Janssen Pharmaceutical K.K.*

Statistical Analysis Plan

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

Protocol CNTO1275TAT3001; Phase 3

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. in Japan.

Status: Approved
Date: 30 June 2023
Prepared by: Janssen Pharmaceutical K.K.
Document No.: EDMS-RIM-478213

Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

TABLE OF CONTENTS

VERSION HISTORY

Table 1: SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1	26 July 2021	Not Applicable	Initial release
2	30 June 2023	1. Section 5.3.5 and Section 5.8: remove alpha spending for interim analyses; Section 5.8: add a sentence "However, the study turned out to be early terminated by sponsor before occurrence of 15 events, and the planned interim analyses will therefore not be performed. " 2. Section 5.3.5 and 5.8: Change significance level of interim analysis to 0.0012, and final analysis to 0.0496 3. Section 4: Split PK, PD analysis set to DB and OLE period 4. Section 5.6.2: add "AEs during receiving study intervention ustekinumab through the Study will also be summarized" 5. Section 5.6.2: add summary for AEs related to COVID-19 6. Section 5.7.1: "In Escape arm OLE period and OLE period, serum ustekinumab concentrations will be summarized by DB period intervention arm (ustekinumab arm or placebo arm) in table." were changed to "In Escape arm OLE period and OLE period, serum ustekinumab concentrations will be summarized by intervention arm (Ustekinumab -> Ustekinumab or Placebo -> Ustekinumab) in table." 7. Section 5.4.2.2: removed "and percent of change from baseline" from "The observed values, change from baseline and percent of change from baseline of inflammatory markers will be descriptively summarized by visit." 8. Section 5.6.2, add "AEs leading to death" and "SAEs by relationship to study intervention" 9. Table 4, add FACIT, PtGA and SF-36 10. Section 5.7.1: Participants who received IV intervention at	Remove alpha spending for interim analyses and some other changes were made due to study early termination before time of interim analysis; Some of the analysis were updated after review of data presentation specification for alignment based on clinical team requests; Also due to protocol amendment 2 and early termination of the study, the SAP was updated accordingly to incorporate the changes and clarifications; Some other minor changes include type error and wordings correction.

SAP Version	Approval Date	Change	Rationale
		Week 0 and continuously received next IV intervention at Week OL-0 (which mean without SC intervention) will be summarized in a separate table which will include serum concentrations at Week 0, 2, 4, ~~8,~~ Week OL-0 and OL-8. 11. Section 4: change "IV intervention of ustekinumab at Week OL-0 or SC intervention of ustekinumab" to "dose" for "Pharmacokinetics Analysis Set in Escape arm OLE period" 12. Add "Time to relapse by 4 categories (Kerr's definition)" in Section 5.4.2.1 13. Appendix 9: Add more parameters for CTCAE table 14. Add endpoint in Section 5.5: Proportion of participants who achieve 7.5mg/day or less during OLE period. 15. Section 5.6.2: add AESI for summary and listing 16. Section 5.4.2.2: add "Last observed GC dose before relapse will also be presented for participants who had relapse. The last observed GC dose (during DB) is the average GC dose in last 7 days before the date of relapse (first visit of relapse will be used for relapse need to be confirmed) for participants who had relapse, or average GC dose in last 7 days on or before end of DB period." and removed "The prednisolone dose that is used at the date of relapse will be also presented." 17. Section 5.3.2, 5.3.3, 5.3.4, 5.3.5,5.4.2.2, And change "95% CIs" to "95% Wald CIs". 18. Appendix 2, Table 4, "18-64 years" was changed to "15-64 years", Section 1.2 and 5.7.8: 18 was changed to 15 19. Section 5.3.5, 5.4.2.2: removed "on or prior to the situation" 20. Section 5.7.8 and Appendix 6.2, add subgroup 5-7 and >=18 for age groups	

SAP Version	Approval Date	Change	Rationale
		21. Section 5.4.2.2 and 5.5.2: add spaghetti plot for GC dose overtime 22. Section 5.1.1, add: For serum ustekinumab concentrations by timepoint summary, if PK assessment is missing at scheduled visit or timepoints, the visit of early termination and unscheduled visit will be mapped to the scheduled visit if it's within protocol specified visit window 23. Section 5.3.5, 5.3.6, 5.3.7, 5.4.2.2: Other (eg, withdrawal of consent to study participation, lost to follow-up) were changed to: other (ie, other participants not included in above situations) 24. Section 5.6.2, add "Serious Infections" 25. Section 5.1.2, change "16 weeks after the follow-up starting date or early discontinuation, whichever comes first" to "Last date of study discontinuation or last participation date" 26. Section 6.9, add "If a laboratory value falls within the grading as specified below but also within the local laboratory normal limits, the value is considered to be normal and will be reset to grade 0." 27. Section 6.2, add categorical variables for BMI, update category for RACE and Ethnicity 28. Section 4: Removed "randomized" in definition for "FAS in OLE period". Add "Safety Analysis Set" and "Full Analysis Set". 29. Section 5.7.2: the definition of "Subject ADA status" was minor changed 30. Section 5.4.4.2, add: Note: for "death or treatment discontinuation": use data on or prior to death or treatment discontinuation through end of DB period; for major protocol deviation and other situations: use data through end of DB period. 31. Other minor changes	

1. INTRODUCTION

This statistical analysis plan (SAP) for the CNTO1275TAT3001 phase 3 trial describes the statistical analyses and definitions to evaluate the efficacy and safety of ustekinumab in patients with Takayasu Arteritis (TAK).

1.1. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of ustekinumab compared to placebo, in combination with oral glucocorticoid (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 • 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

Objectives	Endpoints
• 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
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

1.2. Study 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.

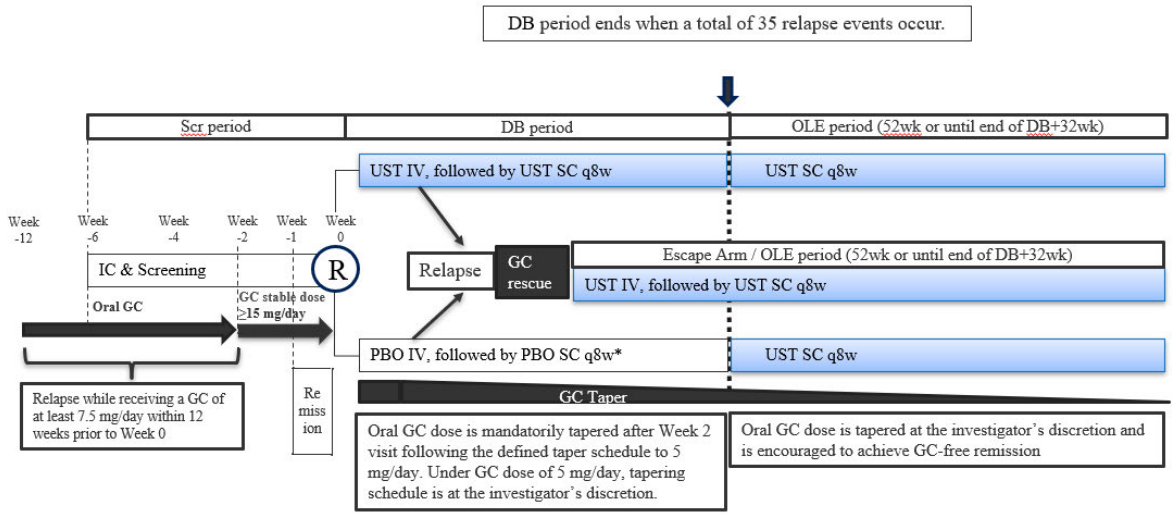
Ustekinumab group: The participants will receive body weight-range based IV administration of ustekinumab (~6 mg/kg) at Week 0 followed by ustekinumab 90 mg SC administered 8 weeks after the initial IV dose and then every 8 weeks (q8w) thereafter.

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 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 IV dose at Week OL-0, 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.

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; UST=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.

2. STATISTICAL HYPOTHESES

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

3. 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 are 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.

4. POPULATIONS (ANALYSIS SETS) FOR ANALYSIS

Analysis Sets	Description
Randomized	The randomized analysis set includes all participants who were randomized in the study.
Full Analysis Set (FAS)	The full analysis set (FAS) includes all randomized participants (or directly enrolled into OLE period without randomization) who received at least 1 dose of study intervention.
FAS in DB period	FAS includes all randomized participants who received at least 1 dose of study intervention through DB period.
FAS in OLE period	FAS includes all participants who received at least 1 dose of study intervention through OLE period.
Safety Analysis Set	The safety analysis set includes all participants who received at least 1 dose of study intervention.
Safety Analysis Set in DB period	The safety analysis set includes all participants who received at least 1 dose of study intervention through DB period.
Safety Analysis Set in OLE period	The safety analysis set includes all participants who received at least 1 dose of study intervention through OLE period.
Pharmacokinetics Analysis Set	The PK analysis set is defined as participants who received at least 1 complete dose of ustekinumab and have at least 1 valid postdose PK data
Pharmacokinetics Analysis Set in DB period	The PK analysis set in DB period is defined as participants who received at least 1 complete dose of ustekinumab and have at least 1 valid postdose PK data through DB period
Pharmacokinetics Analysis Set in Escape arm OLE period	Pharmacokinetics Analysis Set in Escape arm OLE period is defined as participants who experienced relapse in DB period and received at least 1 complete dose of ustekinumab and have at least 1 valid postdose PK data from Week OL-0 to end of OLE-period.
Pharmacokinetics Analysis Set in OLE period	Pharmacokinetics Analysis Set in OLE period is defined as participants who didn't experience relapse in DB period and received at least 1 complete SC intervention of ustekinumab at Week OL-0 and have at least 1 valid postdose PK data from Week OL-0 to end of OLE period.

Analysis Sets	Description
Immunogenicity Analysis Set	The immunogenicity analysis set is defined as all participants who received at least 1 dose of ustekinumab and have at least 1 postdose valid immunogenicity data.
Pharmacokinetics/Pharmacodynamics (PD) Analysis set in DB period	PK/PD Analysis set is defined as all participants (including participants who received placebo intervention) who have at least 1 paired PK and PD data collected at same time point needed for each PK/PD analysis. If participants who receive placebo intervention and have no concentration data during DB period, serum ustekinumab concentrations will be imputed as zero and should be included into PK/PD analyses for DB period as well.
Pharmacokinetics/Pharmacodynamics Analysis set in OLE period	PK/PD Analysis set is defined as all participants who have at least 1 paired PK and PD data collected at same time point needed for each PK/PD analysis.in OLE period.

5. STATISTICAL ANALYSES

5.1. General Considerations

5.1.1. Visit Windows

Unless otherwise specified, nominal visits will be used for all by visit analyses. The study visits scheduled after randomization should occur at the times delineated in the Time and Events Schedule of the protocol.

For serum ustekinumab concentrations by timepoint summary, if PK assessment is missing at scheduled visit or timepoints, the visit of early termination and unscheduled visit will be mapped to the scheduled visit if it's within protocol specified visit window.

5.1.2. Analysis Phase

Analysis phase	Start date	End date
Screening	The date of signing the informed consent	1 day before the first study intervention
Double-blind period (DB period)	Date of the first study intervention	Date of 35th relapse event occurred If participants discontinued study intervention, date of treatment discontinuation will be used for the end date. If participants had relapse and moved to escape arm, then 1 day before date of the first study intervention after

Analysis phase	Start date	End date
		having relapse and moving to escape arm will be used.
Open-label extension period (OLE period)	Date of the first study intervention after having relapse and moving to escape arm or 1 day after the end of DB period	Date of last observed visit or early treatment discontinuation, whichever comes first
Follow-up*	The end of DB period or OLE period, whichever comes later + 1 day	Date of study discontinuation or last participation date

*Note: For summaries and analysis by study period, follow-up period may be analyzed together with DB period (ie, for participants early discontinue study intervention administrations before the end of DB period) or OLE period, rather than analyzing separately.

If the participants received Placebo treatment and achieved GC dose <= 5 mg/day at the end of DB period and discontinued treatment after DB period, the data from date of 1 day after DB period to treatment discontinuation date will be summarized separately for safety, and will not be summarized for efficacy, demographics and concomitant medication and only presented in the listing.

5.1.3. Baseline

The baseline measurement is defined as the closest measurement taken prior to or at the date of the first study intervention.

For patients who did not receive the first study intervention, use the reference date below to obtain baseline measurements.

5.1.4. Reference Date

The reference date is used to calculate relative day variables. It is defined as the date of the initial study intervention. If the administration date is missing or the administration is not done, then the randomization date should be used.

5.1.5. Study Day

Study day is defined as the number of days from the study reference date to the event/visit date. Note that the reference date is referred to as Day 1 and the previous day is Day -1.

5.2. Participant Dispositions

Participant dispositions will be summarized by analysis phase (DB period and OLE period).

The number of participants in the following disposition categories will be summarized by intervention group and overall:

- Participants who completed the study
- Participants who terminated study prematurely at DB period
- Participants who terminated study prematurely at OLE period
- Reasons for termination of study at DB period
- Reasons for termination of study at OLE period
- Participants completed study intervention at DB period
- Participants who discontinued study intervention at DB period
- Reasons for discontinuation of study intervention at DB period
- Participants completed study intervention at OLE period
- Participants who discontinued study intervention at OLE period
- Reasons for discontinuation of study intervention at OLE period

Listings of participants will be provided for the following categories:

- Participants who discontinued study intervention
- Participants who terminated study prematurely
- Participants who were randomized yet did not receive study intervention.

5.3. Primary Endpoint(s) Analysis

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

5.3.1. Definition of Endpoint(s)

Time to relapse of TAK is defined from randomization date to the date of 1st visit of relapse through the end of DB period according to protocol-defined criteria (Protocol Section 8.1.1). Relapse of TAK is defined by 5 categories:

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

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 'ischemic symptoms'.

To evaluate if the symptoms caused by TAK, 2 consecutive evaluations are needed for the relapse judgement. If the relapse is confirmed in both 1st and 2nd visit, 1st visit date will be used for the date of relapse in the analysis. If the following emergent cases are caused by worsening of TAK, the participants will be judged as relapse at 1st visit only, and the 1st visit date will be used for the analysis.

- 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

5.3.2. Primary Estimand

Primary Trial Objective: To evaluate the efficacy of ustekinumab compared to placebo, in combination with oral GC taper regimen, in participants with relapsing TAK**.**

Estimand Scientific Question of Interest: What's the effect on time to relapse of assigning participants with TAK to ustekinumab vs placebo, in combination with protocol allowed oral GC taper regimen?

Primary Estimand, based on the primary objective and scientific question of interest above, 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 through DB period
- **Treatment**: ustekinumab versus placebo, in combination with protocol allowed oral GC taper regimen
- **Intercurrent Events (ICE) and their corresponding strategies:**

Intercurrent Events	**Name of Strategy for Addressing Intercurrent Events and Its Description**
Death or treatment discontinuation at DB period	**While on treatment strategy:** use time to relapse on or before this ICE.
Major protocol deviation (eg, protocol prohibited concomitant medication and therapy)	**Treatment Policy strategy:** use time to relapse through DB period, regardless of major protocol deviations

- **Population level summary**: Hazard ratio for time to relapse

5.3.2.1. Main Estimator of Primary Estimand

- Data included:
  - Without ICE: Time from randomization to relapse through DB period. If no relapse events up to clinical cutoff, censored at last disease assessment through DB period.
  - With ICE: If the ICE is death or treatment discontinuation at DB period, censored at last disease assessment on or prior to the ICE. For major protocol deviation, time from randomization to relapse during study intervention through DB period is used for analysis. If no relapse events up to clinical cutoff, censored at last disease assessment through DB period
- Missing data or data not included: Not applicable.
- Assumptions:
  - Noninformative censoring assumed for all types of censoring
  - Distinct baseline hazard for each stratum, proportional hazard ratio across strata
- Main estimator: A stratified Cox proportional hazard model with study intervention as explanatory variable, and with oral GC dose at Week 0 and the status of previous biologic medication as stratification factors. Hazard ratio and its 95% Wald confidence intervals (CIs) will be estimated.

5.3.3. Supplementary Estimand 1

The supplementary estimand 1 is defined to apply "while on treatment strategy" to major protocol deviation (Protocol prohibited concomitant medication and therapy) of the intercurrent event. Other components are the same as primary estimand.

- **Population**: Same attributes as primary estimand.
- **Endpoint**: Same attributes as primary estimand
- **Treatment**: Same attributes as primary estimand
- **Intercurrent Events (ICE) and their corresponding strategies:**

Intercurrent Events	**Name of Strategy for Addressing Intercurrent Events and Its Description**
Death or treatment discontinuation at DB period	Same strategy as primary estimand
Major protocol deviation (Protocol prohibited concomitant medication and therapy)	**While on treatment strategy:** use time to relapse through DB period, and on or before this ICE

- **Population level summary**: Same attributes as primary estimand

5.3.3.1. Main Estimator of Supplementary Estimand 1

- Data included:
  - Without ICE: Time from randomization to relapse through DB period. If no relapse events up to clinical cutoff, censored at last disease assessment through DB period
  - With ICE: Censored at last disease assessment on or prior to the ICE if no relapse events prior to the ICE. Time from randomization to relapse if relapse occurred prior to the ICE.
- Missing data or data not included: Not applicable.
- Assumptions:
  - Noninformative censoring assumed for all types of censoring
  - Distinct baseline hazard for each stratum, proportional hazard ratio across strata
- Main estimator: A stratified Cox proportional hazard model with study intervention as explanatory variable, and with oral GC dose at Week 0 and the status of previous biologic medication as stratification factors. Hazard ratio and its 95% Wald CIs will be estimated.

5.3.4. Supplementary Estimand 2

The supplementary estimand 2 is defined to apply "composite strategy" to death, treatment discontinuation (due to AE of disease worsening, disease relapse, initiated prohibited medication and lack of efficacy) and major protocol deviation (Protocol prohibited concomitant medication and therapy) of the intercurrent event. Other components are the same as primary estimand.

- **Population**: Same attributes as primary estimand.
- **Endpoint**: Same attributes as primary estimand
- **Treatment**: Same attributes as primary estimand
- **Intercurrent Events (ICE) and their corresponding strategies:**

Intercurrent Events	**Name of Strategy for Addressing Intercurrent Events and Its Description**
Death or treatment discontinuation at DB period (AE of disease worsening, disease relapse, initiated prohibited medication and lack of efficacy)	**Composite strategy:** A participant with this intercurrent event is considered to have a relapse at the time of this event.
Treatment discontinuation at DB period due to other reasons	**While on treatment strategy:** use time to relapse on or before this ICE.
Major protocol deviation (Protocol prohibited concomitant medication and therapy)	**Composite strategy:** A participant with this intercurrent event is considered to have a relapse at the time of this event.

- **Population level summary**: Same attributes as primary estimand

5.3.4.1. Main Estimator of Supplementary Estimand 2

- Data included:
  - Without ICE: Time from randomization to relapse through DB period. If no relaplse events up to clinical cutoff, censored at last disease assessment through DB period
  - With ICE: ICEs with death, treatment discontinuation (due to AE of disease worsening, disease relapse, initiated prohibited medication and lack of efficacy) or major protocol deviation of prohibited concomitant medication are considered as relapse event and time from randomization to ICE through DB period will be used. For treatment discontinuation due to other reason, use data through last disease assessment prior to the ICE.
- Missing data or data not included: Not applicable.
- Assumptions:
  - Noninformative censoring assumed for all types of censoring
  - Distinct baseline hazard for each stratum, proportional hazard ratio across strata
- Main estimator: A stratified Cox proportional hazard model with study intervention as explanatory variable, and with oral GC dose at Week 0 and the status of previous biologic medication as stratification factors. Hazard ratio and its 95% Wald CIs will be estimated.

5.3.5. Analysis Methods of Primary Estimand

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 based on FAS in DB period. Oral GC dose at Week 0 and the status of previous biologic medication will be considered as stratification factors. Oral GC dose at Week 0 will be derived as following formula:

Oral GC dose at Week 0 = Sum of oral GC dose from Day -6 to randomization date (mg) / [Number of days treated with GC dose from Day -6 to Randomization date × Weight at Week 0 (kg)]. If weight at Week 0 is missing, weight at screening period will be used.

The hazard ratio and its 2-sided 95% Wald CIs will be also estimated. Efron's method will be used to handle ties.

The Kaplan-Meier method will be used to estimate the distribution of time to relapse for each treatment. The median relapse event with 95% CI will be provided. In addition, the number and percentage of participants who had relapse event or were censored will be presented.

The definition of censoring is described as below:

Situation	Date of Relapse or Censoring	Outcome
Relapse	Date of 1st visit judged as relapse through end of DB period	Relapse event
Death or treatment discontinuation	Date of last disease assessment on or prior to death or treatment discontinuation through end of DB period	Censored
Major protocol deviation (Protocol prohibited concomitant medication and therapy)	Date of last disease assessment through end of DB period	Censored
Other (ie, other participants not included in above situations)	Date of last disease assessment through end of DB period	Censored

5.3.6. Analysis Methods of Supplementary Estimand 1

Similar analysis will be performed as primary estimand. Censoring definition will be changed from analysis method of primary estimand as below:

Situation	Date of Relapse or Censoring	Outcome
Relapse	Same as analysis method of primary estimand	
Death or treatment discontinuation	Same as analysis method of primary estimand	
Major protocol deviation (Protocol prohibited concomitant medication and therapy)	Date of last disease assessment on or prior to major protocol deviation through end of DB period	Censored
Other (ie, other participants not included in above situations)	Same as analysis method of primary estimand	

If the participant has concomitant medication related major protocol deviation, the censoring date will be the last disease assessment date on or prior to the major protocol deviation. The details of major protocol deviation described in Appendix 8.

5.3.7. Analysis Methods of Supplementary Estimand 2

Similar analysis will be performed as primary estimand. Censoring definition will be changed from analysis method of primary estimand as below:

Situation	Date of Relapse or Censoring	Outcome
Relapse	Same as analysis method of primary estimand	
Treatment discontinuation due to other reasons (ie, other than AE of disease worsening, disease relapse, initiated prohibited medication or lack of efficacy)	Same as analysis method of primary estimand	
Death or treatment discontinuation due to AE of disease worsening, disease relapse, initiated prohibited medication and lack of efficacy	Date of ICE	Relapse event
Major protocol deviation (Protocol prohibited concomitant medication and therapy)	Date of ICE	Relapse event
Other (ie, other participants not included in above situations)	Same as analysis method of primary estimand	

5.3.8. Subgroup Analyses of Primary Efficacy Endpoint

All baseline characteristics described in Section 5.7.8 will be used for subgroup analysis. Hazard ratio and its 95% CIs will be presented. The subgroup analysis will be applied only for the primary estimand.

5.4. Secondary Endpoint(s) Analysis

No key confirmatory secondary endpoints are defined in this study.

5.4.1. Key Confirmatory Secondary Endpoint(s)

Not applicable.

5.4.1.1. Definition of Endpoint(s)

Not applicable.

5.4.1.2. Estimand(s)

Not applicable.

5.4.1.3. Analysis Methods

Not applicable.

5.4.2. Supportive Secondary Endpoint(s)

The supportive secondary endpoints are as following:

- 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

5.4.2.1. Definition of Endpoints

Time to relapse by 5 categories (Protocol-defined criteria)

As described in Section 5.3.1, protocol-defined criteria consist of 5 categories: 1) Systemic symptoms (objective assessment), 2) Systemic symptoms (subjective assessment), 3) Elevated inflammation markers, 4) Vascular signs and symptoms and 5) Ischemic symptoms. Time to relapse will be calculate by each category independently. According to protocol, confirmation visit is not needed for each category, so 1st visit that the criterion met will be used as relapse date. If the participant met at least one criterion described above and it met due to disease worsening, it is considered as relapse event and time from randomization to the date of meeting the criterion will be used in the analysis.

Time to relapse (Kerr's definition)

Time to relapse is defined from the date of randomization to the judged date of relapse through the end of DB period based on Kerr's definition as following.

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.

Time to relapse by 4 categories (Kerr's definition)

As described above, Kerr's definition consists of 4 categories. Time to relapse will be calculate independently. According to protocol, confirmation visit is not needed for each category, so 1st visit that the criterion met will be used as relapse date. Only if the participant meets the criteria and its symptoms comes from worsening of TAK, it is considered to be an event.

Time to relapse (clinical symptoms)

Time to relapse is defined from the date of randomization to the judged date of relapse through end of DB period based on clinical symptoms as following.

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.

Oral GC dose

Oral GC dose (prednisolone or equivalent) used from randomization date to last observed date prior to the date of relapse will be included in the analysis if the participant has relapse. If the participant has no relapse, oral GC dose used from randomization to last observed date through the end of DB period will be included in the analysis.

Inflammatory markers

CRP and ESR will be analyzed as inflammatory markers. Data from central lab will be used for CRP, and local lab data will be used for ESR. For CRP, if central lab data is missing, local lab data will be used for analysis at the same visit.

5.4.2.2. Analysis Methods

Unless otherwise specified, the analysis population will be the FAS in DB period defined in Section 4.

Time to relapse

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% Wald CIs will be estimated using Cox proportional hazard regression model. Oral GC dose at Week 0 and the status of previous biologic medication will be considered as stratification factors. Efron's method will be used to handle ties. Proportion of number of relapsed participants through treatment period will be also summarized by each definition of relapse.

The definition of censoring is described as below:

Situation	Date of Relapse or Censoring	Outcome
Relapse	Date of 1st visit judged as relapse through end of DB period	Relapse event
Death or treatment discontinuation	Date of last disease assessment on or prior to death or treatment discontinuation through end of DB period	Censored
Major protocol deviation (Protocol prohibited concomitant medication and therapy)	Date of last disease assessment through end of DB period	Censored
Other (ie, other participants not included in above situations)	Date of last disease assessment through end of DB period	Censored

Note: for "death or treatment discontinuation": use data on or prior to death or treatment discontinuation through end of DB period; for major protocol deviation and other situations: use data through end of DB period.

Time to relapse by categories

Forest plot including number of participants who have relapse, median time, hazard ratio and its 95% CI will be displayed. Censoring rule will be used as described above.

Oral GC dose

Prednisolone dose or equivalent will be descriptively summarized including cumulative dose and change from baseline. Change from baseline is defined as the change between the GC dose at randomization and the last observed GC dose. Last observed GC dose before relapse will also be presented for participants who had relapse. The last observed GC dose (during DB) is the average GC dose in last 7 days before the date of relapse (first visit of relapse will be used for relapse need to be confirmed) for participants who had relapse, or average GC dose in last 7 days on or before end of DB period. Number and proportion of participants who achieved GC dose of 5mg/day or less through the end of DB period will be also summarized. If actual GC dose average in last 7 days through the end of DB period (for participants with relapse during DB, data before the date of relapse will be used) is 5mg/day or less, the participants are considered to achieve GC dose of 5mg/day or less. A spaghetti plot of oral GC dose (mg/day) overtime through DB period will be provided for individual participants. GC dose after study treatment discontinuation of DB will not be included in summary of analysis.

Inflammatory markers

The observed values, change from baseline of inflammatory markers will be descriptively summarized by visit. These values will be also graphically displayed by line plot.

5.5. Tertiary/Exploratory Endpoint(s) Analysis

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.
- Proportion of participants who achieve 7.5mg/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.

5.5.1. Definition of Endpoints

36-item Short Form

The SF-36 consists of 8 subscales: limitations in physical functioning due to health problems, limitations in usual role activities due to physical health problems, bodily pain, general mental health (psychological distress and well-being), limitations in usual role activities due to personal or emotional problems, limitations in social functioning due to physical or mental health problems, vitality (energy and fatigue), and general health perception. These subscales are scored from 0 to 100 with higher scores indicating better health. Another algorithm yields 2 summary scores, the Physical Component Summary (PCS) and the Mental Component Summary (MCS).

8 subscales and 2 summary score will be calculated by using web scoring system that is provided by Qualitest Inc.

Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-Fatigue):

The Functional Assessment of Chronic Illness Therapy – Fatigue Scale (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 seven days. Subjects 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.

FACIT-Fatigue scale is scored so that a high score is good. To achieve this, the score for negatively-phrased questions will be reversed (4 – item response), then sum the item response. If

there are >= 7 missing items in the FACIT-Fatigue, the score will be set as missing. Otherwise, the total score will be prorated:

FACIT-Fatigue scale score = (Summation of the individual item scores × 13) / Number of items answered.

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.

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.

5.5.2. Analysis Method

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. Unless otherwise specified, analysis of exploratory endpoints for OLE period will be based on FAS in OLE period.

For participants with relapse in OLE period, percentage of participants who experience relapse will be summarized by study intervention. Also, events rate in hundred patient-year will be also summarized and calculated as (the number of relapse × 365.25/ Sum of total duration of disease assessment in OLE period in days) * 100.

For continuous variables of patient reported outcomes (PROs) in DB period, descriptive analysis followed by mixed model repeated measures (MMRM) will be used with change from baseline as dependent variable, baseline score as covariate, and intervention group, GC dose at baseline, previous biologic medication, week, and interaction between treatment and week as fixed effects. An unstructured covariance structure will be used to model the within-patient error. In case of convergence problems, the autoregressive matrix structure and compound symmetry structure will be used till convergence is achieved. Parameters will be estimated using residual (restricted) maximum likelihood, the Kenward-Roger method will be used for calculating the denominator degrees of freedom. Based on the MMRM model described above, treatment effects at each visit in DB period will be estimated based on the differences of least-square (LS) means with 95% CIs. For continuous variables of PROs in OLE period, only descriptive summary will be performed by intervention group and visit, intervention comparison will not be performed.

GC dose during OLE period (on or before treatment discontinuation) will be descriptively summarized as following:

- Cumulative oral GC dose

- GC dose and change from baseline in GC dose by 4 weeks. Baseline is defined as 7 days average from Day -6 to OLE Week 0. GC dose by 4 weeks summary will used the average in 4 weeks.
- Last observed GC dose that is presented as the average in the last 7 days in OLE period
- The number and proportion of participants who achieve 5mg/day or less during at least 7 days, and the duration that these participants achieve 5mg/day or less
- The number and proportion of participants who achieve 5mg/day or less at least 7days and continue until the end of OLE period, and the duration that these participants achieve 5mg/day or less
- The number and proportion of participants who achieve 7.5mg/day or less during at least 7 days, and the duration that these participants achieve 7.5mg/day or less
- The number and proportion of participants who achieve 7.5mg/day or less at least 7days and continue until the end of OLE period, and the duration that these participants achieve 7.5mg/day or less
- A spaghetti plot of oral GC dose (mg/day) overtime during OLE period (including GC dose after treatment discontinuation) will be provided for individual participants.

5.6. Other Safety Analyses

All safety analyses will be based on the safety analysis set in DB/OLE period based on actual intervention received, unless otherwise specified.

For all continuous safety variables, descriptive statistics by intervention group will include the N, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by intervention group using frequency counts and percentages.

5.6.1. Extent of Exposure

Extent of exposure will be summarized by analysis phase (DB period and OLE period) and type of administration (IV and SC).

The number and percentage of participants who receive each study intervention within each analysis phase will be summarized.

Descriptive statistics for duration of study intervention (N, mean, SD, median, and range (minimum, maximum)) will be summarized by study intervention.

Study intervention duration is defined as (date of last dose of study intervention – date of first dose of study intervention) +1.

Number of administrations and Cumulative dose will be also summarized by study intervention.

Study intervention compliance will be summarized descriptively. See Appendix 6 for further details.

5.6.2. Adverse Events

Adverse events will be summarized by analysis phase (DB period and OLE period). AEs during receiving study intervention ustekinumab through the Study will also be summarized.

The verbatim terms used in the CRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Any AE occurring at or after the initial administration of study intervention through the day of last dose is considered to be treatment emergent. If the event occurs on the day of the initial administration of study intervention, and either event time or time of administration are missing, then the event will be assumed to be treatment emergent. If the event date is recorded as partial or completely missing, then the event will be considered to be treatment emergent unless it is known to be prior to the first administration of study intervention based on partial onset date or resolution date. All reported treatment-emergent adverse events will be included in the analysis. For each adverse event, the number and percentage of participants who experience at least 1 occurrence of the given event will be summarized by intervention group.

Summary tables will be provided for treatment-emergent adverse events:

- AEs
- AEs per hundred patient-years of follow-up that will be calculated as (the number of adverse events ×365.25/ Sum of total duration of follow-up in days) * 100
- Serious AEs (SAEs)
- AEs leading to death
- AEs leading to discontinuation of study intervention
- AE with a frequency threshold of 5% or more
- AEs by severity (mild, moderate, severe)
- AEs by relationship to study intervention
- SAEs by relationship to study intervention
- Infections
- Serious Infections
- Infusion reactions
- Injection-site reactions
- Hypersensitivity Reactions (either Infusion reactions or Injection-site reactions)
- AEs related to COVID-19
- Other AESI

In addition to the summary tables, listings will be provided for participants who:

- AEs

- SAEs
- AEs leading to discontinuation of study intervention
- Death
- Infections
- Serious Infections
- Infusion reactions
- Injection-site reactions
- Hypersensitivity Reactions
- Other AESIs

5.6.3. Additional Safety Assessments (if applicable)

5.6.3.1. Clinical Laboratory Tests

Clinical Laboratory Tests will be summarized by analysis phase (DB period and OLE period).

Clinical laboratory tests will be displayed for the participants included in the safety analysis set.

Descriptive statistics and graphical displays will be presented for selected chemistry and hematology laboratory tests at scheduled time points.

Change from baseline over time will be summarized for chemistry and hematology tests and displayed by intervention group. A box plot of change from baseline to over time will be provided for the following laboratory tests:

- Hematology: Hemoglobin, Hematocrit, Red blood cell (RBC) count, White blood cell (WBC), Platelet count, Lymphocytes, Monocytes, Neutrophils, Bands, Eosinophils, Basophils
- Chemistry: Albumin, Alkaline phosphatase, Alanine aminotransferase (ALT/SGPT), Aspartate aminotransferase (AST/SGOT), Total carbon dioxide (CO_2), Total bilirubin, BUN, Calcium, Chloride, Creatinine, Glucose, Potassium, Total protein, Sodium, CK

The National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE; version 5.0) will be used in the summary of laboratory data (Grade 0-4). The proportion of subjects with postbaseline values by maximum toxicity grade for clinical laboratory tests will be summarized by intervention group. Shift summaries from baseline laboratory value to the worst on-treatment grade in chemistry and hematology tests with NCI toxicity grades will be presented. Subjects with toxicity grades ≥ 2 will be listed.

In addition, the incidence of markedly abnormal laboratory values will be presented by intervention group. Additionally, the markedly abnormal laboratory values will be listed. Markedly abnormal criteria are defined as Table 2:

Table 2: Markedly abnormal laboratory criteria

Item	Criterion of markedly abnormal criteria
Hematology & Differential panel	
Hemoglobin	$\leq 10 g/dL$
WBC	Out of normal range
Neutrophils	Out of normal range
Lymphocytes	Out of normal range
Chemistry panel	
ALT	$\geq 3 \times ULN$
AST	$\geq 3 \times ULN$
LDH	$\geq 3 \times ULN$
Creatinine	$\geq 1.5 \times ULN$
Glucose	$\geq 300 mg/dL$

All laboratory values will be listed.

5.6.3.2. Vital Signs

Vital signs will be summarized by analysis phase (DB period and OLE period). Continuous vital sign parameters including temperature, respiratory rate, weight, pulse and blood pressure (systolic and diastolic, right and left hands separately) will be summarized at each assessment time point. Change from baseline will be summarized at each assessment timepoint. Descriptive statistics (mean, standard deviation, median, minimum and maximum) will be presented.

Incidence of clinically important vital signs during intervention, as defined in Table 3, will be summarized for participants who had a baseline assessment and at least 1 postbaseline assessment for that vital sign. A listing of participants with treatment-emergent [clinically important/markedly abnormal] vital signs will be presented, along with a listing of all vital sign measurements.

Table 3: Clinically Important Vital Signs

Vital Sign	**Criteria**
Pulse	>120 bpm and with >15 bpm increase from baseline
	<50 bpm and with >15 bpm decrease from baseline
Systolic blood pressure	>180 mm Hg and with >20 mm Hg increase from baseline
	<90 mm Hg and with >20 mm Hg decrease from baseline
Diastolic blood pressure	>105 mm Hg and with >15 mm Hg increase from baseline
	<50 mm Hg and with >15 mm Hg decrease from baseline
Temperature	>38ºC
Respiratory rate	>24 breaths per minute
Weight	>10% kg increase from baseline
	>10% kg decrease from baseline

5.6.3.3. Electrocardiogram

ECG will be summarized by analysis phase (DB period and OLE period).

The interpretation of the ECGs as determined by a qualified physician (investigator or qualified designee) will be displayed by the number and percentage of participants meeting the normality criteria. The interpretation will be summarized over time by intervention group.

A listing of clinically relevant ECG abnormalities will also be provided.

5.7. Other Analyses

5.7.1. Pharmacokinetics

Blood samples will be collected for serum ustekinumab concentrations at the specified visits as indicated in the Schedule of Activities in protocol. PK analyses will be performed on the PK analysis set (see Section 4).

Serum ustekinumab concentrations summary and analysis will be based on the observed data; therefore, no imputation of missing data will be performed. All participants and samples excluded from the analysis will be clearly documented (eg, unknown or unreliable drug intake information).

All PK data including actual sampling time will be listed. All serum ustekinumab concentrations below the lower limit of quantification (LLOQ) or missing data will be labeled as such in the concentration data listing or statistical analysis system dataset.

Descriptive statistics (N, mean, SD, median, range, CV (%) and IQ range) will be used to summarize serum ustekinumab concentrations at each sampling time point.

For descriptive statistics of serum concentration of ustekinumab, the following data handling rules will be applied;

- Participants will be excluded from the PK analysis if their data do not allow for accurate assessment of the PK. In particular, all serum concentration summaries will exclude, from the time of occurrence, data collected for participants who 1) discontinue ustekinumab, 2) skip an infusion or injection, 3) receive an incomplete infusion or injection, 4) receive an incorrect infusion or injection, 5) receive an additional infusion or injection, and/or 6) receive commercial ustekinumab. **Exclusion data from PK analysis due to such inadequate administration will be specified by PK analyst.** In addition, PK samples taken outside the scheduled visit window (Week 2 and Week 4 visits: **±4 days;** Week 8 and thereafter: **±7 days**) will be excluded from the summaries.
- Serum ustekinumab concentrations below the LLOQ will be imputed as zero in the summary statistics.
- When more than half (>50%) of the serum concentrations of ustekinumab are BQL at each scheduled time point, mean, median, minimum and 25% quartile will be shown as ‘BQL’, and SD, %CV and 75% quartile will be shown as ‘NC’ (not calculated). Maximum observed value will be presented as maximum.
- When all serum concentration data are BQL at each scheduled time point, mean and median will be reported as ‘BQL’; SD and %CV are reported as ‘NC’ (not calculated); IQ range, maximum and minimum will be reported as ‘BQL’.
- When the number of serum concentrations data of ustekinumab at each scheduled time point is less than or equal to 2, N, mean and median will be calculated, and SD, %CV, 25% quartile and 75% quartile will be shown as ‘NC’. Minimum and maximum will be shown as ‘NC’ (quantifiable data=1) or will be reported as observed including BQL (quantifiable data =2).

- At the time point where no observation is obtained, 'NA (not applicable)' is reported.
- Data of samples with no information about the sampling date and time and/or the drug administration (time and dosage) will be excluded from descriptive statistics.
- Sampling time at Week 0 predose will be substituted with "0" in the figure. If, as the result of calculations (eg, descriptive statistics), a concentration value is less than the LLOQ (eg, 0.16880 µg/mL), the value should be reported as calculated.

Definition of analysis period

- DB period: Serum ustekinumab concentration is defined as the data derived from participants who were randomized ustekinumab arm and the duration is from Week 0 to end of DB period (see the definition in Section 5.1.2).
- Escape arm OLE period: Serum ustekinumab concentration is defined as the data derived from participants who experienced relapse in DB period and received IV intervention at Week OL-0 and the duration is from Week OL-0 to end of OLE-period (see the definition in Section 5.1.2).
- OLE period: Serum ustekinumab concentration is defined as the data derived from participants who didn't experience relapse in DB period and received SC intervention at Week OL-0 and the duration is from Week OL-0 to end of OLE period.

Serum ustekinumab concentrations will be summarized in tabular or graphical formats with nominal sampling timepoint.

Table

In DB period, serum ustekinumab concentrations from all patients received the active treatmnet will be summarized in table. In Escape arm OLE period and OLE period, serum ustekinumab concentrations will be summarized by intervention arm (Ustekinumab -> Ustekinumab or Placebo -> Ustekinumab) in table. In addition, to assess the impact of weight-based dosing, serum ustekinumab concentrations up to Week 8 in DB period and up to Week OL-8 in Escape arm OLE period will be summarized in a separate table by weight-range based dose category. Participants who received IV intervention at Week 0 and continuously received next IV intervention at Week OL-0 (which mean without SC intervention) will be summarized in a separate table which will include serum concentrations at Week 0, 2, 4, Week OL-0 and OL-8.

Figure

Serum ustekinumab concentration data may be displayed graphically in separate graph.

- Median (IQR) of serum ustekinumab concentration time profiles through DB period (in linear and semilog scales) will be presented in figure.
- Median (IQR) of serum ustekinumab concentration time profiles through Escape arm OLE period or OLE period (in linear and semilog scales) will be presented in figure by DB period intervention arm.

Serum ustekinumab concentration data may also be displayed graphically, such as median (IQR) of serum ustekinumab concentrations over time by the following subgroups:

- Antibodies to ustekinumab status by subject who have at least one positive ADA sample or no positive ADA sample through DB period or end of OLE period

Listing

The elapsed time[day] from last dosing to next PK sampling point will be described in listing.

Other

If sufficient data are available, then population PK analysis using serum concentration-time data of ustekinumab will be performed using nonlinear mixed-effects modeling. Details will be given in a population PK analysis plan and the results of the analysis will be presented in a separate report.

5.7.2. Immunogenicity

Blood samples will be collected for the detection of antibodies to ustekinumab at the specified visits as indicated in the Schedule of Activities in protocol. Immunogenicity analyses will be performed on the Immunogenicity analysis set (see Section 4).

"Sample ADA status" and sample titer as well as the cumulative "subject ADA status" and peak titer through the visit will be coded and provided by the bioanalytical group.

"Subject ADA status" is defined as below.

- Participants with treatment-emergent ADA positive to ustekinumab include:
  - Participants with treatment-induced antibodies to ustekinumab
  - Participants with treatment-boosted antibodies to ustekinumab
- Participants with treatment-induced antibodies to ustekinumab have a negative sample prior to administration and at least one positive sample after administration.
- Participants with treatment-boosted antibodies to ustekinumab have a positive sample prior to administration and at least one positive sample after administration with increase in titer over baseline.

The analysis will be based on the observed data; therefore, no imputation of missing data will be performed.

Incidence of antibody (evaluable, baseline ADA positive, treatment-emergent ADA positive, treatment-emergent ADA negative) status, neutralizing antibodies (NAb) and the maximum titers of anti-ustekinumab antibodies from Week 0 to OLE period will be summarized by intervention groups. The summary of participants with baseline positive samples is taken from the sample status at baseline. Sample ADA status at baseline is not considered for "subject ADA status". A 'Total' column that combines all intervention groups will be also presented.

The summary of following endpoints (time to relapse of TAK, relapse status, achieving GC dose criteria status, and injection site reactions status) will be presented by intervention group by

treatment-emergent ADA status. For 1 and 2, only DB period data will be assessed. For 3 and 4, both DB and OLE period data will be assessed:

1. Time to relapse of TAK according to protocol-defined criteria through the end of DB period
2. Relapse status through the end of DB period
3. Achieving GC dose criteria (5 mg/day or less or not)
4. Injection-Site Reactions status through DB period/OLE period

5.7.3. Pharmacodynamics

See Section 5.7.5.

5.7.4. Pharmacokinetic/Pharmacodynamic Relationships

Pharmacokinetic/Pharmacodynamic analyses will be based on the PK/PD analysis set (see Section 4). In DB period, the serum ustekinumab concentration data derived from participants who received placebo treatment will be complemented as zero. Exploratory PK-PD analyses, including graphical exploration of PK-PD data, may be performed.

Following PD indicator will be used: time to relapse, the proportions of relapse, the proportions of participants achieving GC dose of 5 mg/day or less and CRP/ESR.

Serum ustekinumab concentrations at DB or OLE relapse timing is defined as serum ustekinumab concentration at 1st relapse visit. If PK sample is not collected at 1st relapse visit, serum ustekinumab concentration at relapse confirmation visit will be used. For participants who didn't experience relapse, serum ustekinumab at end of DB will be treated as those at DB relapse timing. Serum ustekinumab at end of OLE will be treated as those at OLE relapse timing.

The definition of end of DB period and end of OLE period is shown in Section 5.1.2.

Time to relapse at DB period versus serum ustekinumab concentrations at DB relapse timing are plotted using the data from individual subjects for both ustekinumab arm and placebo arm (vertical axis: time to relapse DB period, horizontal axis: serum ustekinumab concentration).

Relationship between the proportions of relapse at end of DB period and end of OLE period and serum ustekinumab concentrations will be tabulated. In case DB period, the following category (ustekinumab arm: <=median or >median) will be used. In case OLE period, the following category (<=median or >median) will be used. DB period and OLE period will be summarized in separate table.

Relationship between the proportions of participants achieving GC dose of 5 mg/day or less through DB period and serum ustekinumab concentrations in ustekinumab arm at end of DB period will be summarized by ustekinumab concentration category (<=median or >median).

CRP/ESR value at DB relapse visit or at OLE relapse visit versus serum ustekinumab concentrations at DB or OLE relapse timing will be plotted using the data from individual

participants (vertical axis: the change from baseline in CRP/ESR, horizontal axis: serum ustekinumab concentration) by intervention arm (DB relapse visit: ustekinumab arm/placebo arm, OLE relapse visit: ustekinumab arm/placebo->ustekinumab arm) and relapse status. For participants who didn't experience relapse, CRP/ESR values at end of DB period or at end of OLE period (date of last observed visit or early discontinuation whichever comes first) will be used.

If deemed feasible and necessary, exposure-response modeling analyses may be performed. The analysis methods may be summarized in a separate analysis plan. Results of such analyses may be presented in a separate technical report.

5.7.5. Biomarkers

Biomarker results will be summarized in a separate technical report. Changes in biomarkers over time may be summarized by intervention group. 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.

5.7.6. Health Economics

Not applicable.

5.7.7. Other Variables and/or Parameters

Not applicable.

5.7.7.1. Definition

Not applicable.

5.7.7.2. Analysis Method

Not applicable.

5.7.8. Definition of Subgroups

Subgroup	Definition
Age Group	• 15-64 • >= 65
	• 15-17 • >= 18
Glucocorticoid at baseline	• <0.5 mg/kg/day • >=0.5 mg/kg/day
Status of previous biologic medication	• Bio-nonfailure • Biofailure
Weight	• <50 kg • >=50kg
Disease duration	• <5 years • >=5years

5.8. Interim Analyses

One efficacy interim analysis is planned to confirm early success 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.

However, the study turned out to be early terminated by sponsor before occurrence of 15 events, and the planned interim analyses will therefore not be performed.

5.8.1. Data Monitoring Committee (DMC) or Other Review Board

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.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 List of Abbreviations

ADA	anti-drug antibody
AE	adverse event
ALT/SGPT	alanine aminotransferase
AST/SGOT	aspartate aminotransferase
ATC	anatomic and therapeutic class
BMI	body mass index
CI	confidence interval
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DB	Double-blind
DMC	Data Monitoring Committee
ECG	electrocardiogram
ESR	erythrocyte sedimentation rate
FACIT	The Functional Assessment of Chronic Illness Therapy
F (%)	absolute SC bioavailability
FAS	full analysis set
GC	glucocorticoid
ICE	Intercurrent events
IQ	interquartile
LLOQ	lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
NAb	neutralizing antibodies
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PtGA	Patient's global assessment
SAEs	serious adverse events
SAP	Statistical Analysis Plan
SD	standard deviation
SF-36	Short form-36
TAK	Takayasu arteritis
TEAEs	treatment-emergent adverse events
VAS	visual analog scale
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary

6.2. Appendix 2 Demographics and Baseline Characteristics

The number of participants in each analysis set will be summarized by intervention group, and overall.

Table 4 presents a list of the demographic variables that will be summarized by intervention group and overall for the randomized analysis set.

Table 4: Demographic Variables

Continuous Variables:	**Summary Type**
Age (years)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum], and IQ range).
Weight (kg)	
Height (cm)	
Body Mass Index (BMI) (kg/m^2)	
Disease duration (years)	
Glucocorticoid at baseline (mg/kg/day)	
Categorical Variables	
Age (15-64 years, and =>65 years; 15-17 years, and >=18 years)	Frequency distribution with the number and percentage of participants in each category.
Weight (<50kg, >=50kg)	
Sex (male, female, unknown, undifferentiated)	
Race[a] (Asian (Japanese), Other)	
Ethnicity (Hispanic or Latino, not Hispanic or Latino)	
BMI (Underweight <18.5, Normal 18.5-<25, Overweight 25-<30, Obese >=30)	
Glucocorticoid at baseline (<0.5 mg/kg/day, =>0.5 mg/kg/day)[b]	
Status of previous biologic medication (Bio-nonfailure, Biofailure)	
Treatment (Tocilizumab, TNF, other)[c]	
Disease duration (< 5 year, >= 5 year)	

[a]If multiple race categories are indicated, the Race is recorded as 'Multiple'
[b]GC dose will be calculated as following formula:
Oral GC dose at Baseline = Sum of oral GC dose from Day -6 to randomization date (mg) / [Number of days treated with GC dose from Day -6 to Randomization date × Weight at Week 0 (kg)]
*Weight at screening may be used in case Weight at Week 0 were not collected.
[c]If the previous medication status is biofailure

6.3. Appendix 3 Protocol Deviations

A listing of participants with major protocol deviations including participant ID, type of deviation, and reasons for deviation will be provided. Major and minor COVID-19 related protocol deviation will also be listed.

6.4. Appendix 4 Prior and Concomitant Medications

Prior and Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD). Prior medications are defined as any therapy used before the day of first dose (partial or complete) of study intervention. Concomitant medications are defined as any therapy used on or after the same day as the first dose of study intervention, including those that started before and continue on after the first dose of study intervention.

Summaries of concomitant medications will be presented by anatomic and therapeutic class (ATC) term and intervention group. The proportion of participants who receive each concomitant medication will be summarized as well as the proportion of participants who receive at least 1 concomitant medication. The concomitant medication that is used through DB period and through the study will be summarized.

Prior medications will be summarized by intervention group and ATC term.

6.5. Appendix 5 Medical History

Medical history will be collected at screening. A summary table and a subject listing will be provided for general medical history and COVID-19 medical history for the randomized analysis set.

6.6. Appendix 6 Intervention Compliance

Intervention compliance will be summarized by analysis phase (DB period and OLE period) and type of administration (IV and SC).

Compliance will be summarized descriptively by study intervention. Compliance to randomized intervention versus actual intervention will be presented in a summary table.

Compliance will be calculated as follows:

100 x (actual amount of study intervention)/ protocol defined amount of study intervention

6.7. Appendix 7 Adverse Events of Special Interest

Opportunistic infection, active tuberculosis and malignancy are defined as special interest AE. AEs are determined by clinical review and detailed definitions are described in Data Presentation Specifications.

6.8. Appendix 8 Major Protocol Deviation for Intercurrent Events

Sequence number	Description [Copy or select the description from the Protocol and/or decide with Study Team on additional Protocol Deviations to be identified]	Protocol Deviation Description (DVTERM) as entered in Study Specific Issue System *This is suggestive wording to ensure review of PDs is consistent.*	PD Criterion (100 character limit required)	Protocol Deviation Coded Term (DVDECOD)	* Check/Listing * Medical Listing ** Source documents (if applicable)	Remarks (optional)
CONCOMITANT MEDICATION *(Study Specific Issue System Category Received a disallowed concomitant treatment)*						
62	**Taken a prohibited medication and regimen after study drug administration** Anti-IL-6 (eg, actemra), anti-TNF therapy (eg, remicade, humira)	Received protocol prohibited medication (Anti-IL-6, anti-TNF therapy) <specify medication >	Received protocol proh bited medication	Received a disallowed concomitant treatment	Source documents Medical Listing	
63	**Taken a prohibited medication and regimen after study drug administration** Anti-IL-23, anti- IL-12/23 p40, anti-IL-17 therapy	Received protocol prohibited medication (Anti-IL-23, anti- IL-12/23 p40, anti-IL-17 therapy) <specify medication>	Received protocol proh bited medication	Received a disallowed concomitant treatment	Source documents Medical Listing	
64	**Taken a prohibited medication and regimen after study drug administration** JAK inhibitors (eg, tofacitinib, upadacitinib)	Received protocol prohibited medication (JAK inhibitors) <specify medication>	Received protocol proh bited medication	Received a disallowed concomitant treatment	Source documents Medical Listing	
65	**Taken a prohibited medication and regimen after study drug administration** Cell-depleting therapies (eg, abatacept, rituximab, alemtuzumab)	Received protocol prohibited medication (Cell-depleting therapies) <specify medication>	Received protocol proh bited medication	Received a disallowed concomitant treatment	Source documents Medical Listing	
66	**Taken a prohibited medication and regimen after study drug administration** Cytotoxic acylating agents (eg, chlorambucil, cyclophosphamide)	Received protocol prohibited medication (Cytotoxic acylating agents) <specify medication>	Received protocol proh bited medication	Received a disallowed concomitant treatment	Source documents Medical Listing	
67	**Taken a prohibited medication and regimen after study drug administration** Immunomodulator (eg, MTX, AZA, MMF, TAC, cyclosporine)	Received protocol prohibited medication (Immunomodulator) <specify medication>	Received protocol proh bited medication	Received a disallowed concomitant treatment	Source documents Medical Listing	
68	**Taken a prohibited medication and regimen after study drug administration** Intra-muscular, intra-articular, intra-bursal, epidural, intra-lesional or IV GC	Received protocol prohibited medication (Intra-muscular, intra-articular, intra-bursal, epidural, intra-lesional or IV GC) <specify medication and route>	Received protocol proh bited medication	Received a disallowed concomitant treatment	Source documents Medical Listing	

Sequence number	Description [Copy or select the description from the Protocol and/or decide with Study Team on additional Protocol Deviations to be identified]	Protocol Deviation Description (DVTERM) as entered in Study Specific Issue System *This is suggestive wording to ensure review of PDs is consistent.*	PD Criterion (100 character limit required)	Protocol Deviation Coded Term (DVDECOD)	* Check/Listing * Medical Listing ** Source documents (if applicable)	Remarks (optional)
CONCOMITANT MEDICATION *(Study Specific Issue System Category Received a disallowed concomitant treatment)*						
69	**Taken a prohibited medication and regimen after study drug administration** Other investigational agents	Received protocol prohibited medication (Other investigational agents) <specify medication>	Received protocol proh bited medication	Received a disallowed concomitant treatment	Source documents	
70	**Violation of Glucocorticoid tapering rules** Week 0 through Week 2: No adjustments in glucocorticoid dose are permitted.	Received a disallowed glucocorticoid therapy at Week 0 through Week 2.	Received a disallowed glucocorticoid therapy	Received a disallowed concomitant treatment	Source documents Check/Listings Medical Listings	If the subject misses a dose or overdose for more than 2 days at the actual daily dose per a week in tapering schedule, it will be handled as Major PD.
71	**Violation of Glucocorticoid tapering rules** 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	Received a disallowed glucocorticoid therapy at Week 2 through participant's relapse or end of DB period.	Received a disallowed glucocorticoid therapy	Received a disallowed concomitant treatment	Source documents Medical Listings	If the subject misses a dose or overdose for more than 2 days at the actual daily dose per a week in tapering schedule, it will be handled as Major PD.

Sequence number	Description [Copy or select the description from the Protocol and/or decide with Study Team on additional Protocol Deviations to be identified]	Protocol Deviation Description (DVTERM) as entered in Study Specific Issue System *This is suggestive wording to ensure review of PDs is consistent.*	PD Criterion (100 character limit required)	Protocol Deviation Coded Term (DVDECOD)	* Check/Listing * Medical Listing ** Source documents (if applicable)	Remarks (optional)
CONCOMITANT MEDICATION *(Study Specific Issue System Category Received a disallowed concomitant treatment)*						
	ultimately at discretion of investigator at 5 mg or less based on disease activities of TAK in participants.					
72	**Anti-platelet or Anti-coagulation Therapy** Participants are newly received anti-platelet therapy (including but not limited to aspirin, clopidogrel, ticlopidine) or anti-coagulation therapy (including but not limited to warfarin) during DB period.	Newly received a disallowed anti-platelet or anti-coagulation therapy during double blind period.	Received a disallowed anti-platelet or anti-coagulation therapy	Received a disallowed concomitant treatment	Source documents Medical Listings	Regardless of whether or not it has been discussed with the sponsor medical monitor in advance, a new use is regarded as Major PD.
73	**Anti-hypertensive Therapy** Participants are newly received anti-hypertensive treatment during DB period.	Newly received a disallowed newly received anti-hypertensive treatment during double blind period.	Received a disallowed anti-hypertensive treatment	Received a disallowed concomitant treatment	Source documents Medical Listings	Regardless of whether or not it has been discussed with the sponsor medical monitor in advance, a new use is regarded as Major PD.
74	**Oral NSAIDs** Participants are newly received oral NSAIDs treatment during DB period.	Newly received a disallowed oral NSAIDs treatment during double blind period.	Received a disallowed oral NSAIDs treatment	Received a disallowed concomitant treatment	Source documents Medical Listings	Regardless of whether or not it has been discussed with the sponsor medical monitor in advance, a new use is regarded as Major PD.

6.9. Appendix 9 Laboratory Toxicity Grading

The grading scale use for lab assessments is based on 'Common Terminology Criteria for Adverse Events (CTCAE) v5.0'.

If a laboratory value falls within the grading as specified below but also within the local laboratory normal limits, the value is considered to be normal and will be reset to grade 0.

Prebaseline measurements will use the same grading ranges as applied to baseline measurements. In case a test has two sets of ranges – one for baseline normal and one for baseline abnormal, the one for baseline normal will be applied for all measurements taken prebaseline and on baseline.

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Janssen implementation notes
Blood and lymphatic system disorders					
Anemia	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hemoglobin (Hgb) <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hemoglobin (Hgb) <8.0 g/dL; <4.9 mmol/L; <80 g/L; *transfusion indicated*	*Life-threatening consequences; urgent intervention indicated*	Clinical signs and symptoms are not taken into consideration for grading.
Leukocytosis	-	-	>100,000/mm3; >100 x 10e9 /L	*Clinical manifestations of leucostasis; urgent intervention indicated*	Clinical signs and symptoms are not taken into consideration for grading; Added ranges in SI unit (x 10e9 /L)
Investigations					
Alanine aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	Ranges defined for "abnormal baseline" are applied only if baseline > ULN. If baseline < LLN, then ranges for "normal baseline" are applied.
Alkaline phosphatase increased	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	Ranges defined for "abnormal baseline" are applied only if baseline > ULN. If baseline < LLN, then ranges for "normal baseline" are applied.
Aspartate aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	Ranges defined for "abnormal baseline" are applied only if baseline > ULN. If baseline < LLN, then ranges for "normal baseline" are applied.
Blood bilirubin increased	>ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal	>1.5 - 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal	>10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal	Ranges defined for "abnormal baseline" are applied only if baseline > ULN. If baseline < LLN, then ranges for "normal baseline" are applied.

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Janssen implementation notes
Cholesterol high	>ULN - 300 mg/dL; >ULN - 7.75 mmol/L	>300 - 400 mg/dL; >7.75 - 10.34 mmol/L	>400 - 500 mg/dL; >10.34 - 12.92 mmol/L	>500 mg/dL; >12.92 mmol/L	
CPK increased	>ULN - 2.5 x ULN	>2.5 x ULN - 5 x ULN	>5 x ULN - 10 x ULN	>10 x ULN	
Creatinine increased	Creatine Kinase >ULN - 1.5 x ULN	Creatine Kinase >1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	Creatine Kinase >3.0 x baseline; >3.0 - 6.0 x ULN	Creatine Kinase >6.0 x ULN	
Hemoglobin increased	Increase in >0 - 2 g/dL; Increase in >0 - 20 g/L	Increase in >2 - 4 g/dL; Increase in >20 - 40 g/L	Increase in >4 g/dL; Increase in >40 g/L	-	The increase indicates the level of increase above normal (above ULN). Applied as, eg, grade 1 (g/dL): >ULN – ULN+2 g/dL; Added ranges in SI unit (g/L).
Lymphocyte count decreased	<LLN - 800/mm3; <LLN - 0.8 x 10e9/L	<800 - 500/mm3; <0.8 - 0.5 x 10e9 /L	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200/mm3; <0.2 x 10e9 /L	
Lymphocyte count increased	-	>4000/mm3 - 20,000/mm3; >4 - 20 x 10e9 /L	>20,000/mm3; >20 x 10e9 /L	-	Added ranges in SI unit (x 10e9 /L).
Neutrophil count decreased	<LLN - 1500/mm3; <LLN - 1.5 x 10e9 /L	<1500 - 1000/mm3; <1.5 - 1.0 x 10e9 /L	<1000 - 500/mm3; <1.0 - 0.5 x 10e9 /L	<500/mm3; <0.5 x 10e9 /L	Both Neutrophils and segmented neutrophils are graded using these criteria.
Platelet count decreased	<LLN - 75,000/mm3; <LLN - 75.0 x 10e9 /L	<75,000 - 50,000/mm3; <75.0 - 50.0 x 10e9 /L	<50,000 - 25,000/mm3; <50.0 - 25.0 x 10e9 /L	<25,000/mm3; <25.0 x 10e9 /L	
White blood cell decreased	<LLN - 3000/mm3; <LLN - 3.0 x 10e9 /L	<3000 - 2000/mm3; <3.0 - 2.0 x 10e9 /L	<2000 - 1000/mm3; <2.0 - 1.0 x 10e9 /L	<1000/mm3; <1.0 x 10e9 /L	
Metabolism and nutrition disorders					
Hypercalcemia	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; Ionized calcium >ULN - 1.5 mmol/L	Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L; Ionized calcium >1.5 - 1.6 mmol/L; *symptomatic*	Corrected serum calcium of >12.5 - 13.5 mg/dL; >3.1 - 3.4 mmol/L; Ionized calcium >1.6 - 1.8 mmol/L; *hospitalization indicated*	Corrected serum calcium of >13.5 mg/dL; >3.4 mmol/L; Ionized calcium >1.8 mmol/L; *life-threatening consequences*	Clinical signs and symptoms are not taken into consideration for grading.

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Janssen implementation notes
Hyperkalemia	Potassium >ULN - 5.5 mmol/L	Potassium >5.5 - 6.0 mmol/L; *intervention initiated*	Potassium >6.0 - 7.0 mmol/L; *hospitalization indicated*	Potassium >7.0 mmol/L; *life-threatening consequences*	Clinical signs and symptoms are not taken into consideration for grading.
Hypermagnesemia	Magnesium >ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L	-	Magnesium >3.0 - 8.0 mg/dL; >1.23 - 3.30 mmol/L	Magnesium >8.0 mg/dL; >3.30 mmol/L; *life-threatening consequences*	Clinical signs and symptoms are not taken into consideration for grading.
Hypernatremia	Sodium >ULN – 150 mmol/L	Sodium >150 – 155 mmol/L; *intervention initiated*	Sodium >155 – 160 mmol/L; *hospitalization indicated*	Sodium >160 mmol/L; *life-threatening consequences*	Clinical signs and symptoms are not taken into consideration for grading.
Hypertriglyceridemia	Triglycerides 150 mg/dL - 300 mg/dL; 1.71 mmol/L - 3.42 mmol/L	Triglycerides >300 mg/dL – 500 mg/dL; >3.42 mmol/L - 5.7 mmol/L	Triglycerides >500 mg/dL – 1000 mg/dL; >5.7 mmol/L - 11.4 mmol/L	Triglycerides >1000 mg/dL; >11.4 mmol/L; *life-threatening consequences*	Clinical signs and symptoms are not taken into consideration for grading.
Hypoalbuminemia	Albumin <LLN - 3 g/dL; <LLN - 30 g/L	Albumin <3 - 2 g/dL; <30 - 20 g/L	Albumin <2 g/dL; <20 g/L	*Life-threatening consequences; urgent intervention indicated*	Clinical signs and symptoms are not taken into consideration for grading.
Hypokalemia	*Potassium <LLN - 3.0 mmol/L*	*Symptomatic with* Potassium <LLN - 3.0 mmol/L; intervention indicated	Potassium <3.0 - 2.5 mmol/L; *hospitalization indicated*	Potassium <2.5 mmol/L; *life-threatening consequences*	"Symptomatic" ranges are applied for grade 2, grade 1 not assigned, ie, worst case applied. Clinical signs and symptoms are not taken into consideration for grading of grade 3 and 4.
Hypomagnesemia	Magnesium <LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	Magnesium <1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	Magnesium <0.9 - 0.7 mg/dL; <0.4 - 0.3 mmol/L	Magnesium <0.7 mg/dL; <0.3 mmol/L; *life-threatening consequences*	Clinical signs and symptoms are not taken into consideration for grading.
Hyponatremia	Sodium <LLN – 130 mmol/L	*Sodium 125-129 mmol/L and asymptomatic*	*Sodium 125-129 mmol/L symptomatic;*	Sodium <120 mmol/L; *life-threatening consequences*	Clinical signs and symptoms are not taken

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Janssen implementation notes
			120-124 mmol/L regardless of symptoms Sodium <130-120 mmol/L		into consideration for grading. Worst case ("<130-120 mmol/L" for grade 3 added by Janssen) is applied across grade 2/3 ranges: 120-129 mol/L assigned to grade 3, grade 2 not used.
Renal and urinary disorders					
Proteinuria	1+ proteinuria; urinary protein ≥ULN - <1.0 g/24 hrs; urinary protein ≥ULN - <1000 mg/day	**Adult:** 2+ and 3+ proteinuria; urinary protein 1.0 - <3.5 g/24 hrs; urinary protein 1000 - <3500 mg/day **Pediatric:** Urine P/C (Protein/Creatinine) ratio 0.5 - 1.9; Urine P/C (Protein/Creatinine) 56.5 – 214.7 g/mol	**Adult:** 4+ proteinuria; urinary protein >=3.5 g/24 hrs; urinary protein >=3500 mg/day; **Pediatric:** Urine P/C (Protein/Creatinine) ratio >1.9; Urine P/C (Protein/Creatinine) >214.7 g/mol	-	In case both 24-h urine collection and dipstick are collected, then worst case is taken, as opposed to having 24-h urine collection take precedence over dipstick. Added ranges in SI unit for urinary protein (mg/day) and for urine P/C (g/mol). Pediatric grading is applied to age range [0-18]. Adult grading is applied for ages [>18].

7. REFERENCES

Not Applicable.