Janssen Pharmaceutical K.K.*

Clinical Protocol

Protocol Title
A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group Study of Ustekinumab in Participants With Takayasu Arteritis

Protocol CNTO1275TAT3001; Phase 3
AMENDMENT 2

CNTO1275 (Ustekinumab)

*This study is being conducted by Janssen Pharmaceutical K.K. in Japan. The term "sponsor" is used throughout the protocol to represent Janssen Pharmaceutical K.K

Status: Approved
Date: 15 August 2022
Prepared by: Janssen Pharmaceutical K.K.
EDMS number: EDMS-RIM-226774, 3.0

GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 2	15 August 2022
Amendment 1	7 April 2021
Original Protocol	12 February 2021

Amendment 2 (15 August 2022)

Overall Rationale for the Amendment: To modify eligibility criteria to include a broader population of Takayasu arteritis patients. Additional minor corrections and clarifying changes are also included in this amendment.

The changes to the protocol are described in the table below. For select changes, additions to the text are indicated by underline; deletion of text is shown in ~~strikethrough~~.

Section Number and Name	Description of Change	Brief Rationale
1.3. Schedule of Activities (SoA) Footnotes o. in Table 1	Relapse Confirmation Visit is the second relapse assessment visit after participants meet the relapse criteria once at scheduled visit or unscheduled visit (This visit will be ~~treated~~ defined as "1st relapse visit"). At Relapse Confirmation Visit, TAK Disease Assessment S&S and CRP/ESR must be performed and the other items are not needed to perform if they already performed at "1st relapse visit". If participants are judged as relapse ~~once~~ at "1st relapse visit" only, all the assessments at Relapse Confirmation Visit should be performed. For PK assessment, PK samples will be collected at 1st relapse visit defined above.	Text was revised to clarify the PK sample collection at relapse.
1.3. Schedule of Activities (SoA) Footnotes j. in Table 2	Relapse Confirmation Visit is the second relapse assessment visit after participants meet the relapse criteria ~~for the first time~~ once at scheduled visit or unscheduled visit (This visit will be ~~treated~~ defined as "1st relapse visit"). At Relapse Confirmation Visit, TAK Disease Assessment S&S and CRP/ESR must be performed and the other items are not needed to perform if they already performed at "1st relapse visit". If participants are judged as relapse ~~at the first assessment only~~ at "1st relapse visit" only, all the assessments at Relapse Confirmation Visit should be performed. For PK assessment, PK samples will be collected at 1st relapse visit defined above.	Text was revised to clarify the PK sample collection at relapse.
1.1. Synopsis	This is a Phase 3, randomized, double-blind, placebo-controlled, multicenter, interventional study in participants ≥~~18~~ 15 years and ≤75 years of age with TAK to evaluate the efficacy, safety, pharmacokinetic (PK), and immunogenicity of intravenous (IV) and subcutaneous (SC) ustekinumab.	Updated the inclusion criteria for age to expand participant population.

Section Number and Name	Description of Change	Brief Rationale
4.1. Overall Design 5.1. Inclusion Criteria 1.	This is a Phase 3, randomized, double-blind, placebo-controlled, parallel, multicenter, interventional study in participants ≥~~18~~15 years and ≤75 years of age with TAK to evaluate the efficacy, safety, PK, and immunogenicity of IV and SC ustekinumab. Criterion modified per Amendment 2: 1.1 ~~18~~15 to 75 years of age, inclusive, (at the time of the first administration of study intervention at Week 0). If participant's disease onset of TAK is over 50 years old, appropriate evaluations should be made to distinguish from giant cell arteritis (GCA).	
5.1. Inclusion Criteria 19.	Criterion modified per Amendment 2: 19.1 Are considered eligible according to the following TB screening criteria: d. Within 6 weeks prior to the first administration of the study intervention, has a negative interferon gamma release assays (IGRAs) result, or have a newly identified positive IGRAs result in which active TB has been ruled out and for which appropriate treatment for latent TB has been initiated at least 3 weeks prior to the first administration of the study intervention. A participant whose first IGRA result is indeterminate should have the test repeated. In the event that the second IGRA result is also indeterminate, the participant ~~should be excluded from the study.~~ may be enrolled without treatment for latent TB if active TB is ruled out, their chest radiograph shows no abnormality suggestive of TB (active or old, inactive TB) and the participant has no additional risk factors for TB as determined by the investigator. This determination must be promptly reported to the sponsor and recorded in the participant's source documents and initialed by the investigator.	Text was revised to clarify the inclusion criteria for TB.
5.1. Inclusion Criteria 22. and 23.	Criterion modified per Amendment 2: 22.1 Must sign an ICF (or their legally acceptable representative must sign) indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study. Parent(s) (preferably both if available	Text was added to clarify assent form in the inclusion criteria for informed consent process.

Section Number and Name	Description of Change	Brief Rationale
	or as per local requirements) (or their legally acceptable representative) must sign an ICF indicating that they understand the purpose of, and procedures required for, the study and is/are willing to allow the child to participate in the study. Assent is also required of children capable of understanding the nature of the study (typically 7 years of age and older) as described in Informed Consent Process and Assent Form in Appendix 8: Regulatory, Ethical, and Study Oversight Considerations. Criterion modified per Amendment 2: 23.1 Must sign a separate informed consent form (or their legally-acceptable representative must sign) if he or she agrees to provide an optional (DNA) sample for research. Refusal to give consent for the optional DNA research sample does not exclude a participant from participation in the study. Parent(s) (preferably both if available or as per local requirements) (or their legally acceptable representative) must sign a separate informed consent form if they agree to the child providing an optional DNA sample for research. Assent is also required of children capable of understanding the nature of the study (typically 7 years of age and older) as described in the Informed Consent Process and Assent Form in Appendix 8: Regulatory, Ethical, and Study Oversight Considerations.	
5.2. Exclusion Criteria 3.	Criterion modified per Amendment 2: 3.1 Has received immunosuppressant (s) (including but not limited to MTX, AZA, mycophenolate mofetil [~~(~~MMF~~)~~], oral TAC, oral cyclosporine A) within 4 weeks of first study intervention.	Text was added to clarify the exclusion criteria for the previous medical therapy.
5.2. Exclusion Criteria 8.	Criterion modified per Amendment 2: 8.1 Has previously been treated with any immunomodulatory biologic agent not described in this protocol within 5 half-lives or 12 weeks, whichever is longer, before the first administration of study intervention (eg, abatacept, agents whose mechanism of action targets B cell [eg, belimumab], IL-1 [eg, canakinumab], IL-2, IL-17 [eg,	Text was added to clarify the exclusion criteria for the previous medical therapy.

Section Number and Name	Description of Change	Brief Rationale
	secukinumab, ixekizumab, brodalumab], or IFN pathways).	
5.2. Exclusion Criteria 10.	Criterion modified per Amendment 2: 10.1 Has previously failed to respond Janus kinase (JAK) inhibitor* for the treatment of TAK (ie, lack of efficacy), including but not limited to tofacitinib, baricitinib, upadacitinib. Has received treatment with JAK inhibitor within 5 half-lives before the first administration of study intervention, if discontinued by any reasons excepting lack of efficacy. *Failed response to JAK inhibitor is defined for participants who have received at least 4 weeks treatment of JAK inhibitor and signs and symptoms of TAK persisted for 2 weeks or more and were not able to taper oral GC dose of 7.5 mg/day (prednisolone or equivalent) or less ~~due to recurrence of disease activity of TAK based on clinical judgment of a treating physician. These signs and symptoms of TAK must have occurred ≥2 weeks after receiving JAK inhibitor~~.	Text was revised to clarify the exclusion criteria for the previous medical therapy.
6.8. Concomitant Therapy	~~Oral~~ NSAIDs Participants are permitted to receive stable doses (≥2 weeks prior to first study intervention administration) of ~~oral~~ NSAIDs treatment according to the local practice at the discretion of the investigator. Participants should not initiate ~~oral~~ NSAIDs therapy during DB period, unless discussed and agreed with the sponsor medical monitor.	Text was revised to clarify how to use NSAIDs.
6.8. Concomitant Therapy Prohibited Therapies	Use of additional investigational or approved biologic or non-biologic immunosuppressant or immunomodulatory agents, other than those explicitly allowed in the inclusion/exclusion criteria, are prohibited until safety follow-up visit including but not limited to, the following:	Text was added to clarify the period of Prohibited Therapies.
7.1. Discontinuation of Study Intervention	• The participant requires a prohibited therapy such as an immunomodulatory biologic, cyclophosphamide, or IV glucocorticoid (see Section 6.8).	Text was added to clarify the discontinuation of study intervention.
8. STUDY ASSESSMENTS AND PROCEDURES	If multiple assessments are scheduled for the same timepoint, it is recommended that procedures be performed in the following sequence: patient-reported outcome (PRO) assessments, ECG and	Text was revised to clarify the sequence of study assessment.

<table>
<tr><th>Section Number and Name</th><th>Description of Change</th><th>Brief Rationale</th></tr>
<tr><td>Overview</td><td>vital signs, ~~patient-reported outcome (PRO) assessments,~~ clinical safety laboratory assessments, PK, immunogenicity, and biomarkers.</td><td></td></tr>
<tr><td>9.3. Populations for Analysis Sets</td><td><table>
<tr><th>Population</th><th>Description</th></tr>
<tr><td>Enrolled</td><td>All participants who sign the ICF.</td></tr>
<tr><td>Randomized</td><td>All participants who were randomized in the study.</td></tr>
<tr><td>FAS</td><td>All randomized participants who take at least 1 dose of study intervention. Full analysis set will be the primary population for efficacy analyses.</td></tr>
<tr><td>~~Per-protocol~~</td><td>~~All participants who take at least 1 dose of study intervention and have no major protocol deviations. More details will be provided in the SAP.~~</td></tr>
<tr><td>Safety</td><td>All participants who take at least 1 dose of study intervention.</td></tr>
<tr><td>PK</td><td>All participants who take at least 1 complete dose of ustekinumab and have at least 1 post-dose sample collection.</td></tr>
<tr><td>Immunogenicity</td><td>All participants who take at least 1 dose of ustekinumab and have at least 1 post-dose sample collection.</td></tr>
</table></td><td>Correction of error in writing</td></tr>
<tr><td>9.4.2. Primary Endpoint</td><td>The Kaplan-Meier method will be used to estimate the distribution of time to relapse for each treatment. One efficacy interim analysis is planned and the type I error rate will be controlled at 5% (2-sided). The significant level is to be determined based on the O'Brien-Fleming alpha spending function. Based on this approach, the interim analysis will be performed at a significance level of ~~0.0028~~0.0012 when exactly 15 of 35 events were observed and if the study is not stopped, the final analysis performed at the ~~0.0491~~0.0496 significance level.</td><td>Correction of error in writing</td></tr>
<tr><td>9.5. Interim Analysis</td><td>One efficacy interim analysis is planned after 15 events have been occurred. The O'Brien-Fleming alpha spending function as implemented by the Lan-DeMets method will be used to determine the statistical boundary for early success (2-sided p-value ≤~~0.0028~~0.0012 for the efficacy interim analysis when exactly 15 of 35 events were observed).</td><td>Correction of error in writing</td></tr>
</table>

Section Number and Name	Description of Change	Brief Rationale
10.5. Appendix 5: Definition of Inadequate Response or Intolerance to Biologics	1. Inadequate response to current or prior therapy with TCZ or anti-TNF therapy b. Was not able to taper oral GC dose to 7.5 mg/day (prednisolone or equivalent) or less due to ~~recurrence of~~ disease activity of TAK based on clinical judgment of a treating physician. The ~~recurrence of~~ disease activity of TAK must have ~~occurred~~ persisted ≥2 weeks after receiving one of the biologic treatments.	Text was revised to clarify the definition of inadequate response to biologics based on current clinical practice.
10.8.6. Committees Structure	One efficacy interim analysis is planned after 15 events have been occurred. The O'Brien-Fleming alpha spending function as implemented by the Lan-DeMets method will be used to determine the statistical boundary for early success (2-sided p-value ≤~~0.00280~~0.0012 for the efficacy interim analysis when exactly 15 of 35 events were observed).	Correction of error in writing
Throughout the protocol	Minor grammatical, formatting, and/or spelling changes were made.	Minor errors were noted.

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1. PROTOCOL SUMMARY

1.1. Synopsis

A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group Study of Ustekinumab in Participants With Takayasu Arteritis

STELARA® (ustekinumab) is a fully human immunoglobulin G1 kappa monoclonal antibody which binds with high affinity to the p40 subunit common to both interleukin (IL)-12 and IL-23. This study is designed to evaluate glucocorticoids (GC) sparing effect of ustekinumab in participants with Takayasu arteritis (TAK). The mechanism of action of ustekinumab is prevention of IL-12/23p40 binding to the IL-12R1 cell surface receptor shared by both cytokines. Through this mechanism of action, ustekinumab effectively neutralizes IL-12 T helper (Th)1- and IL-23 Th17-mediated cellular responses and has the potential to offer patients with relapsing TAK a safe and effective steroid sparing therapy.

OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the efficacy of ustekinumab compared to placebo, in combination with oral GC taper regimen, in participants with relapsing TAK	• Time to relapse of TAK according to protocol-defined criteria (see Section 8.1) through the end of DB period
Secondary	
• To evaluate the safety of ustekinumab, in combination with oral GC taper regimen, in participants with relapsing TAK	• Number/proportion of participants with TEAEs through the end of study • Number/proportion of participants with TEAEs by system organ class with a frequency threshold of 5% or more through the end of study • Number/proportion of participants with treatment-emergent SAEs through the end of study
• To evaluate the efficacy of ustekinumab compared to placebo, in combination with oral GC taper regimen, in participants with relapsing TAK as measured by alternative definitions of relapse criteria, relapse rate, GC sparing effects, and disease activity	• Time to relapse of TAK according to Kerr's definition through the end of DB period • Time to relapse of TAK based on clinical symptoms only through the end of DB period • Time to relapse of TAK in each of the 5 categories through the end of DB period • Relapse rate in each of the 5 categories through the end of DB period • Cumulative oral GC dose (prednisolone or equivalent) through the end of DB period • Change from baseline in oral GC dose (prednisolone or equivalent) through the end of DB period

Objectives	Endpoints
	• Number/proportion of participants achieving oral GC dose of 5 mg/day or less through the end of DB period • Change from baseline in imaging evaluation through the end of DB period • Change from baseline in inflammatory markers (CRP, ESR) through the end of DB period
• To evaluate the PK and immunogenicity of ustekinumab, in combination with oral GC taper regimen, in participants with relapsing TAK	• Serum concentrations of ustekinumab in participants receiving ustekinumab through the end of study • Number/proportion of participants who are positive for anti-ustekinumab antibodies in participants receiving active study intervention through the end of study
Exploratory	
• To explore changes in the PRO instruments and the physician reported outcome	• Changes from baseline PROs through the end of study SF-36 PtGA of disease activity on VAS FACIT-Fatigue • Change from baseline on physician reported outcome: PhGA through the end of study
• To explore the efficacy of ustekinumab in combination with oral GC taper regimen, in participants with relapsing TAK during OLE period	• Number/proportion of participants who experience relapse of TAK according to protocol-defined criteria during OLE period • Number/proportion of participants who experience relapse of TAK according to Kerr's definition during OLE period • Number/proportion of participants who experience relapse of TAK based on clinical symptoms only during OLE period • Number/proportion of participants who experience relapse of TAK in each of the 5 categories during OLE period • Cumulative oral GC dose (prednisolone or equivalent) during OLE period • Change from baseline in oral GC dose (prednisolone or equivalent) during OLE period

	• Number/proportion of participants achieving oral GC dose of 5 mg/day or less during OLE period • Change from baseline in imaging evaluation during OLE period • Change from baseline in inflammatory markers (CRP, ESR) during OLE period

Abbreviations: CRP=C-reactive protein; DB=double-blind; ESR=erythrocyte sedimentation rate; FACIT=Functional Assessment of Chronic Illness Therapy; GC=glucocorticoid; OLE=open-label extension; PK=pharmacokinetic; PRO=patient reported outcome; PhGA=Physician's Global Assessment of Disease Activity; PtGA=Patient's global assessment; TAK=Takayasu arteritis; SAE=serious adverse event; SF-36=short-form 36; TEAE=treatment-emergent adverse event; VAS=visual analog scale

Hypothesis

The hypothesis is that ustekinumab will prolong time to relapse while attempting corticosteroids tapering as compared with placebo in participants with TAK.

OVERALL DESIGN

This is a Phase 3, randomized, double-blind, placebo-controlled, multicenter, interventional study in participants ≥15 years and ≤75 years of age with TAK to evaluate the efficacy, safety, pharmacokinetic (PK), and immunogenicity of intravenous (IV) and subcutaneous (SC) ustekinumab.

The total duration of the study will be approximately 2 years, consisting of (1) a ≤6-week screening period in which a participant's eligibility will be reviewed prior to administration of the first dose of study intervention; (2) a double-blind (DB) period: up to participant's relapse of TAK or end of the DB period (a total of 35 relapse events occur), whichever is earlier; (3) an open-label extension (OLE) period: 52 weeks or 32 weeks from the first SC administration after the end of DB period, whichever is later; and (4) a safety follow-up period: 16 weeks.

Participants must have experienced TAK relapse within 12 weeks prior to administration of study intervention and the relapse must have occurred at oral GC dose of at least 7.5 mg/day (prednisolone or equivalent). The relapse must have been adequately treated with ≥15 mg/day of prednisone or equivalent and participants must subsequently have achieved remission at least 1 week prior to the first administration of the study intervention.

Approximately 50 participants will be randomized at Week 0 in a blind fashion to 1:1 ratio stratified by oral GC dose at Week 0 (<0.5 mg/kg/day, ≥0.5 mg/kg/day of prednisolone or equivalent) and status of previous biologic medication (bio-nonfailure or bio-failure) to receive either ustekinumab or matching placebo with the following treatment regimens during the DB period until participants develop relapse or a total of 35 relapse events have occurred.

Ustekinumab group: The participants will receive body weight-range based IV administration of ustekinumab (~6 mg/kg) at Week 0 followed by ustekinumab 90 mg SC administered 8 weeks after the initial IV dose and then every 8 weeks (q8w) thereafter.

Placebo group: The participants will receive IV administration of placebo at Week 0 followed by placebo SC administered 8 weeks after the initial IV dose and then q8w thereafter.

During the DB period, participants will receive IV administration of study intervention followed by SC administration of study intervention, with starting the protocol defined oral GC taper regimen from Week 2 visit (baseline oral GC dose will be stable until Week 2). Participants who develop relapse will receive rescue medication of oral GC that is at least double the oral GC dose at the relapse. These participants will

be assessed whether they achieve remission at the next scheduled administration visit from the relapse (Week OL-0) to enter OLE phase as the Escape arm regardless of remission status, and then receive IV administration of ustekinumab at Week OL-0 followed by ustekinumab 90 mg SC administered 8 weeks after the initial IV dose, then q8w thereafter. Escape arm is identical to OLE period except participants in Escape arm will receive IV ustekinumab at Week OL-0 instead of SC ustekinumab. Participants in Escape arm may receive continuous administrations of IV ustekinumab with 8-week interval once in the study if they relapse prior to Week 8.

When a total of 35 relapse events occur, the DB period will end and rest of the participants in the DB period will enter OLE period except for participants who reach oral GC dose of 5 mg/day (prednisolone or equivalent) or less in the placebo group to avoid unnecessary administration of ustekinumab for those who are considered to be placebo responders. These participants will continue or switch (if participants receive placebo in DB period) to receive SC ustekinumab administered q8w with maintaining the originally dosing schedule. For these participants, the first dosing visit from the end of DB period will be regarded as Week OL-0. In transition period from the end of DB period to completion of the database lock (DBL), participants who reach oral GC dose of 5 mg/day (prednisolone or equivalent) or less at the end of DB period will continue to receive study intervention assigned in DB period until completion of the DBL for DB period in order to maintain the blind. The data occurred in the transition period will be handled as that of OLE period. Participants assigned to the placebo group who reach oral GC dose of 5 mg/day (prednisolone or equivalent) or less at the end of DB period will terminate the study intervention administration and conduct early-termination (early-term) visit after completion of the DBL for DB period.

When 35 events occur, further recruitment will end.

During OLE period, participants will receive SC administration of ustekinumab at Week OL-0 and followed by SC administration of ustekinumab with oral GC taper of investigator's discretion for 52 weeks (Week OL-52) or until 32 weeks from the first SC administration after the end of DB period, whichever is later. Safety follow-up visit will be conducted 16 weeks after last SC ustekinumab administration.

A long-term extension (LTE) study to evaluate further long-term effects of ustekinumab may be conducted if the sponsor deems that ustekinumab treatment is beneficial to study participants based on results of the primary analysis. Participants who complete their participation in OLE period may be eligible to enter the LTE and continue to receive 90 mg SC ustekinumab q8w. Details will be provided in a separate LTE protocol or amendment of this protocol.

The efficacy interim analysis is planned to determine early success when relapse of TAK occurs in 15 events.

The primary efficacy analysis will be performed when relapse of TAK occurs in 35 events with additional secondary endpoints to be analyzed.

A first DBL will occur after a total of 15 events in relapse of TAK occurred for an interim analysis. A second DBL will occur after a total of 35 events in relapse of TAK occurred. A third DBL will occur approximately 24 weeks after the second DBL. A fourth DBL will occur when all participants have either completed their final study visit or terminated study participation prior to their final visit. Additional DBLs other than the ones specified above may be performed.

Investigative study sites and participants will remain blinded to initial treatment assignment until the end of the study, except the assignment for participants who reach oral GC dose of 5 mg/day (prednisolone or equivalent) or less when a total of 35 relapse events occur will be revealed after the second DBL. Identification of sponsor personnel who will have access to the unblinded participant data will be documented prior to unblinding to the sponsor.

The primary endpoint of this study is the time taken to relapse of TAK according to protocol-defined criteria through the end of DB period.

An external Independent Data Monitoring Committee (IDMC) will be commissioned for this study to ensure the continuous safety and well-being of the participants enrolled in this study.

An interim analysis will be implemented to evaluate early efficacy after 15 relapse events occurred. This efficacy analysis is unblinding and IDMC recommend the continuation or early termination of the DB period based on the results of interim analysis. The sponsor will decide the continuation and termination of DB period based on the recommendation by IDMC. If the sponsor decides early termination of DB period, all participants will be rolled over to the OLE period except for participants assigned to the placebo group who reach oral GC dose of 5 mg/day (prednisolone or equivalent) or less at the end of DB period. In transition period, follow the same process as 35 relapse events occurrence. The sponsor will continue to enroll participants into OLE period until reaching a total of approximately 50 participants. Participants who are eligible according to Inclusion/Exclusion criteria in this protocol will directly enter to OLE period to receive body weight-range based IV administration of ustekinumab (~6 mg/kg) at Week OL-0 and followed by ustekinumab 90 mg SC q8w with oral GC taper at investigator's discretion for 52 weeks (Week OL-52). Safety follow-up visit will be conducted 16 weeks after last SC ustekinumab administration.

NUMBER OF PARTICIPANTS

Approximately 50 participants will be enrolled in this study.

EFFICACY EVALUATIONS

TAK Disease Signs and Symptoms

Efficacy of ustekinumab in TAK will be assessed from the presence of TAK activity including investigator assessment of signs and symptoms of TAK.

Physician Global Activity-Visual Analog Scale (PhGA-VAS)

Physician Global Activity is partially validated tool to measure the global evaluation by the physician of the participant's overall disease activity at the time of assessment using a 10 cm VAS.

Imaging

In this study, imaging assessment will be performed using computed tomography angiography (CTA) or magnetic resonance angiography (MRA), if CTA is not feasible, by the dedicated radiologist or physician from study site (or designee) at specified time point in Schedule of Activities (Section 1.3). Imaging assessment will include the aorta and its major branches from the terminal of the common carotid artery (internal and external carotid branches) to the abdominal aortic terminal (common iliac artery branch) and will be performed in multiple planes using contrast media agent. When imaging assessment has been performed within 12 weeks prior to scheduled imaging assessment visit, imaging assessment may not be performed and the prior results will be used for this scheduled assessment.

(1) Vessel involvement such as stenosis, obstruction, and aneurysm; (2) Arterial wall thickness; and (3) The presence of mural contrast enhancement and oedema (MRA only) will be assessed for imaging evaluation on disease activity of TAK. Study independent central imaging assessment will be used to analyze all computed tomography or MRA scans included in this study. The central imaging assessment of imaging will be blinded to the clinical data.

Short Form 36 (SF-36)

The SF-36 is a widely used tool that assesses the global medical quality of life, functional health, and well-being of general and specific populations.

Patient Global Activity-Visual Analog Scale (PtGA-VAS)

Patient Global Activity is partially validated tool to measure the global evaluation by the participant of the participant's overall disease activity at the time of assessment using a 10 cm VAS.

Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue

The Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scale version 4.0 is a 13-item questionnaire formatted for self-administration that assesses patient- reported fatigue and its impact upon daily activities and functions over the past 7 days.

PHARMACOKINETIC EVALUATIONS

Blood samples will be collected to evaluate the serum PK of ustekinumab as specified in Schedule of Activities (Section 1.3). Serum samples will be analyzed to determine concentrations of ustekinumab using a validated, specific, and sensitive immunoassay method by or under the supervision of the sponsor.

IMMUNOGENICITY EVALUATIONS

Serum samples will be evaluated for the presence of anti-ustekinumab antibodies and the titer according to the Schedule of Activities (Section 1.3). Additionally, serum samples should be collected at the final visit from participants who are discontinued from treatment or withdrawn from the study. Serum samples that test positive for anti-ustekinumab antibodies will be further characterized to determine if anti-ustekinumab antibodies could neutralize the biological effects of ustekinumab in vitro (ie, neutralizing antibodies to ustekinumab). These samples will be tested by the sponsor or sponsor's designee.

PHARMACODYNAMIC AND BIOMARKER EVALUATIONS

Assessments will be performed to identify biomarkers that are relevant to ustekinumab treatment and/or TAK, where local regulations permit. These may include, but are not limited to, the evaluation of relevant biomarkers in serum, whole blood, and peripheral blood mononuclear cells collected as specified in the Schedule of Activities (Section 1.3).

PHARMACOGENOMIC (DNA) EVALUATIONS

A pharmacogenomic blood sample will be collected from participants who consent separately to this component of the study to allow for pharmacogenomic research, where local regulations permit. Participation in the pharmacogenomic research is optional.

Whole blood samples will be collected for genetic analyses at screening as specified in the Schedule of Activities (Section 1.3) if within the maximum blood volume allowed.

SAFETY EVALUATIONS

Safety evaluations will include assessment of adverse events (AEs), concomitant medications, pregnancy testing, administration reactions, chemistry and hematology laboratory tests, immunogenicity, vital signs, and general physical examinations. In addition, electrocardiogram, chest x-ray, chest CT, human immunodeficiency virus, hepatitis B, hepatitis C, and tuberculosis testing will be required at screening.

STATISTICAL METHODS

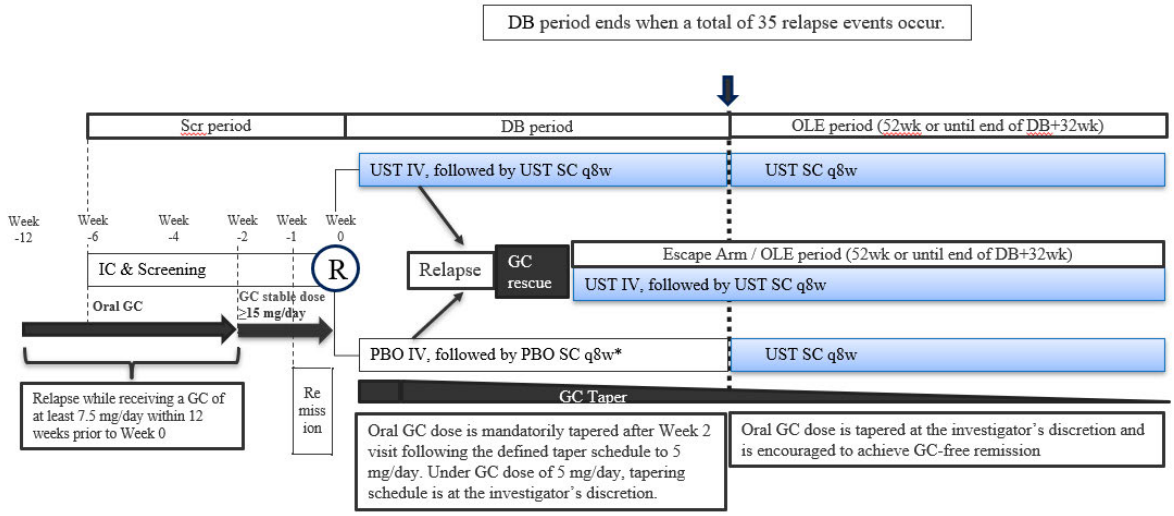
Statistical analysis will be done by the sponsor or under the authority of the sponsor. Specific details of the statistical methods to be used to analyze the efficacy and safety data will be provided in the statistical analysis plan. For the primary endpoint of time to relapse, primary analysis will consist of test using a Cox proportional hazard regression model for comparison between 2 treatment groups. The hazard ratio and its 2-sided 95% confidence intervals will be also presented. The Kaplan-Meier method will be used to estimate the distribution of time to relapse for each treatment. All reported AEs with onset during treatment phase

(ie, treatment adverse events [TEAEs] and AEs that have worsened since baseline) will be included in analysis. For each AE, the percentage of participants who experience at least 1 AE will be summarized by treatment group. Adverse events will also be summarized based on patient-year by treatment group.

Summaries, listings, or participants narratives may be provided, as appropriate, for those participants who die, who discontinue treatment due to AE, or who experience a serious adverse event (SAE). Descriptive statistics will be calculated for each laboratory analyte at baseline and for observed values and changes from baseline at each scheduled time point. Clinically relevant abnormalities will be evaluated by frequency tabulations. Descriptive statistics of weight, temperature, pulse/heart rate, respiratory rate, and blood pressure (right and left hands separately) values and changes from baseline will be summarized at each scheduled time point. Serum ustekinumab concentrations will be summarized with descriptive statistics at each sampling time point. A listing of participants who are positive for anti-ustekinumab antibodies will be provided.

1.2. Schema

Figure 1: Schematic Overview of the Study



Abbreviations: DB=double-blind; DBL=database lock; Early-Term=early-termination; GC=glucocorticoids; IC=informed consent; IV=intravenous; OLE=open-label extension; UST=ustekinumab; PBO=placebo; SC=subcutaneous; Scr=screening; US=ustekinumab; q8w=every 8 weeks.
* When a total of 35 relapse events occur, participants who reach oral GC dose of 5 mg/day (prednisolone or equivalent) or less at the end of the DB period in the placebo group will terminate the study intervention administration and conduct early-term visit.

1.3. Schedule of Activities

Table 1: Schedule of Activities (Screening through the Double-Blind Period)

Study Week	Screening	0	2	4	8	12	16	20	24	Non- dosing Visit from Week 28[n]	Dosing Visit from Week 32[n]	Relapse Confirmation Visit[o]	Early-termination[p]	Safety F/U[p]	Notes
Acceptable deviation (days)	**(≤6weeks)**	**0**	**±4**	**±4**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**0**	**±7**	**±7**	
Study Procedure[a]															
Screening/Administrative															
Informed consent/assent (ICF) [b]	X														Must be signed before first study-related activity.
Pharmacogenomics (DNA) (optional) ICF[c]	X														
Demographics	X														
Review medical history requirements	X														
Inclusion/exclusion criteria[d]	X	X													Minimum criteria for the availability of documentation supporting the eligibility criteria are described in Source Documents section of Section 10.8, Appendix 8: Regulatory, Ethical, and Study Oversight Considerations. Check clinical status again before first dose of study intervention.
Review prestudy therapy	X														
Review preplanned surgery/procedure(s)	X														
Study Intervention Administration															
Dispense/administer study intervention		X			X		X		X		X				

Study Week	Screening	0	2	4	8	12	16	20	24	Non- dosing Visit from Week 28[n]	Dosing Visit from Week 32[n]	Relapse Confirmation Visit[o]	Early-termination[p]	Safety F/U[p]	Notes
Acceptable deviation (days)	**(≤6weeks)**	**0**	**±4**	**±4**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**0**	**±7**	**±7**	
Issue participant diary cards	X	X	X	X	X	X	X	X	X	X	X	X	X		
Participant diary cards returned to clinic		X	X	X	X	X	X	X	X	X	X	X	X	X	
Efficacy Assessments															
ClinROs															
TAK Disease Assessment S&S	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Imaging[e]	X								X		X[e]	X[e]			
PhGA		X			X		X		X		X	X	X		
PROs[f]															
PtGA		X			X		X		X		X	X	X		
SF-36		X			X		X		X		X	X	X		
FACIT-Fatigue		X			X		X		X		X	X	X		
Safety Assessments															
Physical examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Height	X														
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
12-lead ECG[g]	X								X			X	X		
Chest x-ray[h]	X														
TB evaluation[i]	X	X			X		X		X		X	X	X	X	
IGRAs (T-SPOT.TB test or QFT)	X														
HIV, HBV, and HCV screening	X														
Urine pregnancy test[j]	X	X			X		X		X		X	X	X	X	Inclusion Criteria and Section 8, STUDY ASSESSMENTS AND PROCEDURES
Infusion or injection-site reaction evaluation[k]		X			X		X		X		X				
Review concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Glucocorticoid tapering[l]			X	X	X	X	X	X	X	X	X				
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Study Week	Screening	0	2	4	8	12	16	20	24	Non- dosing Visit from Week 28[n]	Dosing Visit from Week 32[n]	Relapse Confirmation Visit[o]	Early-termination[p]	Safety F/U[p]	Notes
Acceptable deviation (days)	**(≤6weeks)**	**0**	**±4**	**±4**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**0**	**±7**	**±7**	
Clinical Laboratory Tests															
Chemistry	X	X		X	X	X	X	X	X	X	X	X	X	X	
Hematology	X	X		X	X	X	X	X	X	X	X	X	X	X	
Coagulation	X														
CRP, ESR	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urine analyses (spot urine)															
Urinalysis (dipstick, all participants)	X				X		X		X		X	X	X	X	
Urine sediment analysis	X														
Pharmacokinetics/Immunogenicity															
Serum ustekinumab concentrations		2X[q]	X	X	X	X	X	X	X	X	X	X	X	X	
Antibodies to ustekinumab		X		X		X			X		X		X		
Pharmacogenomics (DNA)															
HLA-B52, IL-12B (Optional) [m]	X														
Blood sample collection (Optional) [m]	X														
Blood Biomarkers (where local regulations permit)															
Serum biomarkers	X	X			X							X	X		
Whole blood (RNA)	X	X			X							X	X		
PBMC (cellular analysis)	X	X			X							X	X		

Abbreviations: CRP C reactive protein; CTA computed tomography angiography; DB double blind; DNA deoxyribonucleic acid; ECG electrocardiogram; ESR erythrocyte sedimentation rate; FACIT The Functional Assessment of Chronic Illness Therapy; FSH follicle stimulating hormone; F/U follow up; GC glucocorticoid; HBV hepatitis B virus; HCV hepatitis C virus; HIV human immunodeficiency virus; HLA Human leucocyte antigen; HRCT high resolution computer tomography; ICF informed consent form/assent form; IGRA interferon gamma release assay; MRA magnetic resonance angiography; OLE open label extension; PBMC peripheral blood mononuclear cell; PhGA Physician Global Activity; PRO patient reported outcome; PtGA Patient Global Activity; QFT QuantiFERON TB Gold; RNA ribo oxynucleic acid; SF 36 short form 36; S&S Signs and Symptoms, TAK Takayasu arteritis; TB tuberculosis.

Footnotes:

a. Unless otherwise specified, all assessments (except for injection-site evaluation) are to be completed prior to study intervention administration.

b. Must be signed before first study-related activity.

c. To participate in the optional DNA research component of this study, participants must sign the DNA research ICF indicating willingness to participate. Blood samples for pharmacogenomic and epigenetic research will be collected only from participants who give informed consent for DNA research.

d. Minimum criteria for the availability of documentation supporting the eligibility criteria will be described in the full protocol. Check clinical status again before first dose of study intervention.
e. Imaging assessment will be performed during screening period, every 24 weeks from Week 0 (eg, Week 24, 48, 72), and Relapse Confirmation Visit using CTA or MRA, if CTA is not feasible. When imaging assessment has been performed within 12 weeks prior to scheduled imaging assessment visit, imaging assessment may not be performed, and the prior results will be used for this scheduled assessment. Imaging assessment for screening visit should be performed and the prior imaging results for screening assessment will not be allowed. Additional imaging assessment may be performed if investigator deems a need for further evaluation of participant's disease activities. At Relapse Confirmation Visit, imaging assessment will be performed within 4 weeks after the investigator confirms participants meets the relapse criteria and it is recommended to be performed prior to Week OL-0.
f. All PRO assessments should be conducted in the order listed in the above Schedule of Activities table. Whenever possible, PRO assessments should be conducted before any tests, procedures, or other consultations for that visit to prevent influencing participants' perceptions.
g. A 12-lead ECG will be performed locally. Participants should rest in a supine position for at least 5 minutes before ECG recording and should refrain from talking or moving arms or legs.
h. Chest x-ray posterior/anterior and lateral views must be taken within 3 months prior to the first administration of study intervention for TB detection. If x-ray is not feasible, Chest CT can be substituted for x-ray.
i. TB evaluation includes an assessment of recent exposure or risk of TB including new or chronic cough, fever, night sweats, unintentional weight loss or recent contact with someone with active TB. If TB is suspected at any time during the study, a chest x-ray, chest HRCT, and T-SPOT.TB test or QFT should be performed.
j. In addition to the urine screening evaluation, a serum pregnancy test may be conducted at any time at the discretion of Investigator or participant. Urine pregnancy tests may be conducted more frequently (eg, monthly basis). Urine pregnancy tests may not be necessary if a participant is considered a postmenopausal state defined as no menses for 12 months without an alternative medical cause and a high FSH level (>40 IU/L or mIU/mL) during the study.
k. Participants should be monitored for the occurrence of infusion reactions for at least 1 hour after IV infusion and injection-site reactions for at least 30 minutes following SC injection.
l. See Section 6.8 for information on oral GC tapering.
m. The pharmacogenomic (DNA) sample should be collected at the specified time point; however, if necessary, it may be collected at a later time point without constituting a protocol deviation.
n. After Week 24, participants will visit the study site every 4 weeks until they develop relapse or end of DB period, whichever is earlier. For Non-dosing Visit, participants will visit the study site every 8 weeks from Week 28. For Dosing Visit, participants will visit the study site every 8 weeks for study intervention administration from Week 32.
o. Relapse Confirmation Visit is the second relapse assessment visit after participants meet the relapse criteria once at scheduled visit or unscheduled visit (This visit will be defined as "1st relapse visit"). At Relapse Confirmation Visit, TAK Disease Assessment S&S and CRP/ESR must be performed and the other items are not needed to perform if they already performed at "1st relapse visit". If participants are judged as relapse at "1st relapse visit" only, all the assessments at Relapse Confirmation Visit should be performed.
   For PK assessment, PK samples will be collected at 1st relapse visit defined above.
p. Participants, who permanently discontinue study intervention administrations before the end of DB period or their relapse, must undergo procedures for early termination and return approximately 16 weeks after last study intervention administration to undergo procedures for safety F/U visits.
q. At Week 0, 2 separate samples for serum ustekinumab concentrations (indicated by "2X" in the Schedule above) will be collected (1 sample will be collected prior to IV infusion and the other collected 1 hour after the end of the infusion) for all participants.

NOTE
* Participants who do not experience relapse at the end of DB period will enter OLE period at the participants' next dosing visit regarded as Week OL-0.

Table 2: Schedule of Activities (Open-Label Extension Period)

Study Week	OL-0[i]	OL-8	OL-16	OL-24	OL-32	OL-40	OL-48	Relapse Confirmation Visit[j]	OL-52 or Early-termination[k]	Safety F/U[k]	Every 8 week visit from Week OL-56[l]	Notes
Acceptable deviation (days)	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	
Study Procedure[a]												
Study Intervention Administration												
Dispense/administer study intervention	X[m]	X	X	X	X	X	X				X	
Issue participant diary cards	X	X	X	X	X	X	X	X	X		X	
Participant diary cards returned to clinic	X	X	X	X	X	X	X	X	X	X	X	
Efficacy Assessments												
ClinROs												
TAK Disease Assessment S&S	X	X	X	X	X	X	X	X	X	X	X	
Imaging[b]	X			X			X	X[b]			X[b]	
PhGA	X			X			X	X	X		X	
PROs[c]												
PtGA	X			X			X	X	X		X	
SF-36	X			X			X	X	X		X	
FACIT-Fatigue	X			X			X	X	X		X	
Safety Assessments												
Physical examination	X	X	X	X	X	X	X	X	X	X	X	
Vital signs	X	X	X	X	X	X	X	X	X	X	X	
Height	X											
Weight	X	X	X	X	X	X	X	X	X	X	X	
12-lead ECG[d]	X			X			X	X	X			
TB evaluation[e]	X	X	X	X	X	X	X	X	X	X	X	
Urine pregnancy test[f]	X	X	X	X	X	X	X	X	X	X	X	
Infusion or injection-site reaction evaluation[g]	X	X	X	X	X	X	X				X	
Review concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	

Study Week	OL-0[i]	OL-8	OL-16	OL-24	OL-32	OL-40	OL-48	Relapse Confirmation Visit[j]	OL-52 or Early-termination[k]	Safety F/U[k]	Every 8 week visit from Week OL-56[l]	Notes
Acceptable deviation (days)	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	
Glucocorticoid tapering[h]	X	X	X	X	X	X	X		X[n]		X	
Adverse events	X	X	X	X	X	X	X	X	X	X	X	
Clinical Laboratory Tests												
Chemistry	X	X	X	X	X	X	X	X	X	X	X	
Hematology	X	X	X	X	X	X	X	X	X	X	X	
CRP, ESR	X	X	X	X	X	X	X	X	X	X	X	
Urine analyses (spot urine)												
Urinalysis (dipstick, all participants)	X		X		X		X		X	X		
Pharmacokinetics/ Immunogenicity												
Serum ustekinumab concentrations	2X[o]	X	X	X	X	X	X	X	X	X	X	
Antibodies to ustekinumab	X	X		X		X					X	
Blood Biomarkers (where local regulations permit)												
Serum biomarkers	X							X	X			
Whole blood (RNA)	X							X	X			
PBMC (cellular analysis)	X							X	X			

Abbreviations: CRP C reactive protein; CTA computed tomography angiography; DB double blind; DNA deoxyribonucleic acid; ESR erythrocyte sedimentation rate; ICF informed consent form/assent form; ECG electrocardiogram; FACIT The Functional Assessment of Chronic Illness Therapy Fatigue; FSH follicle stimulating hormone; F/U follow up; HRCT high resolution computer tomography; MRA magnetic resonance angiography; OLE open label extension; PBMC peripheral blood mononuclear cell; PRO patient reported outcome; PhGA Physician Global Activity; PtGA Patient Global Activity; RNA ribonucleic acid; SF 36 short form 36; S&S Signs and Symptoms, TAK Takayasu arteritis; TB tuberculosis; QFT QuantiFERON TB Gold.

Footnotes:

a. Unless otherwise specified, all assessments (except for injection-site evaluation) are to be completed prior to study intervention administration.

b. Imaging assessment will be performed at Week OL-0 and every 24 weeks from Week OL-0 (eg, Week OL-24, 48, 72, 96,120), and Relapse Confirmation Visit using CTA or MRA, if CTA is not feasible. When imaging assessment has been performed within 12 weeks prior to scheduled imaging assessment visit, imaging

assessment will not be performed and the prior results will be used for this scheduled assessment. At Relapse Confirmation Visit, imaging assessment will be performed within 4 weeks after the investigator confirms participant meets the relapse criteria.

c. All PRO assessments should be conducted in the order listed in the above Schedule of Activities table. Whenever possible, PRO assessments should be conducted before any tests, procedures, or other consultations for that visit to prevent influencing participants' perceptions.

d. A 12-lead ECG will be performed locally. Participants should rest in a supine position for at least 5 minutes before ECG recording and should refrain from talking or moving arms or legs.

e. TB evaluation includes an assessment of recent exposure or risk of TB including new or chronic cough, fever, night sweats, unintentional weight loss or recent contact with someone with active TB. If TB is suspected at any time during the study, a chest x-ray, chest HRCT, and T-SPOT.TB test or QFT should be performed.

f. In addition to the urine screening evaluation, a serum pregnancy test may be conducted at any time at the discretion of Investigator or participant. Urine pregnancy tests may be conducted more frequently (eg, monthly basis). Urine pregnancy tests may not be necessary if a participant is considered a postmenopausal state defined as no menses for 12 months without an alternative medical cause and a high FSH level (>40 IU/L or mIU/mL) during the study.

g. Participants should be monitored for the occurrence of infusion reactions for at least 1 hour after IV infusion and injection-site reactions for at least 30 minutes following SC injection.

h. See Section 6.8 for information on oral GC tapering.

i. Week OL-0 is the participant's next dosing visit from Relapse Confirmation Visit or the end of DB period.

j. Relapse Confirmation Visit is the second relapse assessment visit after participants meet the relapse criteria once at scheduled visit or unscheduled visit (This visit will be defined as "1st relapse visit"). At Relapse Confirmation Visit, TAK Disease Assessment S&S and CRP/ESR must be performed and the other items are not needed to perform if they already performed at "1st relapse visit". If participants are judged as relapse at "1st relapse visit" only, all the assessments at Relapse Confirmation Visit should be performed.
For PK assessment, PK samples will be collected at 1st relapse visit defined above.

k. Participants, who permanently discontinue study intervention administrations before Week OL-52, must undergo procedures for early termination and return approximately 16 weeks after last study intervention administration to undergo procedures for safety F/U visits.

l. OLE period continues through Week OL-52 or until 32 weeks from the first SC administration after the end of DB period , whichever is later. If participants complete Week OL-52 visit earlier than 32 weeks from the first SC administration after the end of DB period, they will be continuing to visit the study site every 8 weeks from Week OL-56 until the end of OLE period.

m. Participants who are in escape arm will receive IV ustekinumab. Participants who are rolled over from DB period will receive SC ustekinumab.

n. At early-termination visit, GC tapering is not needed.

o. At Week OL-0, 2 separate samples for serum ustekinumab concentrations (indicated by "2X" in the Schedule above) will be collected (1 sample will be collected prior to IV infusion and the other collected 1 hour after the end of the infusion) for all participants. For participants who receive SC administration at Week OL-0, a single blood sample at predose will be collected.

2. INTRODUCTION

STELARA® (ustekinumab) is a fully human immunoglobulin G1 kappa monoclonal antibody which binds with high affinity to the p40 subunit common to both interleukin (IL)-12 and IL-23. The mechanism of action of ustekinumab is prevention of IL-12/23p40 binding to the IL-12Rβ1 cell surface receptor shared by both cytokines. Through this mechanism of action, ustekinumab effectively neutralizes IL-12 T helper (Th)1- and IL-23 Th17-mediated cellular responses.

Ustekinumab (subcutaneous [SC] formulation) has been approved globally for the treatment of psoriasis in adults and pediatric and for psoriatic arthritis (PsA) in adults. Ustekinumab has also been approved for the treatment of Crohn's disease (CD) and ulcerative colitis (UC) in adults using intravenous (IV) induction dosing followed by SC maintenance dosing.

Takayasu arteritis is a rare, chronic large vessel vasculitis that affects the aorta and its primary branches, coronary arteries, and pulmonary arteries. Its principal manifestations are systemic inflammation, pain due to vasculitis, vascular stenosis, occlusion, dilatation, and poses problems including disorders of various organs due to disturbance of the blood flow and aneurysms even after remission of inflammation. The symptoms are not only diverse but also often non-specific and many cases are still considered to be left undiagnosed. Frequently observed symptoms include signs of ischemia of the upper limbs such as a difference in blood pressure between the left and right arms and the absence of pulses in the upper limb, fever, malaise, neck pain, pain in various regions, and dizziness. In refractory cases, vascular remodeling progresses and leads to serious outcomes. Complications vary widely including those caused by stenotic lesions and dilated lesions such as aortic insufficiency, aortic aneurysm, aortic dissection, ischemic attacks of the brain, pulmonary infarction, angina pectoris, subclavian steal syndrome, atypical coarctation of the aorta, and renovascular hypertension and tend to occur in large numbers.

Takayasu arteritis is considered to be caused by destruction of elastic arteries, particularly aorta, by autoimmune mechanisms triggered by environmental factors including infection based on genetic factors. Human leucocyte antigen (HLA)-B52 has been reported to be related to the pathogenesis of this disease (Isohisa 1978; Kimura 1996). In addition, one genome-wide association study identified a locus near the IL-12B gene (lead variant rs6871626) was significantly associated with disease susceptibility for TAK (Terao 2013). This lead variant is within a poorly characterized long non-coding ribonucleic acid (RNA) gene (69 KB) close to the IL-12B gene. No functional data is available to link this single nucleotide polymorphisms (SNP) directly to IL-12B; however, the same lead SNP has been reported to be associated with inflammatory bowel disease (IBD), UC, and ankylosing spondylitis. Thus, although the role of the IL-12/23 pathway in TAK pathophysiology has been suggested, more data is needed to understand the link between the genetic signal and the IL-12B gene.

Additionally, inflammatory cells, particularly Th17 and Th1 cells and cytokines, including IL-6 (Alibaz 2015; Park 2006), IL-8 (Alibaz 2015), IL-12 (Verma 2005), IL-18 (Alibaz 2015; Park 2006), IL-23 (Misra 2016), and tumor necrosis factor (TNF)-α (Park 2006) are elevated in

patients with TAK (Alibaz 2015; Verma 2005; Misra 2016). Furthermore, IL-6, IL-12, IL-17, and interferon (IFN)-γ are highly expressed in the aortic tissues in patients with TAK (Kong 2016).

There are strong associations between TAK and IBD. Several case series reported that TAK patients also have IBD, and frequency of IBD in TAK patients was reported to be between 6.3% and 9.3% (Kilic 2016). This co-existence of these 2 diseases cannot be accepted as incidental considering prevalence of these 2 diseases. In addition, 1 literature review identified 144 patients with large vessel vasculitis and IBD, of which 133 patients were with TAK and IBD (Sy 2016). TAK and IBD have many common characteristics, including the age of onset, female predominance, granulomatous inflammation, and benefit from anti-TNF treatment. HLA-B52, HLA-DR2, and IL-12B were suggested to be the genetic determinants for both UC and TAK (Morita 1996; Terao 2015). Furthermore, recently autoantibodies specific to TAK have been identified among autoimmune rheumatic diseases (autoantibodies against endothelial protein C receptor [EPCR] and scavenger receptor class B type 1 [SR-B1]), and each accounted for one-third of the patients with TAK. Surprisingly, 68.6% of 35 primary UC patients had anti-EPCR autoantibodies, suggesting common pathophysiology among TAK and UC (Mutoh 2020). IL-12/23 inhibition has been shown to be effective in UC and CD thus supporting a potential case for its investigation in TAK.

TAK is prevalent in Asia and Middle East and females tend to be more often affected in both regions.

In Japan, approximately 4,433 patients with this disease have been registered (Japan Intractable Disease Information Center). The male/female ratio is about 1:9 and the age of onset in women peaks around 20 years.

Glucocorticoids are used empirically as the first-line treatment to induce remission in TAK, however, due to the known increased risk with long term use of GC (eg, cataracts, osteoporosis, infection, adrenal insufficiency) forces to taper GC dose to at least physiological level (7.5 mg/day [prednisolone or equivalent]) with maintaining remission.

It is reported that supraphysiological doses of GC (above 7.5 mg/day [prednisolone or equivalent]) increases the 10-year risk of some complications (Dora 2013). High relapse rate has been reported during GC taper in TAK. Immunosuppressants such as methotrexate, azathioprine (AZA), tacrolimus (TAC), cyclosporine A, and mycophenolate mofetil has been used as a concomitant therapy to enhance or spare GC effects in TAK, but evidence of their GC sparing effects is limited. To date, tocilizumab (TCZ) has been the only approved biologic agent demonstrating a trend of its GC sparing effects in patients with TAK in Japan while attempting GC taper. However, treatment with TCZ is still insufficient as a GC sparing agent in TAK since 49.4% of the subjects relapsed at Week 24 during GC taper in the TAKT trial (Nakaoka 2018). A combination therapy of GC and TCZ notably increased the risk of infections, which requires careful attention to potential infections during TCZ treatment in TAK (Common Technical Document Module 2). In addition, bowel perforation, laboratory abnormalities in liver function, lipids, and other parameters are often associated with TCZ treatments, which would limit a wide usage of TCZ in TAK management. Furthermore, IL-6 receptor blockade with TCZ abrogates the hepatic synthesis of

acute-phase reactants and renders C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) measurement unreliable for the purpose of monitoring disease activity in TAK. Considering that TAK often affects relatively younger women, less frequent dosing would be preferred to the currently approved weekly SC administration with TCZ in terms of convenience as well as work productivity.

Taken together, significant unmet medical needs still exist for the development of new treatment options for TAK that provide higher GC sparing effect with favorable safety profiles.

There have been several reports that ustekinumab was investigated in TAK. Small case series suggested a potential therapeutic effect of ustekinumab: 1 pilot study in 3 Japanese patients with refractory TAK showed all patients responded to ustekinumab 45 mg SC administered at Days 0 and 28, of which 2 patients with elevated acute-phase reactants at baseline showed significantly decreased levels of CRP and ESR, and the other patients with symptomatic burdens showed considerable symptomatic relief. Despite the response to ustekinumab, vascular imaging performed on Day 84 did not observe any change in vascular wall enhancement (Terao 2016); a Caucasian patient with GC-, immunosuppressant-, and biologics-resistant TAK was successfully treated with ustekinumab 90 mg SC administered at Weeks 1 and 4. Three months later, her symptoms resolved and acute-phase reactants normalized. Her daily GC requirements were significantly reduced and a repeat CT angiogram showed full resolution of wall thickening and re-establishment of the normal smooth contours of the aorta (Yachoui 2018).

In summary, several lines of evidence suggest pathogenic association between IL-12/23 and clinical manifestation of TAK, although data demonstrating causal role of IL-12/23 pathway in disease pathogenesis are still lacking. Given the totality of available scientific evidence and favorable safety and efficacy profile established in other indications, ustekinumab has the potential to offer patients with relapsing TAK a safe and effective steroid sparing therapy.

For the most comprehensive nonclinical and clinical information regarding ustekinumab, refer to the latest version of the Investigator's Brochure (IB) (IB Ustekinumab 2020) and Addenda for ustekinumab.

The term “study intervention” throughout the protocol, refers to treatment with active drug or placebo.

The term "sponsor" used throughout this document refers to the entities listed in the Contact Protocol Supplementary Information, which will be provided as a separate document.

The term "participant" throughout the protocol refers to the common term "subject".

2.1. Study Rationale

This is double-blind, placebo-controlled, multicenter trial, designed to evaluate GC sparing effect of ustekinumab in participants with TAK. Participants must have experienced TAK relapse within 12 weeks prior to administration of study intervention and the relapse must have occurred at a dose of at least 7.5 mg/day (prednisolone or equivalent). The relapse must have been adequately treated

with ≥15 mg/day of prednisone or equivalent and participants must subsequently have achieved remission 1 week prior to the first administration of study intervention to ensure that GC sparing effects of ustekinumab can be reliably investigated.

Time to TAK relapse is selected as the primary endpoint because this is a sensitive parameter to distinguish GC sparing effects between ustekinumab and placebo while attempting GC taper. The DB phase will complete once a total of 35 TAK relapses occur allowing relatively faster study conclusion while securing sufficient statistical power. Participants who experience TAK relapse will be rescued with increased GC and be rolled over to the escape arm to receive ustekinumab. Participants who do not experience TAK relapse at the end of DB period, except for participants who reach GC dose of 5 mg/day or less in the placebo group at which 35 relapse events occur, will be rolled over to the OLE period and receive ustekinumab at least 52 weeks in order to investigate long-term safety and efficacy of ustekinumab in TAK participants.

2.2. Background

Human Pharmacokinetics and Immunogenicity

The pharmacokinetic (PK) of ustekinumab has been evaluated in healthy participants and in Phase 1, Phase 2, and Phase 3 studies that included adult participants with psoriasis, PsA, multiple sclerosis, CD, UC, primary biliary cirrhosis, sarcoidosis, and rheumatoid arthritis. The PK of ustekinumab has also been evaluated in Asian studies (Japanese, Chinese, Korean, and Taiwanese) with psoriasis and Japanese participants with atopic dermatitis. In addition, the PK of ustekinumab has been evaluated in a Phase 3 study in pediatric participants (≥6 to <18 years of age) with moderate to severe plaque psoriasis.

The PK of ustekinumab was generally comparable across different disease indications when consideration was given to differences in participant body weight.

Immunogenicity data from the completed studies show a generally low incidence of antibodies to ustekinumab. In most of these studies, the majority of participants who were positive for antibodies had neutralizing antibodies, however, the presence of antibodies did not preclude clinical response. Participants who were positive for antibodies to ustekinumab generally had lower serum concentrations of ustekinumab than those participants who were negative for antibodies to ustekinumab.

Efficacy/Safety Studies

The efficacy of ustekinumab has been evaluated for psoriasis, PsA, CD, and UC. Most of these studies showed superiority over placebo in achieving primary endpoints.

In all the studies conducted so far, the safety was comparable across ustekinumab and placebo.

For the most comprehensive nonclinical and clinical information regarding ustekinumab, refer to the latest version of the IB for ustekinumab.

2.3. Benefit-risk Assessment

More detailed information about the known and expected benefits and risks of ustekinumab may be found in the IB.

2.3.1. Risks for Study Participation

Potential Risks of Clinical Significance	Summary of Data/ Rationale for Risk	Mitigation Strategy
Risks Due to Study Intervention (Ustekinumab)		
Serious infections	Ustekinumab is a selective immunosuppressant and may have the potential to increase the risk of infections and reactivate latent infections.	• Participants with a history of, or ongoing, chronic, or recurrent infectious disease, including HIV, HBV, or HCV will be excluded from the study. Similarly, participants with evidence of active or untreated latent TB will be excluded from the study (Section 5.2). • Throughout the protocol, participants will be monitored for signs and symptoms of infection, including, but not limited to, TB, sepsis, and pneumonia. • Live viral or live bacterial vaccinations will be restricted during the study as described in Section 5.2.
Hypersensitivity reactions, including serious hypersensitivity reactions	Serious hypersensitivity reactions, including anaphylaxis and angioedema have been reported in post-marketing experience with ustekinumab.	• Participants with known allergy, hypersensitivity, or intolerance to ustekinumab or its excipients will be excluded from the study. Any participant who develops a serious hypersensitivity reaction such as anaphylaxis must discontinue study intervention (Section 7.1). • For injections that occur at the site, appropriately trained personnel and medications must be available to treat hypersensitivity reactions, including anaphylaxis.
Malignancy	Ustekinumab is a selective immunosuppressant. Immunosuppressive agents have	• Participants who have the presence or history of any malignancy including

Potential Risks of Clinical Significance	Summary of Data/ Rationale for Risk	Mitigation Strategy
	the potential to increase the risk of malignancy. Some participants who received ustekinumab in clinical studies developed cutaneous and non-cutaneous malignancies	lymphoproliferative disease including lymphoma, or signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphadenopathy of unusual size or location, and monoclonal gammopathy of undetermined significance, or clinically significant hepatomegaly or splenomegaly will be excluded from the study (Section 5.2). • Participants who develop a malignancy during the study (with the exception of ≤2 localized basal cell skin cancers that are treated with no evidence of recurrence or residual disease) will be discontinued from study intervention (Section 7.1).

Abbreviations: HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency syndrome; PK=pharmacokinetic; TB=tuberculosis.

2.3.2. Benefits for Study Participation

Clinical data of ustekinumab supports the notion that it will provide clinical benefits to TAK participants with manageable safety profile.

More detailed information about the known and expected benefits and risks of ustekinumab may be found in the IB.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the efficacy of ustekinumab compared to placebo, in combination with oral GC taper regimen, in participants with relapsing TAK	• Time to relapse of TAK according to protocol-defined criteria through the end of DB period
Secondary	
• To evaluate the safety of ustekinumab in combination with oral GC taper regimen, in participants with relapsing TAK	• Number/proportion of participants with TEAEs through the end of study • Number/proportion of participants with TEAEs by system organ class with a frequency threshold of 5% or more through the end of study

Objectives	Endpoints
	• Number/proportion of participants with treatment-emergent SAEs through the end of study
• To evaluate the efficacy of ustekinumab compared to placebo, in combination with oral GC taper regimen, in participants with relapsing TAK as measured by alternative definitions of relapse criteria, relapse rate, GC sparing effects, and disease activity	• Time to relapse of TAK according to Kerr's definition through the end of DB period • Time to relapse of TAK based on clinical symptoms only through the end of DB period • Time to relapse of TAK in each of the 5 categories through the end of DB period • Relapse rate in each of the 5 categories through the end of DB period • Cumulative oral GC dose (prednisolone or equivalent) through the end of DB period • Change from baseline in oral GC dose (prednisolone or equivalent) through the end of DB period • Number/proportion of participants achieving GC dose of 5 mg/day or less through the end of DB period • Change from baseline in imaging evaluation through the end of DB period • Change from baseline in inflammatory markers (CRP, ESR) through the end of DB period
• To evaluate the PK and immunogenicity of ustekinumab in combination with oral GC taper regimen, in participants with relapsing TAK	• Serum concentrations of ustekinumab in participants receiving ustekinumab through the end of study • Number/proportion of participants who are positive for anti-ustekinumab antibodies in participants receiving ustekinumab through the end of study

Objectives	Endpoints
Exploratory	
• To explore changes in the PRO instruments and the physician reported outcome	• Changes from baseline on PROs through the end of study SF-36 PtGA of disease activity on VAS FACIT-Fatigue • Change from baseline on physician reported outcome: PhGA through the end of study
• To explore the efficacy of ustekinumab in combination with oral GC taper regimen, in participants with relapsing TAK during OLE period	• Number/proportion of participants who experience relapse of TAK according to protocol-defined criteria during OLE period • Number/proportion of participants who experience relapse of TAK according to Kerr's definition during OLE period • Number/proportion of participants who experience relapse of TAK based on clinical symptoms only during OLE period • Number/proportion of participants who experience relapse of TAK in each of the 5 categories during OLE period • Cumulative oral GC dose (prednisolone or equivalent) during OLE period • Change from baseline in oral GC dose (prednisolone or equivalent) during OLE period • Number/proportion of participants achieving GC dose of 5 mg/day or less during OLE period • Change from baseline in imaging evaluation during OLE period • Change from baseline in inflammatory markers (CRP, ESR) during OLE period

Abbreviations: CRP=C-reactive protein; DB=double-blind; ESR=erythrocyte sedimentation rate; FACIT=Functional Assessment of Chronic Illness Therapy; GC=glucocorticoid; OLE=open-label extension; PK=pharmacokinetic; PRO=patient reported outcome; PhGA= Physician's Global Assessment of Disease Activity; PtGA=Patient's global assessment; TAK=Takayasu arteritis; SAE=serious adverse event; SF-36=short-form-36; TEAE=treatment-emergent adverse event; VAS=visual analog scale.

Refer to Section 8, STUDY ASSESSMENTS AND PROCEDURES for evaluations related to endpoints.

HYPOTHESIS

Efficacy:

The clinical cure rate with ustekinumab is superior to a regimen of placebo for participants with relapsing TAK with effective steroid sparing property.

The primary hypothesis of this study is that ustekinumab took more time to relapse of TAK according to protocol-defined criteria through the end of DB period.

Safety:

The safety of intervention with ustekinumab is similar to a regimen of placebo in TAK participants.

Benefit-risk:

The ustekinumab is safe and tolerated for participants with relapsing TAK with effective steroid sparing property.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 3, randomized, double-blind, placebo-controlled, parallel, multicenter, interventional study in participants ≥15 years and ≤75 years of age with TAK to evaluate the efficacy, safety, PK, and immunogenicity of IV and SC ustekinumab.

Participants must have experienced TAK relapse within 12 weeks prior to administration of study intervention and the relapse must have occurred at oral GC dose of at least 7.5 mg/day (prednisolone or equivalent).

A target of approximately 50 participants will be randomized at Week 0 in a blind fashion to 1:1 ratio stratified by oral GC dose at Week 0 (<0.5 mg/kg/day, ≥0.5 mg/kg/day of prednisolone or equivalent) and status of previous biologic medication (bio-nonfailure or bio-failure) to receive either ustekinumab or matching placebo with the following treatment regimens during the DB period until participants develop relapse or a total of 35 relapse events have occurred.

Ustekinumab group: Body weight-range based IV administration of ustekinumab (~6 mg/kg) at Week 0 followed by ustekinumab 90 mg SC administered 8 weeks after the initial IV dose, then every 8 weeks (q8w) thereafter.

Placebo group: IV administration of placebo at Week 0 followed by placebo SC administered 8 weeks after the initial IV dose, then q8w thereafter.

Before randomization, participants must have experienced TAK relapse within 12 weeks prior to administration of study intervention and the relapse must have occurred at oral GC dose of at least 7.5 mg/day (prednisolone or equivalent). The relapse must have been adequately treated with ≥15 mg/day of prednisone or equivalent and participants must subsequently have achieved remission at least 1 week prior to the first administration of study intervention.

During the DB period, participants will receive IV administration of study intervention followed by SC administration of study intervention, with starting the protocol defined oral GC taper regimen from Week 2 visit (baseline oral GC dose will be stable until Week 2). Participants who develop relapse will receive rescue medication of oral GC that is at least doubling the oral GC dose at the relapse. These participants will be assessed whether they achieve remission at the next scheduled administration visit from the relapse (Week OL-0) to enter OLE phase as the Escape arm regardless of remission status, and then receive IV administration of ustekinumab at Week OL-0 followed by ustekinumab 90 mg SC administered 8 weeks after the initial IV dose, then q8w thereafter. Escape arm is identical to OLE period except participants in Escape arm will receive IV ustekinumab at Week OL-0 instead of SC ustekinumab. Participants in Escape arm may receive continuous administrations of IV ustekinumab with 8-week interval once in the study if they relapse prior to Week 8.

When a total of 35 relapse events occur, the DB period will end and rest of the participants in the DB period will enter OLE period except for participants who reach oral GC dose of 5 mg/day (prednisolone or equivalent) or less in the placebo group to avoid unnecessary administration of ustekinumab for those who are considered to be placebo responders. These participants will continue or switch (if participants receive placebo in DB period) to receive SC ustekinumab administered q8w with maintaining the originally dosing schedule. For these participants, the first dosing visit from the end of DB period will be regarded as Week OL-0. In transition period from the end of DB period to completion of the DBL, participants who reach to oral GC 5 mg/day (prednisolone or equivalent) or less at the end of DB period will continue to receive study intervention assigned in DB period until completion of the DBL for DB period in order to maintain the blind. Participants assigned to the placebo group who reach oral GC dose of 5 mg/day (prednisolone or equivalent) or less at the end of DB period will terminate the study intervention administration and conduct early-term visit after completion of the DBL for DB period.

When 35 events occur, further recruitment will end.

During OLE period, participants will receive SC administration of ustekinumab at Week OL-0, and followed by SC administration of ustekinumab with oral GC taper at investigator's discretion for 52 weeks (Week OL-52) or until 32 weeks from the first SC administration after the end of DB period, whichever is later. Safety follow-up visit will be conducted 16 weeks after last SC ustekinumab administration.

A long-term extension (LTE) study to evaluate further long-term effects of ustekinumab may be conducted if the sponsor deems that ustekinumab treatment is beneficial to study participants based on results of the primary analysis. Participants who complete their participation in OLE period may be eligible to enter the LTE and continue to receive 90 mg SC ustekinumab q8w. Details will be provided in a separate LTE protocol or amendment of this protocol.

The efficacy interim analysis is planned to determine early success when relapse of TAK occurs in 15 events.

The primary efficacy analysis will be performed when relapse of TAK occurs in 35 events with additional secondary endpoints to be analyzed.

A first DBL will occur after a total of 15 events in relapse of TAK occurred for an interim analysis. A second DBL will occur after a total of 35 events in relapse of TAK occurred. A third DBL will occur approximately 24 weeks after the second DBL. A fourth DBL will occur when all participants have either completed their final study visit or terminated study participation prior to their final visit. Additional DBLs other than the ones specified above may be performed.

Investigative study sites and participants will remain blinded to initial treatment assignment until the end of the study, except the assignment for participants who reach oral GC dose of 5 mg/day (prednisolone or equivalent) or less when a total of 35 relapse events occur will be revealed after the second DBL. Identification of sponsor personnel who will have access to the unblinded participant data will be documented prior to unblinding to the sponsor.

An external, independent data monitoring committee (IDMC) will be commissioned for this study to ensure the continuous safety and well-being of the participants enrolled in this study. Refer to Committees Structure in Section 10.8, Appendix 8: Regulatory, Ethical, and Study Oversight Considerations for details.

An interim analysis will be implemented to evaluate early efficacy after 15 relapse events occurred. This efficacy analysis is unblinding and IDMC recommend the continuation or early termination of the DB period based on the results of interim analysis. The sponsor will decide the continuation and termination of DB period based on the recommendation by IDMC. If the sponsor decides early termination of DB period, all participants will be rolled over to the OLE period except for participants assigned to the placebo group who reach oral GC dose of 5 mg/day (prednisolone or equivalent) or less at the end of DB period. In transition period, follow the same process as 35 relapse events occurrence. The sponsor continues to enroll participants into OLE period until reaching a total of approximately 50 participants. Participants who are eligible according to Inclusion/Exclusion criteria in this protocol will directly enter to OLE period to receive body weight-range based IV administration of ustekinumab (~6 mg/kg) at Week OL-0 and followed by ustekinumab 90 mg SC q8w with GC taper of investigator's discretion for 52 weeks (Week OL-52). Safety follow-up visit will be conducted 16 weeks after last SC ustekinumab administration.

A diagram of the study design is provided in Section 1.2, Schema.

4.2. Scientific Rationale for Study Design

Blinding, Control, Study Phase/Periods, Intervention Groups

A placebo control will be used to establish the frequency and magnitude of changes in clinical endpoints that may occur in the absence of active intervention. Randomization will be used to minimize bias in the assignment of participants to intervention sequence groups, to increase the likelihood that known and unknown participant attributes (eg, demographic and baseline characteristics) are evenly balanced across intervention sequence groups, and to enhance the

validity of statistical comparisons across intervention groups. Blinded intervention will be used to reduce potential bias during data collection and evaluation of clinical endpoints.

DNA and Biomarker Collection

Optional pharmacogenomic samples may be obtained from participants only when specific consent is provided by signing the optional genetic research informed consent form /assent form (ICF). It is recognized that genetic variation can be an important contributory factor to interindividual differences in intervention distribution and response and can also serve as a marker for disease susceptibility and prognosis. Pharmacogenomic research may help to explain interindividual variability in clinical outcomes and may help to identify population subgroups that respond differently to an intervention. The goal of the pharmacogenomic component is to collect deoxyribonucleic acid (DNA) to allow the identification of genetic factors that may influence the PK, pharmacodynamics (PD), efficacy, safety, or tolerability of ustekinumab and to identify genetic factors associated with TAK.

Biomarker samples will be collected to evaluate the mechanism of action of ustekinumab or help to explain interindividual variability in clinical outcomes or may help to identify population subgroups that respond differently to an intervention. The goal of the biomarker analyses is to evaluate the PD of ustekinumab and aid in evaluating the intervention-clinical response relationship.

DNA and biomarker samples may be used to help address emerging issues and to enable the development of safer, more effective, and ultimately individualized therapies.

4.2.1. Study-specific Ethical Design Considerations

Potential participants will be fully informed of the risks and requirements of the study and, during the study, participants will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only participants who are fully able to understand the risks, benefits, and potential adverse events (AEs) of the study and provide their consent voluntarily will be enrolled.

When referring to the signing of the ICF, the terms legal guardian and legally acceptable representative refer to the legally appointed guardian of the child with authority to authorize participation in research. For each participant, his or her parent(s) (preferably both parents, if available) or legally acceptable representative(s), as required by local regulations, must give written consent (permission) according to local requirements after the nature of the study has been fully explained and before the performance of any study-related assessments. Assent must be obtained from children (minors) capable of understanding the nature of the study, typically participants 7 years of age and older, depending on the institutional policies. For the purposes of this study, all references to participants who have provided consent (and assent as applicable) refers to the participants and his or her parent(s) or the participant's legal guardian(s) or legally acceptable representative(s) who have provided consent according to this process. Minors who assent to a study

and later withdraw that assent must not be maintained in the study against their will, even if their parent(s) still want them to participate.

The total blood volume to be collected is considered to be an acceptable amount of blood to be collected over this time period from the population in this study based upon the standard of the Japanese Red Cross blood donation.

4.3. Justification for Dose

The proposed dose regimen is a body weight-range based IV administration of ustekinumab (~6 mg/kg) at Week 0 followed by ustekinumab 90 mg SC administered 8 weeks after the initial IV dose, then q8w thereafter.

The ustekinumab dose regimen for this Phase 3 study was selected based on the approved posology in IBD (CD and UC) in which strong association with TAK is suggested and the investigating posology in polymyositis (PM) and dermatomyositis (DM), which can maximize efficacy of ustekinumab possible for treatment of TAK.

The proposed choice of IV administration of ustekinumab at Week 0 followed by ustekinumab SC administered q8w follows the approved dose regimen in inflammatory diseases with target tissue that is more difficult to penetrate (eg, CD). The proposed dose regimen is the highest approved dose with substantial safety and tolerability data available. Evaluating this dose regimen optimizes probability of demonstrating efficacy with an acceptable safety profile. As TAK causes irreversible fibrosis of vascular intima and adventitia due to inflammation of aorta and potentially results in serious complications observed in organs other than large blood vessel, it is important that ustekinumab treatment should rapidly and sufficiently suppress inflammation in large blood vessel to prevent relapse and consequent serious complications.

The proposed dose regimen has been studied in IBD patients with an established favorable safety profile and is being further investigated in ongoing clinical trials with PM/DM.

Given the favorable safety and efficacy profile of ustekinumab established in other indications and several lines of evidence suggesting pathogenic association between IL-12/23 and clinical manifestation of TAK and reported genetic and clinical links between TAK and IBD, ustekinumab has the potential to offer participants with relapsing TAK a safe and effective steroid sparing therapy with a single IV induction dose followed by maintenance SC dosing.

4.4. End of Study Definition

End of Study Definition

The end of study is considered as the last safety follow-up assessment visit shown in the Schedule of Activities (Section 1.3) for the last participant in the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final participant safety follow-up assessment visit at that study site, in the time frame specified in the clinical trial agreement.

Study Completion Definition

A participant will be considered to have completed the study if he or she has completed assessments at Week 16 of the safety follow-up phase.

Participants who prematurely discontinue study intervention for any reason before completion of the DB phase will not be considered to have completed the study.

5. STUDY POPULATION

Screening for eligible participants will be performed within 42 days before administration of the study intervention. Refer to Section 5.4, Screen Failures for conditions under which the repeat of any screening procedures is allowed.

The inclusion and exclusion criteria for enrolling participants in this study are described below. If there is a question about these criteria, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a participant in the study. Waivers are not allowed.

For a discussion of the statistical considerations of participant selection, refer to Section 9.2, Sample Size Determination.

5.1. Inclusion Criteria

Each potential participant must satisfy all of the following criteria to be enrolled in the study:

Age

1. Criterion modified per Amendment 2:

   1.1 15 to 75 years of age, inclusive, (at the time of the first administration of study intervention at Week 0). If participant's disease onset of TAK is over 50 years old, appropriate evaluations should be made to distinguish from giant cell arteritis (GCA).

Type of Participant and Disease Characteristic

2. Must be medically stable on the basis of physical examination, medical history, vital signs, and 12-lead ECG performed at screening. Any abnormalities, must be consistent with the underlying illness in the study population and this determination must be recorded in the participant's source documents and initialed by the investigator.

3. Must be medically stable on the basis of clinical laboratory tests performed at screening. If the results of the serum chemistry panel including liver enzymes, other specific tests, blood coagulation, hematology, or urinalysis are outside the normal reference ranges, the participant may be included only if the investigator judges the abnormalities or deviations from normal to be not clinically significant or to be appropriate and

reasonable for the population under study. This determination must be recorded in the participant's source documents and initialed by the investigator.

4. Must have a diagnosis of TAK made or confirmed by a physician (such as a rheumatologist or cardiovascular specialist) experienced in treatment of TAK.

5. Must have a documented medical history that participant met the diagnostic criteria of definite TAK according to JCS 2017 Guidelines on Management of Vasculitis Syndrome (Section 10.2, Appendix 2: Diagnostic criteria for Takayasu arteritis according to JCS 2017 guideline on management of vasculitis syndrome) before signature on an ICF.

6. Must have developed a relapse of TAK within 12 weeks prior to administration of study intervention and the relapse must have occurred at a dose of at least 7.5 mg/day (prednisolone or equivalent).

7. Must have achieved remission* with an oral GC treatment at least 1 week prior to the first administration of study intervention and maintain remission of clinical symptoms** at the first administration of study intervention.

   *Remission is defined as assessment of 'absence of any of the signs and symptoms' as judged by the investigator for 5 following categories: objective systemic symptoms; subjective systemic symptoms; elevated inflammation markers; vascular signs and symptoms; ischemic symptoms (Section 10.3, Appendix 3: Definitions of relapse/remission of TAK).

   **Remission of clinical symptoms is defined as assessment of 'absence of any of the signs and symptoms' as judged by the investigator for 4 following categories: objective systemic symptoms; subjective systemic symptoms; vascular signs and symptoms; ischemic symptoms (Section 10.3, Appendix 3: Definitions of relapse/remission of TAK).

Allowed concomitant or previous medical therapies for TAK

8. Must be receiving oral GC treatment of ≥15 mg/day (prednisolone or equivalent), inclusive for the treatment of relapsing TAK and be on a stable dose for at least 2 weeks prior to the first administration of study intervention.

9. Criterion modified per Amendment 1

   9.1 If receiving an oral anti-platelet therapy (including but not limited to aspirin, clopidogrel, ticlopidine) or anti-coagulation therapy (including but not limited to warfarin) for treatment of TAK, the dose must have been stable for at least 2 weeks prior to first administration of the study intervention. In terms of warfarin, the dose should be controlled 1-5mg/day to maintain PT-INR target range between 2.0-3.0

(if participants are over 70 years old, PT-INR target range should be between 1.6-2.6).

10. Criterion modified per Amendment 1

10.1 If receiving topical medication such as non-steroidal anti-inflammatory interventions (NSAIDs), GC to treat skin lesions of TAK, the dose must have been stable for ≥2 weeks prior to first administration of the study intervention.

11. If receiving an oral anti-hypertensive therapy for treatment of TAK, the dose must have been stable for at least 2 weeks prior to first administration of the study intervention.

12. If receiving an oral NSAIDs therapy for treatment of TAK or other pain (including menstrual pain and migraine), the dose must have been stable for at least 2 weeks prior to first administration of the study intervention.

Sex and Contraceptive/Barrier Requirements

13. Male or female

A woman must be (as defined in Section 10.10, Appendix 10: Contraceptive and Barrier Guidance),

a. Not of childbearing potential

b. Of childbearing potential and

- Practicing a highly effective method of contraception (failure rate of <1% per year when used consistently and correctly) and agrees to remain on a highly effective method throughout the study and for at least 16 weeks after the last dose of the study intervention- the end of relevant systemic exposure after the last dose - the end of relevant systemic exposure. The investigator should evaluate the potential for contraceptive method failure (eg, noncompliance, recently initiated) in relationship to the first dose of study intervention. Examples of highly effective methods of contraception are located in Section 10.10, Appendix 10: Contraceptive and Barrier Guidance.
- Pregnancy testing (serum or urine) at the end of study intervention.

Note: If childbearing potential changes after start of the study (eg, a woman who is not heterosexually active becomes active or a premenarchal woman experiences menarche) a woman must begin a highly effective method of birth control, as described above.

14. A woman of childbearing potential must have a negative highly sensitive serum (β-human chorionic gonadotropin [β-hCG]) at screening and then have a negative urine pregnancy test at Week 0 prior to study intervention administration.

15. A woman using oral contraceptives must use an additional contraceptive method (above that required in Inclusion Criterion #13).

16. A woman must agree not to donate eggs (ova, oocytes) or freeze for future use for the purposes of assisted reproduction during the study and for a period of 4 months.

17. A male participant must wear a condom when engaging in any activity that allows for passage of ejaculate to another person and a man who has not had a vasectomy, he must agree to use a barrier method of birth control eg, either condom with spermicidal foam/gel/film/cream/suppository or partner with occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository. Male participants should also be advised of the benefit for a female partner to use a highly effective method of contraception as condom may break or leak.

18. A male participant must agree not to donate sperm for the purpose of reproduction during the study and for a minimum 20 weeks after receiving the last dose of study intervention.

Tuberculosis

19. Criterion modified per Amendment 2:

    19.1 Are considered eligible according to the following TB screening criteria:

    a. Have no history of latent or active TB prior to screening. An exception is made for participants who have a history of latent TB and are currently receiving treatment for latent TB, will initiate treatment for latent TB at least 3 weeks prior to the first administration of the study intervention, or have documentation of having completed appropriate treatment for latent TB within 3 years prior to the first administration of the study intervention. It is the responsibility of the investigator to verify the adequacy of previous antituberculous treatment and provide appropriate documentation.

    b. Have no signs or symptoms suggestive of active TB upon medical history and/or physical examination.

    c. Have had no recent close contact with a person with active TB or, if there has been such contact, will be referred to a physician specializing in TB to undergo additional evaluation and, if warranted, receive appropriate treatment for latent TB at least 3 weeks prior to the first administration of the study intervention.

    d. Within 6 weeks prior to the first administration of the study intervention, has a negative interferon gamma release assays (IGRAs) result, or have a newly identified positive IGRAs result in which active TB has been ruled out and for which appropriate treatment for latent TB has been initiated at least 3 weeks prior to the first administration of the study intervention. A participant whose first IGRA result is indeterminate should have the test repeated. In the event that the second IGRA result is also indeterminate, the participant may be

enrolled without treatment for latent TB if active TB is ruled out, their chest radiograph shows no abnormality suggestive of TB (active or old, inactive TB) and the participant has no additional risk factors for TB as determined by the investigator. This determination must be promptly reported to the sponsor and recorded in the participant's source documents and initialed by the investigator.

NOTE: IGRA is not required at screening for participants with a history of latent TB and ongoing treatment for latent TB or documentation of having completed adequate treatment as described above. Participants with documentation of having completed adequate treatment as described above are not required to initiate additional treatment for latent TB.

e. Have a chest radiograph (both posterior-anterior and lateral views) or chest CT, taken within 3 months prior to the first administration of the study intervention and read by a radiologist or pulmonologist, with no evidence of current, active TB or old, inactive TB.

Screening laboratory tests

20. Have screening laboratory test results within the following parameters. If 1 or more of the laboratory parameters is out of range, a single retest of laboratory values is permitted during 6-week screening period:

a) Hemoglobin ≥8.0 g/dL (International System of Units [ISI]: ≥80 g/L)

b) White blood cells $\geq 3.0 \times 10^3/\mu L$ (ISI: ≥3.0 GI/L)

c) Lymphocytes $\geq 0.5 \times 10^3/\mu L$ (ISI: ≥0.5 GI/L)

d) Neutrophils $\geq 1.5 \times 10^3/\mu L$ (ISI: ≥1.5 GI/L)

e) Platelets $\geq 100 \times 10^3/\mu L$ (ISI: ≥75 GI/L)

f) Serum creatinine ≤1.8 mg/dL (ISI: ≤170 µmol/L)

A one-time repeat of these screening laboratory tests (ie, hemoglobin, white blood cells, lymphocytes, neutrophils, platelets, serum creatinine) is allowed during the 6-week screening period and the investigator may consider the participant eligible if the previously abnormal laboratory test result is within an acceptable range on repeat testing at the central laboratory. A screening laboratory test analyzed by the central laboratory may be repeated more than once in the event of suspected error in sample collection or analysis as long as the result is obtained within the 6-week screening period.

21. Participants with other marked disease-associated laboratory abnormalities may be included only if the investigator judges the abnormalities or deviations from normal to be not clinically significant or to be appropriate and reasonable for the population under study. This determination must be recorded in the participant's source documents and initialed by the investigator. Participants with Common Terminology Criteria for Adverse Events

(CTCAE) Grade 3 or Grade 4 laboratory abnormalities must be discussed with the sponsor to determine eligibility for enrollment.

Informed Consent

22. Criterion modified per Amendment 2:

    22.1 Must sign an ICF (or their legally acceptable representative must sign) indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study. Parent(s) (preferably both if available or as per local requirements) (or their legally acceptable representative) must sign an ICF indicating that they understand the purpose of, and procedures required for, the study and is/are willing to allow the child to participate in the study. Assent is also required of children capable of understanding the nature of the study (typically 7 years of age and older) as described in Informed Consent Process and Assent Form in Appendix 8: Regulatory, Ethical, and Study Oversight Considerations.

23. Criterion modified per Amendment 2:

    23.1 Must sign a separate informed consent form (or their legally-acceptable representative must sign) if he or she agrees to provide an optional (DNA) sample for research. Refusal to give consent for the optional DNA research sample does not exclude a participant from participation in the study. Parent(s) (preferably both if available or as per local requirements) (or their legally acceptable representative) must sign a separate informed consent form if they agree to the child providing an optional DNA sample for research. Assent is also required of children capable of understanding the nature of the study (typically 7 years of age and older) as described in the Informed Consent Process and Assent Form in Appendix 8: Regulatory, Ethical, and Study Oversight Considerations.

24. Be willing and able to adhere to the lifestyle restrictions specified in this protocol.

5.2. Exclusion Criteria

Any potential participant who meets any of the following criteria will be excluded from participating in the study:

TAK Diagnosis and Status:

1. Has currently any known severe or uncontrolled TAK complications (eg, hypertension not responding to adequate treatment, aortic incompetence with cardiac insufficiency, progressing aortic aneurysm, coronary artery lesions with severe stenosis).

2. Has any other active rheumatic disease other than TAK including but not limited to granulomatosis with polyangiitis (Wegener's), rheumatoid arthritis, systemic lupus

erythematosus, and Behcet's disease that could interfere with assessment of TAK. GCA and polymyalgia rheumatica are not eligible to participate to the study.

Concomitant or previous medical therapies received:

3. Criterion modified per Amendment 2:

   3.1 Has received immunosuppressant (s) (including but not limited to MTX, AZA, mycophenolate mofetil [MMF], oral TAC, oral cyclosporine A) within 4 weeks of first study intervention.

4. Has received oral cyclophosphamide within 12 weeks or IV cyclophosphamide within 24 weeks prior to the first dose of the study intervention.

5. Has previously received ustekinumab, guselkumab, risankizumab, and agents whose mechanism of action targets IL-23.

6. Has received treatment with an anti-TNF agent: (including but not limited to infliximab, etanercept, adalimumab, golimumab, certolizumab pegol) within 8 weeks before the first administration of study intervention.

7. Has received treatment with an IL-6 inhibitor (including but not limited to TCZ, sarilumab) within 6 weeks before the first dose of study intervention.

8. Criterion modified per Amendment 2:

   8.1 Has previously been treated with any immunomodulatory biologic agent not described in this protocol within 5 half-lives or 12 weeks, whichever is longer, before the first administration of study intervention (eg, abatacept, agents whose mechanism of action targets B cell [eg, belimumab], IL-1 [eg, canakinumab], IL-2, IL-17 [eg, secukinumab, ixekizumab, brodalumab], or IFN pathways).

9. Has received rituximab or B cell depletion treatment within 24 weeks before the first administration of the study intervention.

10. Criterion modified per Amendment 2:

    10.1 Has previously failed to respond Janus kinase (JAK) inhibitor* for the treatment of TAK (ie, lack of efficacy), including but not limited to tofacitinib, baricitinib, upadacitinib. Has received treatment with JAK inhibitor within 5 half-lives before the first administration of study intervention, if discontinued by any reasons excepting lack of efficacy.

    *Failed response to JAK inhibitor is defined for participants who have received at least 4 weeks treatment of JAK inhibitor and signs and symptoms of TAK

persisted for 2 weeks or more and were not able to taper oral GC dose of 7.5 mg/day (prednisolone or equivalent) or less.

11. Use of apheresis therapy (including but not limited to plasmapheresis, photopheresis, leukocytapheresis) or immunoadsorption is prohibited within 2 weeks prior to the first administration of the study intervention.

12. Having a condition that is steroid dependent (eg, steroid dependent asthma, chronic obstructive pulmonary disease, etc) that is not amenable to tapering oral GC.

13. Has received an investigational intervention (including investigational vaccines) within 5 half-lives or 12 weeks before (whichever is longer) the planned first dose of study intervention or is currently enrolled in an investigational study.

14. Taken any disallowed therapies as noted in Section 6.8, Concomitant Therapy before the planned first dose of study intervention.

Infections or predisposition to infections:

15. Has had a Bacille Calmette-Guérin (BCG) vaccination within 12 months of screening.

16. Has received a live virus or live bacterial vaccination within 16 weeks prior to the first administration of the study intervention.

17. Has a history of active granulomatous infection, including but not limited to histoplasmosis or coccidioidomycosis.

18. Has a chest radiograph or chest high-resolution computer tomography (HRCT) within 3 months prior to the first administration of the study intervention that shows an abnormality suggestive of a malignancy or current active infection, including TB. Radiographic findings such as pulmonary nodules should be evaluated by an experienced radiologist and/or pulmonologist to determine whether the presentation is suggestive of infection or active malignancy and final assessment documented by the investigator prior to randomization.

19. Has had a nontuberculous mycobacterial infection or opportunistic infection (eg, cytomegalovirus, pneumocystosis, aspergillosis).

20. Has a history of, or ongoing, chronic or recurrent infectious disease, including but not limited to, chronic renal infection, chronic chest infection (eg, bronchiectasis), chronic infectious sinusitis, recurrent urinary tract infection (eg, recurrent pyelonephritis), an open, draining, or infected skin wound or ulcer.

21. Has a history of HIV antibody positive or tests positive for HIV at screening.

22. Has a hepatitis B infection. Participants must undergo screening for hepatitis B virus (HBV). At a minimum, this includes testing for HBV surface antigen (HBsAg), HBV surface antibody (anti-HBs), and HBV core antibody total (anti-HBc total).

23. Is seropositive for antibodies to HCV, unless has 2 negative HCV ribonucleic acid (RNA) test results 6 months apart prior to screening and has a third negative HCV RNA test result at screening.

24. Has experienced a recent single dermatomal herpes zoster eruption within the past 4 months. Has ever had multi-dermatomal herpes zoster (defined as appearance of lesion outside the primary or adjacent dermatome) or central nervous system zoster infection prior to the first administration of the study intervention.

25. Within 8 weeks prior to the first administration of the study intervention, has had a serious infection (eg, pneumonia, sepsis, or pyelonephritis), or has been hospitalized for an infection, or has been treated with IV antibiotics for an infection. Less serious infections (eg, acute upper respiratory tract infection, simple urinary tract infection) need not be considered exclusionary at the discretion of the investigator.

26. Is a potential participant with the following features will be excluded from participating in the study:

    During the 6 weeks prior to baseline, have had ANY of the following:

    a. confirmed severe acute respiratory syndrome-corona virus-2 (SARS-CoV)-2 corona virus disease (COVID-19) infection (test positive), OR
    b. suspected SARS-CoV-2 infection (clinical features [eg, symptoms] without documented test results), OR
    c. close contact with a person with known or suspected SARS-CoV-2 infection

    Exception: may be included with a documented negative result for a validated SARS-CoV-2 test:

    - If obtained at least 2 weeks after conditions (a), (b), (c) above (timed from resolution of key clinical features if present, eg, fever, cough, dyspnea)

    AND

    - With absence of ALL conditions (a), (b), (c) above during the period between the negative test result and the baseline study visit.

Concurrent medical conditions or past medical history and procedures:

27. Has known allergies, hypersensitivity, or intolerance to ustekinumab or its excipients (see the ustekinumab IB).

28. Any major illness/condition or evidence of an unstable clinical condition (eg, history of liver or renal insufficiency (estimated creatinine clearance below 60 mL/min); significant cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurologic,

hematologic, rheumatologic, psychiatric, or metabolic disturbances), disease of any organ system or active acute or chronic infection/infectious illness that, in the investigator's judgment, will substantially increase the risk to the participant if he or she participates in the study.

29. Had major surgery (eg, requiring general anesthesia) within 1 month before screening, or will not have fully recovered from surgery, or has surgery planned during the time the participant is expected to participate in the study or within 1 month after the last dose of study intervention administration.

    Note: Participants with planned surgical procedures to be conducted under local anesthesia may participate after discussion with the sponsor.

30. Has a transplanted organ (except for a corneal transplant performed >3 months prior to the first administration of the study intervention).

31. Has or has had a substance abuse (intervention or alcohol) problem within the previous 3 years.

32. Is unwilling or unable to undergo multiple venipunctures because of poor tolerability or lack of easy venous access.

Malignancy or increased potential for malignancy:

33. Presence or history of malignancy within 5 years before screening (exceptions are squamous and basal cell carcinomas of the skin that has been treated with no evidence of recurrence for at least 3 months before the first study drug administration and carcinoma in situ of the cervix that has been documented to be surgically cured).

34. Has a known history of lymphoproliferative disease, including lymphoma or signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphadenopathy of unusual size or location, clinically significant splenomegaly, history of splenectomy, or history of monoclonal gammopathy of undetermined significance.

Others

35. Is pregnant, or breast-feeding, or planning to become pregnant while enrolled in this study or within 4 months after the last dose of study intervention.

36. Is employee of the investigator or study site, with direct involvement in the proposed study or other studies under the direction of that investigator or study site, as well as family members of the employees or the investigator.

37. Any condition for which, in the opinion of the investigator, participation would not be in the best interest of the participant (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study intervention is given such that he or she no longer meets all eligibility criteria, then the participant should be excluded from participation in the study. Section 5.4, Screen Failures, describes options for retesting. The required source documentation to support meeting the enrollment criteria are noted in Section 10.8, Appendix 8: Regulatory, Ethical, and Study Oversight Considerations.

5.3. Lifestyle Considerations

Potential participants must be willing and able to adhere to the following lifestyle restrictions during the course of the study to be eligible for participation:

1. Refer to Section 6.8, Concomitant Therapy for details regarding prohibited and restricted therapy during the study.

2. Agree to follow all requirements that must be met during the study as noted in the Inclusion and Exclusion Criteria (eg, contraceptive requirements).

3. Must agree not to receive a live virus or live bacterial vaccination during the study. Participants must also agree not to receive BCG vaccination for 12 months after last dose of study agent, or any other live vaccine for 3 months after receiving the last administration of study agent.

5.4. Screen Failures

Participant Identification, Enrollment, and Screening Logs

The investigator agrees to complete a participant identification and enrollment log to permit easy identification of each participant during and after the study. This document will be reviewed by the sponsor study site contact for completeness.

The participant identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure participant confidentiality, no copy will be made. All reports and communications relating to the study will identify participants by participant identification and age at initial informed consent/assent. In cases where the participant is not randomized into the study, the date seen and age at initial informed consent/assent will be used.

If, during the screening period, a participant has not met all inclusion criteria or has met any exclusion criteria or is unable or unwilling to adhere to the lifestyle considerations of the study, the participant is considered to be a screen failure and is not eligible to be enrolled in the study.

In general, if a participant is a screen failure, but at some timepoint in the future meets all of the participant eligibility criteria, the participant may be rescreened after a new informed consent/assent has been obtained. Participants who are rescreened should be assigned a new participant number and will restart a new screening period.

Completion of screening and randomization procedures must occur within the specified screening window of 6 weeks.

If any delay leads to the expiration of time-specific assessments (eg, TB, chest radiograph), further discussion with the sponsor should occur before the participant is considered for rescreening. The participant will be considered a screen failure because he/she will not meet eligibility criteria and the expired assessments (along with the non-time-specific laboratory tests) will have to be repeated on rescreening.

Additional criteria for retesting and rescreening are outlined below.

Retesting

Retesting of abnormal laboratory values that may lead to exclusion will be allowed once. Retesting can occur at an unscheduled visit during the screening period, as long as this is done within the specified screening window of 6 weeks.

Rescreening

Participants who do not meet the criteria for participation in this study (screen failure) may be rescreened 1 time and only after consultation with the sponsor. Participants who are rescreened will be assigned a new participant number, undergo the informed consent/assent process, and then start a new screening period.

5.5. Criteria for Temporarily Delaying Enrollment, Randomization, and/or Administration of Study Intervention

Additional information for delayed enrollment randomization and/or administration of study intervention will be considered on a case-by-case basis after consultation with the sponsor.

6. STUDY INTERVENTION AND CONCOMITANT THERAPY

6.1. Study Intervention Administered

Study intervention administration must be captured in the source documents and the electronic case report form (eCRF).

Ustekinumab will be manufactured and provided under the responsibility of the sponsor. Refer to the IB for a list of excipients.

For details on rescue medications, refer to Section 6.8.1, Rescue Medication. For a definition of study intervention overdose, refer to Section 6.7, Treatment of Overdose.

Description of Interventions

Table 3: Study Intervention

☒ Intervention(s)						
Arm Name	Ustekinumab Group		Placebo Group		Ustekinumab Group/ Placebo Group	
Period	DB				OLE / Escape arm**	
Intervention Name	Ustekinumab	Ustekinumab	Placebo	Placebo	Ustekinumab	Ustekinumab
Type	INTERVENTION: INCLUDING PLACEBO					
Dose Formulation Unit Dose Strength(s)	A single-use, sterile solution in 30 mL vials with 1 dose strength (ie, 130 mg in 26 mL nominal volume)	A single-use PFS in a strength of 90 mg in 1 mL nominal volume for SC administration	A single-use, sterile solution in 30 mL vials with a 26 mL nominal volume	A single-use PFS for SC administration	A single-use, sterile solution in 30 mL vials with 1 dose strength (ie, 130 mg in 26 mL nominal volume)	A single-use PFS in a strength of 90 mg in 1 mL nominal volume for SC administration
Dosage Level(s) and Frequency	At Week 0 Body weight-range based IV dosing*	At Week 8 and q8w until developing relapse or end of DB period 90 mg	At Week 0 Body weight-range based IV dosing*	At Week 8 and q8w until developing relapse or end of DB period	At Week OL-0 after developing relapse only Body weight-range based IV dosing*	At Week OL-0 after the end of DB period. At Week OL-8 and q8w until Week OL-48, or 32 weeks from the first SC administration after the end of DB period, whichever is later. 90 mg
Route of Administration	IV infusion	SC injection	IV infusion	SC injection	IV infusion	SC injection
Dosing instructions	*The body weight-range based doses are based on the following: Body weight ≤55 kg: 260 mg ustekinumab (2 vials) Body weight >55 kg and ≤85 kg: 390 mg ustekinumab (3 vials) Body weight >85 kg: 520 mg ustekinumab (4 vials)					
Use	Experimental	Experimental	Placebo comparator	Placebo comparator	Experimental	Experimental
Investigational Medicinal Product (IMP)	☒ Yes ☐ No	☒ Yes ☐ No	☒ Yes ☐ No	☒ Yes ☐ No	☒ Yes ☐ No	☒ Yes ☐ No

Abbreviations: DB=double blind; IV=intravenous; OLE=open-label extension; PFS=prefilled syringe; SC=subcutaneous.

**Participants who experienced relapse in DB period and entered in Escape arm will receive IV infusion at Week OL-0, while participants who didn't experience relapse in DB period and entered in OLE period will receive SC administration at Week OL-0.

6.2. Preparation/Handling/Storage/Accountability

Preparation/Handling/Storage

All study intervention must be stored at controlled temperatures ranging from 36°F to 46°F (2°C to 8°C), not frozen, and protected from light.

Vigorous shaking of product should be avoided. The formulation does not contain preservatives. Ustekinumab can be administered either by SC route (without dilution) or IV route after being diluted to an appropriate concentration using an appropriate diluent. Prior to administration, the solution should be visually inspected for particulate matter or discoloration prior to SC administration. The solution is clear to slightly opalescent, colorless to light yellow, and may contain a few small translucent particles of protein. This appearance is not unusual for proteinaceous solutions. The medicinal product should not be used if the solution is discolored or cloudy or if foreign particulate matter is present.

The needle cover on the prefilled syringe contains dry natural rubber (a derivative of latex), which may cause allergic reactions in individuals sensitive to latex.

For SC administration, the liquid intervention is supplied with 90 mg/1 mL PFS.

For IV administration, ustekinumab 5 mg/mL LIV can be administered after being diluted to an appropriate concentration using an appropriate diluent. Aseptic procedures must be used during the preparation and administration of the study material. Exposure to direct sunlight should be avoided during preparation and administration.

Refer to the pharmacy manual/study site investigational product and procedures manual for additional guidance on study intervention preparation, handling, and storage.

Accountability

The investigator is responsible for ensuring that all study intervention received at the site is inventoried and accounted for throughout the study. The study intervention administered to the participant must be documented on the intervention accountability form. All study intervention will be stored and disposed of according to the sponsor's instructions. Study site personnel must not combine contents of the study intervention containers.

Study intervention must be handled in strict accordance with the protocol and the container label and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study intervention and study intervention returned by the participant, must be available for verification by the sponsor's study site monitor during on-site monitoring visits. The return to the sponsor of unused study intervention or used returned study intervention for destruction, will be documented on the intervention return form. When the study site is an authorized destruction unit and study intervention supplies are destroyed on-site, this must also be documented on the intervention return form.

Potentially hazardous materials containing hazardous liquids, such as used ampules, needles, syringes, and vials should be disposed of immediately in a safe manner and therefore will not be retained for intervention accountability purposes.

Study intervention should be dispensed under the supervision of the investigator, or a qualified member of the study site personnel, or by a hospital/clinic pharmacist. Study intervention will be supplied only to participants participating in the study. Returned study intervention must not be dispensed again, even to the same participant. Whenever a participant brings his or her study intervention to the study site for pill count, this is not seen as a return of supplies. Study intervention may not be relabeled or reassigned for use by other participants. The investigator agrees neither to dispense the study intervention from, nor store it at, any site other than the study sites agreed upon with the sponsor. Further guidance and information for the final disposition of unused study interventions are provided in the study reference manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

Intervention Allocation

Procedures for Randomization and Stratification

Central randomization will be implemented in this study. Participants will be randomly assigned to 1 of study intervention sequence groups based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization will be balanced by using randomly permuted and will be stratified by GC dose at Week 0 (<0.5 mg/kg/day, ≥0.5 mg/kg/day of prednisolone or equivalent) and status of previous biologic medication (bio-nonfailure or bio-failure). The interactive web response system (IWRS) will assign a unique intervention code, which will dictate the intervention assignment and matching study intervention kit for the participant. The requestor must use his or her own user identification and personal identification number when contacting the IWRS and will then give the relevant participant details to uniquely identify the participant.

Blinding

The investigator will not be provided with randomization codes. The codes will be maintained within the IWRS, which has the functionality to allow the investigator to break the blind for an individual participant.

Data that may potentially unblind the intervention assignment (ie, study intervention serum concentrations, anti-ustekinumab antibodies, study intervention preparation/accountability data, intervention allocation, biomarker or other specific laboratory data) will be handled with special care to ensure that the integrity of the blind is maintained and the potential for bias is minimized. This can include making special provisions, such as segregating the data in question from view by the investigators, clinical team, or others as appropriate until the time of DBL and unblinding.

Under normal circumstances, the blind should not be broken until all participants have completed DB period of the study and the database is finalized. The investigator may in an emergency determine the identity of the intervention by contacting the IWRS. While the responsibility to

break the intervention code in emergency situations resides solely with the investigator, it is recommended that the investigator contact the sponsor or its designee if possible, to discuss the particular situation, before breaking the blind. Telephone contact with the sponsor or its designee will be available 24 hours per day, 7 days per week. In the event the blind is broken, the sponsor must be informed as soon as possible. The date, time, and reason for the unblinding must be documented by the IWRS, in the appropriate section of the eCRF, and in the source document. The documentation received from the IWRS indicating the code break must be retained with the participant's source documents in a secure manner.

Participants who have had their intervention assignment unblinded will not be eligible to receive further study intervention but should complete evaluations specified in the appropriate Schedule of Activities (Section 1.3) for participants who discontinue study intervention.

In this study, 4 DBLs are planned. A first DBL will occur after a total of 15 events in relapse of TAK occurred. A second DBL will occur after a total of 35 events in relapse of TAK occurred. A third DBL will occur approximately 24 weeks after the second DBL. A fourth DBL will occur when all participants have either completed their final study visit or terminated study participation prior to their final visit. Additional DBLs other than the ones specified above may be performed. Investigative study sites and participants will remain blinded to initial treatment assignment until after the fourth DBL, except for participants who can taper oral GC dose to 5 mg/day (prednisolone or equivalent) or less at which 35 relapse events occur. After the first DBL, the data will be unblinded to IDMC for analysis while participants are still participating in the study. Identification of sponsor personnel who will have access to the unblinded participant data will be documented prior to unblinding to sponsor.

6.4. Study Intervention Compliance

Ustekinumab will be administered as an IV and SC injection.

The details of each study intervention administration will be recorded in the eCRF, including date and time of IV and SC injection.

All visits will occur within a range of ±4 days of the scheduled visit through Week 4 and then ±7 days of the scheduled visit until safety follow-up (Section 1.3). Any visits outside of these ranges should be discussed with the sponsor and should be documented in the eCRF.

Study-site personnel will maintain a log of all study intervention administered. Study intervention supplies for each participant will be inventoried and accounted for. Information regarding study intervention administrations that are administered outside of the scheduled windows or missed will be recorded. Participant charts and worksheets may be reviewed and compared with the data entries on the eCRFs to ensure accuracy. Although it is understood that treatment may be interrupted for many reasons, compliance with the treatment schedule is strongly encouraged.

6.5. Dose Modification

This section is not applicable.

6.6. Continued Access to Study Intervention After the End of the Study

Long-term extension study to evaluate further long-term effects of ustekinumab may be conducted if the sponsor deems that ustekinumab treatment is beneficial to study participants based on results of the primary analysis. Participants who complete their participation in OLE period may be eligible to enter the LTE and continue to receive 90 mg SC ustekinumab q8w. Details will be provided in a separate LTE protocol or amendment of this protocol.

6.7. Treatment of Overdose

For this study, any dose of ustekinumab greater than the highest dosing visit at a single dosing visit specified in this protocol will be considered an overdose. The sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator or treating physician should:

- Contact the medical monitor immediately.
- Evaluate the participant to determine, in consultation with the medical monitor, whether study intervention should be interrupted or whether the dose should be reduced.
- Closely monitor the participant for AE/serious adverse event (SAE) and laboratory abnormalities.
- Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

6.8. Concomitant Therapy

Prestudy therapies administered up to 12 weeks before having obtained the consent/assent must be recorded at screening.

Concomitant therapies must be recorded throughout the study beginning with start of the screening process and through final safety visit in the eCRF. Concomitant therapies should also be recorded beyond the final safety follow-up visit only in conjunction with serious adverse events (SAEs) that meet the criteria outlined in Section 8.3.1, for Collecting Adverse Event and Serious Adverse Event Information.

All therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements; non-pharmacologic therapies such as electrical stimulation, acupuncture, special diets, exercise regimens, or other specific categories of interest) different from the study intervention must be recorded in the eCRF. Medications given for imaging such as contrast media agent must also be recorded. Recorded information will include a description of the type of therapy, duration of use, dosing regimen, route of administration, and indication. Modification of an effective preexisting therapy should not be made for the explicit purpose of entering a participant into the study.

Every reasonable effort should be made to keep doses of concomitant medications stable through the end of DB period unless otherwise specified in the following sections.

If necessary, a concomitant medication may be reduced or temporarily discontinued because of abnormal laboratory values, safety and tolerability issues, concurrent illness, or the performance of a surgical procedure, but the change and reason for the medication change should be clearly documented in the participant's medical record. Adjustments in permitted therapies (anti-platelet or anti-coagulation therapy, anti-hypertensive therapy, NSAIDs, and topical medications) that do not comply with the study protocol should not be allowed through the end of DB period except for reduction of the concomitant therapies due to improvement of the symptoms and safety considerations. During OLE, adjustments in concomitant therapies are allowed based on the discretion of the investigator.

If protocol-prohibited immunosuppressants, biologics (such as TCZ), cytotoxic agents (such as cyclophosphamide) or IV GC are initiated for severe, progressive, or unstable TAK disease activity, the participant should be discontinued from the study.

Any questions or concerns with the use of concomitant therapies should be discussed with the study sponsor and/or medical monitor. The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

Permitted Therapy

Oral Glucocorticoid and Protocol-defined Taper for TAK

Table 4 outlines oral glucocorticoid dose requirements prior to randomization and throughout the study.

Table 4: Glucocorticoid dose requirements for each study period

Study period	Allowable dose
Before randomization	Daily dose must be ≥15 mg/day of prednisolone or equivalent at randomization with stable dosing ≥2 weeks prior to the first study intervention administration.
Week 0 through Week 2	No adjustments in GC dose are permitted.
Week 2 through participant's relapse or end of DB period	GC tapering will start from Week 2 based on defined GC taper schedule (See Table 5). If current daily prednisolone or equivalent dose is ≥30 mg/day, GC dose will be tapered by 5 mg/week. If current prednisolone or equivalent dose is <30 mg/day and >20 mg/day, GC dose will be tapered by 2.5 mg/week. If current prednisolone or equivalent dose is ≤20 mg/day and ≥5 mg/day, GC dose will be tapered by 10%/week according to the below formula. Dose* of Week N=Dose of Week "N-1" ×0.9 *Should be rounded decimals to the nearest whole number. Once the daily prednisolone dose (or equivalent) reaches 5 mg/day, while GC taper by 1 mg/4-8 weeks is encouraged to achieve GC-free remission, GC taper regimen is ultimately at discretion of investigator at 5 mg or less based on disease activities of TAK in participants.
OLE period including Escape arm	GC taper regimen is at the investigator's discretion and is encouraged to achieve GC-free remission.

Abbreviations: GC=glucocorticoid; OLE=open-label extension; TAK=Takayasu arteritis.

Table 5: Glucocorticoid Taper Schedule (Daily Dose [mg] of Prednisolone or Equivalent) (Table shows only up to Week 24)

	Week																								
Baseline	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
60	60	60	55	50	45	40	35	30	25	22.5	20	18	16	14	13	12	11	10	9	8	7	6	5*	5*	5*
50	50	50	45	40	35	30	25	22.5	20	18	16	14	13	12	11	10	9	8	7	6	5*	5*	5*	5*	5*
40	40	40	35	30	25	22.5	20	18	16	14	13	12	11	10	9	8	7	6	5*	5*	5*	5*	5*	5*	5*
35	35	35	30	25	22.5	20	18	16	14	13	12	11	10	9	8	7	6	5*	5*	5*	5*	5*	5*	5*	5*
30	30	30	25	22.5	20	18	16	14	13	12	11	10	9	8	7	6	5*	5*	5*	5*	5*	5*	5*	5*	5*
25	25	25	22.5	20	18	16	14	13	12	11	10	9	8	7	6	5*	5*	5*	5*	5*	5*	5*	5*	5*	5*
20	20	20	18	16	14	13	12	11	10	9	8	7	6	5*	5*	5*	5*	5*	5*	5*	5*	5*	5*	5*	5*
15	15	15	14	13	12	11	10	9	8	7	6	5*	5*	5*	5*	5*	5*	5*	5*	5*	5*	5*	5*	5*	5*

* Once the daily prednisolone dose (or equivalent) reaches 5 mg/day, while GC taper by 1 mg/4-8 weeks is encouraged to achieve GC-free remission, GC taper regimen is ultimately at discretion of investigator based on disease activities of TAK in participants.

Participants that are on GC other than prednisolone during screening should preferably be switched to prednisolone to follow the GC taper in Table 5. If the participant continues on GC other than prednisolone, the investigator should contact the sponsor to ensure that the taper is appropriately adjusted for the GC equivalency compared with prednisolone (Refer to Section 10.6, Appendix 6: Glucocorticoid Conversion Table). If participants have GC-induced side effects such as osteoporosis and hyperglycemia, appropriate treatment must be given in the judgment of the investigator.

Additional consideration of oral GC use during the study is as follow:

- It is recommended that participants be educated about and monitored for symptoms of GC adrenal insufficiency/deficiency (eg, Addisonian symptoms such as fatigue, muscle weakness, decreased appetite, nausea, vomiting, joint and muscle pain) by study staff during periods of GC tapering, as appropriate. Investigators should monitor participants at the regular study visits for any signs and symptoms of Addisonian crisis.

Anti-platelet or Anti-coagulation Therapy

Participants are permitted to receive stable doses (≥2 weeks prior to first study intervention administration) of anti-platelet therapy (including but not limited to aspirin, clopidogrel, ticlopidine) or anti-coagulation therapy (including but not limited to warfarin) according to the local practice at the discretion of the investigator. In terms of warfarin, the dose should be controlled 1-5mg/day in order to maintain PT-INR target range between 2.0-3.0 (if participants are over 70 years old, PT-INR target range should be between 1.6-2.6). Participants should not initiate anti-platelet or anti-coagulation therapy during DB period, unless discussed and agreed with the sponsor medical monitor.

Anti-hypertensive Therapy

Participants are permitted to receive stable doses (≥2 weeks prior to first study intervention administration) of anti-hypertensive treatment according to the local practice at the discretion of the investigator. Participants should not initiate anti-hypertensive therapy during DB period, unless discussed and agreed with the sponsor medical monitor.

NSAIDs

Participants are permitted to receive stable doses (≥2 weeks prior to first study intervention administration) of NSAIDs treatment according to the local practice at the discretion of the investigator. Participants should not initiate NSAIDs therapy during DB period, unless discussed and agreed with the sponsor medical monitor.

Topical Medications

Participants are permitted to receive stable doses (≥2 weeks prior to first study intervention administration) of topical medications according to the local practice at the discretion of the investigator. Participants should not initiate topical medications during DB period, unless discussed and agreed with the sponsor medical monitor.

Prohibited Therapies

Use of additional investigational or approved biologic or non-biologic immunosuppressant or immunomodulatory agents, other than those explicitly allowed in the inclusion/exclusion criteria, are prohibited until safety follow-up visit including but not limited to, the following:

Anti-IL-6 (eg, actemra), anti-TNF therapy (eg, remicade, humira)

Anti-IL-23, anti- IL-12/23 p40, anti-IL-17 therapy

JAK inhibitors (eg, tofacitinib, upadacitinib)

Cell-depleting therapies (eg, abatacept, rituximab, alemtuzumab)

Cytotoxic akylating agents (eg, chlorambucil, cyclophosphamide)

Immunosuppressant (eg, MTX, AZA, MMF, TAC, cyclosporine)

Intra-muscular, intra-articular, intra-bursal, epidural, intra-lesional or IV GC

Other investigational agents

Oral Glucocorticoids

Oral GCs other than for the protocol-define taper, are prohibited during the study, with the exception of use for GC rescue therapy. The use of oral GCs (or other systemic GCs) for indications other than TAK during the study should be limited to only situations for which, in the opinion of the treating physician, there are no adequate alternatives. This should be discussed with the medical monitor or designee prior to providing these and may require discontinuation of study intervention.

Intra-muscular, Intra-articular, Intra-bursal, Epidural, Intra-lesional, or IV Glucocorticoids

Intra-muscular, intra-articular, intra-bursal, epidural, intra-lesional, or IV GCs are prohibited within 6 weeks prior to first study intervention and during the study.

6.8.1. Rescue Medication

The study site will supply rescue medication that will be obtained locally.

Glucocorticoid rescue therapy is defined as a GC therapy for participants who meet the criteria of protocol-defined relapse.

During the DB period, participants who develop a TAK relapse should stop GC taper and be treated with GC rescue therapy that is at least double the dose at the relapse by discretion of the investigator. When considering use of GC rescue therapy, a careful assessment should be made by the investigator whether the symptoms are related to a TAK relapse or are more likely due to non-inflammatory symptoms which could represent adrenal insufficiency or other comorbidities.

After receiving a GC rescue therapy, the participant will enter Escape arm to receive IV ustekinumab at next study intervention administration visit and followed by SC ustekinumab

administered 8 weeks after the IV dose, then q8w thereafter. If the participant will not be able to receive IV ustekinumab at next study administration visit due to any reasons including his/her disease activity and logistical reasons, the participant should be rearranged the visit within the allowance if feasible. If it's not feasible, the investigator should discuss with the sponsor. During Escape arm, GC taper regimen is at the investigator's discretion.

During the OLE period, participants who develop a TAK relapse will be treated GC rescue at discretion of the investigator.

Oral NSAIDs rescue therapy for treatment of TAK in addition to GC rescue therapy is also allowed as needed.

The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

A participant's study intervention must be discontinued if:

- The participant withdraws consent or assent (or the participant's parent/legal representative) to receive study intervention
- The investigator believes that for safety reasons or tolerability reasons (eg, AE) it is in the best interest of the participant to discontinue study intervention
- The participant becomes pregnant
- Noncompliance with study intervention administration defined as multiple episodes of missing the window in which to receive study intervention
- The participant experiences an AE temporally associated with study intervention infusion or injection, resulting in bronchospasm with wheezing and/or dyspnea requiring ventilatory support or symptomatic hypotension with a greater than 40 mmHg decrease in systolic blood pressure
- The participant develops study intervention hypersensitivity (eg, anaphylaxis, angioedema) reaction that is reported as serious or severe
- The participant is deemed ineligible according to the following TB criteria:

  A diagnosis of active TB is made.

  A participant has symptoms suggestive of active TB based on follow-up assessment questions and/or physical examination or has had recent close contact with a person with active TB and cannot or will not continue to undergo additional evaluation.

  A participant undergoing evaluation has a chest radiograph with evidence of current active TB and/or a positive IGRA result, unless active TB can be ruled out and appropriate treatment for latent TB can be initiated prior to the next administration of study intervention and continued to completion. Indeterminate IGRA results should be handled

as in Section 10.7, Appendix 7: Clinical Laboratory Tests. Participants with persistently indeterminate IGRA results may continue without treatment for latent TB if active TB is ruled out, their chest radiograph shows no abnormality suggestive of TB (active or old, inactive TB) and the participant has no additional risk factors for TB as determined by the investigator. This determination must be promptly reported to the sponsor and recorded in the participant's source documents and initialed by the investigator.

A participant receiving treatment for latent TB discontinues this treatment prematurely or is noncompliant with the therapy.

- The participant develops a serious opportunistic infection.
- The participant has a malignancy including squamous cell skin cancer. Consideration may be given to allowing participants who develop ≤2 basal cell skin cancers that are adequately treated with no evidence of residual disease to continue to receive study intervention.
- The participant who reaches oral GC dose of 5 mg/day (prednisolone or equivalent) or less in the placebo group when a total of 35 relapse events occurs.
- The participant requires a prohibited therapy such as an immunomodulatory biologic, cyclophosphamide, or IV glucocorticoid (see Section 6.8).

Note: Any serious infection should be discussed with the medical monitor or designee and study intervention should be withheld until the clinical assessment is complete.

If a participant discontinues study intervention for any reason before the end of the DB phase, then the end-of-treatment assessments should be obtained and scheduled assessments of study intervention should be continued.

7.1.1. Liver Chemistry Stopping Criteria

Discontinuation of study intervention for abnormal liver tests is required by the investigator when a participant meets one of the conditions outlined in Section 10.11, Appendix 11: Liver Safety: Suggested Actions and Follow-up Assessments and Study Intervention Rechallenge Guidelines or in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules if the investigator believes that it is in best interest of the participant.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant will be withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent or assent
- Death
- Other

When a participant withdraws before study completion, the reason for withdrawal is to be documented in the eCRF and in the source document. If the reason for withdrawal from the study is withdrawal of consent or assent, then no additional assessments are allowed.

Withdrawal of Consent

A participant declining to return for scheduled visits does not necessarily constitute withdrawal of consent. Alternate follow-up mechanisms that the participant agreed to when signing the consent/assent form apply (eg, consult with family members, contacting the participant's other physicians, medical records, database searches, and use of locator agencies at study completion) as local regulations permit.

7.3. Lost to Follow-up

To reduce the chances of a participant being deemed lost to follow-up, prior to randomization attempts should be made to obtain contact information from each participant, eg, home, work, and mobile telephone numbers and email addresses for both the participant as well as appropriate family members.

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. A participant cannot be deemed lost to follow-up until all reasonable efforts made by the study site personnel to contact the participant are deemed futile. The following actions must be taken if a participant fails to return to the study site for a required study visit:

- The study site personnel must attempt to contact the participant to reschedule the missed visit as soon as possible, to counsel the participant on the importance of maintaining the assigned visit schedule, to ascertain whether the participant wishes to or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every reasonable effort to regain contact with the participant (where possible, 3 telephone calls, e-mails, fax, and, if necessary, a certified letter to the participant's last known mailing address, or local equivalent methods). These contact attempts should be documented in the participant's medical records.
- Should the participant continue to be unreachable, they will be considered to have withdrawn from the study.
- Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

Should a study site close, eg, for operational, financial, or other reasons and the investigator cannot reach the participant to inform them, their contact information will be transferred to another study site.

8. STUDY ASSESSMENTS AND PROCEDURES

Overview

The Schedule of Activities (Section 1.3) summarizes the frequency and timing of efficacy, PK, immunogenicity, PD, biomarker, pharmacogenomic, and safety measurements applicable to this study.

If multiple assessments are scheduled for the same timepoint, it is recommended that procedures be performed in the following sequence: patient-reported outcome (PRO) assessments, ECG and vital signs, clinical safety laboratory assessments, PK, immunogenicity, and biomarkers. Urine and blood collections for PK and PD assessments should be kept as close to the specified time as possible. Other measurements may be done earlier than specified timepoints if needed. Actual dates and times of assessments will be recorded in the source documentation and eCRF.

Guidelines for handling of assessments affected by the COVID-19 pandemic are found in (Section 10.12, Appendix 12: Guidance on study conduct during COVID-19 pandemic).

Blood Sample Collection

As this study is event driven design and DB period for each participant depends on when they relapse, the total blood volume will differ.

The total blood volume for the study is approximately 570 mL for participants who go through DB period for 24 weeks and OLE period for 52 weeks.

The estimated maximum amount of blood drawn from each participant in this study will not exceed 850 mL for patients who go through the estimated longest DB period (Assuming 104 weeks) and OLE period for 52 weeks.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the eCRF or laboratory requisition form. If blood samples are collected via an indwelling cannula, an appropriate amount (1 mL) of serosanguineous fluid slightly greater than the dead space volume of the lock will be removed from the cannula and discarded before each blood sample is taken. After blood sample collection, the cannula will be flushed with 0.9% sodium chloride, United States Pharmacopeia (USP) (or equivalent) sodium heparin of 10 U/mL and charged with a volume equal to the dead space volume of the lock. If a mandarin (obturator) is used, blood loss due to discard is not expected.

Refer to the Schedule of Activities (Section 1.3) for the timing and frequency of all sample collections.

Instructions for the collection, handling, storage, and shipment of samples are found in the laboratory manuals that will be provided. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in laboratory manuals.

Study-specific Materials

The investigator will be provided with the following supplies:

- Ustekinumab IB
- Pharmacy manual/study site investigational product and procedures manual
- Laboratory manual
- National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5
- IWRS Manual
- Electronic data capture (eDC) Manual
- Sample ICF
- Participant diaries

8.1. Efficacy and Immunogenicity Assessments

The Schedule of Activities (Section 1.3) summarizes the frequency and timing of efficacy measurements applicable to this study.

8.1.1. TAK Disease Signs and Symptoms

Efficacy of ustekinumab in TAK will be assessed from the presence of TAK activity including investigator assessment of signs and symptoms of TAK.

Clinical signs and symptoms will be evaluated in the following items to assess if participants meet the criteria of protocol-defined relapse by investigator or designee at specified time points in the Schedule of Activities (Section 1.3). When 2 or more categories meets the criteria, participants will be judged as relapse. Even if signs of relapse are not present in 2 of 5 categories, participants will be judged as relapse if emergent hospitalization caused by worsening of TAK and GC treatment required or if severe aortic valve incompetence accompanied by symptoms of cardiac failure occurs under ‘vascular signs and symptoms’ or if CTCAE grade 2 or higher (grade ≥3 for myocardial infarction) occurs under ‘ischaemic symptoms’. Definition of relapse are described in Section 10.3, Appendix 3: Definitions of relapse/remission of TAK.

- Systemic symptoms (objective assessment).
- Systemic symptoms (subjective assessment).
- Elevated inflammation markers (CRP, ESR).
- Vascular signs and symptoms.

- Ischemic symptoms.

In assessment of disease activities of TAK, cause of relapse will be confirmed by eliminating other causes such as infections, allergic disorders, and unexplained physical symptoms. Even participants meet the definition of relapse once, they will not receive a GC rescue therapy and continue to receive protocol-defined GC taper regimen except for the following cases. In the following cases, participants will be judged as relapse once.

- Emergent hospitalization caused by worsening of TAK and GC treatment required
- Severe aortic valve incompetence accompanied by symptoms of cardiac failure occurs under 'vascular signs and symptoms'
- CTCAE grade 2 or higher (grade ≥3 for myocardial infarction) occurs under 'ischemic symptoms'
- Both categories 'vascular signs and symptoms' and 'ischemic symptoms' meet the criteria

Except for above cases, the investigators will reconfirm whether the participant meets definition of relapse including the same items of the first assessment at least and the relapse was caused by worsening of TAK to make a final judgement of the relapse at Relapse Confirmation Visit. Completion of confirmation for relapse must occur within the allowed window of 2 weeks (Refer to Section 10.4, Appendix 4: Relapse Judgement Flow). After completion of confirmation, the first relapse visit date will be regarded as relapse date.

In addition, if participants meet the definition of relapse by having only non-specific signs and symptoms once, clinical and laboratory evidence (and imaging results if available) of the non-specific signs and symptoms will be adjudicated by the blinded sponsor medical monitor to verify that these are derived by worsening of TAK prior to the investigator's final judgement of the relapse. The sponsor's medical monitor may request additional information as necessary. Definition of relapse by having non-specific symptoms are described in Section 10.3, Appendix 3: Definitions of relapse/remission of TAK.

8.1.2. Physician Global Activity-Visual Analog Scale (PhGA-VAS)

Physician Global Activity is partially validated tool to measure the global evaluation by the physician of the participant's overall disease activity at the time of assessment using a 10 cm VAS.

8.1.3. Imaging

Computed tomography angiography (CTA) and magnetic resonance angiography (MRA) are imaging modalities of choice for the assessment of the vessels' lumen in terms of caliber irregularities or stenosis, the vessels' wall in terms of thickening and contrast enhancement, and assessment of the surrounding tissue, using a venous contrast phase (Dejaco 2018). CT is suitable for detecting structural lesions and wall inflammation with a higher resolution and shorter procedural time than magnetic resonance imaging (MRI), however it entails radiation exposure (Lariviere 2016).

In this study, imaging assessment will be performed using CTA or MRA, if CTA is not feasible, by the dedicated radiologist or physician from study site (or designee) at specified time point in Schedule of Activities (Section 1.3). The same imaging modality will be used for the same participant throughout the study. Imaging assessment will include the aorta and its major branches from the terminal of the common carotid artery (internal and external carotid branches) to the abdominal aortic terminal (common iliac artery branch) and will be performed in multiple planes using contrast media agent. When imaging assessment has been performed within 12 weeks prior to scheduled imaging assessment visit, imaging assessment may not be performed, and the prior results will be used for this scheduled assessment. Imaging assessment for screening visit should be performed and the prior imaging results for screening assessment will not be allowed.

(1) Vessel involvement such as stenosis, obstruction, and aneurysm; (2) Arterial wall thickness; and (3) The presence of mural contrast enhancement and oedema (MRA only) will be assessed for imaging evaluation on disease activity of TAK. Study independent central imaging assessment will be used to analyze all computed tomography or MRA scans included in this study. The central imaging assessment of imaging will be blinded to the clinical data. Procedural details are described in a separate manual.

8.1.4. Short Form 36 (SF-36)

The SF-36 is a widely used tool that assesses the global medical quality of life, functional health, and well-being of general and specific populations. It has shown evidence of content, concurrent, criterion, construct, and predictive validity in many different chronic diseases and extensive normative data are available.

8.1.5. Patient Global Activity-Visual Analog Scale (PtGA-VAS)

Patient Global Activity is partially validated tool to measure the global evaluation by the participant of the patient's overall disease activity at the time of assessment using a 10 cm VAS.

8.1.6. Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue

The FACIT-Fatigue version 4.0 is a 13-item questionnaire formatted for self-administration that assesses patient-reported fatigue and its impact upon daily activities and function over the past 7 days. Participants will be asked to answer each question using a 5-point Likert-type scale (0 Not at all; 1 A little bit; 2 Somewhat; 3 Quite a bit; and 4 Very Much). The interpretation of FACIT-Fatigue scores is such that a higher score indicates less fatigue, with a range of possible scores of 0-52, with 0 being the worst possible score and 52 the best.

8.1.7. Endpoint Definitions

Time to relapse of TAK for primary endpoint is defined as assessment of ‘signs of relapse present’ as judged by the investigator for at least 2 of 5 categories: objective systemic symptoms, subjective systemic symptoms, elevated inflammation markers, vascular signs and symptoms, or ischemic symptoms.

Time to relapse of TAK according to Kerr’s definition (Kerr 1994) is defined as assessment of ‘signs of relapse present’ as judged by the investigator for at least 2 of 4 categories: systemic

symptoms (objective or subjective), elevated inflammation markers, vascular signs, and symptoms and ischemic symptoms.

8.2. Safety Assessments

Safety evaluations will include assessment of AEs, concomitant medications, pregnancy testing, administration reactions, chemistry and hematology laboratory tests, immunogenicity, vital signs, and general physical examinations. In addition, ECG, chest x-ray, chest CT, HIV, hepatitis B, hepatitis C, and TB testing will be required at screening.

Adverse events will be reported and followed by the investigator as specified in Section 10.9, Appendix 9: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

Any clinically relevant changes occurring during the study must be recorded on the AE section of the eCRF.

Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable condition is reached.

The study will include the following evaluations of safety and tolerability according to the time points provided in the Schedule of Activities (Section 1.3).

8.2.1. Physical Examinations

Physical Examinations

Physical examinations will be performed by the investigator or designated physician, nurse practitioner, or physician assistant as specified in the Schedule of Activities (Section 1.3). Any new, clinically significant finding (in the opinion of the investigator) must be captured as an AE. In addition, resolution of any abnormal findings during the study will be noted in the source document.

The full physical examination will be performed including: the head and neck, chest, abdomen, and extremities, as well as including examinations based on the individual's medical history and manifestations of TAK. Specific assessment of TAK related signs and symptoms will be performed by a clinical assessor as described in Section 10.2, Appendix 2: Diagnostic criteria for Takayasu arteritis according to JCS 2017 guideline on management of vasculitis syndrome, and at time points specified in the Schedule of Activities (Section 1.3).

Assessment of the participants for safety may require some physical examination by an investigator.

Height and Weight

Height and weight will be measured as specified in the Schedule of Activities (Section 1.3). Participants will be instructed to remove shoes and outdoor apparel and gear prior to this measurement.

8.2.2. Vital Signs

Weight, temperature, pulse/heart rate, respiratory rate, blood pressure (right and left hands separately) will be assessed.

Blood pressure and pulse/heart rate measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

Blood pressure and pulse/heart rate measurements should be preceded by at least 5 minutes of rest in a quiet setting without distractions (eg, television, cell phones).

8.2.3. Electrocardiograms

During the collection of ECGs, participants should be in a quiet setting without distractions (eg, television, cell phones). Participants should rest in a supine position for at least 5 minutes before ECG collection and should refrain from talking or moving arms or legs. If blood sampling or vital sign measurement is scheduled for the same time point as ECG recording, the procedure should be performed as in the following order: ECG(s), vital signs, blood draw.

8.2.4. Clinical Safety Laboratory Assessments

Blood samples for serum chemistry and hematology will be collected as noted in Section 10.7, Appendix 7: Clinical Laboratory Tests. The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents.

With prior sponsor approval, local laboratories may be used in the event of a safety concern or if initiation of treatment is critical and the central laboratory results are not expected to be available before the need to provide study intervention or take action to ensure participant safety.

8.2.5. Pregnancy Testing

Additional urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participation in the study.

8.2.6. Infections

Participants will be counseled on the signs and symptoms of infections and will be instructed to contact the site between scheduled visits should any signs and symptoms occur. At each site visit, investigators or other site personnel are required to evaluate participants for any signs or symptoms of infection and ask about symptoms of infection or other AEs that may have occurred between

site visits. Investigators need to consider additional laboratory examination (such as test for fungal or viral antigen) based on each participant's risk of opportunistic infection.

8.2.6.1. Tuberculosis

In addition to general evaluation for infection, monitoring for TB will be performed with chest x-ray or chest HRCT and IGRAs as scheduled in Schedule of Activities (Section 1.3).

8.2.7. Infusion- or Injection-site Reactions

Participants should be monitored for the occurrence of infusion reactions for at least 1 hour after IV infusion and injection-site reactions for at least 30 minutes following SC injection.

8.3. Adverse Events, Serious Adverse Events, and Other Safety Reporting

Timely, accurate, and complete reporting and analysis of safety information, including AEs, SAEs, and product quality control (PQC), from clinical studies are crucial for the protection of participants, investigators, and the sponsor and are mandated by regulatory agencies worldwide. The sponsor has established standard operating procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally acceptable representative) for the duration of the study.

Further details on AEs, SAEs, and PQC can be found in Section 10.9, Appendix 9: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

8.3.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All Adverse Events

All AEs and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until completion of the participant's last study-related procedure, which may include contact for follow-up of safety.

Serious Adverse Events

All SAEs, as well as PQC, occurring during the study must be reported to the appropriate sponsor contact person by study site personnel within 24 hours of their knowledge of the event.

Serious adverse events, including those spontaneously reported to the investigator within 16 weeks after the last dose of study intervention, must be reported. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

Information regarding SAEs will be transmitted to the sponsor using the SAE Form, which must be completed and signed by a physician from the study site and transmitted to the sponsor within 24 hours. The initial and follow-up reports of an SAE should be made by facsimile (fax). Telephone reporting should be the exception and the reporter should be asked to complete the appropriate form(s) first.

8.3.2. Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting AEs or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

Solicited Adverse Events

Solicited AEs are predefined local (at the infusion or injection site) and systemic events for which the participant is specifically questioned and which are noted by participants in their diary (see Section 8, STUDY ASSESSMENTS AND PROCEDURES).

Unsolicited Adverse Events

Unsolicited AEs are all AEs for which the participant is not specifically questioned in the participant diary.

8.3.3. Follow-up of Adverse Events and Serious Adverse Events

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and evaluations as medically indicated to elucidate the nature and causality of the AE, SAE, or PQC as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

Adverse events, including pregnancy, will be followed by the investigator as specified in Section 10.9, Appendix 9: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

8.3.4. Regulatory Reporting Requirements for Serious Adverse Events and Anticipated Events

The sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). The investigator (or sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB. A SUSAR will be reported to regulatory authorities unblinded. Participating investigators and IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified.

8.3.5. Pregnancy

All initial reports of pregnancy in female participants or partners of male participants must be reported to the sponsor by the study site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and must be reported using an SAE reporting form. Any participant who becomes pregnant during the study must be promptly withdrawn from the study and discontinue further study intervention.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

8.3.6. Infections

The study intervention should not be administered to a participant with a clinically important, active infection. Treatment with the study intervention should be withheld until serious and/or severe infections are completely resolved. If a participant develops a serious or severe infection, including but not limited to sepsis or pneumonia, discontinuation of the study intervention must be considered. Treatment must be permanently discontinued for participants who develop a serious opportunistic infection. This should be discussed with the sponsor. For active varicella zoster infection or a significant exposure to varicella zoster infection in a participant without history of chickenpox, the participant should be evaluated for symptoms of infection and if the participant has received appropriate treatment and/or recovered or has no symptoms of infection, he/she may continue the study intervention after discussion with the sponsor.

8.3.7. Tuberculosis

Any newly identified case of active TB occurring after the first administration of the study intervention in participants participating in this study must be reported by the investigator according to the local procedures. These events are to be considered serious only if they meet the definition of an SAE. Treatment must be permanently discontinued for participants with active TB.

8.3.8. Infusion- or Injection-site Reactions

An infusion reaction is defined as an AE that occurs during or within 1 hour following the infusion of the study intervention, excluding laboratory abnormalities. Permanent discontinuation of the study intervention must be considered for participants who experience an AE of infusion reaction that is considered serious or severe by the investigator.

8.3.9. Events of Special Interest

Adverse events of special interest: opportunistic infection (ie, infection by an organism that normally is not pathogenic or does not cause invasive infection in immunocompetent hosts), case of active TB, or malignancy occurring after the first administration of study intervention in participants in this study must be reported by the investigator following procedures. Investigators are also advised that active TB is considered a reportable disease required by local regulations. These events are to be considered serious only if they meet the definition of an SAE as shown in

Section 10.9, Appendix 9: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

8.3.10. Disease-related Events and Disease-related Outcomes Not Qualifying as Adverse Events or Serious Adverse Events

All events that meet the definition of an SAE will be reported as SAEs, regardless of whether they are protocol-specific assessments.

8.4. Pharmacokinetics

Serum samples will be used to evaluate the PK of ustekinumab. Serum collected for PK may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period. Genetic analyses will not be performed on these serum samples. Participant confidentiality will be maintained.

8.4.1. Evaluations

At visit for measurement of ustekinumab concentrations in PK only evaluations (ie, no anti-ustekinumab antibodies will be evaluated), venous blood samples of 5 mL should be collected and each sample will be divided into 2 aliquots (1 for serum ustekinumab concentration and 1 for back-up). At visit for serum concentration of PK and immunogenicity, venous blood samples of 7.5 mL should be collected, and each sample will be divided into 3 aliquots (1 each for serum concentration of ustekinumab, for anti-ustekinumab antibodies, and for back-up). Additional information about the collection, handling, and shipment of biological samples can be found in the laboratory manual.

8.4.2. Analytical Procedures

Pharmacokinetics

Blood samples will be collected to evaluate the serum PK of ustekinumab as specified in Schedule of Activities (Section 1.3). Serum samples will be analyzed to determine concentrations of ustekinumab using a validated, specific, and sensitive method by or under the supervision of the sponsor.

8.5. Genetics and Pharmacogenomics

Pharmacogenomics

A pharmacogenomic blood sample will be collected from participants who consent separately to this component of the study to allow for pharmacogenomic research, as necessary. Participant participation in pharmacogenomic research is optional.

HLA-B and IL-12B genotype

The genotypes of the HLA-B and IL-12B genes will be tested for participants who consent separately to this component of the study. The genotyping tests may include, but are not limited to, the presence of HLA-B*52:01 allele (for HLA-B) and rs6871626 polymorphism (for IL-12B).

Genetic (DNA) variation may be an important contributory factor to interindividual variability in drug response and associated clinical outcomes. Genetic factors may also serve as markers for disease susceptibility and prognosis and may identify population subgroups that respond differently to an intervention.

DNA samples may be analyzed for identification of genetic and epigenetic factors that may be associated with the disease and/or the responses to the treatment. This research may consist of the analysis of 1 or more candidate genes, or the analysis of genetic and epigenetic markers throughout the genome, or analysis of the entire genome (as appropriate) in relation to ustekinumab intervention and/or TAK. Whole blood samples will be collected for genetic analyses at screening as specified in the Schedule of Activities (Section 1.3) if within the maximum blood volume allowed.

8.6. Biomarkers

Biomarker assessments will be performed to identify biomarkers that are relevant to ustekinumab treatment and/or TAK. These may include, but are not limited to, the evaluation of relevant biomarkers in serum, whole blood, and peripheral blood mononuclear cell (PBMC) samples collected as specified in the Schedule of Activities (Section 1.3). Data collected from these samples will be used for exploratory research that will include the following objectives:

- To understand the molecular effects of ustekinumab.
- To understand TAK pathogenesis.
- To understand why individual participants may respond differently to ustekinumab.
- To understand the impact of treatment with ustekinumab on vascular or systemic inflammation.

Stopping Analysis

Biomarker analyses are dependent upon the availability of appropriate biomarker assays and clinical response rates. Biomarker analysis may be deferred or not performed, during or at the end of the study, if it becomes clear that the analysis will not have sufficient scientific value for biomarker evaluation or if there are not enough samples or responders to allow for adequate biomarker evaluation. In the event the study is terminated early or shows poor clinical efficacy, completion of biomarker assessments will be based on justification and intended utility of the data.

8.6.1. Pharmacodynamics

Samples for the analysis of pharmacodynamic biomarkers will be collected from all participants. Serum level of IL-12, IL-23, IL-17A, IL-17F, and IL-22 may be measured to assess the pharmacodynamic effect of ustekinumab.

8.6.2. Serum biomarkers

Blood samples will be collected from all participants for serum-based biomarker analyses, where local regulations permit. Serum may be analyzed for levels of specific proteins, autoantibodies,

other inflammation-related molecules, and/or broad panel of analytes relevant to TAK pathogenesis and ustekinumab treatment.

8.6.3. Whole Blood Gene Expression Profile

Whole blood will be collected by venipuncture from participants for RNA expression analysis, where local regulations permit. Total RNA will be isolated and used for differential gene expression analyses to identify gene expression patterns that are relevant to ustekinumab treatment and/or TAK and to evaluate markers that can predict clinical response. Transcriptomic studies may be conducted using microarray and/or alternative equivalent technologies, which facilitate the simultaneous measurement of the relative abundances of multiple RNA species resulting in a transcriptome profile for each blood sample. The samples may also be used for targeted assessment of genes relevant to the disease and/or the treatment. These analyses may be used to evaluate the changes in gene expression profiles that may correlate with biologic response relating to TAK and/or the action of ustekinumab and may also be used to identify population subgroups that respond differently to an intervention.

8.6.4. Peripheral Blood Mononuclear Cells

Whole blood will also be collected and processed for peripheral blood mononuclear cells (PBMC) isolation and cryopreserved for later analysis. Analysis may include but is not limited to flow cytometric assessment of cell populations, single cell transcriptomics, or functional assessment of cells in response to ustekinumab treatment and/or related to TAK pathogenesis. These analyses may not be performed if cryopreserved PBMC samples do not meet the quality or quantity standard required for the assessments.

8.7. Immunogenicity Assessments

Anti-ustekinumab antibodies will be evaluated in serum samples collected from all participants according to the Schedule of Activities (Section 1.3). Additionally, serum samples should also be collected at the safety follow-up visit from participants who discontinued study intervention or were withdrawn from the study. These samples will be tested by the sponsor or sponsor's designee.

Serum samples will be screened for antibodies binding to ustekinumab and the titer of confirmed positive samples will be reported. Serum samples that test positive for anti-ustekinumab antibodies will be further characterized to determine if anti-ustekinumab antibodies could neutralize the biological effects of ustekinumab in vitro (ie, neutralizing antibodies [NAbs] to ustekinumab). Other analyses may be performed to verify the stability of antibodies to ustekinumab and/or further characterize the immunogenicity of ustekinumab.

Samples collected for immunogenicity analyses may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period. Genetic analyses will not be performed on these serum samples. Participant confidentiality will be maintained.

Analytical Procedures

The detection and characterization of anti-ustekinumab antibodies will be performed using a validated assay method by or under the supervision of the sponsor. All samples collected for

detection of anti-ustekinumab antibodies will also be evaluated for ustekinumab serum concentration to enable interpretation of the antibody data. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the study intervention(s). Samples may be stored up to 15 years (or according to local regulations) following the last participant's last visit for the study at a facility selected by the sponsor to enable further analysis of immune responses to ustekinumab.

8.8. Medical Resource Utilization and Health Economics

Medical resource utilization and health economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the statistical analysis plan (SAP).

9.1. Statistical Hypotheses

The hypothesis is that ustekinumab will prolong time to relapse while attempting corticosteroids tapering as compared with placebo in participants with TAK.

9.2. Sample Size Determination

Thirty-five events of relapse will have a power of 80% to detect a hazard ratio of 0.371 at a 2-sided alpha level of 0.05 (fixed design with no interim analysis is assumed) assuming a relapse-free rate of 55% in ustekinumab group and 20% in placebo group at Week 24. The assumptions of relapse-free rate at Week 24 is based on the results of clinical trial of TCZ showing trend of its steroid sparing effects in moderate to severe TAK participants. Total sample size is approximately 50 (25/treatment group) participants with which 35 events will occur 105 weeks after the first participant was enrolled. Regarding study duration, enrollment speed is assumed uniform every 6 months for 2 years; 5 participants for the first 6 months, 12 participants for the next 6 months, 18 participants for the next 6 months, and 15 participants for the last 6 months. Relapse free rate will carefully be monitored by using blind data during DB period and the actual number of participants enrolled in this study will be flexibly determined through the trial.

9.3. Populations for Analysis Sets

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign the ICF.
Randomized	All participants who were randomized in the study.
FAS	All randomized participants who take at least 1 dose of study intervention. Full analysis set will be the primary population for efficacy analyses.
Safety	All participants who take at least 1 dose of study intervention.
PK	All participants who take at least 1 complete dose of ustekinumab and have at least 1 post-dose sample collection.
Immunogenicity	All participants who take at least 1 dose of ustekinumab and have at least 1 post-dose sample collection.

Abbreviations: FAS=full analysis set; ICF=informed consent form; PK=pharmacokinetic

9.4. Statistical Analyses

The SAP will be finalized prior to DBL and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1. Primary Estimand

The primary estimand, the main clinical quantity of interest to be estimated in this study, is defined by the following 5 components:

- Population: Participants with TAK who have not adequately responded to conventional therapy
- Endpoint: Time from randomization to relapse
- Treatment: Stelara versus placebo
- Intercurrent Events (ICE)

  Death or treatment discontinuation: Use time to ICE (While on treatment strategy)

  Major protocol deviation: Use time to relapse regardless of the occurrence of major protocol deviations (Treatment policy strategy)
- Population level summary: Hazard ratio for time to relapse

9.4.2. Primary Endpoint

Primary analysis will be performed after 35 events of relapse occurred. For the primary endpoint of time to relapse, primary analysis will consist of test using a Cox proportional hazard regression model for comparison between 2 treatment groups. GC dose at Week 0 and the status of previous biologic medication will be considered as stratification factors. The hazard ratio and its 2-sided 95% confidence intervals will be also presented. The Kaplan-Meier method will be used to estimate the distribution of time to relapse for each treatment. One efficacy interim analysis is planned and the type I error rate will be controlled at 5% (2-sided). The significant level is to be determined based on the O'Brien-Fleming alpha spending function. Based on this approach, the interim analysis will be performed at a significance level of 0.0012 when exactly 15 of 35 events were observed and if the study is not stopped, the final analysis performed at the 0.0496 significance level.

9.4.3. Secondary Endpoints

Other time-to-event efficacy endpoints

Time-to-relapse using other definitions such as Kerr's definition, based on clinical symptoms only and each of 5 categories will be estimated by Kaplan-Meier method. The hazard ratio and its 2-sided 95% confidence intervals will be estimated using Cox proportional hazard regression model. GC dose at Week 0 and the status of previous biologic medication will be considered as stratification factors. Proportion of number of relapsed participants through treatment period will be also summarized by each definition of relapse.

GC tapering

Prednisolone dose will be descriptively summarized including cumulative dose and change from baseline through the end of DB period. Proportion of participants who achieved GC dose of 5mg/day or less will be also summarized.

Imaging

Change from baseline in imaging evaluation through the end of DB period will be calculated.

Inflammatory makers

Change from baseline in inflammatory markers (CRP and ESR) through the end of DB period will be descriptively summarized.

9.4.4. Exploratory Endpoints

For exploratory endpoints, the continuous variables will be summarized by intervention group and week using descriptive statistics, which will include the number of participants (N), mean, standard deviation (SD), median, minimum, and maximum. The categorical variables will be summarized by intervention group and week using frequencies and percentages. The further details will be described in SAP.

Exploratory endpoints are as follows:

- Proportion of participants who experienced relapse using each definition such as protocol-defined criteria, Kerr's definition, based on clinical symptoms only and each of five categories during OLE period.
- Changes from baseline on PROs through the end of study (SF-36, PtGA of disease activity on VAS, FACIT-Fatigue) through the end of study.
- Change from baseline PhGA through the end of study.
- Cumulative oral GC dose during OLE period.
- Change from baseline in oral GC dose during OLE period.
- Proportion of participants achieving oral GC dose of 5 mg/day or less during OLE period.
- Change from baseline in imaging evaluation during OLE period.
- Change from baseline in inflammatory markers (CRP, ESR) during OLE period.

For continuous variables of patient reported outcomes, descriptive analysis followed by mixed model repeated measures will be used. No adjustment for multiple comparison will be made.

9.4.5. Safety Analyses

Adverse Events

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs are AEs with onset during the treatment phase or that are a consequence of a preexisting condition that has

worsened since baseline. All reported AEs with onset during treatment phase (ie, TEAEs and AEs that have worsened since baseline) will be included in the analysis. For each AE, the percentage of participants who experience at least 1 occurrence of the given event will be summarized by intervention group.

Summaries, listings, datasets, or participant narratives may be provided, as appropriate, for those participants who die, who discontinue intervention due to an AE, or who experience a severe or an SAE.

All safety analyses will be performed on the safety population.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Reference ranges and markedly abnormal results (specified in the SAP) will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte at baseline and for observed values and changes from baseline at each scheduled time point. Frequency tabulations of the changes from baseline will be presented in pre- versus post-intervention cross-tabulations (with classes for below, within, and above normal ranges). Frequency tabulations of the laboratory abnormalities will be made. A listing of participants with any laboratory results outside the reference ranges will be provided. A listing of participants with any markedly abnormal laboratory results will also be provided.

Electrocardiogram

Clinically relevant abnormalities will be evaluated by frequency tabulations.

Vital Signs

Vital signs including descriptive statistics of weight, temperature, pulse/heart rate, respiratory rate, and blood pressure (right and left hands separately, systolic and diastolic) values and changes from baseline will be summarized over time at each scheduled time point, using descriptive statistics and/or graphically. The percentage of participants with values beyond clinically important limits will be summarized.

Physical Examinations

Descriptive statistics of changes from baseline will be summarized at each scheduled time point.

Physical examination findings will be summarized at each scheduled time point. Descriptive statistics will be calculated at baseline and for observed values and changes from baseline at each scheduled time point. Frequency tabulations of the abnormalities will be made.

9.4.6. Other Analyses

Pharmacokinetics analysis

Pharmacokinetic analyses for ustekinumab will be performed on the PK analysis population.

Serum ustekinumab concentrations will be summarized with descriptive statistics, including arithmetic mean, SD, coefficient of variation%, median, interquartile range, minimum, and maximum at each nominal sampling timepoint. All concentrations below the lowest quantifiable sample concentration of the assay or missing data will be labeled as such in the concentration data listing or statistical analysis system dataset. Below the lowest quantifiable concentrations will be treated as zero in the summary statistics.

Detailed rules for the analysis including exclusion from the PK analyses will be specified in the SAP. If feasible, population PK analysis of ustekinumab may be performed using nonlinear mixed-effect modeling. Further details will be provided in a population PK analysis plan and the results will be provided in a separate report.

Immunogenicity Analyses

Anti-ustekinumab antibodies will be analyzed on the immunogenicity analysis population.

A listing of participants who are positive for anti-ustekinumab antibodies will be provided. The maximum titers of anti-ustekinumab antibodies will be summarized for participants who are positive for anti-ustekinumab antibodies. The incidence of NAbs to ustekinumab will be summarized for participants who are positive for anti-ustekinumab antibodies and have samples evaluable for NAbs to ustekinumab.

Pharmacodynamic and Biomarker Analyses

The biomarker analyses will be used to understand TAK, characterize the effects of ustekinumab, to identify PD markers and biomarkers relevant to treatment, and to determine if these markers can predict response to ustekinumab. The biomarker analyses may include but are not limited to serum cytokines, inflammatory markers, whole blood RNA profile, and other categories of biomarkers potentially involved in the development and the progression of TAK.

Changes in biomarkers over time may be summarized by treatment group. Associations between baseline levels and changes from baseline in selected markers and clinical response may be explored. Results of biomarker analyses may be presented in a separate technical report.

Planned biomarker analyses may be deferred if emerging study data show no likelihood of providing useful scientific information or insufficient number of samples are available for analyses. Any biomarker samples received by the contract vendor or sponsor after the cutoff date will not be analyzed and therefore, excluded from the biomarker analysis.

Pharmacokinetic/Pharmacodynamic Analyses

If data permit, the relationship between serum ustekinumab concentration and efficacy/safety measures, biomarkers, and immunogenicity will be analyzed graphically. In addition, PK/PD modeling may be performed to characterize the relationship between serum ustekinumab exposure and efficacy/safety measures. Analyses plan and results may be provided in a separate report.

Pharmacogenomic Analyses

Genetic (DNA) analyses may be conducted only in participants who sign the consent/assent form to participate in the pharmacogenomic sampling. These analyses are considered exploratory. DNA samples may be used for research related to ustekinumab or TAK. They may also be used to develop tests/assays related to ustekinumab and TAK. Pharmacogenomic research may consist of the analysis of one or more candidate genes or of the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate) in relation to ustekinumab TAK clinical endpoints. Analyses results may be summarized in a separate technical report.

9.5. Interim Analysis

An IDMC will be established to monitor data on an ongoing basis to ensure the continuous safety and well-being of the participants enrolled in this study. The committee will meet periodically to review safety data and provide recommendation to the sponsor on continuing the trial. The IDMC responsibilities, authorities, and procedures will be documented in the IDMC charter.

One efficacy interim analysis is planned after 15 events have been occurred. The O'Brien-Fleming alpha spending function as implemented by the Lan-DeMets method will be used to determine the statistical boundary for early success (2-sided p-value $\leq$0.0012 for the efficacy interim analysis when exactly 15 of 35 events were observed). Specific details will be provided in the IDMC Charter and IDMC SAP.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations and Definitions

AE	Adverse event
anti-HBc total	HBV core antibody total
anti-HBs	HBV surface antibody
Aza	Azathioprine
β-hCG	β-human chorionic gonadotrophin
CD	Crohn's disease
COVID-19	Coronavirus Disease 2019
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
CTA	Computed tomography angiography
CT	Computed tomography
DB	Double-blind
DBL	database lock
DM	dermatomyositis
DNA	deoxyribonucleic acid
ECG	electrocardiogram
EPCR	endothelial protein C receptor
ESR	erythrocyte sedimentation rate
eCRF	electronic case report forms
eDC	electronic data capture
FACIT	The Functional Assessment of Chronic Illness Therapy
FSH	Follicle stimulating hormone
GC	glucocorticoid
GCA	Giant Cell Arteritis
GCP	Good Clinical Practice
HBsAg	HBV surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HLA	Human leucocyte antigen
HRCT	high-resolution computer tomography
IB	Investigator's Brochure
IBD	inflammatory bowel disease
ICE	Intercurrent events
ICF	informed consent form/assent form
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDMC	Independent data monitoring committee
IDMJE	International Committee of Medical Journal Editors
IEC	International ethics committee
IFN	Interferon
Ig	Immunoglobulin
IGRA	interferon gamma release assay
IL	Interleukin
INR	international normalized ratio
IRB	Institutional Review Board
ISI	International System of Units
IV	Intravenous
IWRS	interactive web response system
JAK	Janus kinase
LIV	liquid in vial
LTE	Long-term extension
NCI-CTCAE	National Cancer Institute - Common Terminology Criteria for Adverse Events
NSAID	non-steroidal anti-inflammatory drug

MedDRA	Medical Dictionary for Regulatory Activities
MMF	mycophenolate mofetil
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
MTX	methotrexate
NAbs	neutralizing antibodies
OLE	open-label extension
PBMC	peripheral blood mononuclear cell
PD	Pharmacodynamic
PFS	prefilled syringe
PK	Pharmacokinetic
PM	polymyositis
PQC	product quality complaint
PRO	patient-reported outcome
PsA	psoriatic arthritis
PtGA	Patient's global assessment
QFT	QuantiFERON-TB Gold
Q8W	Every 8 weeks
RA	rheumatoid arthritis
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome-corona virus
SC	Subcutaneous
SD	standard deviation
SF-36	Short form-36
SI	International System of Units
SLE	systemic lupus erythematosus
SNPs	single nucleotide polymorphisms
SR-B1	scavenger receptor class B type 1
SUSAR	suspected unexpected serious adverse reactions
TAC	Tacrolimus
TAK	Takayasu arteritis
TB	Tuberculosis
TCZ	tocilizumab
TEAE	treatment-emergent adverse events
TNF	Tumor necrosis factor
UC	ulcerative colitis
ULN	upper limit of normal
VAS	visual analog scale
WBC	white blood cell

Definitions of Terms

COA	An umbrella term encompassing different types of outcomes assessments
Electronic source system	Contains data traditionally maintained in a hospital or clinic record to document medical care or data recorded in a eCRF as determined by the protocol. Data in this system may be considered source documentation.
PRO	Reports directly from the participant without interpretation by clinician or anyone else

10.2. Appendix 2: Diagnostic criteria for Takayasu arteritis according to JCS 2017 guideline on management of vasculitis syndrome

The diagnostic criteria of definite is at least 1 of the items in A+ any of the conditions in B are observed, and conditions in C can be excluded.

A. Signs and symptoms

- Systemic signs and symptoms: Fever, generalized malaise, easy fatigability, lymphadenopathy (cervical), hypertension in younger patients (≥140/90 mmHg)
- Pain: Carotidynia, chest pain, back pain, lower back pain, shoulder pain, upper limb pain, lower limb pain
- Visual signs and symptoms: Transient or persistent visual impairment, preocular bright or dark sensation, loss of vision, fundus changes (hypotensive changes, hypertensive changes)
- Head and neck signs and symptoms: Headache, toothache, jaw claudication,*[a] dizziness, hearing impairment, tinnitus, syncope, cervical vascular murmurs, hemiplegia
- Upper limb signs and symptoms: Numbness, cold sensation, difficulty in arm raising, claudication,*[b] abnormal pulse and blood pressure (weakness or loss of radial artery pulse or left-right difference of ≥10 mmHg), increased pulse pressure (related to aortic insufficiency)
- Lower limb signs and symptoms: Numbness, cold sensation, weakness, claudication, abnormal pulse and blood pressure (augmented or weakened pulse of lower limb arteries, reduced blood pressure, blood pressure difference between upper and lower limbs*[c])
- Chest symptoms: Shortness of breath, palpitation, dyspnea, bloody sputum, sensation of chest compression, anginal symptoms, arrhythmia, cardiac murmur, back vascular murmur
- Abdominal signs and symptoms: Abdominal vascular murmur, complication by ulcerative colitis
- Skin signs and symptoms: Erythema nodosum

*a. Intermittent mastication due to pain caused by mastication
*b. Intermittent exertion of the upper limbs due to pain and weakness caused by exertion
*c. Instances other than "10–30 mmHg higher in the lower limb than upper limb"

B. Examination findings

Imaging examination findings: In the aorta or its primary branches*[a] or both, multiple*[b] or diffuse hypertrophic lesions,*[c] stenotic lesions (including occlusions),*[d] or dilated lesions (including aneurysms)*[d] detected.

*a. The aorta and its primary branches corresond to the aorta (ascending, arch, thoracic descending, abdominal descending), primary branches of the aorta (including the coronary artery), and pulmonary artery.
*b. Multiple lesions are defined as those that involve two or more of the above arteries or sites or two or more segments of the aorta.
*c. Hypertrophic lesions are detected by ultrasonography (macaroni sign of the common carotid artery), contrast-enhanced CT, contrast-enhanced MRI (circumferential contrast enhancement of the arterial wall), and PET-CT (circumferential FDG uptake of the arterial wall).
*d. Stenotic lesions and dilated lesions are detected by chest radiography (wave-like deformation of the descending aorta), CT angiography, MR angiography, echocardiography (aortic insufficiency), and angiography. They are accompanied by dilatation of the ascending aorta and frequently also by aortic insufficiency. In the chronic stage, circumferential calcification of the arterial wall is visualized by CT, and the development of collateral circulation is detected by CT angiography and MR angiography

Points of attention in imaging diagnosis: Contrast-enhanced CT is performed in the late phase of contrast enhancement. CT angiography is performed in the early phase of contrast enhancement with 3-

dimensional image processing. Angiography is usually performed when other procedures such as endovascular treatment and coronary artery angiography or left ventriculography are simultaneously intended.
C. Conditions to be included in the differential diagnoses of Takayasu arteritis
Arteriosclerosis, congenital vascular anomaly, inflammatory abdominal aortic aneurysm, infectious aneurysm, syphilitic mesaortitis, giant cell arteritis (temporal arteritis), vascular Behçet's disease, IgG4-related diseases.

10.3. Appendix 3: Definitions of relapse/remission of TAK

Definitions of relapse of TAK (Inclusion criteria definition/Efficacy evaluation definition)

Category	Inclusion criteria definition When 2 or more categories in the following 5 categories meet the criteria, participants will be judged as relapse.	Efficacy evaluation definition When 2 or more categories in the following 5 categories meet the criteria, participants will be judged as relapse. Even if signs of relapse were not present in 2 of 5 categories, relapse was considered to have occurred if emergent hospitalization caused by worsening of TAK and GC treatment required or if severe aortic valve incompetence accompanied by symptoms of cardiac failure occurred under 'vascular signs and symptoms' or if CTCAE grade 2 or higher (grade ≥3 for myocardial infarction) occurred under 'ischaemic symptoms'.
1. Systemic symptoms (objective assessment)	An assessment of 'signs of relapse present' should be made for this category if any of the following are observed; • Fever: body temperature ≥38.0°C • Weight loss: weight loss >2 kg in 4 weeks • Arthritis: joint symptoms in ≥2 joints (arthralgia, swelling and tenderness in joints)	An assessment of 'signs of relapse present' should be made for this category if any of the following are observed; • Fever: body temperature ≥38.0°C • Weight loss: weight loss >2 kg since the previous measurement • Arthritis: joint symptoms in ≥2 joints (arthralgia, swelling, and tenderness in joints)
2. Systemic symptoms (subjective assessment)	An assessment of 'signs of relapse present' should be made for this category if any of the following symptoms are observed at grade 2 or higher • Malaise • Myalgia • Headache • Dizziness/vertigo	An assessment of 'signs of relapse present' should be made for this category if there is an increase in the CTCAE grade from baseline for any of the following • Malaise • Myalgia • Headache • Dizziness/vertigo
3. Elevated inflammation markers	An assessment of 'signs of relapse present' should be made for this category if the following is observed • CRP ≥1.0 mg/dL and ESR ≥30 mm/h	An assessment of 'signs of relapse present' should be made for this category if the following is observed • CRP ≥1.0 mg/dL and ESR ≥30 mm/h
4. Vascular signs and symptoms	An assessment of 'signs of relapse present' should be made for this category if any of the following are observed; • Renovascular hypertension Normal blood pressure <120/80 mm Hg: has risen to 140/90 mm Hg or higher	• An assessment of 'signs of relapse present' should be made for this category if any of the following are observed; • If severe aortic valve incompetence accompanied by symptoms of cardiac failure occurs, it should be deemed that relapse of TAK has

	Normal blood pressure ≥120/80 mm Hg: diastolic blood pressure has risen by ≥20 mm Hg • New vascular bruits (carotid artery, subclavian artery, renal artery) • New loss of pulse (carotid artery, subclavian artery, brachial artery, radial artery, femoral artery, popliteal artery, posterior tibial artery, dorsalis pedis artery) • New difference in blood pressure between left and right: new difference in systolic blood pressure between left and right ≥10 mm Hg • Tenderness or spontaneous pain in carotid artery: symptoms of CTCAE grade 2 or higher • Spontaneous pain in chest region or back region: symptoms of CTCAE grade 2 or higher • Onset of aortic valve incompetence (moderate or severe)	occurred, even if none of the criteria for categories 1-3 or 5 are met • Renovascular hypertension <120/80 mm Hg at baseline: has risen to ≥140/90 mm Hg ≥120/80 mm Hg at baseline: diastolic blood pressure has risen by ≥20 mm Hg • New vascular bruits (carotid artery, subclavian artery, renal artery) • New loss of pulse (carotid artery, subclavian artery, brachial artery, radial artery, femoral artery, popliteal artery, posterior tibial artery, dorsalis pedis artery) • New difference in blood pressure between left and right: new difference in systolic blood pressure between left and right of ≥10 mm Hg • Tenderness or spontaneous pain in carotid artery: increase in CTCAE grade since baseline • Spontaneous pain in chest region or back region: increase in CTCAE grade since baseline • Aortic valve incompetence (worsening from 'no symptoms' or 'mild' to at least 'moderate' or worsening from 'moderate' to 'severe')
5. Ischaemic symptoms	An assessment of 'signs of relapse present' should be made for this category if any of the following symptoms are observed at grade 2 or higher • Abdominal pain • Seizure • Syncope • Intermittent claudication • Ischaemic cardiac pain	An assessment of 'signs of relapse present' should be made for this category if there is an increase in the CTCAE grade from baseline for any of the following events. If symptoms of grade 2 or higher (grade 3 or higher for myocardial infarction) occur, it should be deemed that TAK has occurred, even if none of the criteria for categories 1-4 are met • Abdominal pain • Stroke • Seizure • Syncope • Intermittent claudication • Ischaemic cardiac pain • Myocardial infarction

Definitions of another relapse of TAK

	Definition
Relapse of TAK by having non-specific symptoms	Participants meet 2 or more categories in the following 5 categories without meeting 4) or 5) will be considered as relapse per non-specific symptoms: 1) Objective systemic symptoms; 2) Subjective systemic symptoms; 3) Elevated inflammation markers; 4) Vascular signs and symptoms; 5) Ischemic symptoms.
Relapse of TAK according to Kerr's definition	Participants meet 2 or more categories in the following 4 categories will be considered as relapse per Kerr's definition: 1) Objective systemic symptoms or subjective systemic symptoms, 2) Elevated inflammation markers, 3) Vascular signs and symptoms or ischemic symptoms, 4) Imaging evaluation*. *Imaging evaluation: whether typical imaging features is present (eg, long segments of critical stenoses [>70%])
Relapse of TAK based on clinical symptoms only	Participants meet at least 1 category in the following 4 clinical categories are considered as relapse per clinical symptom only definition: 1) Objective systemic symptoms; 2) Subjective systemic symptoms; 3) Vascular signs and symptoms; 4) Ischemic symptoms.

Definitions of remission of TAK

Category	When the following 5 categories are assessed 'absence of any of the signs and symptoms' as judged by the investigator, participants will be judged as remission.
1. Systemic symptoms (objective assessment)	An assessment of 'absence of signs' should be made for this category if any of the following are not observed • Fever: body temperature ≥38.0°C • Weight loss: weight loss >2 kg in 4 weeks • Arthritis: joint symptoms in ≥2 joints (arthralgia, swelling, and tenderness in joints)
2. Systemic symptoms (subjective assessment)	An assessment of 'absence of signs' should be made for this category if any of the following symptoms are not observed at grade 2 or higher • Malaise • Myalgia • Headache • Dizziness/vertigo
3. Elevated inflammation markers*	An assessment of 'absence of signs' should be made for this category if the following is not observed • CRP ≥1.0 mg/dL and ESR ≥30 mm/h
4. Vascular signs and symptoms	An assessment of 'absence of signs' should be made for this category if any of the following are not observed • Tenderness or spontaneous pain in carotid artery: symptoms of CTCAE grade 2 or higher • Spontaneous pain in chest region or back region: symptoms of CTCAE grade 2 or higher

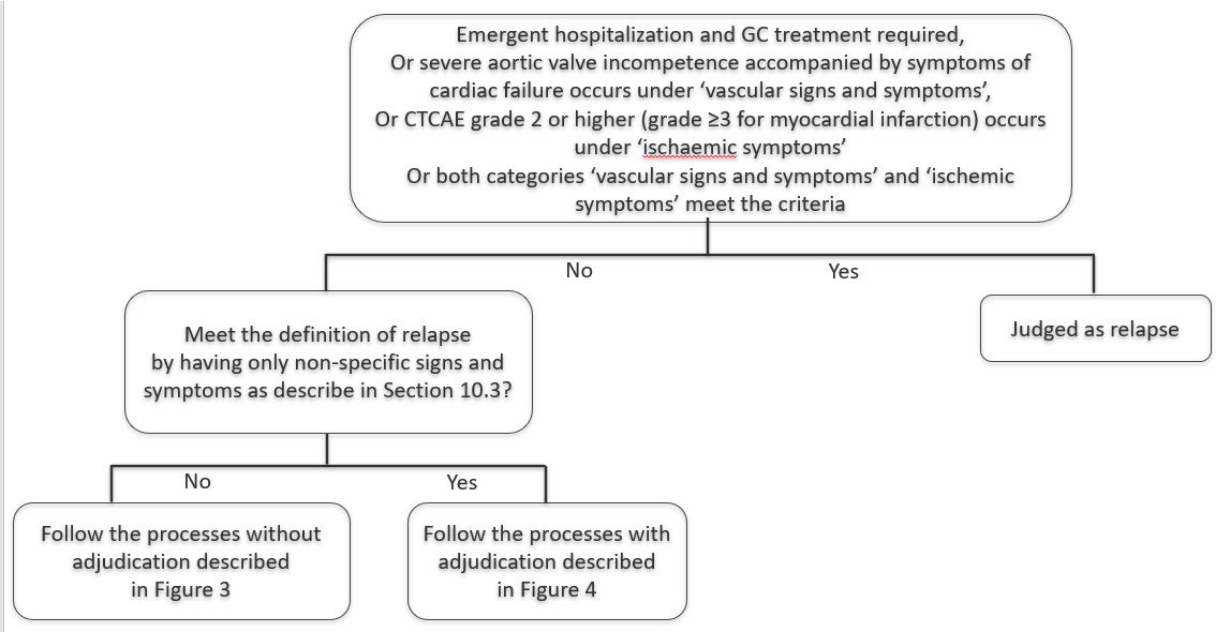
5. Ischaemic symptoms	An assessment of 'absence of signs' should be made for this category if any of the following symptoms are not observed at grade 2 or higher • Abdominal pain • Seizure • Syncope • Intermittent claudication • Ischaemic cardiac pain

*"3. Elevated inflammation markers" is not included in Assessment of "Remission of clinical symptoms".

10.4. Appendix 4: Relapse Judgement Flow

When participants meet the criteria of the TAK relapse described in Section 10.3 after administration of study intervention during the study, the investigators will follow the processes below to judge the relapse of TAK. The processes are shown in Figure 2.

Figure 2: Flow Chart For Relapse Judgement Process



The flows of relapse judgement without adjudication and with adjudication are described below:

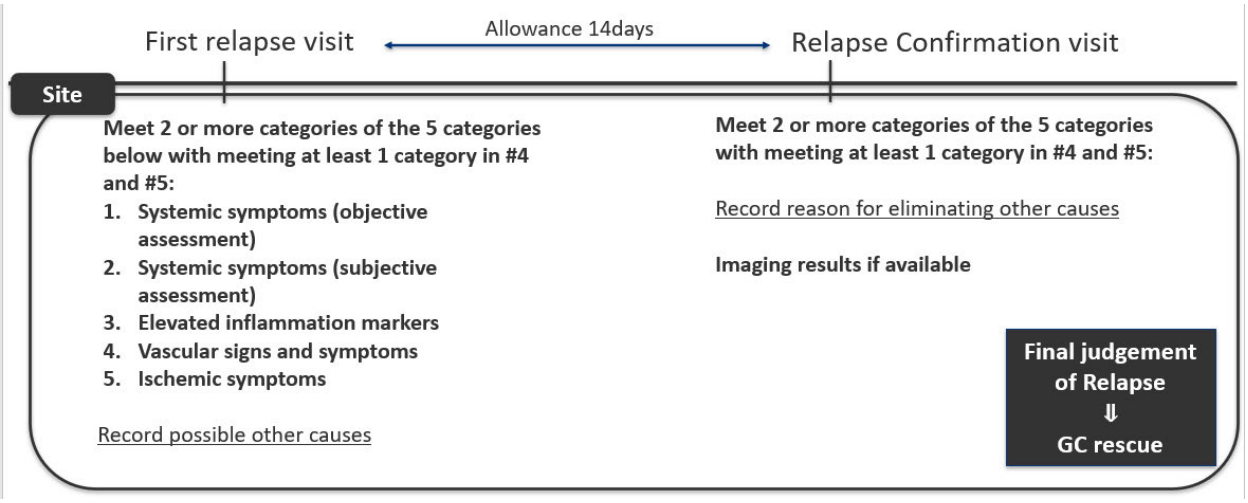
Relapse judgement process without adjudication

The schematic flow of relapse judgement process without adjudication is shown in Figure 3.

For the first relapse visit, the investigator or designee will record possible other causes on the Source Document. For the Relapse Confirmation Visit, the investigator or designee will record the reason for eliminating other causes in the eDC.

Inflammation marker results (ie, CRP) provided by central lab is encouraged to be used to judge relapse of TAK in this process.

Figure 3: The flow of relapse judgement without adjudication



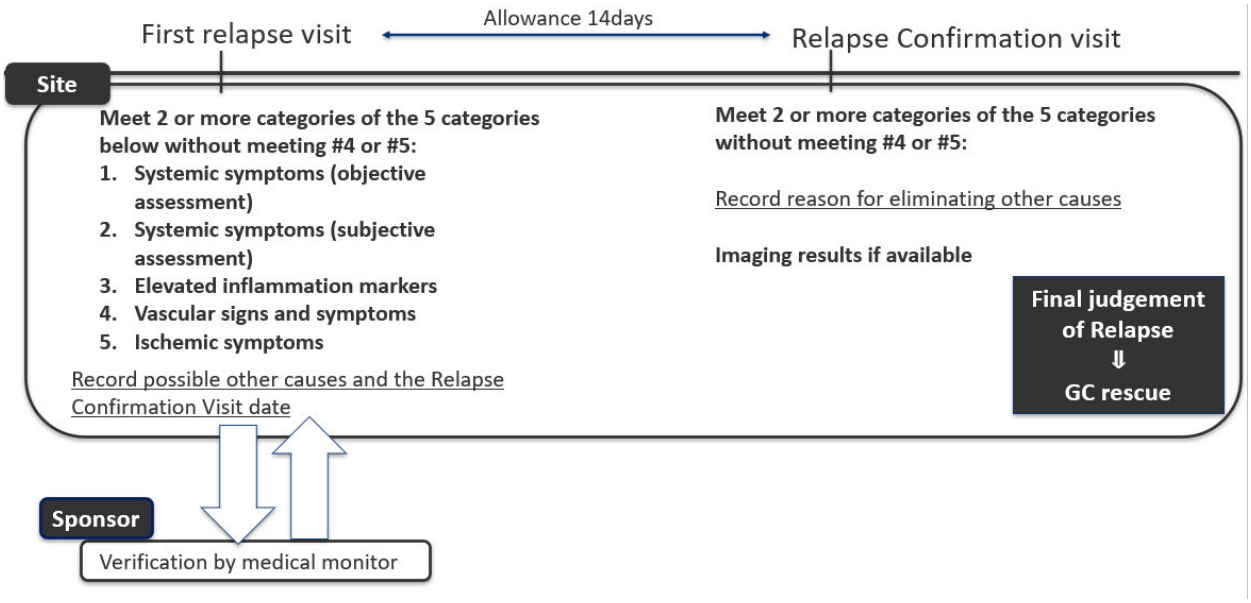
Relapse judgement process with adjudication

The schematic flow of relapse judgement process with adjudication is shown in Figure 4.

For the first relapse visit, the investigator or designee will record the possible other causes, and the Relapse Confirmation Visit date on the Source Document, and will submit these information to the sponsor within 3 working days. The sponsor's medical monitor will verify it and may request additional information as necessary until the Relapse Confirmation Visit. If the Relapse Confirmation Visit is scheduled within 5 working days of the first relapse visit, the investigator or designee should contact sponsor. For the Relapse Confirmation Visit, the investigator or designee will record the reason for eliminating other causes in the eDC.

Inflammation marker results (ie, CRP) provided by central lab is encouraged to be used to judge relapse of TAK in this process.

Figure 4: The flow of relapse judgement with adjudication



10.5. Appendix 5: Definition of Inadequate Response or Intolerance to Biologics

The criteria for inadequate response or intolerance to biologics (TCZ or anti-TNF therapies [infliximab, adalimumab, certolizumab pegol, etanercept, etc]) are described in items 1 and 2, below. Participants who meet 1 of the 2 items are considered to be bio-failure.

1. Inadequate response to current or prior therapy with TCZ or anti-TNF therapy

Eligible participants must satisfy criteria a, b, c.

a. Have received at least 4 weeks treatment of:

1) Tocilizumab (at SC dose of 162 mg/week)

or

2) Anti-TNF therapy (infliximab, adalimumab, certolizumab pegol, golimumab, etc)

AND

b. Was not able to taper oral GC dose to 7.5 mg/day (prednisolone or equivalent) or less due to disease activity of TAK based on clinical judgment of a treating physician.

The disease activity of TAK must have persisted ≥2 weeks after receiving one of the biologic treatments.

AND

c. Have documentation available to the investigator that meets the following 2 requirements:

1) Provide the dates and doses of the failed TCZ or anti-TNF therapy.

2) Documents that the participant had inadequate response to TCZ or anti-TNF therapy.

Examples of acceptable documents include: medical records, letter provided by a referring physician, or other "reason for referral" documents (eg, insurance authorization form).

2. Current or prior intolerance to therapy with TCZ or anti-TNF therapy

Eligible participants must satisfy criteria a and b.

a. Have had an adverse reaction that meets 1 of the following 3 criteria: 1) significant acute infusion/administration reaction; 2) significant delayed infusion/administration reaction (eg, delayed hypersensitivity or serum sickness-like reaction); or 3) significant injection-site reaction. Definitions of these 3 criteria are provided below.

Adverse reactions also must have followed 1 dose of TCZ, or anti-TNF therapy and, in the treating physician's opinion, precluded continued use of the therapy.

1) A significant acute infusion/administration reaction is defined as an adverse reaction that was:

- Manifested through 1 of the following symptoms.
  a. Fever greater than 100 F (37.8 C)
  b. Chills or rigors
  c. Itching
  d. Rash
  e. Flushing
  f. Urticaria or angioedema
  g. Breathing difficulties (dyspnea, chest paint or tightness, shortness of breath, wheezing, stridor)
  h. Clinical hypotension (pallor, diaphoresis, faintness, syncope), blood pressure less than 90 mm Hg systolic and 60 mm Hg diastolic, or a systemic or orthostatic drop in systolic blood pressure of greater than 20 mm Hg

and

- Occurred within 24 hours after infusion/administration of tocilizumab or anti-TNF therapy.

and

- Was considered related to the infusion/administration of TCZ or anti-TNF therapy.

2) A significant delayed infusion/administration reaction is defined as an adverse reaction that:

- Was manifested through 1 or more of the following symptoms:
  a. Myalgias
  b. Arthralgias
  c. Fever greater than 100 F (37.8 C)
  d. Malaise
  e. Rash

  and

- Occurred >24 hours and <15 days after infusion/administration of TCZ or anti-TNF therapy.

  and

- Was considered related to the infusion/administration of TCZ or anti-TNF therapy.

3) A significant injection-site reaction is defined as an adverse reaction that:

- Was manifested through 1 or more of the following symptoms:
  a. Significant bruising
  b. Erythema
  c. Hemorrhage
  d. Irritation
  e. Pain
  f. Pruritus
  g. "Injection-site reaction"

  and
- Occurred within 24 hours of infusion/administration of TCZ or anti-TNF therapy.

  and
- Was considered related to the injection.

b. Have documentation available to the investigator that meets the following 2 requirements:

1) Provides the date of discontinuation of TCZ or anti-TNF therapy.
2) Documents that the participant had intolerance to TCZ or anti-TNF therapy.

Examples of acceptable documents include: medical records, letter provided by a referring physician, or other "reason for referral" documents (eg, insurance authorization form).

10.6. Appendix 6: Glucocorticoid Conversion Table

GC	Replacement/Equivalence
Cortisone acetate	25 mg
Hydrocortisone	20 mg
Prednisolone	5 mg
Triamcinolone	4 mg
Methylprednisolone	4 mg
Dexamethasone	0.75 mg
Betamethasone	0.75 mg

10.7. Appendix 7: Clinical Laboratory Tests

The following tests will be performed according to the Schedule of Activities by the central laboratory:

Protocol-required Safety Laboratory Assessments

<table>
<tr><th>Laboratory Assessments</th><th colspan="3">Parameters</th></tr>
<tr><td rowspan="2">Hematology</td><td>Platelet count
Red blood cell (RBC) count
Hemoglobin
Hematocrit</td><td><u>RBC Indices:</u>
Mean corpuscular volume
Mean corpuscular hemoglobin
% Reticulocytes</td><td><u>White Blood Cell (WBC) count with Differential:</u>
Neutrophils
Lymphocytes
Monocytes
Eosinophils
Basophils</td></tr>
<tr><td colspan="3">Note: A WBC evaluation may include any abnormal cells, which will then be reported by the laboratory. An RBC evaluation may include abnormalities in the RBC count, RBC parameters, or RBC morphology, which will then be reported by the laboratory. In addition, any other abnormal cells in a blood smear will also be reported.</td></tr>
<tr><td rowspan="2">Clinical Chemistry</td><td colspan="2">Sodium
Potassium
Chloride
Bicarbonate
Blood urea nitrogen
Creatinine
Glucose nonfasting
Aspartate aminotransferase (AST)/Serum glutamic-oxaloacetic acid
Alanine aminotransferase (ALT)/Serum glutamic-oxaloacetic
Gamma-glutamyltransferase
FSH as needed</td><td>Total bilirubin, and if total bilirubin is abnormally elevated, then direct bilirubin and indirect bilirubin
Alkaline phosphatase
Creatine phosphokinase
Lactic acid dehydrogenase
Uric acid
Calcium
Phosphate
Albumin
Total protein
Cholesterol
Triglycerides
Magnesium</td></tr>
<tr><td colspan="3">Note: Details of liver chemistry stopping criteria and required actions and follow-up are given in Section 10.11, Appendix 11, Liver Safety. All events of ALT (or AST) ≥3× upper limit of normal (ULN) and total bilirubin ≥2× ULN (>35% direct bilirubin) or ALT (or AST) ≥3× ULN and international normalized ratio (INR) >1.5, if INR measured which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).</td></tr>
<tr><td>Routine Urinalysis</td><td colspan="2"><u>Dipstick</u>
Specific gravity
pH
Glucose
Protein
Blood
Ketones
Bilirubin
Urobilinogen
Nitrite
Leukocyte esterase</td><td><u>Sediment (if dipstick result is abnormal)</u>
RBCs
WBCs
Epithelial cells
Crystals
RBC, WBC, or heme-granular Casts
Bacteria</td></tr>
</table>

	If dipstick result is abnormal, microscopy will be used to measure sediment. In the microscopic examination, observations other than the presence of WBC, RBC, and casts may also be reported by the laboratory. Dipstick and sediment analysis of the urine samples will be performed in parallel at screening, ie, in the same sample at the same time. Specific gravity, pH, glucose, protein (eg, myoglobin), blood, ketones, bilirubin, and urobilinogen will be determined using a dipstick. Red blood cells, WBC, epithelial cells, crystals, casts, and bacteria will be measured using flow cytometry or microscopy. If there is discordance between the dipstick results and the flow cytometric results, the sediment will be examined microscopically. Crystals, casts, and bacteria will only be reported if they are present.
Genetic test	• HLA-B52 at screening only • IL-12B at screening only
Other Screening Tests	• Urine pregnancy testing for women of childbearing potential only • Serum pregnancy test (at the discretion of the investigator) • Viral serology (HIV antibody, HBsAg, anti-HBs, anti-HBc total, and HCV antibody) at screening only • Coagulation (prothrombin time [PT], activated partial thromboplastin time [aPTT], and international normalized ratio) at screening only • IGRA (performed locally) • CRP and ESR

10.8. Appendix 8: Regulatory, Ethical, and Study Oversight Considerations

10.8.1. Regulatory and Ethical Considerations

Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines on good clinical practice (GCP) and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human participants. Compliance with this standard provides public assurance that the rights, safety, and well-being of study participants are protected, consistent with the principles that originated in the Declaration of Helsinki and that the study data are credible.

Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the participants, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involve only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative listed in the Protocol Supplementary Information page(s), which will be provided as a separate document. Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the eCRF and source documents will reflect any departure from the protocol and the source documents will describe this departure and the circumstances requiring it.

Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study intervention to the study site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, participant compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations

The following documents must be provided to the sponsor before enrollment of the first participant:

- Completed investigator financial disclosure forms from all subinvestigators
- Documentation of subinvestigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study and a dated copy of current laboratory normal ranges for these tests, if applicable
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the participants)
- IB (or equivalent information) and amendments/addenda
- Sponsor-approved participant recruiting materials

- Information on compensation for study-related injuries or payment to participants for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for participants
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for participants, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and participant compensation programs and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

Approval for the collection of optional samples for research and for the corresponding ICF must be obtained from the IEC/IRB. Approval for the protocol can be obtained independent of this optional research component.

During the study, the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data, or study conduct)
- Revision(s) to ICF and any other written materials to be provided to participants
- If applicable, new or revised participant recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to participants for participation in the study, if applicable
- New edition(s) of the IB and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of AEs that are serious, unlisted/unexpected, and associated with the study intervention
- New information that may adversely affect the safety of the participants or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the participants
- Report of deaths of participants under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this study, where required.

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion (if applicable, the notification will be submitted through the head of investigational institution).

Other Ethical Considerations

For study-specific ethical design considerations, refer to Section 4.2.1.

10.8.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information in accordance with local regulations to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Refer to Required Prestudy Documentation (above) for details on financial disclosure.

10.8.3. Informed Consent Process and Assent Form

Each participant (or a legally acceptable representative) must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) that is used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the participant can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the study site personnel must explain to potential participants (or their legally acceptable representatives) the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Participants will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the participant will receive for the treatment of his or her disease. Participants will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a participant identification register for the purposes of long-term follow up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the participant, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the participant or legally acceptable

representative is authorizing such access, which includes permission to obtain information about his or her survival status. It also denotes that the participant agrees to allow his or her study physician to recontact the participant for the purpose of obtaining consent for additional safety evaluations and subsequent disease-related treatments, if needed. The physician may also recontact the participant for the purpose of obtaining consent to collect information about his or her survival status.

The participant or legally acceptable representative will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of either the participant's or his or her legally acceptable representative's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the participant.

Participants who are rescreened are required to sign a new ICF.

Participants will be asked for consent to provide optional samples for research (where local regulations permit). After informed consent for the study is appropriately obtained, the participant or his or her legally acceptable representative will be asked to sign and personally date a separate ICF indicating agreement to participate in the optional research component. Refusal to participate in the optional research will not result in ineligibility for the study. A copy of this signed ICF will be given to the participant.

Where local regulations require, a separate ICF may be used for the required DNA component of the study.

If the participant or legally acceptable representative is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the ICF after the oral consent of the participant or legally acceptable representative is obtained.

Children (minors) or participants who are unable to comprehend the information provided can be enrolled only after obtaining consent of a legally acceptable representative. Assent must be obtained from children (minors) capable of understanding the nature of the study, typically participants 7 years of age and older, depending on the institutional policies. Assent must be obtained from participants who are able to write. A separate assent form in the language the participant can understand must be developed for adolescents. After having obtained the assent, a copy of the assent form must be given to the participant, and to the participant's parent(s) or if applicable legally acceptable representative.

10.8.4. Data Protection

Privacy of Personal Data

The collection and processing of personal data from participants enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of participants confidential.

The informed consent obtained from the participant (or his or her legally acceptable representative) includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The participant has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

Exploratory biomarker, PK, and immunogenicity research is not conducted under standards appropriate for the return of data to participants. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to participants or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

10.8.5. Long-term Retention of Samples for Additional Future Research

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand ustekinumab, to understand TAK, to understand differential intervention responders, and to develop tests/assays related to ustekinumab and TAK. The research may begin at any time during the study or the post-study storage period.

10.8.6. Committees Structure

Data Monitoring Committee

A Data Monitoring Committee (DMC) will be established to monitor data on an ongoing basis to review interim data to ensure the continuing safety of the participants enrolled in this study and to meet efficacy objectives. The committee will meet periodically to review safety data and provide recommendation to the sponsor on continuing the trial. The IDMC responsibilities, authorities, and procedures will be documented in the IDMC charter.

One efficacy interim analysis is planned after 15 events have been occurred. The O'Brien-Fleming alpha spending function as implemented by the Lan-DeMets method will be used to determine the statistical boundary for early success (2-sided p-value ≤ 0.0012 for the efficacy interim analysis when exactly 15 of 35 events were observed). Specific details will be provided in the IDMC

Charter and IDMC SAP. This committee will consist of at least one medical expert in the relevant therapeutic area and at least one statistician; committee membership responsibilities, authorities, and procedures will be documented in its charter. The committee will meet periodically to review interim data. After the review, the DMC will make recommendations regarding the continuation of the study.

10.8.7. Publication Policy/Dissemination of Clinical Study Data

All information, including but not limited to information regarding ustekinumab or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including pharmacogenomics and biomarker research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of ustekinumab and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a clinical study report generated by the sponsor and will contain data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator for the study. Results of any analyses performed after the clinical study report has been issued will be reported in a separate report and will not require a revision of the clinical study report.

Study participant identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors (ICMJE) guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will

not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and sub-study approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 18 months after the study end date or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the ICMJE Recommendations for the conduct, reporting, editing, and publication of scholarly work in medical journals, which state that the named authors must have made a significant contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work; and drafted the work or revised it critically for important intellectual content and given final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and disclose the existence of and the results of clinical studies as required by law. The disclosure of the final study results will be performed after the end of study in order to ensure the statistical analyses are relevant.

10.8.8. Data Quality Assurance

Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study site personnel before the study, periodic monitoring visits by the sponsor, and direct transmission of clinical laboratory data from a central laboratory into the sponsor's data base. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for eCRF completion will be provided and reviewed with study site personnel before the start of the study.

The sponsor will review eCRF for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

10.8.9. Case Report Form Completion

Case report forms are prepared and provided by the sponsor for each participant in electronic format. All data relating to the study must be recorded in eCRF. All eCRF entries, corrections, and alterations must be made by the investigator or authorized study site personnel. The investigator must verify that all data entries in the eCRF are accurate and correct.

The study data will be transcribed by study site personnel from the source documents onto an electronic eCRF, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor.

Worksheets may be used for the capture of some data to facilitate completion of the eCRF. Any such worksheets will become part of the participant's source documents. Data must be entered into eCRF in English. The eCRF must be completed as soon as possible after a participant visit and the forms should be available for review at the next scheduled monitoring visit.

All participative measurements (eg, pain scale information or other questionnaires) will be completed by the same individual who made the initial baseline determinations whenever possible.

If necessary, queries will be generated in the eDC tool. If corrections to an eCRF are needed after the initial entry into the eCRF, this can be done in either of the following ways:

- Investigator and study site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Sponsor or sponsor delegate can generate a query for resolution by the investigator and study site personnel.

10.8.10. Source Documents

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: participant identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all AEs and follow-up of AEs; concomitant medication; intervention receipt/dispensing/return records; study intervention administration information; and date of study completion and reason for early discontinuation of study intervention or withdrawal from the study, if applicable.

The author of an entry in the source documents should be identifiable. Given that PROs are reports of a patient's health condition that come directly from the patient, without interpretation by a clinician or anyone else, the responses to PRO measures entered by trial participants into source records cannot be overridden by site staff or investigators.

Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

The following data will be recorded directly into the eCRF and will be considered source data:

- Race
- Blood pressure and pulse/heart rate
- Height and weight

- Investigator-completed scales and assessments
- PROs

The minimum source documentation requirements for Section 5.1, Inclusion Criteria and Section 5.2, Exclusion Criteria that specify a need for documented medical history are as follows:

- Referral letter from treating physician or
- Complete history of medical notes at the site
- Discharge summaries.

Inclusion and exclusion criteria not requiring documented medical history must be verified at a minimum by participant interview or other protocol required assessment (eg, physical examination, laboratory assessment) and documented in the source documents.

An eSource system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. This data is electronically extracted for use by the sponsor. If eSource is utilized, references made to the eCRF in the protocol include the eSource system but information collected through eSource may not be limited to that found in the eCRF.

10.8.11. Monitoring

The sponsor will use a combination of monitoring techniques central, remote, or on-site monitoring to monitor this study.

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the eCRF with the source documents (eg, hospital/clinic/physician's office medical records). At these visits, the monitor will compare data entered into the eCRF with the source documents (eg, hospital/clinic/physician's office medical records); a sample may be reviewed. The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the sponsor and study site personnel and are accessible for verification by the sponsor study site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will be discussed with the study site personnel. The sponsor expects that, during monitoring visits, the relevant study site personnel will be available, the source documents will be accessible and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study site personnel will be available to provide an update on the progress of the study at the site.

Central monitoring will take place for data identified by the sponsor as requiring central review.

10.8.12. On-site Audits

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. Participant privacy must, however, be respected. The investigator and study site personnel are responsible for being present and available for consultation during routinely scheduled study site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

10.8.13. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all eCRF and all source documents that support the data collected from each participant, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

10.8.14. Study and Site Start and Closure

First Act of Recruitment

The first site open is considered the first act of recruitment and it becomes the study start date.

Study/Site Termination

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

The investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

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

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

10.9. Appendix 9: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.9.1. Adverse Event Definitions and Classifications

Adverse Event

An AE is any untoward medical occurrence in a clinical study participant administered a pharmaceutical (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product (Definition per ICH).

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects AEs starting with the signing of the ICF (refer to All Adverse Events under Section 8.3.1, Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information, for time of last AE recording).

Serious Adverse Event

A SAE based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  (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
- Is a suspected transmission of any infectious agent via a medicinal product
- Is medically important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

If a serious and unexpected AE occurs for which there is evidence suggesting a causal relationship between the study intervention and the event (eg, death from anaphylaxis), the event must be reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (eg, all-cause mortality).

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An AE is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For ustekinumab, the expectedness of an AE will be determined by whether or not it is listed in the IB.

10.9.2. Attribution Definitions

Assessment of Causality

The causal relationship to study intervention is determined by the investigator. The following selection should be used to assess all AEs.

Related

There is a reasonable causal relationship between study intervention administration and the AE.

Not Related

There is not a reasonable causal relationship between study intervention administration and the AE.

The term "reasonable causal relationship" means there is evidence to support a causal relationship.

10.9.3. Severity Criteria

An assessment of severity grade will be made using the following general categorical descriptors:

Mild: Awareness of symptoms that are easily tolerated, causing minimal discomfort, and not interfering with everyday activities.

Moderate: Sufficient discomfort is present to cause interference with normal activity.

Severe: Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the participant (eg, laboratory abnormalities).

10.9.4. Special Reporting Situations

Safety events of interest on a sponsor study intervention in an interventional study that may require expedited reporting or safety evaluation include, but are not limited to:

- Overdose of a sponsor study intervention

- Suspected abuse/misuse of a sponsor study intervention
- Accidental or occupational exposure to a sponsor study intervention
- Any failure of expected pharmacologic action (ie, lack of effect if used according to the local label) of a sponsor study intervention (to be reported as a PQC for marketed products)
- Unexpected therapeutic or clinical benefit from use of a sponsor study intervention
- Medication error, intercepted medication error, or potential medication error involving a Johnson & Johnson medicinal product (with or without participant exposure to the Johnson & Johnson medicinal product, eg, product name confusion, product label confusion, intercepted prescribing or dispensing errors)
- Exposure to a sponsor study intervention from breastfeeding

Special reporting situations should be recorded in the eCRF. Any special reporting situation that meets the criteria of an SAE should be recorded on the SAE page of the eCRF.

10.9.5. Procedures

All Adverse Events

All AEs, regardless of seriousness, severity, or presumed relationship to study intervention, must be recorded using medical terminology in the source document and the eCRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the eCRF their opinion concerning the relationship of the AE to study therapy. All measures required for AE management must be recorded in the source document and reported according to sponsor instructions.

For all studies with an outpatient phase, including open-label studies, the participant must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the participant is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical personnel only)
- Site number
- Participant number
- Any other information that is required to do an emergency breaking of the blind

Serious Adverse Events

All SAEs that have not resolved by the end of the study or that have not resolved upon the participant's discontinuation from the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline if a baseline value/status is available
- The event can be attributed to agents other than the study intervention or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (participant or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Any event requiring hospitalization (or prolongation of hospitalization) that occurs during participation in the study must be reported as an SAE, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or AE (eg, social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the eCRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered SAEs. Any AE that results in a prolongation of the originally planned hospitalization is to be reported as a new SAE.

For convenience the investigator may choose to hospitalize the participant for the duration of the intervention period. The cause of death of a participant in a study within 16 weeks of the last dose of study intervention, whether or not the event is expected or associated with the study intervention, is considered an SAE.

Information regarding SAEs will be transmitted to the sponsor using an SAE reporting form, which must be completed and signed by a physician from the study site and transmitted in a secure manner to the sponsor within 24 hours. The initial and follow-up reports of an SAE should be made by facsimile (fax). Telephone reporting should be the exception and the reporter should be asked to complete the appropriate form(s) first.

10.9.6. Product Quality Complaint Handling

Definition

A PQC is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, reliability, or performance of a distributed product, including its labeling, drug delivery system, or package integrity. A PQC may have an impact on the safety and efficacy of the product. In addition, it includes any technical complaints, defined as any complaint that indicates a potential quality issue

during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product or the drug delivery system.

Procedures

All initial PQCs must be reported to the sponsor by the study site personnel within 24 hours after being made aware of the event.

A sample of the suspected product should be maintained under the correct storage conditions until a shipment request is received from the sponsor.

10.9.7. Contacting Sponsor Regarding Safety, Including Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues, PQC, or questions regarding the study are listed in the 'Protocol Supplementary Information page(s), which will be provided as a separate document.

10.10. Appendix 10: Contraceptive and Barrier Guidance

Participants must follow contraceptive measures as outlined in Section 5.1, Inclusion Criteria. Pregnancy information will be collected and reported as noted in Section 8.3.5, Pregnancy and Section 10.9, Appendix 9: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

Definitions

Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Woman Not of Childbearing Potential

- **Premenarchal**
  A premenarchal state is one in which menarche has not yet occurred.
- **Postmenopausal**
  A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level (>40 IU/L or mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT), however in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. If there is a question about menopausal status in women on HRT, the woman will be required to use one of the non-estrogen-containing hormonal highly effective contraceptive methods if she wishes to continue HRT during the study.
- **Permanently sterile (for the purpose of this study)**
  Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Note: If the childbearing potential changes after start of the study (eg, a premenarchal woman experiences menarche) or the risk of pregnancy changes (eg, a woman who is not heterosexually active becomes active), a woman must begin a highly effective method of contraception, as described throughout the inclusion criteria.

If reproductive status is questionable, additional evaluation should be considered.

Contraceptive (birth control) use by men or women should be consistent with local regulations regarding the acceptable methods of contraception for those participating in clinical studies.

Typical use failure rates may differ from those when used consistently and correctly.

Examples of Contraceptives

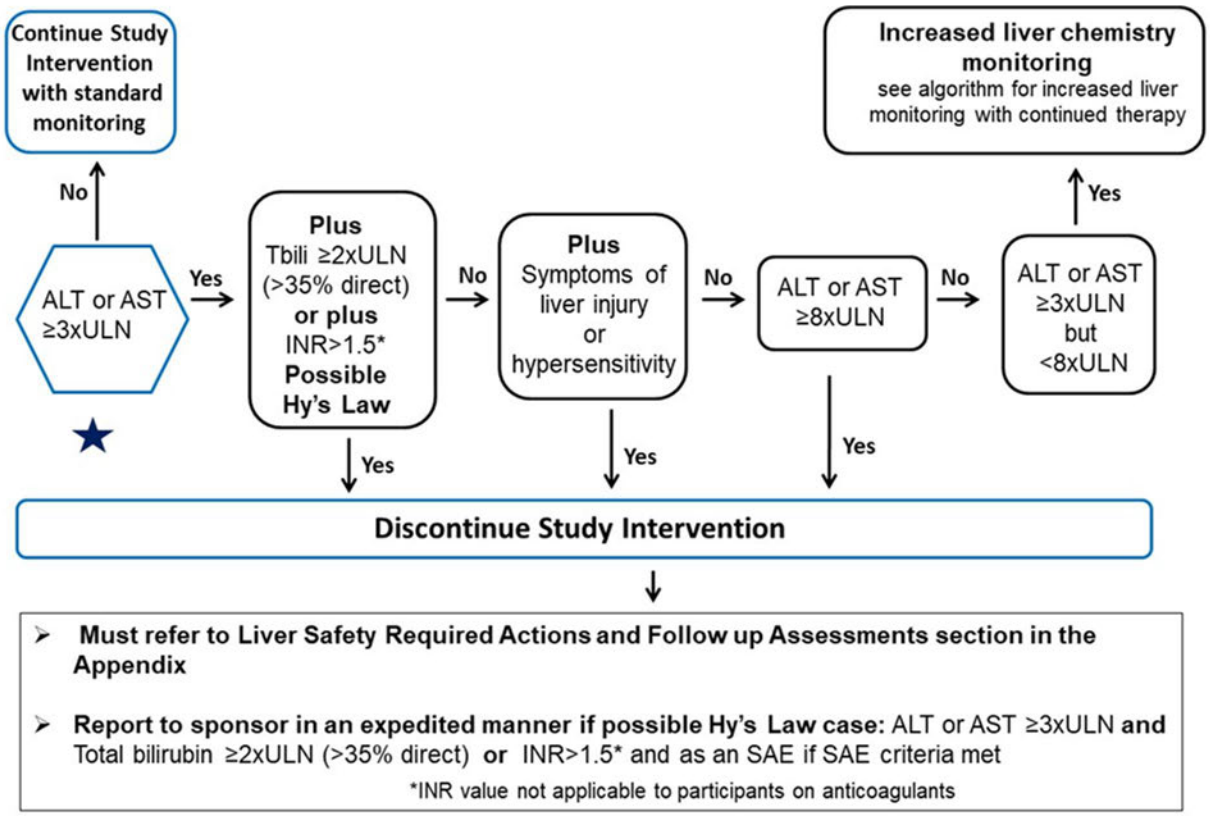
EXAMPLES OF CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
USER INDEPENDENT **Highly Effective Methods That Are User Independent** *Failure rate of <1% per year when used consistently and correctly.*
• Intrauterine device
• Intrauterine hormone-releasing system
• Bilateral tubal occlusion
• Azoospermic partner *(vasectomized or due to medical cause)* *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 74 days)*
USER DEPENDENT **Highly Effective Methods That Are User Dependent** *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] Oral
• Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*
NOT ALLOWED AS SOLE METHOD OF CONTRACEPTION DURING THE STUDY (not considered to be highly effective - failure rate of ≥1% per year)
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.
• Male condom with or without spermicide
• Periodic abstinence (calendar, symptothermal, post-ovulation methods)
• Withdrawal (coitus-interruptus)
• Lactational amenorrhea method
a) Typical use failure rates may differ from those when used consistently and correctly. b) Hormonal contraception may be susceptible to interaction with the study intervention, which may reduce the efficacy of the contraceptive method. In addition, consider if the hormonal contraception may interact with the study intervention.

10.11. Appendix 11: Liver Safety: Suggested Actions and Follow-up Assessments

A. STOPPING ALGORITHM

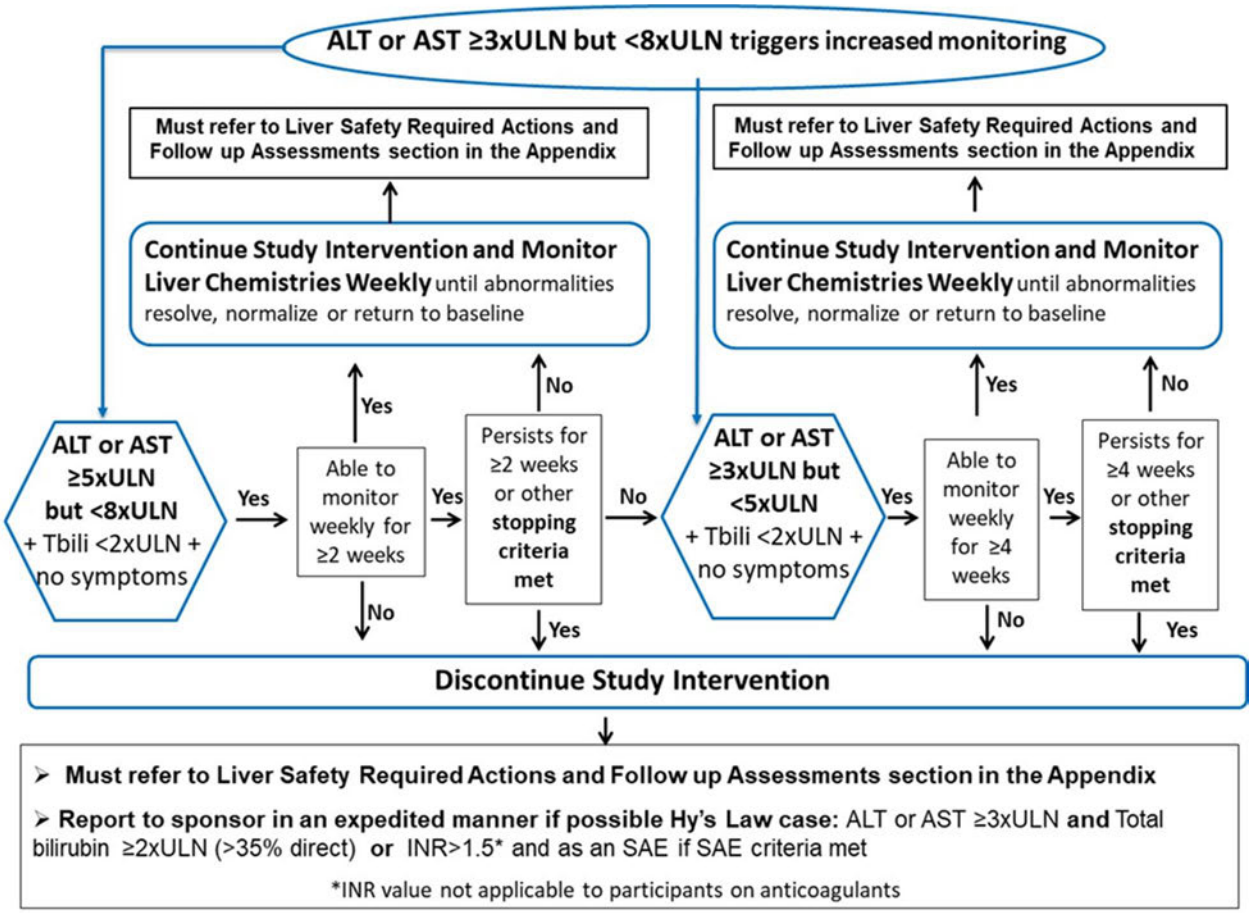
Study intervention will be discontinued for a participant if liver chemistry stopping criteria are met.

Phase 3-4 Liver Chemistry Stopping Criteria and Increased Monitoring Algorithm



Abbreviations: ALT=alanine transaminase; AST=aspartate transaminase; INR=international normalized ratio; SAE=serious adverse event; ULN=upper limit of normal; Tbili=Total bilirubin.

Phase 3-4 Liver Chemistry Increased Monitoring Algorithm with Continued Study Intervention for Participants with ALT or AST ≥3xULN but <8xULN



Abbreviations: ALT=alanine transaminase; AST=aspartate transaminase; INR=international normalized ratio; SAE=serious adverse event; ULN=upper limit of normal; Tbili=Total bilirubin.

10.12. Appendix 12: Guidance on study conduct during COVID-19 pandemic

It is recognized that the COVID-19 pandemic may have an impact on the conduct of this clinical study due to, for example, self-isolation/quarantine by participants and study-site personnel; travel restrictions/limited access to public places, including hospitals; study site personnel being reassigned to critical tasks. In alignment with recent health authority guidance, the sponsor is providing options for study-related participant management in the event of disruption to the conduct of the study. This guidance does not supersede any local or government guidelines or requirements or the clinical judgement of the investigator to protect the health and well-being of participants and site staff. If at any time a participant's safety is considered to be at unacceptable risk, study intervention will be discontinued, and study follow-up will be conducted. Scheduled visits that cannot be conducted in person at the study site will be performed to the extent possible remotely/virtually or delayed until such time that on-site visits can be resumed. At each contact, participants will be interviewed to collect safety data. Key efficacy endpoint assessments should be performed if required and as feasible. Participants will also be questioned regarding general health status to fulfill any physical examination requirement. Every effort should be made to adhere to protocol-specified assessments for participants on study intervention, including follow-up. Modifications to protocol-required assessments may be permitted after consultation between the participant, and investigator and with the agreement of the sponsor (see below).

The sponsor will continue to monitor the conduct and progress of the clinical study, and any changes will be communicated to the sites and to the health authorities according to local guidance. If a participant has tested positive for COVID-19, the investigator should contact the sponsor's medical officer or designee to discuss plans for study intervention and follow-up. Modifications made to the study conduct as a result of the COVID-19 pandemic should be summarized in the clinical study report.

ADDITIONAL ELEMENTS, WHERE APPLICABLE:

Certain protocol-mandated visits to the study site may not be possible during the COVID-19 outbreak. Therefore, temporary measures may be implemented if considered appropriate by the sponsor and investigator to maintain continuity of patient care and study integrity. Certain measures, such as those listed below, may be necessary and should be instituted in accordance with applicable (including local) laws, regulations, guidelines, and procedures:

- Remote (eg, by phone / telemedicine) or in person, off-site (eg, in-home) interactions between site staff (or designees) and patients for study procedures eg, those related to safety monitoring/efficacy evaluation/study intervention storage and administration (including training where pertinent)
- Procurement of study intervention by patients (or designee) or shipment of study intervention from the study site directly to patients for at home administration
- Laboratory assessments using a suitably accredited local laboratory; for selected measures (eg, urine pregnancy), home testing may be employed
- Other procedures may be conducted at an appropriate facility, missed assessments/visits will be captured in the clinical trial management system for protocol deviations. Discontinuations

of study interventions and withdrawal from the study should be documented with the prefix "COVID-19-related" in the electronic case report form (eCRF).

- Other relevant study data elements impacted by the pandemic should also be documented/labeled as "COVID-19-related" in eCRFs and/or other study systems, as directed by detailed sponsor guidance. These may include missed/delayed/modified study visits/assessments/dosing and instances where temporary measures such as those above are implemented.

NOTES on COVID-related exclusion:

1. If a participant is excluded due to recent COVID-19-related features, the reason for screen failure should be documented in the case report form under the exclusion criterion of having a condition for which participation would not be in the participant's interest or could confound study assessments.
2. The field of COVID-related testing (for presence of, and immunity to, the SARS-CoV-2 virus) is rapidly evolving. Additional testing may be performed as part of screening and/or during the study if deemed necessary by the investigator and in accordance with current regulations/guidance from authorities/SOC. The sponsor will evaluate the totality of impact of COVID-19 on collection of key study data and additional data analyses will be outlined in study SAP(s).

Precaution: for those who may carry a higher risk for severe COVID-19 illness (eg, those aged over 65 years), follow guidance from local health authorities when weighing the potential benefits and risks of enrolling in the study and during participation in the study.

10.13. Appendix 13: Hepatitis B Virus screening

Participants must undergo screening for hepatitis B virus (HBV). At a minimum, this includes testing for HBsAg, anti-HBs (HBV surface antibody), and anti-HBc total (HBV core antibody total):

Participants who test negative for all HBV screening tests (ie, HBsAg-, anti-HBc-, and anti-HBs-) ***are eligible*** for this study.

Participants who test **positive** for surface antigen (HBsAg+) ***are not eligible*** for this study, regardless of the results of other hepatitis B tests.

Participants who test **negative** for surface antigen (HBsAg-) and test **positive** for core antibody (anti-HBc+) ***and/or*** surface antibody (anti-HBs+) must undergo further testing for hepatitis B deoxyribonucleic acid (HBV DNA test). If the HBV DNA test is **positive**, the patient ***is not eligible*** for this study. If the HBV DNA test is **negative**, the patient ***is eligible*** for this study. In the event the HBV DNA test cannot be performed, the patient ***is not eligible*** for this study. If core antibody (anti-HBc) and/or surface antibody (anti-HBs) are positive and the HBV DNA test is negative, HBV DNA quantitation should be monitored at least every 3 months or shorter.

Eligibility based on Hepatitis B virus test results				
	Hepatitis B test result			
Action	**Hepatitis B surface antigen (HBsAg)**	**Hepatitis B surface antibody (anti-HBs)**	**Hepatitis B core antibody (anti-HBc total)**	**Hepatitis B viral DNA (HBV DNA) ***
Exclude	+	— *or* +	— *or* +	NA
	—	—	+	+
	—	+	—	+
	—	+	+	+
Include	—	—	—	NA
	—	—	+	—
	—	+	—	—
	—	+	+	—
* If HBV DNA is detectable, exclude from clinical trial. If HBV DNA testing cannot be performed or there is evidence of chronic liver disease, exclude from clinical trial.				

Reference;

Japan College of Rheumatology: Recommendations on Immunosuppressive Therapy in Patients with Rheumatic Disease and Hepatitis B Virus Infection, Revised Version; Oct. 18. 2011.

10.14. Appendix 14: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment 1 (7 April 2021)

Overall Rationale for the Amendment: To clarify the process related to relapse confirmation and put minor modifications throughout the protocol.

Section Number and Name	Description of Change	Brief Rationale
1.3. Schedule of Activities, Table 1	e. Imaging assessment will be performed during screening period, every 24 weeks from Week 0 (eg, Week 24, 48, 72), and ~~relapse visit~~ Relapse Confirmation Visit using CTA or MRA, if CTA is not feasible. When imaging assessment has been performed within 12 weeks prior to scheduled imaging assessment visit, imaging assessment may not be performed, and the prior results will be used for this scheduled assessment. Imaging assessment for screening visit should be performed and the prior imaging results for screening assessment will not be allowed. Additional imaging assessment may be performed if investigator deems a need for further evaluation of participant's disease activities. At ~~relapse visit~~ Relapse Confirmation Visit, imaging assessment will be performed within 4 weeks after the investigator confirms participants meets the relapse criteria and it is recommended to be performed prior to Week OL-0.	Text was added to clarify the potential additional imaging assessment.
1.3. Schedule of Activities, Table 1	~~p. When participants meet the relapse criteria, the cause of relapse will be evaluated at relapse visit unless the investigator deems to require urgent GC treatment. The relapse visit will be made at participants' next visit or unscheduled visit prior to the next visit at investigator's discretion.~~ o. Relapse Confirmation Visit is the second relapse assessment visit after participants meet the relapse criteria once at scheduled visit or unscheduled visit (This visit will be treated as "1st relapse visit"). At Relapse Confirmation Visit, TAK Disease Assessment S&S and CRP/ESR must be performed and the other items are not needed to perform if they already performed at "1st relapse visit". If participants are judged as relapse once, all the assessments at Relapse Confirmation Visit should be performed.	Updated to clarify "Relapse Confirmation Visit" (Footnote p on the initial protocol was updated as Footnote o on the amendment 1 due to footnote order change).
1.3. Schedule of Activities, Table 2	j. Relapse Confirmation Visit is the second relapse assessment visit after participants meet the relapse criteria for the first time at scheduled visit or unscheduled visit (This visit will be treated as "1st relapse visit"). At Relapse Confirmation Visit, TAK Disease Assessment S&S and CRP/ESR must	Updated to clarify "Relapse Confirmation Visit".

Section Number and Name	Description of Change	Brief Rationale
	be performed and the other items are not needed to perform if they already performed at "1st relapse visit". If participants are judged as relapse once, all the assessments at Relapse Confirmation Visit should be performed.	
5.1. Inclusion Criteria 9.	Criterion modified per Amendment 1 9.1 If receiving an oral anti-platelet therapy (including but not limited to aspirin, clopidogrel, ticlopidine) or anti-coagulation therapy (including but not limited to warfarin) for treatment of TAK, the dose must have been stable for at least 2 weeks prior to first administration of the study intervention. In terms of warfarin, the dose should be controlled 1-5 mg/day to maintain PT-INR target range between 2.0-3.0 (if participants are over 70 years old, PT-INR target range should be between 1.6-2.6).	Text was added to clarify the dose of warfarin based on medical practice in Japan.
6.8. Concomitant Therapy Anti-platelet or Anti-coagulation Therapy	Participants are permitted to receive stable doses (>2 weeks prior to first study intervention administration) of anti-platelet therapy (including but not limited to aspirin, clopidogrel, ticlopidine) or anti-coagulation therapy (including but not limited to warfarin) according to the local practice at the discretion of the investigator. In terms of warfarin, the dose should be controlled 1-5mg/day in order to maintain PT-INR target range between 2.0-3.0 (if participants are over 70 years old, PT-INR target range should be between 1.6-2.6).	Text was added to clarify the dose of warfarin based on medical practice in Japan.
8.1.1. TAK Disease Signs and Symptoms	In assessment of disease activities of TAK, cause of relapse will be confirmed by eliminating other causes such as infections, allergic disorders, and unexplained physical symptoms~~, unless the investigator deems to require emergent GC treatment~~. Even participants meet the definition of relapse once, they will not receive a GC rescue therapy and continue to receive protocol-defined GC taper regimen ~~unless~~ except for the following cases. In the following cases, participants will be judged as relapse once. · Emergent hospitalization caused by worsening of TAK and GC treatment required · Severe aortic valve incompetence accompanied by symptoms of cardiac failure occurs under 'vascular signs and symptoms' · CTCAE grade 2 or higher (grade ≥3 for myocardial infarction) occurs under 'ischemic symptoms' · Both categories 'vascular signs and symptoms' and 'ischemic symptoms' meet the criteria Except for above cases, the investigators will	Text was added to clarify the conditions which participants are judged as relapse once.

Section Number and Name	Description of Change	Brief Rationale
	reconfirm whether the participants meets definition of relapse including the same items of the first assessment at least and the relapse was caused by worsening of TAK to make a final judgement of the relapse at Relapse Confirmation Visit ~~next visit or unscheduled visit prior to the next visit~~.	
10.4. Appendix 4: Relapse Judgement Flow	Relapse judgement process without adjudication The schematic flow of relapse judgement process without adjudication is shown in Figure 3. For the first relapse visit, the investigator or designee will record ~~the evidence of worsening TAK and~~ possible other causes on the Source Document ~~in the electronic data capture (eDC)~~. For the ~~second relapse visit~~ Relapse Confirmation Visit, the investigator or designee will record the ~~evidence of worsening TAK and~~ reason for eliminating other causes in the eDC. Inflammation marker results (ie, CRP) provided by central lab is encouraged to be used ~~will be used~~ to judge relapse of TAK in this process.	"Relapse judgement process without adjudication" was updated for clarification.
10.4. Appendix 4: Relapse Judgement Flow	Relapse judgement process with adjudication The schematic flow of relapse judgement process with adjudication is shown in Figure 4. For the first relapse visit, the investigator or designee will record ~~the evidence of worsening TAK,~~ possible other causes, and the Relapse Confirmation Visit date on the Source Document, and will submit these information to the sponsor ~~next scheduled relapse visit in the eDC~~ within 3 working days. The sponsor's medical monitor will verify it ~~the evidence~~ and may request additional information as necessary until the Relapse Confirmation Visit ~~next scheduled visit~~. If the Relapse Confirmation Visit ~~second relapse visit~~ is scheduled within 5 working days of the first relapse visit, the investigator or designee should contact sponsor. For the ~~second relapse visit~~ Relapse Confirmation Visit, the investigator or designee will record the reason for ~~evidence of worsening TAK and~~ eliminating other causes in the eDC. Inflammation marker results (ie, CRP) provided by central lab is encouraged to be used to judge relapse of TAK in this process. ~~Inflammation marker results (ie, CRP) provided by central lab will be used to judge relapse of TAK for both visits (turnaround time for central lab result of CRP is generally 1 business day), unless participants require emergent GC rescue therapy. If~~	"Relapse judgement process with adjudication" was updated for clarification.

Section Number and Name	Description of Change	Brief Rationale
	~~emergent GC rescue is needed, local CRP result will be permitted to judge relapse of TAK for both visits. The rationale for emergent therapy required and the value of local CRP will be recorded in eDC.~~	
10.9. Appendix 9: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	~~Disease progression should not be recorded as an AE or SAE term; instead, signs and symptoms of clinical sequelae resulting from disease progression/lack of efficacy will be reported if they fulfill the SAE definition (refer to Adverse Event Definitions and Classifications in Section 10.9, Appendix 9: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting). Expected progression of disease should not be considered an AE (or SAE). However, if determined by the investigator to be more likely related to the study intervention than the underlying disease, the clinical signs or symptoms of progression and the possibility that the study intervention is enhancing disease progression, should be reported per the usual reporting requirements.~~	Text was deleted to collect safety information adequately based on the PMDA feedback.
Throughout the protocol	Minor grammatical, formatting, and/or spelling changes were made.	Minor errors were noted.

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INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study intervention, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD

Institution: Janssen Pharmaceutical K.K.

Signature: electronic signature appended at the end of the protocol Date: _____

(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

Signature

User	Date	Reason
PPD	15-Aug-2022 08:46:15 (GMT)	Document Approval