Statistical Analysis Plan for Study M19-944

A Phase 3 Randomized, Placebo-Controlled, Double-Blind Program to Evaluate Efficacy and Safety of Upadacitinib in Adult Subjects with Axial Spondyloarthritis Followed by a Remission-Withdrawal Period

Remission-Withdrawal Period

Version 2.0

Table of Contents

List of Tables

List of Figures

List of Appendices

1.0 Introduction

The Statistical Analysis Plans (SAPs) describe the statistical analyses for the upadacitinib Study M19-944 entitled "A Phase 3 Randomized, Placebo-Controlled, Double-Blind Program to Evaluate Efficacy and Safety of Upadacitinib in Adult Subjects with Axial Spondyloarthritis Followed by a Remission-Withdrawal Period."

Study Protocol M19-944 is a global, multicenter, protocol ("master protocol") with a common screening platform for determining subject eligibility into 2 separate studies: Study 1 examines the efficacy and safety of upadacitinib in ankylosing spondylitis (AS) subjects who had an inadequate response to biologic disease-modifying antirheumatic drug therapy (bDMARD-IR). Study 2 examines the efficacy and safety of upadacitinib in non-radiographic axial spondyloarthritis (nr-axSpA) subjects.

This SAP is for the Remission-Withdrawal Period. The SAPs for Study 1 (AS, bDMARD-IR) and Study 2 (nr-axSpA) are described in separate documents.

The SAP will not be updated in case of administrative changes or amendments to the protocol unless the changes impact the analyses described in this SAP. If future protocol amendment impacts statistical analyses, this SAP will be amended accordingly. Details of SAP versions are outlined in Section 14.0.

Unless noted otherwise, all analyses will be performed using SAS Version 9.4 (SAS Institute Inc., Cary, NC 27513) or later under the UNIX operating system.

2.0 Study Objectives and Design

2.1 Study Objectives

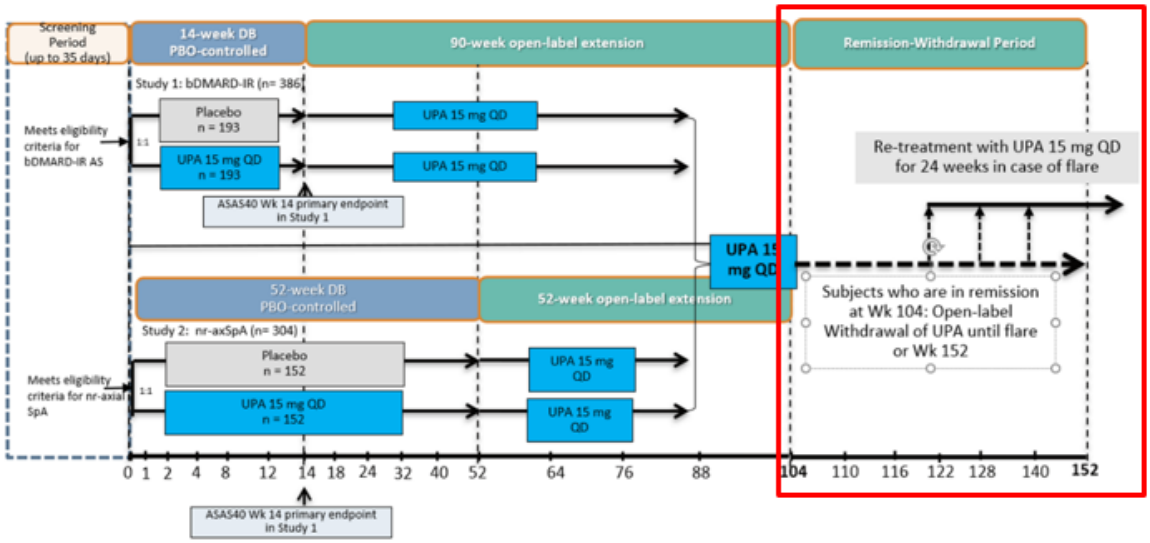
Remission Withdrawal Period:

- To evaluate the maintenance of disease control after withdrawal of upadacitinib in those who achieved Ankylosing Spondylitis Disease Activity Score (ASDAS) < 1.3 at Week 104 and ASDAS < 2.1 at Week 88.

2.2 Study Design Overview

Figure 1 shows the design of Study M19-944. Remission-Withdrawal Period is illustrated in the right portion.

Figure 1. Study Schematic



AS ankylosing spondylitis; ASAS Assessment of Spondyloarthritis International Society; bDMARD IR biologic disease modifying antirheumatic drug inadequate responder; EMA European Medicines Agency; FDA Food and Drug Administration; MRI magnetic resonance imaging; nr axSpA non radiographic axial spondyloarthritis; QD once daily; SI sacroiliac; UPA upadacitinib

Subjects in Study M19-944 from both Study 1 (AS bDMARD-IR) and Study 2 (nr-axSpA) who reach Week 104 on study drug (upadacitinib 15 mg QD) will be assessed whether they are in remission, with an ASDAS (CRP) < 1.3 at Week 104 and an ASDAS (CRP) < 2.1 at Week 88.

Subjects in remission at Week 104 will be eligible for the Remission-Withdrawal Period. Subjects will be followed without study drug treatment and assessed for disease flare through Week 152. Flare is defined as an ASDAS (CRP) ≥ 2.1 at 2 consecutive visits (based on observed records), which are at least 2 weeks apart, or an ASDAS (CRP) > 3.5 at one visit. Subjects who flare will receive open-label re-treatment upadacitinib

15 mg QD from the time of flare for 24 weeks (re-treatment) or longer per local country requirements. Subjects who do not flare will be followed without upadacitinib treatment until Week 152 at which point they will have the option to receive open label upadacitinib for the predefined time period, if Week 152 is before the end of the Open-Label Extension Period for their respective country. If Week 152 is after the end of the Open-Label Extension Period, the subject will complete the study at Week 152.

Efficacy analyses will be performed to characterize subject response to treatment withdrawal up to 48 weeks and response to upadacitinib re-treatment for 24 weeks respectively. Safety analyses will be performed to access safety of reinitiated upadacitinib 15 mg QD after treatment withdrawal, including re-treatment after flare and treatment during Open-Label Extension Period after withdrawal.

An additional safety analysis will be performed to access the totality of upadacitinib safety in the M19-944 study.

For the purposes of subject disposition and efficacy analysis, the duration of withdrawal from treatment is defined as the Withdrawal Period. The 24 weeks of exposure to treatment after flare is defined as the Re-treatment Period.

For the purposes of baseline characteristics, efficacy analysis and safety analysis, Original Baseline is defined as the value last observed prior to the first administration of study drug in the parent study, Study 1 or Study 2. The Original Baseline is used as the baseline value for all change or percent change from baseline efficacy analyses in the Withdrawal Period and for all safety summaries. For the purposes of efficacy analysis, Re-treatment Baseline is defined as the baseline value of the Re-treatment Period, which is the value last observed prior to the first administration of re-treatment study drug in the Remission-Withdrawal Period. The Re-treatment Baseline is used as the baseline value for all change or percent change from baseline efficacy analyses in the Re-treatment Period.

All analyses and summary will be performed and presented for overall (all eligible subjects) and by indication for Study 1 (bDMARD-IR AS) and Study 2 (nr-axSpA) subgroups (eligible subjects enrolled in Study 1 and Study 2, respectively).

2.3 Treatment Assignment and Blinding

Subjects will be followed without study drug treatment from Week 104 to Week 152. Subjects who flare will receive open-label upadacitinib 15 mg QD from the time of flare for 24 weeks (re-treatment) or longer per local country requirements. Subjects who do not flare will be followed without upadacitinib treatment until Week 152 at which point they will have the option to receive open label upadacitinib for the predefined time period, if Week 152 is before the end of the Open-Label Extension Period for their respective country. If Week 152 is after the end of the Open-Label Extension Period, the subject will complete the study at Week 152.

3.0 Endpoints for Remission-Withdrawal Study

3.1 Endpoints for Withdrawal Period

During the Withdrawal Period, the time-to-flare endpoint is defined as follows:

- Flare event criterion is defined as ASDAS (CRP) score > 2.1 at two consecutive visits, which are at least 2 weeks apart, or ASDAS (CRP) score > 3.5 at one visit
- Time-to-flare is defined as the number of days between the first day of treatment withdrawal and the day on which the criterion is met.

Additional endpoints during the Withdrawal Period include the following measurements assessed at scheduled time points in the Withdrawal Period:

Binary variables:

- Assessment of SpondyloArthritis international Society (ASAS) 20 response*;
- ASAS40 response*

- Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) 50 response*;
- ASAS Partial Remission (PR);
- Inactive Disease based on ASDAS(CRP) (ASDAS score < 1.3)
- Low Disease Activity based on ASDAS(CRP) (ASDAS score < 2.1);
- Major Improvement based on ASDAS(CRP) (a change from Original Baseline of ≤ 2.0);
- Clinically Important Improvement based on ASDAS(CRP) (a change from Original Baseline of ≤ 1.1);

* *Relative to Original Baseline.*

Change from Original Baseline in:

- ASDAS(CRP) and components;
- BASDAI and BASDAI components including mean of question 5 and 6 of the BASDAI (Score 0 10);
- Bath Ankylosing Spondylitis Functional Index (BASFI) (Score 0 10);
- Linear Bath Ankylosing Spondylitis Metrology Index ($BASMI_{lin}$);
- Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) for subjects with baseline enthesitis (MASES > 0);
- Patient's Assessment of Total Back Pain NRS score 0 - 10;
- Patient's Assessment of Nocturnal Back Pain NRS score 0 - 10;
- Patient's Global Assessment of Pain NRS score 0 - 10;
- Physician's Global Assessment of Disease Activity (PGA) Numeric Rating Scale (NRS) score 0 - 10;
- Patient's Global Assessment of Disease Activity (PtGA) NRS score 0 - 10;
- Tender joint count (TJC68) and swollen joint count (SJC66);
- ASAS Health Index (HI).

3.2 Endpoints for Re-Treatment Period

During the Re-treatment Period, endpoints include the following measurements assessed at scheduled time points in Re-treatment Period:

Binary variables:

- ASAS20 response*;
- ASAS40 response*;
- BASDAI 50 response*;
- ASAS PR;
- Inactive Disease based on ASDAS(CRP) (ASDAS score < 1.3)
- Low Disease Activity based on ASDAS(CRP) (ASDAS score < 2.1);
- Major Improvement based on ASDAS(CRP) (a change from Re-treatment Baseline of ≤ 2.0);
- Clinically Important Improvement based on ASDAS(CRP) (a change from Re-treatment Baseline of ≤ 1.1);

* *Relative to Re treatment Baseline.*

Change from Re-treatment Baseline in:

- ASDAS(CRP) and components;
- BASDAI and BASDAI components including mean of question 5 and 6 of the BASDAI (Score 0 10);
- BASFI (Score 0 10);
- $BASMI_{lin}$;
- MASES for subjects with baseline enthesitis (MASES > 0);
- Patient's Assessment of Total Back Pain NRS score 0 - 10;
- Patient's Assessment of Nocturnal Back Pain NRS score 0 - 10;
- Patient's Global Assessment of Pain NRS score 0 - 10;
- Physician's Global Assessment of Disease Activity (PGA) NRS score 0 - 10;
- Patient's Global Assessment of Disease Activity (PtGA) NRS score 0 - 10;

- Tender joint count (TJC68) and swollen joint count (SJC66);
- ASAS HI.

3.3 Safety Endpoints

The following safety evaluations will be performed for each period in the Remission-Withdrawal study as well as Open-Label Extension Period: adverse events (AEs), serious adverse events (SAEs), AE of special interest (AESI), AEs leading to discontinuation, vital signs, laboratory tests, and physical examination findings.

4.0 Analysis Populations

The Analysis Populations are defined in Table 1 and Table 2 below.

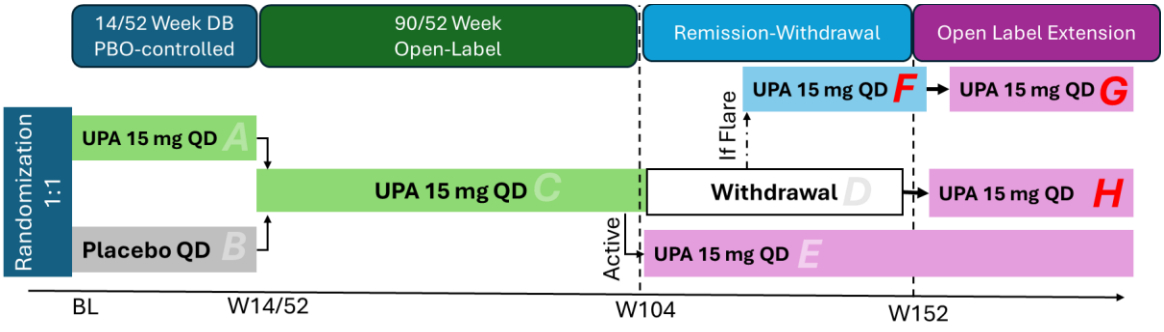
Table 1. Analysis Population for Efficacy Analyses

Analyses Population	Definition	Analyses Group
Withdrawal Analysis Set (WAS)	All subjects who entered the Remission-Withdrawal Period	Off Upadacitinib Treatment
Re-treatment Analysis Set (RAS)	All subjects who entered the Remission-Withdrawal Period and received at least one dose of Upadacitinib re-treatment in the Remission-Withdrawal Period	Upadacitinib 15 mg Re-treatment in RW

Table 2. Analysis Population for Safety Analyses

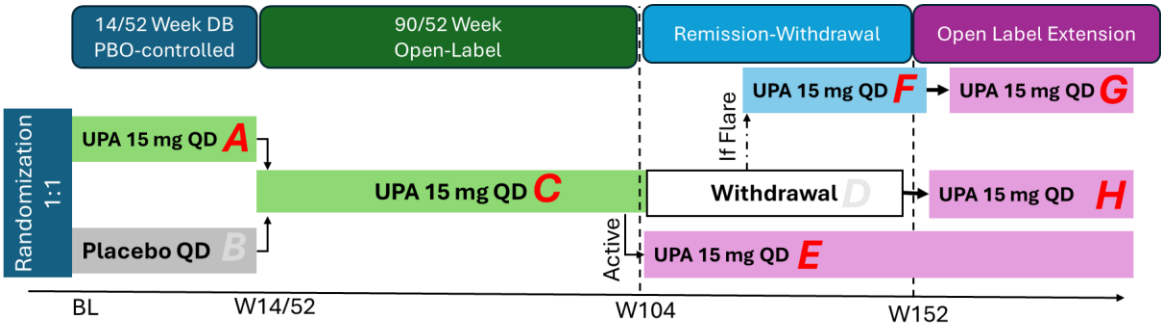
Analyses Population	Definition	Analyses Group	Data for Analyses
UPA reinitiation	All subjects who received at least one dose of reinitiated upadacitinib	Upadacitinib 15 mg	Safety data after reinitiation of upadacitinib (i.e., F+G+H as shown in Figure 2) will be included in safety analyses for summary of safety after reinitiating upadacitinib.
ALL UPA	All subjects who received at least one dose of upadacitinib in M19-944.	Any Upadacitinib 15 mg	Safety data under upadacitinib exposure in M19-944 (i.e., A+C+E+F+G+H in Figure 3) will be included in safety analyses for the totality of upadacitinib safety in M19-944.

Figure 2. Study Drug Exposure for Reinitiated Upadacitinib (UPA reinitiation)



Study 1 includes 14 week double blind placebo controlled period with 90 week open label period. Study 2 includes 52 week double blind placebo controlled period with 52 week open label period.

Figure 3. Study Drug Exposure for All Upadacitinib (ALL UPA)



Study 1 includes 14 week double blind placebo controlled period with 90 week open label period. Study 2 includes 52 week double blind placebo controlled period with 52 week open label period.

5.0 Subject Disposition

A summary of subject accountability will be provided where the number of subjects in each of the following categories will be summarized for overall and for Study 1 and Study 2 respectively:

- Subjects enrolled in the Withdrawal Period
- Subjects who completed Withdrawal Period
- Subjects who prematurely discontinued study during the Withdrawal Period
- Subjects who entered Re-treatment Period
- Subjects who completed Re-treatment Period
- Subjects who prematurely discontinued study drug during Re-treatment Period
- Subjects who entered Open-Label Extension Period

6.0 Study Treatment Duration and Compliance

The duration of treatment will be summarized for the UPA reinitiation and ALL UPA populations.

Study Drug Duration (in Days) (UPA_reinitiation):

- Duration of Upadacitinib 15 mg: Last dose date of reinitiated upadacitinib 15 mg − first dose date of reinitiated upadacitinib 15 mg + 1

Study Drug Duration (in Days) (ALL_UPA):

- Duration of Any Upadacitinib 15 mg: Last dose date of upadacitinib 15 mg − first dose date of upadacitinib 15 mg + 1, excluding the duration of withdrawal

The duration of exposure to study drug will be summarized as specified above, with the number of subjects, mean, standard deviation, median, minimum and maximum values. In addition, the number and percentage of subjects exposed to study drug will be summarized for the following cumulative duration intervals:

- ≥ 2 weeks
- ≥ 4 weeks
- ≥ 12 weeks
- ≥ 24 weeks
- ≥ 9 months
- ≥ 12 months
- ≥ 18 months
- ≥ 2 years
- ≥ 2.5 years
- ≥ 3 years
- ≥ 3.5 years
- ≥ 4 years

Study drug compliance will not be summarized for the Remission-Withdrawal Study.

7.0 Demographics, Baseline Characteristics, Medical History, and Prior/Concomitant Medications

Demographics, baseline or disease characteristics and medical history will be summarized relative to the start of the original study (Study 1 or Study 2), and prior and concomitant medications will be summarized relative to the start of the Remission-Withdrawal Period overall and for Study 1 and Study 2 subgroups. Categorical variables will be summarized with the number and percentage of subjects. Continuous variables will be summarized with descriptive statistics (number of non-missing observations, mean and standard deviation, median, minimum and maximum).

7.1 Demographics and Baseline Characteristics

Main Demographic and Original Baseline Characteristics

- Sex (male, female)
- Age (years)
- Age Categories (< 40, ≥ 40 and < 65, ≥ 65 years)
- Race (White, Non-White)
- Geographic Region (North America, South/Central America, Western Europe, Eastern Europe, Asia, Other)
- Weight (kg)
- Weight Categories (< 60, ≥ 60 and < 80 kg, ≥ 80 kg)
- Height (cm)
- Body Mass Index (BMI) (kg/m^2)
- Body Mass Index (BMI) Category (kg/m^2) (BMI < 25, BMI ≥ 25)

Axial SpA Medical History and Characteristics at Original Baseline

- Duration (years) of Axial SpA symptoms
- Duration (years) since Axial SpA diagnosis
- Duration since Axial SpA diagnosis categories (< 5 years, ≥ 5 - 10 years, ≥ 10 years)

- Duration of Axial SpA symptoms categories (< 5 years, ≥ 5 - 10 years, ≥ 10 years)
- HLA-B27 (positive, negative)
- Oral Corticosteroids use at baseline
- csDMARDs use at baseline
- Opioid use at baseline
- NSAID score at baseline

Table 3. ASAS and/or ASDAS Components at Original Baseline

ASAS only components	• Patient's assessment of total back pain (NRS score 0 - 10) • Function – Represented by the BASFI (NRS score 0 - 10) • Inflammation – (mean of items 5 and 6 of the BASDAI NRS score 0 – 10)
ASDAS only components	• Patient's assessment of back pain (BASDAI Question 2 NRS score 0 – 10) • Peripheral pain/swelling (BASDAI Question 3 NRS score 0 – 10) • High sensitivity C-reactive protein (hs-CRP) in mg/L • Erythrocyte sedimentation rate (ESR) (mm/hr) • Duration of morning stiffness (BASDAI Question 6 NRS score 0 – 10)
Components for both ASAS and ASDAS	• Patient global assessment of disease activity (NRS score 0 – 10)

Other Original Baseline Axial SpA Disease Characteristics

- ASDAS (CRP)
- ASDAS(CRP) categories (ASDAS(CRP) > 3.5 vs ≤ 3.5)
- Physician's Global Assessment of Disease Activity (NRS score 0 - 10)
- $BASMI_{lin}$
- MASES for subjects with baseline enthesitis (MASES > 0)
- Presence of enthesitis (MASES > 0)
- Tender Joint Count (TJC68)
- Swollen Joint Count (SJC66)
- High Sensitivity C-reactive Protein (hsCRP) (mg/L) at Screening
- Screening hsCRP levels (> ULN vs ≤ ULN, > 5mg/L vs ≤ 5mg/L)

- MRI (SI joints) inflammation at screening (positive vs negative)*
- MRI+/hsCRP > ULN, MRI+/hsCRP ≤ ULN, and MRI-/hsCRP > ULN at screening*
- Prior failed bDMARDs (yes or no)

* *For Study 2 only.*

Patient Reported Outcomes and Measures at Original Baseline

- BASDAI (Score 0-10)
- ASAS HI
- Patient's Assessment of Nocturnal Back Pain (NRS score 0 - 10)
- Patient's Global Assessment of Pain (NRS score 0 - 10)

7.2 Medical History and Prior and Concomitant Medications

Medical history data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The actual version of the MedDRA coding dictionary will be noted in the statistical tables and clinical study report. The number and percentage of subjects in each medical history category (by MedDRA system organ class and preferred term) will be summarized overall and for Study 1 and Study 2 subgroups for the WAS. The system organ class (SOC) will be presented in alphabetical order, and the preferred terms will be presented in alphabetical order within each SOC. Subjects reporting more than one PT within a SOC will be counted only once for that SOC. No statistical comparison will be performed for medical history reporting.

Concomitant medications during the Withdrawal Period and the Re-treatment Period will be summarized for the WAS and RAS respectively. Generally concomitant medications are those medications, other than study drug, taken after the first dose of study drug and within 1 day of the last dose of study drug. This includes medications with a start date between first study drug administration and last study drug administration + 1 day, as well as medications with a start date prior to first dose of study drug and which are ongoing after first dose of study drug. Medications taken on the day of the first dose of study drug

are counted as concomitant medications. For the purposes of Withdrawal Period summary, medications other than upadacitinib taken on or after Week 104 visit during treatment withdrawal will be considered as concomitant medications.

7.3 Protocol Deviations

Protocol deviations for Remission-Withdrawal study are described in Appendix B.

8.0 Handling of Potential Intercurrent Events

For the Withdrawal Period, the potential intercurrent event is upadacitinib re-treatment. The following strategies will be used to handle the intercurrent event in efficacy analysis:

- For time-to-flare endpoint, the composite strategy will be used. Subjects who receive upadacitinib re-treatment without meeting disease flare criterion will be considered flared at the time of first dose.
- For binary endpoints, the composite strategy will be used to handle intercurrent events. Subjects who receive upadacitinib re-treatment will be considered as non-responder for all Withdrawal Period visits after first dose date.
- For continuous endpoints, the hypothetical strategy will be used to handle intercurrent events. All data after first dose date of upadacitinib re-treatment will be excluded from analysis and will be implicitly imputed by the statistical model.

For the Re-treatment Period, the potential intercurrent event is premature discontinuation of re-treatment study drug. The following strategy will be used to handle the intercurrent event in efficacy analysis:

- For all endpoints, the treatment-policy strategy will be used to handle intercurrent events. All collected efficacy data will be used as observed, regardless of whether the subject discontinued re-treatment study drug prior to the completion of the Re-treatment Period.

9.0 Efficacy Analyses

9.1 General Considerations

There are two sets of planned efficacy analysis: efficacy analysis for the Withdrawal Period (from Week 104 up to Week 152) and efficacy analysis for the Re-treatment Period.

Efficacy analyses will be performed after all subjects have completed or discontinued from M19-944 study. Efficacy analyses will be performed overall and by indication for Study 1 (bDMARD-IR AS) and Study 2 (nr-axSpA) subgroups. There will be no statistical testing for efficacy analyses in the Remission-Withdrawal Period; only descriptive statistics will be provided.

Unless otherwise specified, binary variables will be summarized using descriptive statistics and 95% confidence intervals (CI) using normal approximation. Continuous variables will be analyzed using Mixed-Effect Model Repeat Measurement (MMRM) method. Time-to-flare will be analyzed using a Kaplan-Meier (KM) estimator.

9.2 Withdrawal Period Efficacy Analysis

9.2.1 Handling of Missing Data

Missing data will be handled as described below for the Withdrawal Period efficacy analysis.

9.2.1.1 Time-to-Flare

After handling of intercurrent events, for subjects without observed flare event, time-to-flare will be censored at the last available flare assessment at or prior to Week 152 visit.

9.2.1.2 Binary Endpoints

Non-responder Imputation (NRI) will be used, in which all missing data after handling of intercurrent events will be categorized as non-responders.

9.2.1.3 Continuous Endpoints

After handling of intercurrent events, Mixed -Effect Model Repeat Measurement (MMRM) will be used as the primary approach for handling missing data.

Mixed-Effect Model Repeat Measurement (MMRM)

MMRM will be utilized in the analysis of continuous endpoints (refer to Section 9.2.2). The MMRM analysis will be conducted based on observed data, and includes the categorical fixed effect of visit and the continuous fixed covariates of Original Baseline measurement. For summary of the overall subjects, an additional fixed effect of parent study (Study 1 or Study 2) will be considered. An unstructured variance covariance matrix will be used. The MMRM analysis is based on the assumption of data being missing at random (MAR).

9.2.2 Efficacy Analyses in the Withdrawal Period

The distribution of event-free survival defined in Section 3.1 will be estimated using Kaplan-Meier (KM) method. Subjects who did not have flare event will be censored at the last available flare assessment visit at or prior to Week 152 visit. If a subject discontinued prior to flare or Week 152 visit, the data will be censored at the date of last flare assessment. The KM estimator for median survival time for the flare-free rate during the Withdrawal period will be provided. The corresponding 95% CI will be derived based on Greenwood's formula for variance derivation and the log-log transformation applied on the survival function. The KM plot will be provided.

Binary and continuous endpoints defined in Section 3.1 and Section 3.2 will be analyzed at scheduled time points during the Withdrawal Period.

For binary endpoints, NRI will be used for missing data handling (see Section 9.2.1.2). Descriptive statistics, including point estimate and 95% CI by normal approximation, will be provided.

For continuous endpoints, MMRM model (as described in Section 9.2.1.3) will be used based on observed data. Mean estimates with associated 95% CI will be provided. In addition, descriptive statistics based on observed data will be provided, including the number of observations, mean, and standard deviation.

Plots of efficacy endpoints by visit during the Withdrawal Period will be provided for selected endpoints.

9.3 Re-Treatment Period Efficacy Analysis

9.3.1 Handling of Missing Data

Missing data will be handled as described below for the Re-treatment Period efficacy analysis.

9.3.1.1 Binary Endpoints

All reported data will be used with no missing data imputation.

9.3.1.2 Continuous Endpoints

Mixed-Effect Model Repeat Measurement (MMRM) analysis based on all observed data will be conducted with categorical fixed effect of visit and Re-treatment Baseline as the continuous fixed covariate. For summary in the overall subjects, an additional fixed effect of parent study (Study 1 or Study 2) will be considered. An unstructured variance covariance matrix will be used.

9.3.2 Efficacy Analyses in the Re-Treatment Period

Binary and continuous endpoints defined in Section 3.2 will be analyzed at scheduled time points during the Re-treatment Period.

For binary endpoints within the Re-treatment Period, descriptive statistics based on all observed data will be provided (see Section 9.3.1.1). Descriptive statistics include the point estimate and 95% CI by normal approximation.

For continuous endpoints within the Re-treatment Period, MMRM method (as described in Section 9.3.1.2) will be used based on all observed data. Mean estimates with 95% confidence intervals will be provided. In addition, descriptive statistics will be provided, including the number of observations, mean, and standard deviation.

Plots of efficacy endpoints by visit during the Re-treatment Period will be provided for selected endpoints.

10.0 Safety Analyses

10.1 General Considerations

Safety data will be summarized for the safety populations defined in Section 4.0.

The safety analyses will include reporting of adverse events (AEs), adverse events of special interest (AESI), laboratory, and vital sign measurements. Exposure-adjusted event rate (EAER) over 100 patient-years for subjects with treatment-emergent adverse events (TEAEs) will be provided to adjust for potentially different follow-up time between subjects. For the purpose of event rate calculation, the numerator will be the total number of AEs reported for the event (i.e., a subject can contribute more than one event to the numerator) and the denominator will be the total exposure time among subjects. The number of AEs reported (numerator), the total number of years of exposure (denominator calculated as total number of days of exposure for all treated subjects divided by 365.25), and the exposure-adjusted AE event rate per 100 patient-years calculated as ([numerator (number of AEs)/denominator]) • 100 will be presented.

In addition, exposure-adjusted incidence rate (EAIR) will be provided for AE Overview and Adverse Events of Special Interest (AESI) as deemed appropriate for long-term analysis. For the purpose of incidence rate calculation, the numerator will be the number

of subjects with AE reported for the event (i.e., a subject can contribute at most once to the numerator) and the denominator will be the total exposure time among subjects in the treatment group and at risk of an initial occurrence of the event, i.e., for subjects with no event, it is the total exposure time under the treatment group; for subjects with an event, it is the exposure time to the first event. The numerator, denominator (calculated as total number of days exposed to study drug for all treated subjects divided by 365.25), and the exposure-adjusted incidence rate per 100 patient-years calculated as ([numerator/denominator]) • 100 will be presented for each treatment group.

10.2 Adverse Events

A treatment-emergent Adverse Event (TEAE) is defined as an adverse event with an onset date that is after the first dose of study drug, and no more than 30 days after the last dose of study drug. Events where the onset date is the same as the study drug start date are assumed to be treatment-emergent, unless the study drug start time and the adverse event start time are collected, and the adverse event start time is prior to the study drug start time. If an incomplete onset date was collected for an adverse event, the event will be assumed to be treatment-emergent unless there is other evidence that confirms that the event was not treatment-emergent (e.g., the event end date was prior to the study drug start date).

AEs will be summarized and presented using primary MedDRA System Organ Classes (SOCs) and preferred terms (PTs) using MedDRA Version 27.1 or most up to date version. The actual version of the MedDRA coding dictionary used will be noted in the AE tables and in the clinical study report. Specific adverse events will be counted once for each subject for calculating percentages, unless stated otherwise. In addition, if the same adverse event occurs multiple times within a subject, the highest severity and level of relationship to investigational product will be reported.

10.2.1 Adverse Event Overview

An overview of TEAEs per 100 patient-years of study drug exposure will be presented for the following categories:

- Any TEAE
- Any TEAE related to study drug according to investigator assessment
- Any Severe TEAE
- Any Serious TEAE
- COVID-19 TEAE
- Any TEAE leading to discontinuation of study treatment
- Any TEAE Leading to Death
- All Deaths

The number of TEAEs reported, the total number of years of study drug exposure, and the TEAE rate per 100 patient-years will be presented. An overview of TEAE incidence rate per 100 patient-years of exposure will also be presented.

10.2.2 Treatment-Emergent Adverse Events by SOC and PT

TEAEs per 100 patient-years of study drug exposure will be summarized by SOC and PT. The following summaries of adverse events will be generated:

- All TEAEs
- Serious TEAEs
- Severe TEAEs
- TEAEs related to study treatment according to the investigator
- TEAEs leading to discontinuation of study treatment
- TEAE leading to death
- COVID-19 TEAE

TEAEs will be summarized by SOC and PT; by maximum relationship to study treatment as assessed by the investigator (e.g., reasonable possibility or no reasonable possibility) and SOC and PT; by maximum severity and SOC and PT.

10.2.3 Deaths, Serious Adverse Events, and Adverse Events Leading to Study Treatment Discontinuation

Treatment-emergent serious adverse events (SAEs), TEAEs leading to premature discontinuation of study treatment, and TEAEs leading to death will be summarized by SOC and PT.

Tabular listings will be provided for all deaths, all SAEs, TEAEs leading to death, TEAEs leading to premature discontinuation of study treatment.

10.2.4 Adverse Events of Special Interest

Adverse events of special interest will be summarized by SOC and PT and will be based on standardized or AbbVie-defined company MedDRA queries (SMQs or CMQs), or based on adjudication results. Adjudicated cardiovascular events will be summarized using the CAC adjudicated categories. Adverse events of special interest categories and detailed information about the search criteria are listed in Table 4.

A summary of non-treatment-emergent malignancy events will also be presented.

Tabular listings of treatment-emergent adverse events of special interest will be provided.

An overview of AESIs per 100 patient-years of study exposure will be presented. The number of TEAEs reported, the total number of years of study drug exposure, and the TEAE rate per 100 patient-years will be presented. Additionally, an overview of AESIs Incidence rate per 100 patient-years of study drug exposure will be also presented.

Table 4. AESI for Upadacitinib with SMQs/CMQs/PTs Searches

AESI	Type of MedDRA Query	Broad or Narrow Search	SMQ/CMQ Search Criteria
Serious Infections	CMQ		"Infections" – Subset for SAEs
Opportunistic Infection excluding Tuberculosis and Herpes Zoster	CMQ		"Opportunistic Infection excluding Tuberculosis and Herpes Zoster"
Possible Malignancy	SMQ	Narrow	"Malignancies"
Malignancy	SMQ	Narrow	"Malignant tumours"
Non-Melanoma Skin Cancer (NMSC)	SMQ	Narrow	Skin Malignant tumours (Narrow SMQ) removing Melanoma CMQ
Malignancy excluding NMSC			"Malignant tumours" SMQ (Narrow) removing NMSC output
Lymphoma	SMQ	Broad	"Malignant Lymphomas"
Hepatic Disorder	SMQ	Narrow	"Drug Related Hepatic Disorders" comprehensive search
Adjudicated Gastrointestinal Perforations	Output from adjudication		
Anemia	CMQ		"Non-Hemolytic and Non-Aplastic Anemias"
Neutropenia	CMQ		"Hematological Toxicity – Neutropenia"
Lymphopenia	CMQ		"Hematological Toxicity – Lymphopenia"
Herpes Zoster	CMQ		"Herpes Zoster"
Renal Dysfunction	SMQ	Narrow	"Acute Renal Failure"
Active Tuberculosis	CMQ		"Active Tuberculosis"
Bone Fracture	CMQ		"Bone Fracture"
Serious Hypersensitivity Reaction	SMQ	Narrow	"Anaphylactic Reaction" (SMQ narrow) including "Angiodema" (SMQ Narrow) – subset to SAEs
Retinal Detachment	CMQ		"Retinal Detachment"
Acute Renal Failure	SMQ	Narrow	"Acute Renal Failure"

AESI	Type of MedDRA Query	Broad or Narrow Search	SMQ/CMQ Search Criteria
Adjudicated Cardiovascular Events	Output from CAC		
MACE*			
Cardiovascular Death			
Non-fatal Myocardial Infarction			
Non-fatal Stroke			
Undetermined/Unknown Cause of Deaths			
Other Cardiovascular events			
Adjudicated Thrombotic Events	Output From CAC		
Venous Thromboembolic Events**			
Deep Vein Thrombosis			
Pulmonary Embolism			
Other Venous Thrombosis			
Arterial Thromboembolic Events (non-cardiac, non-neurologic)			

CAC Cardiovascular Adjudication Committee; CMQ company MedDRA query; PT preferred term; SMQ standard MedDRA query

* MACE; Major Adverse Cardiovascular Events, defined as cardiovascular death, non fatal myocardial infarction and non fatal stroke.

** Venous thromboembolic events (VTE) include deep vein thrombosis (DVT) and pulmonary embolism (PE) (fatal and non fatal).

Additional AEs may be considered for summary based on recommendations from Clinical and Safety as deemed appropriate.

10.3 Analysis of Laboratory Data

Data collected from central and local laboratories, including additional laboratory testing due to an SAE, will be used in all analyses, except for period baseline where SAE-related laboratory assessments on or before the first dose of study drug will be excluded.

10.3.1 Variables and Units

Safety laboratory parameters to be summarized in this study are listed below. Laboratory parameters will be reported using the standard international (SI) units.

Table 5. List of Safety Laboratory Variables

Laboratory Variables
Hematology
Leukocytes (White Blood Cell Count)
Erythrocytes (Red Blood Cell Count)
Hemoglobin
Hematocrit
Platelets
Neutrophils
Basophils
Eosinophils
Lymphocytes
Monocytes
Erythrocytes Mean Corpuscular Volume
Reticulocytes/Erythrocytes

Laboratory Variables
Chemistry
Total Bilirubin
Alkaline Phosphatase (ALP)
Aspartate aminotransferase (AST)
Alanine aminotransferase (ALT)
Total Protein
Albumin
Glucose
Triglycerides
Blood Urea Nitrogen (BUN)
Creatinine
Uric acid
Sodium
Potassium
Calcium
Inorganic Phosphorus
Chloride
Bicarbonate
Cholesterol
LDL cholesterol
HDL cholesterol
LDL/HDL ratio
Cholesterol/HDL ratio
Urinalysis
Specific Gravity
pH

10.3.2 Assessment of Mean Change from Baseline in Clinical Laboratory Variables

For UPA reinitiation, each laboratory variable will be summarized for all time points (starting with visit at first dose of reinitiated upadacitinib) with the number of non-missing observations, mean and standard deviation, median, minimum and maximum.

Mean change from Original Baseline to each applicable post-baseline visit will be summarized for selected laboratory variables, with the number of observations, reinitiation baseline mean, and visit mean. The change from Original Baseline mean, standard error, and 95% confidence interval will be presented for the mean change from Original Baseline overall and for Study 1 and Study 2 subgroups.

No summary of laboratory data by visit will be provided for ALL UPA.

10.3.3 Assessment of Potentially Clinically Important Laboratory Values

The criteria for potentially clinically important laboratory values will be determined by CTCAE v4.03 criteria of Grade 3 or higher.

Laboratory abnormalities will be evaluated based on Potentially Clinically Important (PCI) criteria (Appendix D). For each laboratory PCI criterion, the number and percentage of subjects who have a laboratory value meeting CTCAE v4.03 criteria Grade 3 and 4 will be summarized. Listings will be provided to summarize subject-level laboratory data for subjects meeting PCI criteria. A listing of possible Hy's Law cases will be provided.

10.3.4 Assessment of Liver Elevations

According to FDA's Guidance for Industry "Drug-Induced Liver Injury: Premarketing clinical evaluation" (July 2009), when aminotransferase (AT) abnormalities indicating hepatocellular injury are accompanied by evidence of impaired hepatic function (Total bilirubin elevation > 2 × ULN), in the absence of evidence of biliary obstruction (i.e., significant elevation of ALP) or some other explanation of the injury (e.g., viral hepatitis, alcohol hepatitis), the combined finding (i.e., Hy's Law cases) represents a signal of a potential for the drug to cause severe DILI.

For the purpose of assessing for potential Hy's law cases, the frequencies and percentages of subjects with post baseline liver specific function test values that meet the following criteria of potential clinical interest will be summarized. Listings will be provided to

summarize subject-level laboratory data for subjects meeting liver elevations based on criteria specified below:

- ALT ≥ 3 × ULN
- ALT ≥ 5 × ULN
- ALT ≥ 10 × ULN
- ALT ≥ 20 × ULN
- AST ≥ 3 × ULN
- AST ≥ 5 × ULN
- AST ≥ 10 × ULN
- AST ≥ 20 × ULN
- TBL ≥ 2 × ULN
- Alkaline phosphatase ≥ 1.5 × ULN
- ALT and/or AST ≥ 3 × ULN and TBL ≥ 1.5 × ULN
- ALT and/or AST ≥ 3 × ULN and TBL ≥ 2 × ULN

For criteria involving multiple parameters, the values do not need to be concurrent to meet the defined criteria.

10.4 Analysis of Vital Signs

Vital sign measurements of systolic and diastolic blood pressure, pulse rate, respiratory rate, body temperature, and weight will be summarized.

For UPA reinitiation, each vital sign variable will be summarized for all visits (starting with visit at first dose of reinitiated upadacitinib) with the number of non-missing observations, mean and standard deviation, median, minimum and maximum. Mean change from Original Baseline to each applicable post-baseline visit will be summarized for each vital sign variable, with the number of observations, Original Baseline mean, and visit mean. The change from Original Baseline mean, standard error, and 95% confidence interval will be presented for the mean change from baseline.

No summary of vital sign data by visit will be provided for ALL UPA.

Vital sign variables will be evaluated based on potentially clinically important (PCI) criteria (Appendix D). For each vital sign PCI criterion, the number and percentage of subjects who have a vital sign value meeting the criteria will be summarized. Listings will be provided to summarize subject-level vital sign data for subjects meeting PCI criteria.

11.0 Other Analyses

Not Applicable.

12.0 Interim Analyses

Not Applicable.

13.0 Overall Type-I Error Control

There is no formal statistical testing in the Remission-Withdrawal study. Thus, no Type-I error control is planned in this study.

14.0 Version History

Table 6. SAP Version History Summary

Version	Date	Summary
1.0	08 August 2022	Original version
2.0	11 December 2024	The following changes have been made: • Redefined safety analysis populations in Section 4.0 to collectively summarize patient safety of reinitiated upadacitinib after treatment withdrawal and to summarize patient safety of any upadacitinib in Study M19-944. • Updated treatment exposure duration in Section 6.0 to reflect the redefined safety analysis populations. • Moved description of intercurrent event handling to Section 8.0. • Removed estimand language in Section 9.0. • Streamlined safety analysis description in Section 10.0 for redefined safety analysis populations. • Aligned AESI categories in Section 10.2.4 to the most updated upadacitinib PSSAP (Version 8.0). • Removed COVID-19 or geo-political conflict language in Section 5.0, Section 9.2 and Section 9.3, and NRI-MI in Appendix as they are no longer applicable.

15.0 References

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Appendix A. List of SAP Signatories

Name	Title	Role/Functional Area
[redacted]	[redacted]	Author
[redacted]	[redacted]	Clinical Statistics
[redacted]	[redacted]	Statistical Programming
[redacted]	[redacted]	Medical/Scientific Monitor

Appendix B. Protocol Deviations

Protocol deviations include eligibility criteria violations, receipt of wrong treatment or incorrect dose of study treatment, development of withdrawal criteria without being withdrawn, and use of excluded concomitant medications. A listing of subjects with protocol deviations will be provided.

For each of the following protocol deviation categories and across all categories, the number and percentage of randomized subjects with at least one protocol deviation will be summarized overall and by treatment group:

- Subject entered into the study even though did not satisfy entry criteria;
- Subject developed withdrawal criteria during the study but was not withdrawn;
- Subject received wrong treatment or incorrect dose of study treatment;
- Subject took excluded concomitant medication.

Appendix C. EAER and Normal Approximation Based 95% Confidence Interval

Assume the occurrence of TEAE of special interest follows a Poisson distribution and let λ denote the rate of occurrence of TEAE under the total exposure time for a treatment group. Let n be the number of AEs reported in Any upadacitinib 15 mg QD group. Let T be the total time exposed to study drug summed across all treated subjects in Any upadacitinib 15 mg QD group. Under the assumption that n follow Poisson distribution with parameters λT, the $\hat{\lambda}$ n/T.

Using normal approximation, the 95% confidence interval can be calculated by (Liu GF et al. 2006.[10]):

$$\hat{\lambda} \pm Z_{\alpha/2}\hat{\sigma}$$

Where $\hat{\sigma} = \sqrt{\frac{n}{T^2}}$

Appendix D. Potentially Clinically Important Criteria for Safety Endpoints

The criteria for Potentially Clinically Important (PCI) laboratory findings are described in Table D-1 and Table D-2, and the PCI criteria for vital sign findings are described in Table D-3.

Table D-1. Criteria for Potentially Clinically Important Hematology Values

Hematology Variables	Units	Definition of Potentially Clinically Important	
		Very Low	Very High
Hemoglobin	g/L	< 80	---
Neutrophils	10^9/L	< 1.0	---
Lymphocytes	10^9/L	< 0.5	---
Platelets	10^9/L	< 50.0	---
Leukocytes	10^9/L	< 2.0	---

Note: A post baseline value must be more extreme than the baseline value to be considered a potentially clinically important finding.

Table D-2. Criteria for Potentially Clinically Important Chemistry Values

Chemistry Variables	Units	Definition of Potentially Clinically Important	
		Very Low	Very High
Creatinine	umol/L	---	>3.0 × baseline; >3.0 × ULN
ALT	U/L	---	>5.0 × ULN
AST	U/L	---	>5.0 × ULN
Bilirubin	umol/L	---	>5.0 × ULN
CPK	U/L	---	>5.0 × ULN

Note: A post baseline value must be more extreme than the baseline value to be considered a potentially clinically important finding.

Table D-3. Criteria for Potentially Clinically Important Vital Sign Values

Vital Signs Variables	Criterion	Definition of Potentially Clinically Important
Systolic Blood Pressure (mmHg)	Low	Value ≤ 90 mmHg and decrease ≥ 20 mmHg from Baseline
	High	Value ≥ 160 mmHg and increase ≥ 20 mmHg from Baseline
Diastolic Blood Pressure (mmHg)	Low	Value ≤ 50 mmHg and decrease ≥ 10 mmHg from Baseline
	High	Value ≥ 100 mmHg and increase ≥ 10 mmHg from Baseline
Pulse (bpm)	Low	> 7% increase from baseline
	High	> 7% decrease from baseline