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Protocol for Study M19-944

Axial Spondyloarthritis: Evaluation of Upadacitinib in Adult Subjects – SELECT-AXIS 2

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1 SYNOPSIS

Title: 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	
Background and Rationale:	Axial spondyloarthritis (axSpA) encompasses a spectrum of inflammatory involvement of the axial skeleton. Also, based on the Assessment of SpondyloArthritis international Society (ASAS) axSpA criteria, axSpA can be further divided into non-radiographic axial spondyloarthritis (nr-axSpA) or ankylosing spondylitis (AS). Patients with nr-axSpA and AS share common epidemiological, genetic, and clinical disease characteristics, particularly with regard to disease activity, and similar response to treatment. There remains a significant unmet medical need in the treatment of axSpA. Evidence from Phase 2 studies and one Phase 3 study with Janus kinase (JAK) inhibitors suggest that inhibition of JAK-mediated pathways may be a promising approach for the treatment of subjects with AS. More selective JAK inhibitors may decrease the risk for infection (including viral reactivation) and/or malignancy that are observed with pan JAK inhibitors or less selective JAK inhibitors. Upadacitinib is a novel oral selective and reversible JAK-1 inhibitor being developed for axSpA and treatment of other immune-mediated inflammatory diseases. The results from the Phase 2/3 study in AS (Study M16-098, SELECT-AXIS 1) showed that upadacitinib 15 mg once daily (QD) had an efficacy profile that can benefit patients with AS through one year, and no new safety risks were identified.[1] Study Protocol M19-944 is a global, multicenter, protocol ("master protocol") with a common screening platform for determining subject eligibility into 2 separate studies with many overlapping eligibility criteria within the same protocol: Study 1 is in subjects with active AS who had an inadequate response to biologic disease-modifying antirheumatic drug therapy (bDMARD-IR) and Study 2 is in subjects with active nr-axSpA. The ability to use a common screening platform is considered to be one of the main advantages of incorporating these 2 studies into a single protocol, resulting in a decreased patient burden during screening and a more efficient recruitment of subjects and use of resources. A subject in screening may be eligible for and randomized into 1 of the 2 studies without the need to screen-fail and rescreen for the other study. The requirement for subjects to meet the modified New York criteria using confirmation of radiographic evidence by a central reader is necessary for eligibility into the AS study; however, those subjects who do not meet these radiographic criteria may still be eligible for the nr-axSpA study. Although this protocol includes a common screening process and other operational elements for Study 1 and Study 2, randomization and data collection will be conducted for each study independently. Each study has its own objective, hypothesis testing, and adequate power for primary and secondary endpoints. The analyses and reporting for the 2 studies will therefore be separate. The success of each study in its corresponding subject population will be determined separately and independently of the other study. Each study represents a standalone study for regulatory purposes with the ability to report interim and final data independently.

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	The treatment goal in axial SpA is to achieve a state of sustained remission in patients with active axial SpA.[2,3] Once disease activity is under control, one key clinical question is whether treatment with immunosuppressive treatment can be safely withdrawn without causing disease flares. Several studies with bDMARDs have shown that active axial SpA patients who achieved sustained remission and in whom immunosuppressive treatment was withdrawn, were less likely to stay in sustained remission compared to those who continued treatment.[4,5,6] However, there is a lack of withdrawal studies with JAK-inhibitor treatment in axial SpA.
Objective(s) and Endpoint(s):	**Objectives:** Double-Blind Period: • To evaluate the efficacy of upadacitinib compared with placebo on reduction of signs and symptoms in adult subjects with active axSpA including bDMARD-IR AS (Study 1) and nr-axSpA (Study 2); • To assess the safety and tolerability of upadacitinib in adult subjects with active axSpA including bDMARD-IR AS (Study 1) and with nr-axSpA (Study 2). Open-Label Extension Period: To evaluate the safety and tolerability of upadacitinib in extended treatment in adult subjects with active axSpA including bDMARD-IR AS who have completed the Double-Blind Period (Study 1) and with nr-axSpA who have completed the Double-Blind Period (Study 2). Remission-Withdrawal Period: To evaluate the maintenance of disease control after withdrawal of upadacitinib [redacted] **Primary Endpoint:** Study 1 (bDMARD-IR AS): The primary endpoint is ASAS40 response at Week 14. Study 2 (nr-axSpA): The primary endpoint is ASAS40 response at Week 14.
Investigator(s):	Multi-center
Study Site(s):	Approximately 230 sites in approximately 25 countries between 2 studies
Study Population and Number of Subjects to be Enrolled:	Approximately 386 subjects with AS who are bDMARD-IR (Study 1) and approximately 304 subjects with nr-axSpA (Study 2)
Investigational Plan:	Study 1 (bDMARD-IR AS) is comprised of a 35-day Screening Period; a 14-week randomized, double-blind, parallel-group, placebo-controlled period (the Double-Blind Period); a 90-week open-label, long-term extension period (the Open-Label Extension Period); and a 30-day Follow-Up Visit (F/U Visit). Study 2 (nr-axSpA) is comprised of a 35-day Screening Period; a 52-week randomized, double-blind, parallel-group, placebo-controlled period (the Double-Blind Period); a 52-week open-label, long-term extension period (the Open-Label Extension Period); and a 30-day F/U Visit.

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	In the Double-Blind Period for both studies, subjects will be randomized in a 1:1 ratio to 1 of 2 treatment groups: Study 1 (bDMARD-IR AS): • Group 1: upadacitinib 15 mg QD (N = 193) • Group 2: placebo QD (N = 193) Study 2 (nr-axSpA): • Group 1: upadacitinib 15 mg QD (N = 152) • Group 2: placebo QD (N = 152) Subjects in the placebo group will be switched to upadacitinib 15 mg QD at Week 14 in the Open-Label Extension Period for Study 1 (bDMARD-IR AS) and Week 52 in the Open-Label Extension Period for Study 2 (nr-axSpA). Remission-Withdrawal Period: • [redacted] will be eligible for the open-label remission-withdrawal period. Subjects will be followed and assessed for potential flare through Week 152. Subjects who flare during this period (flare defined as ASDAS [CRP] ≥ 2.1 at 2 consecutive visits, which are at least 2 weeks apart, or ASDAS [CRP] > 3.5 at one visit) will be eligible to receive open-label upadacitinib 15 mg QD for 24 weeks (re-treatment) from the timepoint of flare. Subjects who do not flare through Week 152 during the withdrawal period, will have reached the end of the study. • Subjects not eligible for the withdrawal period will have reached the end of the study after the 30 day follow up visit.
Key Eligibility Criteria:	Eligible subjects will be adult females and males who are at least 18 years of age at Screening with a clinical diagnosis of AS, meet the modified New York Criteria for AS, and are without total spinal ankylosis (Study 1, bDMARD-IR AS); or with a clinical diagnosis of nr-axSpA fulfilling the 2009 ASAS classification criteria for axSpA but not meeting the radiologic criterion of the modified New York criteria for AS and have objective signs of active inflammation on magnetic resonance imaging of sacroiliac joints or based on high sensitivity C-reactive protein > upper limit of normal (Study 2, nr-axSpA). Eligible study subjects for Study 1 and Study 2 must have a Bath Ankylosing Spondylitis Disease Activity Index score ≥ 4 and a Patient's Assessment of Total Back Pain score ≥ 4 based on a 0 – 10 numerical rating scale at the Screening and Baseline Visits. For Study 1 (bDMARD-IR AS), subjects must have been previously exposed to 1 or 2 biologic disease modifying antirheumatic drugs (bDMARDs) (at least 1 tumor necrosis factor [TNF] inhibitor or 1 interleukin [IL]-17 inhibitor), and the subject must have discontinued the bDMARD therapy due to either lack of efficacy (after at least 12 weeks of treatment with a bDMARD at an adequate dose) or intolerance (irrespective of treatment duration). Prior exposure to a 2nd bDMARD is allowed for no more than 30% of subjects. Subjects who have had lack of efficacy to 2 bDMARDs (including both a TNF inhibitor and IL-17 inhibitor) are not eligible. For Study 2 (nr-axSpA), subjects with prior failure of nonsteroidal anti-inflammatory drugs (NSAIDs) may be enrolled, and prior treatment with at

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	most 1 bDMARD (either 1 TNF inhibitor or 1 IL-17 inhibitor) is allowed in a subset of subjects (at least 20%, but not exceeding 35% of total enrolled subjects). Subjects who received prior treatment with a bDMARD must have discontinued the bDMARD due to either lack of efficacy (after at least 12 weeks of treatment with a bDMARD at an adequate dose) or intolerance (irrespective of treatment duration). Subjects who have had lack of efficacy to both a TNF inhibitor and IL-17 inhibitor are not eligible. Eligible subjects for Study 1 and Study 2 are to have had an inadequate response to at least 2 NSAIDs over an at least 4-week period in total at maximum recommended or tolerated doses or have an intolerance to or contraindication for NSAIDs as defined by the Investigator.
Study Drug and Duration of Treatment:	Upadacitinib 15 mg QD film-coated tablets for oral administration, 90 or 104 weeks in duration for Study 1 (bDMARD-IR AS) and 52 or 104 weeks in duration for Study 2 (nr-axSpA). Placebo for upadacitinib QD film-coated tablets for oral administration, 14 weeks in duration for Study 1 (bDMARD-IR AS) and 52 weeks in duration for Study 2 (nr-axSpA).
Date of Protocol Synopsis:	12 July 2021

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2 INTRODUCTION

2.1 Background and Rationale

Why Is This Study Being Conducted

Spondyloarthritis (SpA) is represented by a group of diseases that share common genetic, clinical, and radiographic features.[7,8] Adult SpA patients are commonly categorized by the 2 predominant manifestations of disease: either axial spondyloarthritis (axSpA), which primarily involves the spine and sacroiliac (SI) joints, or peripheral SpA, which primarily involves peripheral joints. Axial spondyloarthritis encompasses a spectrum of inflammatory involvement of the axial skeleton. Also, based on the Assessment of SpondyloArthritis international Society (ASAS) axSpA criteria, the disease can be further divided into 2 categories by radiographic findings: 1) non-radiographic axial spondyloarthritis (nr-axSpA), which is axSpA that does not meet the 1984 modified New York imaging criteria, and 2) ankylosing spondylitis (AS), which by definition meets the modified New York criteria.[9] Patients with nr-axSpA and AS share common epidemiological, genetic, and clinical disease characteristics, particularly with regard to disease activity, and similar response to treatment.[10,11] The presence of sacroiliitis on plain radiographs of at least Grade 2 bilateral or Grade 3 unilateral are required by the modified New York criteria for the classification of AS.

Per international treatment recommendations, nonsteroidal anti-inflammatory drugs (NSAIDs) are the first-line therapy in axSpA.[2,12] After failure of 2 NSAIDs given over a maximum of 4 weeks, biologic disease-modifying antirheumatic drugs (bDMARDs) are the next recommended treatment option. Analgesics are also considered standard of care treatment for patients with pain from axSpA and are in line with current treatment guidelines. In axSpA, conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) and long-term corticosteroids are not efficacious and therefore not recommended for treatment of axial symptoms.[2]

The prevalence of AS differs between regions and has been estimated to be up to 0.5%[13,14,15] with similar estimated prevalence rates for nr-axSpA, resulting in an overall prevalence for axSpA in the United States (US) of approximately up to 1% or even higher in the overall population.[16,17] In contrast to other regions of the world, the prevalence in Japan has only been estimated to be 0.0065%.[18]

There remains a significant unmet medical need in the treatment of axSpA as only approximately 45% to 50% of patients show an ASAS40 response and only approximately 15% to 20% achieve a state of remission in biologic-naïve patients, and response rates are even less in axSpA patients who had an inadequate response to bDMARDs (bDMARD-inadequate responders [bDMARD-IR]).[19,20,21,22] To date, there have been no oral targeted therapies approved for the treatment of axSpA. Data from patients with rheumatoid arthritis (RA) suggest that an oral therapy could provide a preferred administration alternative to injectable biologic medications.[23] Evidence from Phase 2 studies with the Janus kinase (JAK) inhibitors, tofacitinib or filgotinib, suggests that inhibition of JAK-mediated pathways may be a promising approach for the treatment of subjects with AS.[24,25]

More selective JAK inhibitors may decrease the risk for infection (including viral reactivation) and/or malignancy that are observed with pan JAK inhibitors or less selective JAK inhibitors. Upadacitinib is a novel oral selective and reversible JAK inhibitor being developed for axSpA and treatment of other

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immune-mediated inflammatory diseases including RA, Crohn's disease, ulcerative colitis, atopic dermatitis, psoriatic arthritis (PsA), giant cell arteritis, and juvenile idiopathic arthritis. In the Phase 2/3 study in AS (Study M16-098, SELECT-AXIS 1), the primary endpoint (ASAS40 at Week 14) was met with a statistically significantly higher ASAS40 response in the upadacitinib 15 mg once daily (QD) group compared to the placebo group.[26] Through Week 64, no new safety risks were identified.[1]

Per international treatment recommendations, the treatment goal in axial SpA is to achieve remission or Low Disease Activity (LDA).[2,3,12,27] One important clinical question in axial SpA patients who achieve clinical remission on a certain drug-treatment is whether the remission can be sustained even after the drug is withdrawn.

Clinical Hypothesis for Study 1 (bDMARD-IR AS)

Upadacitinib is expected to provide better efficacy compared to placebo and is expected to be well tolerated in adult subjects with active AS who are bDMARD-IR.

Clinical Hypothesis for Study 2 (nr-axSpA)

Upadacitinib is expected to provide better efficacy compared to placebo and is expected to be well tolerated in adult subjects with active nr-axSpA.

Rationale for Master Protocol Approach

Study Protocol M19-944 is a global, multicenter, protocol ("master protocol") with a common screening platform for determining subject eligibility into 2 separate studies with many overlapping eligibility criteria within the same protocol. The ability to use a common screening platform is considered to be one of the main advantages of incorporating these 2 studies into a single protocol, resulting in a decreased patient burden during screening and a more efficient recruitment of subjects and use of resources. A subject who is a bDMARD-IR in screening may be eligible for and randomized into 1 of the 2 studies without the need to screen-fail and rescreen for the other study. The requirement for subjects to meet the modified New York criteria using confirmation of radiographic evidence by a central reader is necessary for eligibility into the AS study; however, those subjects who do not meet these radiographic criteria may still be eligible for the nr-axSpA study.

Although this protocol includes a common screening process and other operational elements (Appendix G) for Study 1 and Study 2, randomization and data collection will be conducted for each study independently. There is no overlap in subject population, nor is there a shared control group. Each study has its own objective, hypothesis testing, and adequate power for primary and secondary endpoints. The analyses and reporting for the 2 studies will therefore be separate. The success of each study in its corresponding subject population will be determined separately and independently of the other study. Each study represents a standalone study for regulatory purposes with the ability to report interim and final data independently.

2.2 Benefits and Risks to Subjects

Primary results from the ongoing upadacitinib Phase 2/3 Study M16-098 (SELECT-AXIS 1) in bDMARD-naïve AS demonstrated superior efficacy of upadacitinib with an acceptable safety profile at the selected dose for Phase 3 (15 mg QD) compared to placebo (data on file). Since AS and nr-axSpA are

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conditions along the spectrum of axSpA and patients with either condition share similar disease characteristics and similar response to treatment (see Section 2.1),[10,11] it is expected that the safety profiles of upadacitinib in the bDMARD-IR AS and nr-axSpA populations would be similar.[28] The available long-term safety data from the Phase 3 RA studies with upadacitinib did not show any new significant safety concerns compared to the marketed JAK inhibitors.[29] The findings of an increased risk of infections, herpes zoster, and abnormal laboratory changes have been observed (e.g., increases in serum transaminases, lipids, and creatine phosphokinase [CPK], small mean decreases from Baseline in hemoglobin, and small mean changes from Baseline in absolute lymphocyte count [ALC]) with upadacitinib therapy. The incidence rates of other clinically important adverse events (AEs) such as cardiovascular events, malignancies, and mortality reported during the RA studies were within the expected range for the general population or for a population of patients with moderately to severely active RA.[30] Events of deep vein thrombosis and pulmonary embolism have been reported in patients receiving JAK inhibitors including upadacitinib.

When treated with available therapies, safety events are typically fewer in AS patients compared to RA or PsA patients.[28,31,32,33] The reason for fewer safety events might be due to the fact that patients with axSpA are, on average, younger, use fewer concomitant immunosuppressants given that corticosteroids and csDMARDs are not efficacious and not recommended for the treatment of axial symptoms (see Section 2.1), and generally have fewer comorbidities such as hypertension, hypercholesterolemia, or diabetes.[34,35]

The results of genetic toxicology testing indicate that upadacitinib is not genotoxic; however, upadacitinib is teratogenic based on animal studies, which necessitates avoidance of pregnancy in females of childbearing potential. Based on the calculated safety margins for human fetal exposure with seminal fluid transfer, there is judged to be no risk to the pregnancy of female partners of male subjects who are treated with upadacitinib.

A detailed discussion of the pre-clinical and clinical toxicology, metabolism, pharmacology, and safety experience with upadacitinib can be found in the current Investigator's Brochure.[30]

Taken together, the safety and efficacy data from upadacitinib studies to date show a favorable benefit:risk profile for upadacitinib and support the continued investigation of upadacitinib in adult subjects with active axSpA including bDMARD-IR AS (Study 1) and nr-axSpA (Study 2).

In view of the coronavirus disease 2019 (COVID-19) pandemic, the benefit:risk profile of various immunomodulatory therapies on COVID-19 is being evaluated. At this time, the effects of upadacitinib on the course of COVID-19 are not well defined.

3 OBJECTIVES AND ENDPOINTS

3.1 Objectives

Double-Blind Period:

- To evaluate the efficacy of upadacitinib compared with placebo on reduction of signs and symptoms in adult subjects with active axSpA including bDMARD-IR AS (Study 1) and nr-axSpA (Study 2);

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- To assess the safety and tolerability of upadacitinib in adult subjects with active axSpA including bDMARD-IR AS (Study 1) and with nr-axSpA (Study 2).

Open-Label Extension Period:

To evaluate the safety and tolerability of upadacitinib in extended treatment in adult subjects with active axSpA including bDMARD-IR AS who have completed the Double-Blind Period (Study 1) and with nr-axSpA who have completed the Double-Blind Period (Study 2).

Remission-Withdrawal Period:

To evaluate the maintenance of disease control after withdrawal of upadacitinib [redacted]

3.2 Primary Endpoint

Study 1 (bDMARD-IR AS):

The primary endpoint is ASAS40 response at Week 14.

Study 2 (nr-axSpA):

The primary endpoint is ASAS40 response at Week 14.

3.3 Secondary Endpoints

Study 1 (bDMARD-IR AS):

The multiplicity-controlled secondary endpoints at Week 14 are:

1. Change from Baseline in Ankylosing Spondylitis Disease Activity Score (ASDAS);
2. Change from Baseline in magnetic resonance imaging (MRI) Spondyloarthritis Research Consortium of Canada (SPARCC) score (spine);
3. Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) 50 response;
4. ASAS20 response;
5. ASDAS Inactive Disease (ID) (ASDAS score < 1.3);
6. Change from Baseline in Patient's Assessment of Total Back Pain (Total Back Pain);
7. Change from Baseline in Patient's Assessment of Nocturnal Back Pain (Nocturnal Back Pain);
8. ASDAS LDA (ASDAS score < 2.1);
9. Change from Baseline in Bath Ankylosing Spondylitis Functional Index (BASFI);
10. ASAS partial remission (PR) (an absolute score of ≤ 2 units for each of the 4 domains identified in ASAS40);
11. Change from Baseline in Ankylosing Spondylitis Quality of Life (ASQoL);

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12. Change from Baseline in ASAS Health Index (HI);
13. Change from Baseline in Linear Bath Ankylosing Spondylitis Metrology Index ($BASMI_{lin}$);
14. Change from Baseline in Maastricht Ankylosing Spondylitis Enthesitis Score (MASES).

Additional secondary endpoint at Week 14:

- Change from Baseline in MRI SPARCC score (SI joints).

Study 2 (nr-axSpA):

The multiplicity-controlled secondary endpoints at Week 14 (unless otherwise noted) are:

1. Change from Baseline in ASDAS;
2. Change from Baseline in MRI SPARCC score (SI joints);
3. BASDAI 50 response;
4. ASDAS ID (ASDAS score < 1.3);
5. Change from Baseline in Patient's Assessment of Total Back Pain (Total Back Pain);
6. Change from Baseline in Patient's Assessment of Nocturnal Back Pain (Nocturnal Back Pain);
7. ASDAS LDA (ASDAS score < 2.1);
8. ASAS PR (an absolute score of ≤ 2 units for each of the 4 domains identified in ASAS40);
9. Change from Baseline in BASFI;
10. Change from Baseline in ASQoL;
11. Change from Baseline in ASAS HI;
12. ASAS20 response;
13. Change from Baseline in $BASMI_{lin}$;
14. Change from Baseline in MASES;
15. ASAS40 response at Week 52 (for European Union [EU]/European Medicines Agency [EMA] regulatory purposes).

For US/Food and Drug Administration (FDA) regulatory purposes, the last multiplicity-controlled secondary endpoint is change from Baseline in MASES.

Additional secondary endpoints are:

- Change from Baseline in MRI SPARCC score (spine) at Week 14;
- Initiation of rescue between Week 24 and Week 52;
- ASDAS Major Improvement (a change from Baseline of ≤ –2.0) at Week 52 (for EU/EMA regulatory purposes);

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- ASDAS ID (ASDAS score < 1.3) at Week 52 (for EU/EMA regulatory purposes);
- ASDAS LDA (ASDAS score < 2.1) at Week 52 (for EU/EMA regulatory purposes).

3.4 Additional Endpoints

Study 1 (bDMARD-IR AS):

Additional endpoints are the following measurements assessed at scheduled time points other than those specified for the primary and secondary endpoints:

Binary variables:

- ASAS20 response;
- ASAS40 response;
- BASDAI 50 response;
- ASAS PR;
- ASDAS ID (ASDAS score < 1.3);
- ASDAS LDA (ASDAS score < 2.1);
- ASDAS Major Improvement (a change from Baseline of ≤ –2.0);
- ASDAS Clinically Important Improvement (a change from Baseline of ≤ –1.1);
- Discontinuation of opioids among subjects with opioid use at Baseline.

Change from Baseline in:

- ASAS HI;
- ASDAS;
- ASQoL;
- BASDAI and BASDAI components including mean of question 5 and 6 of the BASDAI;
- BASFI;
- $BASMI_{lin}$;
- High sensitivity C-reactive protein (hsCRP);
- EuroQoL-5D-5L (EQ-5D-5L);
- Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F);
- MASES;
- Modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) with conventional radiograph;
- MRI SPARCC score of SI joints;
- MRI SPARCC score of spine;

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- Patient's Assessment of Total Back Pain (Total Back Pain);
- Patient's Assessment of Nocturnal Back Pain (Nocturnal Back Pain);
- Patient's Global Assessment of Pain;
- Physician's Global Assessment of Disease Activity (PGA);
- Patient's Global Assessment of Disease Activity (PtGA);
- 36-Item Short Form Health Survey (SF-36);
- Tender joint count (TJC) and swollen joint count (SJC);
- Work Productivity and Activity Impairment (WPAI);
- NSAID score;
- Physical Activity Assessment (step count, physical activity, and spinal range of motion tasks) as measured by a wearable device (except in countries where the digital health technology device is not available or is not allowed to be used in the study by the local regulatory authority).

Additional endpoint relating to the assessment of disease flare for subjects on upadacitinib treatment who achieve an ASDAS C-reactive protein (CRP) < 1.3 at Week 52 and an ASDAS (CRP) < 2.1 at Week 40:

- Time to flare during Week 52 to Week 104

Study 2 (nr-axSpA):

Additional endpoints are the following measurements assessed at scheduled time points other than those specified for the primary and secondary endpoints:

Binary variables:

- ASAS20 response;
- ASAS40 response;
- BASDAI 50 response;
- ASAS PR;
- ASDAS ID (ASDAS score < 1.3);
- ASDAS LDA (ASDAS score < 2.1);
- ASDAS Major Improvement (a change from Baseline of ≤ –2.0);
- ASDAS Clinically Important Improvement (a change from Baseline of ≤ –1.1);
- Discontinuation of opioids among subjects with opioid use at Baseline.

Change from Baseline in:

- ASAS HI;
- ASDAS;

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- ASQoL;
- BASDAI and BASDAI components including mean of question 5 and 6 of the BASDAI;
- BASFI;
- $BASMI_{lin}$;
- hsCRP;
- EQ-5D-5L;
- FACIT-F;
- MASES;
- mSASSS with conventional radiograph;
- MRI SPARCC score of SI joints;
- MRI SPARCC score of spine;
- Total Back Pain;
- Nocturnal Back Pain;
- Patient's Global Assessment of Pain;
- PGA;
- PtGA;
- SF-36;
- TJC and SJC;
- WPAI;
- NSAID score.

Additional endpoint relating to the assessment of disease flare for subjects in the upadacitinib group who achieved an ASDAS (CRP) < 1.3 at Week 52 and an ASDAS (CRP) < 2.1 at Week 40:

- Time to flare during Week 52 to Week 104

Study 1 and Study 2: Remission-Withdrawal Period

Additional endpoint relating to the assessment of disease flare:

- Time to flare during the withdrawal period

Additional endpoints assessed at scheduled visits during the withdrawal period:

Binary variables:

- ASDAS (CRP) ID/LDA
- ASDAS (CRP) Major Improvement/Clinically Important Improvement

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- ASAS 40/20/PR
- BASDAI 50

Change from baseline (of Double-Blind Period) in:

- ASDAS (CRP) (and components)
- BASDAI (and components)
- Total back pain
- BASFI
- PtGA
- Patient's Global Assessment of Pain
- Nocturnal back pain
- ASAS HI
- TJC/SJC
- $BASMI_{lin}$
- MASES
- PGA

Additional endpoints assessed at scheduled visits during re-treatment of upadacitinib after disease flare:

Binary variables:

- ASDAS (CRP) ID/LDA
- ASDAS (CRP) Major Improvement/Clinically Important Improvement
- ASAS 40/20/PR
- BASDAI 50

Change from re-treatment baseline (i.e., at the time of flare) in:

- ASDAS (CRP) (and components)
- BASDAI (and components)
- Total back pain
- BASFI
- PtGA
- Patient's Global Assessment of Pain
- Nocturnal back pain
- ASAS HI

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- TJC/SJC
- $BASMI_{lin}$
- MASES
- PGA

3.5 Patient Experience Data (PED)

PED will be collected for Study 1 and Study 2 at each subject's Baseline Visit only.

3.6 Safety Endpoints

Study 1 and Study 2 will be analyzed and reported independently for safety. The following safety evaluations will be performed during Study 1 and Study 2: treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), AE of special interest (AESI), AEs leading to discontinuation, vital signs, laboratory tests, and physical examination findings.

3.7 Pharmacokinetic Endpoints

Study 1 and Study 2 will be analyzed and reported independently for pharmacokinetic (PK) endpoints. PK samples will be collected from approximately 30% of subjects at select sites at the visits indicated in Appendix D. Using the data available from these subjects, a nonlinear mixed-effects modeling approach will be used to estimate the population central values and the empirical Bayesian estimates of the individual values of upadacitinib oral clearance (CL/F) and apparent volume of distribution (V/F). Additional parameters may be estimated if useful in the interpretation of the data. Data from these studies may be combined with data from other studies for the population PK analyses.

3.8 Biomarker Research

Optional samples for biomarker research will be collected in Study 1 and Study 2 as described in Appendix D to evaluate known and/or novel disease-related or drug-related biomarkers. Types of biomarkers may include nucleic acids, proteins, lipids, and/or metabolites. The objective of the research is to analyze samples for biomarkers that will help to understand axSpA, related conditions, and response to treatment with upadacitinib or similar compounds. Research may also include changes in epigenetics, gene expression, and proteomics that may associate with axSpA, related conditions, or the subject's response to treatment. This research is exploratory in nature, and the results may not be included with clinical study reports.

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4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a global Phase 3, multicenter, protocol with a common screening platform and other operational elements of study conduct. The master protocol includes 2 independent studies for subjects with active axSpA including bDMARD-IR AS (Phase 3 study, Study 1) and nr-axSpA (Phase 3 study, Study 2).

Although this protocol includes a common screening process and other operational elements of study conduct for Study 1 and Study 2, randomization and data collection will be conducted for each study independently. The analyses and reporting for the 2 studies will also be separate. Each study represents a standalone study which may be reported individually for regulatory purposes.

Study 1 (bDMARD-IR AS) is comprised of a 35-day Screening Period; a 14-week randomized, double-blind, parallel-group, placebo-controlled period (the Double-Blind Period); a 90-week open-label, long-term extension period (the Open-Label Extension Period); and a 30-day Follow-Up Visit (F/U Visit).

Study 2 (nr-axSpA) is comprised of a 35-day Screening Period; a 52-week randomized, double-blind, parallel-group, placebo-controlled period (the Double-Blind Period); a 52-week open-label, long-term extension period (the Open-Label Extension Period); and a 30-day F/U Visit.

For both studies, a 30-day F/U phone call may be performed in place of a visit to determine the status of any ongoing AEs/SAEs or the occurrence of any new AEs/SAEs is required; these subjects will be considered as having completed the study.

Up to and including Week 14 of each study, a ± 3 day window is permitted around scheduled study visits. After Week 14 of each study, a ± 7 day window is permitted around scheduled study visits. If a subject has an out of window visit, the next visit should occur as originally scheduled based on the first date of study drug administration (Baseline Visit).

In the Double-Blind Period, subjects will be randomized in a 1:1 ratio to 1 of 2 treatment groups:

Study 1 (bDMARD-IR AS):

- Group 1: upadacitinib 15 mg QD (N = 193)
- Group 2: placebo QD (N = 193)

Study 2 (nr-axSpA):

- Group 1: upadacitinib 15 mg QD (N = 152)
- Group 2: placebo QD (N = 152)

Subjects in the placebo group will be switched to upadacitinib 15 mg QD at Week 14 in the Open-Label Extension Period for Study 1 (bDMARD-IR AS) and to upadacitinib 15 mg QD at Week 52 in the Open-Label Extension Period for Study 2 (nr-axSpA).

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The AbbVie study team will be unblinded to perform the Week 14 primary analysis for both studies. Reporting will be performed independently for Study 1 and Study 2. For Study 1 and Study 2, the unblinding will take place after all subjects in the study have completed the Week 14 visit or have prematurely discontinued prior to Week 14. For both Study 1 and Study 2, sites and subjects will remain blinded to the Double-Blind Period treatment assignments for the duration of the study.

Information on the Data Monitoring Committee (DMC) and Cardiovascular Adjudication Committee (CAC) are described in Section 6.3 and Section 6.1, respectively.

See Section 5 for information regarding eligibility criteria and Section 5.8 for information on stratification.

The schematic of Study 1 and Study 2 is shown in Figure 1. Further details regarding study procedures are located in the operations manual (Appendix G).

Remission-Withdrawal Period

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, [redacted]

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. [redacted] 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 (See Appendix F for more details).

Subjects who do not flare, will be followed without upadacitinib treatment until Week 152.

Subjects who are not in remission at Week 104 will complete the study after the 30 day follow up visit OR, if applicable, will have the option to enter open-label treatment with upadacitinib until a predefined time period only per local country requirements (See Appendix F).

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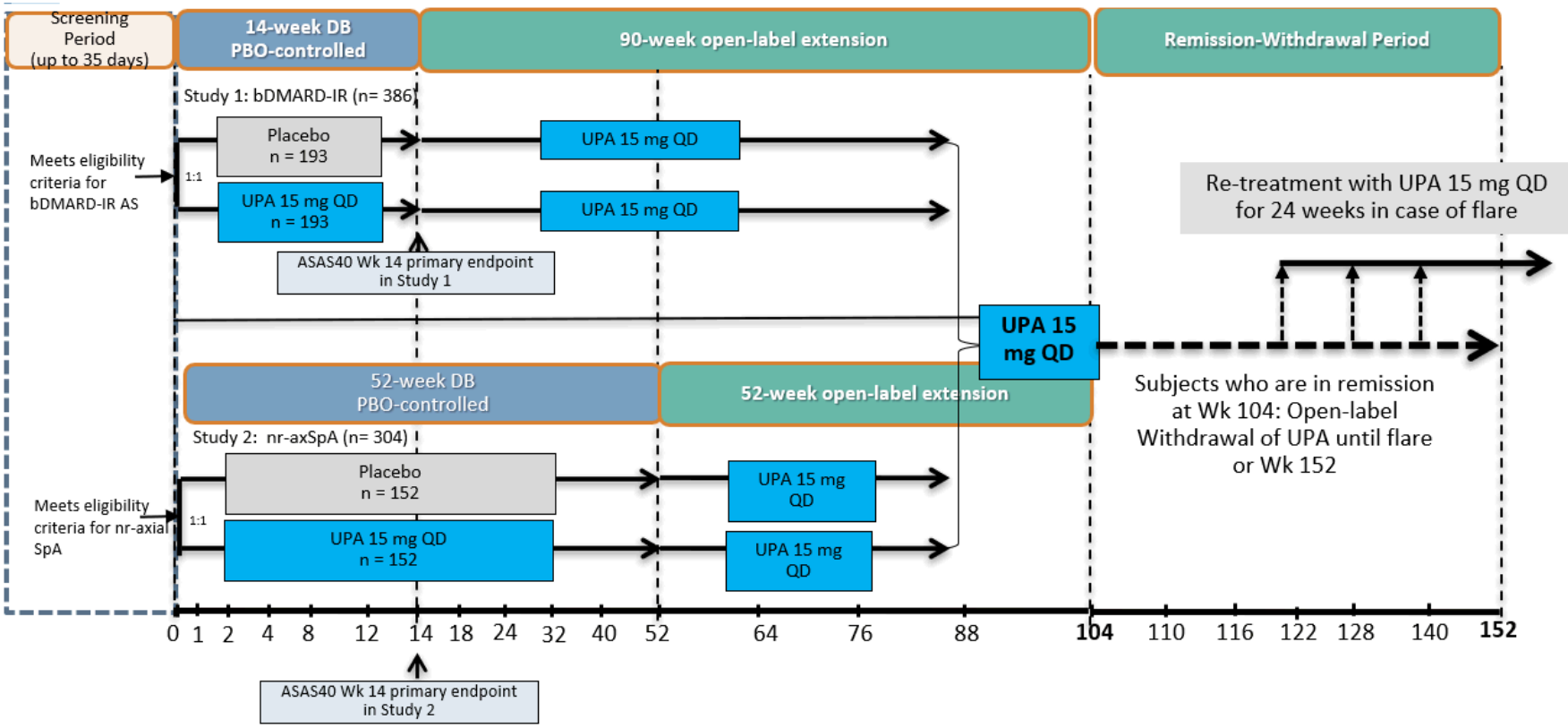
Figure 1. Study Schematic



AS = ankylosing spondylitis; ASAS = Assessment of SpondyloArthritis International Society; DB = double-blind; bDMARD-IR = biologic disease-modifying antirheumatic drug inadequate responder; MRI = magnetic resonance imaging; nr-axSpA = non-radiographic axial spondyloarthritis; PBO = placebo; QD = once daily; SI = sacroiliac; UPA = upadacitinib; Wk = week

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4.2 Discussion of Study Design

Master Protocol Design

The Study M19-944 master protocol utilizes a common screening platform to operationally streamline the screening and enrollment of similar but noncompeting subject populations into independent studies within the master protocol. Please refer to Section 2.1 for the rationale for the master protocol approach.

Choice of Control Group

Placebo control will be used in Study 1 and Study 2. Comparative studies utilizing a double-blind, placebo-control design provides an unbiased assessment of the efficacy and safety profile of upadacitinib.

Appropriateness of Measurements

Standard statistical, clinical, and laboratory procedures will be utilized in Study 1 and Study 2. All efficacy measurements are standard for assessing disease activity in subjects with AS or nr-axSpA. All clinical and laboratory procedures are standard and generally accepted.

Suitability of Subject Population

The intended study populations are subjects with active AS who are bDMARD-IR (Study 1) or with active nr-axSpA (Study 2). These 2 specific populations chosen were based on the unmet medical need of these subjects. Key entry criteria are to enroll adult female and male subjects who are at least 18 years of age with a clinical diagnosis of AS, meet the modified New York Criteria for AS, and are without total spinal ankylosis (Study 1) or with a clinical diagnosis of nr-axSpA fulfilling the 2009 ASAS classification criteria for axSpA but not meeting the radiologic criterion of the modified New York criteria for AS and have objective signs of active inflammation on MRI of SI joints or based on hsCRP > upper limit of normal (ULN) (Study 2). Eligible study subjects for both studies must have a BASDAI score ≥ 4 and a Total Back Pain score ≥ 4 based on a 0 – 10 numerical rating scale (NRS) at the Screening and Baseline Visits. Subjects who enter a study on permitted concomitant medication(s) must have been on a stable dose for the amount of time specified in the eligibility criteria (Section 5.1) prior to the Baseline Visit.

Selection of Doses in the Study

Study 1 and Study 2 will evaluate 1 dose of upadacitinib (15 mg QD) versus placebo. Dose selection was informed by results of the Phase 2/3 study of upadacitinib in AS (Study M16-098, SELECT-AXIS 1) including exposure-response analyses from that study, as well as the results from the exposure-response analyses conducted based on data from upadacitinib Phase 2 and Phase 3 studies in RA (Studies M13-537, M13-550, M13-549, M13-542, M15-555, M14-465, and M13-545).

In Study M16-098, upadacitinib 15 mg QD was studied versus placebo over a period of 14 weeks in subjects with active AS who failed treatment with NSAIDs and who were bDMARD-naïve. The study met its primary endpoint, ASAS40 response at Week 14. No new safety risks were identified in this study. Efficacy and safety data in Japanese subjects were overall consistent with global data in this study.

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Exposure-response relationships between upadacitinib plasma exposures (average concentrations [C_{avg}]) and ASAS response rates (i.e., ASAS20 and ASAS40) and safety variables (i.e., herpes zoster infections; pneumonia; any infection; serious infections; decrease in hemoglobin, lymphocytes, or neutrophils from Baseline; and increase in platelet counts from Baseline) were evaluated using data from Study M16-098. Results of these analyses showed that upadacitinib C_{avg} values with the 15 mg QD dose were associated with higher ASAS20 and ASAS40 response rates compared to placebo, with no evidence of exposure-dependent increase in ASAS20 or ASAS40 response within subjects treated with upadacitinib.[36] These results indicate that upadacitinib exposures resulting from the 15 mg QD dose maximize efficacy in subjects with AS.

Similarly, evaluation of exposure-response relationships between upadacitinib plasma exposures and safety variables indicated no exposure-dependent changes in the occurrence of safety events, except for decrease in hemoglobin levels by > 1 g/dL compared to Baseline. Similar to results previously observed in subjects with RA, higher upadacitinib exposures (especially those associated with the 30 mg QD dose) were associated with higher incidence of hemoglobin decrease of > 1 g/dL.

Overall, results from Study M16-098 (including exposure-response evaluations) indicate that upadacitinib 15 mg QD provides the optimal balance of efficacy and safety in treatment of AS.

Likewise, exposure-response analyses of upadacitinib Phase 2 and 3 studies in RA have previously shown that upadacitinib 15 mg QD dosing result in near maximal efficacy in RA, with 30 mg QD dosing resulting in only modest incremental efficacy benefit (≤ 5% increase in American College of Rheumatology or LDA/clinical remission responses from 15 mg QD to 30 mg QD across all populations).[37] More importantly, these results were consistent across subjects with inadequate response to a csDMARD (csDMARD-IR) and bDMARD-IR populations and whether upadacitinib is used as monotherapy or on background treatment of csDMARDs.

Overall, AS patients and nr-axSpA patients show similar and comparable response to treatment. For this reason, treatment recommendations were published for axSpA as a whole including AS and nr-axSpA.[19,38,39] Based on the historically similar treatment responses in AS patients and nr-axSpA patients, and the consistent benefit:risk profile for upadacitinib 15 mg QD dose across the different RA populations, the 15 mg QD dose was selected for both AS and nr-axSpA populations and is expected to provide optimal benefit:risk balance.

5 STUDY ACTIVITIES

5.1 Eligibility Criteria

Subjects must meet all of the following criteria specific to each study in order to be included in the study.

Study 1: bDMARD-IR AS specific criteria:

- 1. Subject must have a clinical diagnosis of AS and subjects must meet the modified New York criteria for AS.
- 2. Subject must not have total spinal ankylosis.

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- 3. Subject must have been previously exposed to 1 or 2 bDMARDs (at least 1 tumor necrosis factor [TNF] inhibitor or 1 interleukin [IL]-17 inhibitor), and the subject must have discontinued the bDMARD therapy due to either lack of efficacy (after at least 12 weeks of treatment with a bDMARD at an adequate dose) or intolerance (irrespective of treatment duration). Prior exposure to a 2nd bDMARD is allowed for no more than 30% of subjects. Subjects who have had lack of efficacy to 2 bDMARDs (including both a TNF inhibitor and IL-17 inhibitor) are not eligible.

Study 2: nr-axSpA-specific criteria:

- 4. Subject must have a clinical diagnosis of nr-axSpA fulfilling the 2009 ASAS classification criteria for axSpA but not meeting the radiologic criterion of the modified New York criteria for AS.
- 5. Subjects with or without prior exposure to a bDMARD may be enrolled.
  - For the subset of subjects with prior bDMARD exposure (at least 20%, but not exceeding 35% of total enrolled subjects), prior treatment with at most 1 bDMARD (either 1 TNF inhibitor or 1 IL-17 inhibitor) is allowed, and the subject must have discontinued the bDMARD due to either lack of efficacy (after at least 12 weeks of treatment with a bDMARD at an adequate dose) or intolerance (irrespective of treatment duration). Subjects who have had lack of efficacy to both a TNF inhibitor and IL-17 inhibitor are not eligible.
- 6. Subject must have objective signs of active inflammation consistent with axSpA on MRI of SI joints or hsCRP > ULN at Screening.

The following eligibility criteria are applicable for Study 1 and Study 2:

Consent and Demographics

- 7. Subject must be able to understand and willing to adhere to all protocol requirements and voluntarily sign and date an informed consent, approved by an Independent Ethics Committee (IEC)/institutional review board (IRB), prior to the initiation of any screening or study-specific procedures.
- 8. Subject must be an adult male or female, at least 18 years of age at Screening.

Disease Activity and Prior and Concomitant Treatment

- 9. Subject must meet the following scores at Screening and Baseline Visits:
  - BASDAI score ≥ 4 and
  - Total Back Pain score ≥ 4 based on a 0 – 10 NRS.
- 10. Subject has had an inadequate response to at least 2 NSAIDs over an at least 4-week period in total at maximum recommended or tolerated doses, or subject has an intolerance to or contraindication for NSAIDs as defined by the Investigator.
- 11. The washout period for biologics prior to the first dose of study drug is specified below:
  - ≥ 4 weeks for etanercept;

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- ≥ 8 weeks for adalimumab, infliximab, certolizumab, golimumab, abatacept, tocilizumab, and ixekizumab;
- ≥ 12 weeks for ustekinumab;
- ≥ 16 weeks for secukinumab;
- ≥ 1 year for rituximab OR ≥ 6 months if B cells have returned to pre-treatment level or normal reference range (central lab) if pre-treatment levels are not available;
- ≥ 12 weeks or at least 5 times the mean terminal elimination half-life, whichever is longer, for other biologics.

12. If entering the study on the following concomitant csDMARDs, subject must be on a stable dose as indicated below for at least 28 days prior to the Baseline Visit. A combination of up to 2 background csDMARDs is allowed EXCEPT the combination of methotrexate (MTX) and leflunomide.
    - MTX (≤ 25 mg/week); or
    - Sulfasalazine (≤ 3 g/day); or
    - Hydroxychloroquine (≤ 400 mg/day); or
    - Chloroquine (≤ 400 mg/day); or
    - Leflunomide (≤ 20 mg/day); or
    - Apremilast (≤ 60 mg/day).
13. If entering the study on concomitant oral corticosteroids, subject must be on a stable dose of prednisone (≤ 10 mg/day) or oral corticosteroid equivalent for at least 14 days prior to the Baseline Visit.
14. If entering the study on concomitant NSAIDs, tramadol, combination of acetaminophen/paracetamol and codeine or combination of acetaminophen/paracetamol and hydrocodone, and/or non-opioid analgesics, subject must be on stable dose(s) for at least 14 days prior to the Baseline Visit.
15. Subject must not have been exposed to any JAK inhibitor (including but not limited to upadacitinib [Rinvoq®], tofacitinib [Xeljanz®], baricitinib [Olumiant®], filgotinib, ruxolitinib [Jakafi®], abrocitinib [PF-04965842], and peficitinib [Smyraf®]).
16. Subject must not have used the following prohibited concomitant treatments within the specified timeframe prior to Baseline Visit:
    - Intra-articular joint injections, spinal/paraspinal injection(s), or parenteral administration of corticosteroids (including intramuscular and intravenous injections) within 28 days prior to the Baseline Visit. Inhaled or topical corticosteroids are allowed;
    - Any other csDMARDs (other than those allowed per eligibility criterion 12), including thalidomide, within 28 days or 5 half-lives (whichever is longer) of the drug prior to the Baseline Visit;
    - Opioid analgesics (except for combination of acetaminophen/paracetamol and codeine or combination of acetaminophen/paracetamol and hydrocodone which are allowed) within 14 days prior to the Baseline Visit.

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- 17. Subject must not have received a live vaccine within 28 days (or longer if required locally) prior to the first dose of study drug or have expected need of live vaccination during study participation including at least 30 days (or longer if required locally) after the last dose of study drug.
- 18. Subject must have no systemic use of known strong cytochrome P450 3A (CYP3A) inhibitors from Screening through the end of study drug administration or strong CYP3A inducers 30 days prior to study drug administration through the end of study drug administration (refer to Table 1 is Section 5.3 for examples of commonly used strong CYP3A inhibitors and inducers). Subjects must not use herbal therapies or other traditional medicines with unknown effects on CYP3A from Screening through the end of study drug administration.
- 19. Subject must not have been treated with any investigational drug of chemical or biologic nature within a minimum of 30 days or 5 half-lives of the drug (whichever is longer) prior to the first dose of study drug or is currently enrolled in another interventional study.
- 20. Subject must not have a history of an allergic reaction or significant sensitivity to constituents of the study drug (and its excipients) and/or other products in the same class.

Contraception

- 21. For all females of childbearing potential: must not have a positive serum pregnancy test at the Screening Visit and must have a negative urine pregnancy test at Baseline prior to the first dose of study drug (local practices may require serum pregnancy testing at Baseline). Subjects with a borderline pregnancy test at Screening must have absence of clinical suspicion of pregnancy or other pathological causes of borderline results and a serum pregnancy test ≥ 3 days later to document continued lack of a positive result (unless prohibited by local requirements).
- 22. Female subjects of childbearing potential must practice at least 1 protocol-specified method of birth control that is effective from Study Day 1 through at least 30 days after the last dose of study drug (local practices may require 2 methods of birth control). Female subjects of non-childbearing potential do not need to use birth control.
- 23. Females must not be pregnant, breastfeeding, or considering becoming pregnant during the study or for approximately 30 days after the last dose of study drug.

Laboratory Values

- 24. Laboratory values must meet the following criteria within the Screening Period prior to the first dose of study drug:
  - Serum aspartate transaminase (AST) ≤ 2 × ULN;
  - Serum alanine aminotransferase (ALT) ≤ 2 × ULN;
  - eGFR by simplified 4-variable Modification of Diet in Renal Disease (MDRD) formula ≥ 30 mL/min/1.73 m^2;
  - Total white blood cell (WBC) count ≥ 2,500/µL;
  - Absolute neutrophil count (ANC) ≥ 1,200/µL;

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- Platelet count ≥ 100,000/µL;
- ALC ≥ 750/µL;
- Hemoglobin ≥ 9 g/dL.

Subject History

- 25. Subject is judged to be in good health as determined by the Principal Investigator, based upon the results of medical history, laboratory profile, physical examination, chest x-ray (CXR), and a 12-lead electrocardiogram (ECG) performed during Screening.
- 26. Subject must not have a history of clinically significant (per Investigator's judgment) drug or alcohol abuse within the last 6 months.
- 27. Subject must have no current or past history of infection including:
  - Recurrent or disseminated (even a single episode) herpes zoster;
  - Disseminated (even a single episode) herpes simplex;
  - Human immunodeficiency virus (HIV) defined as confirmed positive anti-HIV antibody (Ab) test;
  - Active tuberculosis (TB) or meets TB exclusionary parameters (specific requirements for TB testing are provided in Section 5.10);
  - For subjects in Japan only: Positive result of beta-D-glucan (screening for pneumocystis jirovecii infection) or 2 consecutive indeterminate results of beta-D-glucan during the Screening Period;
  - Active infection(s) requiring treatment with intravenous anti-infectives within 30 days, or oral/intramuscular anti-infectives within 14 days prior to the Baseline Visit;
  - Chronic recurring infection and/or active viral infection that, based on the Investigator's clinical assessment, makes the subject an unsuitable candidate for the study;
  - Confirmed COVID-19: the Baseline Visit must be at least 14 days from onset of signs/symptoms or positive SARS-CoV-2 test; symptomatic subjects must have recovered, defined as resolution of fever without use of antipyretics and improvement in symptoms;
  - Suspected COVID-19: subjects with signs/symptoms suggestive of COVID-19, known exposure, or high risk behavior should undergo molecular (e.g., polymerase chain reaction [PCR]) testing to rule out SARS-CoV-2 infection or must be asymptomatic for 14 days from a potential exposure;
  - Subject must not have evidence of:
    - Hepatitis B virus (HBV): hepatitis B surface antigen (HBs Ag) positive (+) test or detected sensitivity on the HBV DNA PCR qualitative test for subjects who are hepatitis B core Ab (HBc Ab) positive (+) (and for Hepatitis B surface Ab positive [+] subjects where mandated per local requirements);
    - Hepatitis C virus (HCV): HCV RNA detectable in any subject with anti-HCV Ab.

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- 28. Subject must not have any of the following medical diseases or disorders:
  - Recent (within past 6 months) cerebrovascular accident, myocardial infarction, coronary stenting;
  - History of an organ transplant which requires continued immunosuppression;
  - History of gastrointestinal (GI) perforation (other than appendicitis or mechanical injury), diverticulitis, or significantly increased risk for GI perforation per Investigator judgment;
  - Conditions that could interfere with drug absorption including but not limited to short bowel syndrome or gastric bypass surgery; subjects with a history of gastric banding/segmentation are not excluded;
  - History of any malignancy except for successfully treated non-melanoma skin cancer (NMSC) or localized carcinoma in situ of the cervix;
  - History of inflammatory arthritis of different etiology other than axial SpA (including but not limited to RA, PsA, mixed connective tissue disease, systemic lupus erythematosus, reactive arthritis, scleroderma, polymyositis, dermatomyositis), or any arthritis with onset prior to 17 years of age;
  - Fibromyalgia (currently with active symptoms);
  - Extra-articular manifestations (e.g., psoriasis, uveitis, or inflammatory bowel disease) that are not clinically stable for at least 30 days prior to study entry.
- 29. There must be no reason the Investigator believes that the subject is an unsuitable candidate to participate in the study or receive study drug or would place the subjects at risk by participating in the study.

Remission-Withdrawal Period Specific Criteria:

[redacted]

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5.2 Contraception Recommendations

Contraception Requirements for Females Only

Subjects must follow the following contraceptive guidelines as specified:

- Females, Non-Childbearing Potential
  - Females do not need to use birth control during or following study drug treatment if considered of non-childbearing potential due to meeting any of the following criteria:
    - Postmenopausal, age > 55 years with no menses for 12 or more months without an alternative medical cause.
    - Postmenopausal, age ≤ 55 years with no menses for 12 or more months without an alternative medical cause AND a follicle-stimulating hormone (FSH) level > 40 IU/L.
    - Permanently surgically sterile (bilateral oophorectomy, bilateral salpingectomy, or hysterectomy).
- Females of Childbearing Potential
  - Females of childbearing potential must avoid pregnancy while taking study drug and for at least 30 days after the last dose of study drug. Females must commit to one of the following methods of birth control:
    - Combined (estrogen- and progestogen-containing) hormonal birth control (oral, intravaginal, transdermal, injectable) associated with inhibition of ovulation initiated at least 30 days prior to study Baseline Day 1.
    - Progestogen-only hormonal birth control (oral, injectable, implantable) associated with inhibition of ovulation initiated at least 30 days prior to study Baseline Day 1.
    - Bilateral tubal occlusion/ligation (can be via hysteroscopy, provided a hysterosalpingogram confirms success of the procedure) (For Japan: bilateral tubal ligation).
    - Intrauterine device.
    - Intrauterine hormone-releasing system.
    - Vasectomized sexual partner (the partner has received medical confirmation of the surgical success of the vasectomy and is the sole sexual partner of the trial subject).
    - Practice true abstinence (unless not acceptable per local practices), defined as: refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable).

If required per local practices, females of childbearing potential must commit to using 2 methods of contraception (either 2 highly effective methods or 1 highly effective method combined with 1 effective method). Effective methods of birth control are the following:

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- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action, initiated at least 30 days prior to Study Day 1.
- Male or female condom with or without spermicide.
- Cap, diaphragm, or sponge with spermicide.
- A combination of male condom with a cap, diaphragm, or sponge with spermicide (double barrier method).

Contraception recommendations related to use of concomitant therapies prescribed per standard of care should be based on the local label.

5.3 Prohibited Medications and Therapy

JAK Inhibitors

Prior and concomitant oral and topical exposure to any other JAK inhibitors (including but not limited to the investigational drug, upadacitinib [Rinvoq®]; tofacitinib [Xeljanz®]; baricitinib [Olumiant®]; filgotinib; ruxolitinib [Jakafi®]; abrocitinib [PF-04965842]; and peficitinib [Smyraf®]) is not allowed.

Targeted Biologic Therapies

Concomitant biologic therapies and biosimilar versions of biologic drugs are prohibited during treatment with study drug and in the Remission-Withdrawal Period. Examples of biologic therapies include but are not limited to the following:

- Abatacept
- Adalimumab
- Anakinra
- Belimumab
- Bimekizumab
- Certolizumab pegol
- Dupilumab
- Efalizumab
- Etanercept
- Golimumab
- Guselkumab
- Infliximab
- Ixekizumab
- Natalizumab
- Rituximab

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- Risankizumab
- Secukinumab
- Tildrakizumab
- Tocilizumab
- Ustekinumab

Other Non-Biologic Systemic Therapy

Initiation of additional systemic immunomodulating therapy for the treatment of axSpA is prohibited during treatment with study drug outside of rescue parameters (refer to Section 5.4) and in the Remission-Withdrawal Period.

Corticosteroids

Spinal/paraspinal and SI joint injection(s) or parenteral administration of corticosteroids (including intramuscular and intravenous injections) or prednisone (or oral corticosteroid equivalents) > 10 mg/day are not allowed during treatment with study drug outside of rescue parameters (refer to Section 5.4) and in the Remission-Withdrawal Period; the following exceptions apply: short-term use (≤ 10 days) of corticosteroids for conditions that are not related to axSpA, such as exacerbation of asthma or chronic obstructive pulmonary disease, allergic reactions, or serious infection when additional corticosteroids may be required to prevent adrenal insufficiency, a total of up to 100 mg of prednisolone or equivalent is allowed during each study.

Investigational Drugs

Subjects who have been treated with any investigational drug within 30 days or 5 half-lives of the drug (whichever is longer) prior to the first dose of study drug are excluded from participation in the studies. Investigational drugs are also prohibited during the studies including the Remission-Withdrawal Period.

Vaccines

If the subject and Investigator choose to receive/administer live vaccines, these vaccinations must be completed (per local label) at least 28 days (or longer if required locally) before first dose of study drug. Live vaccinations are prohibited during study participation prior to Week 14 for Study 1 (bDMARD-IR AS) and prior to Week 52 for Study 2 (nr-axSpA), including at least 30 days (or longer if required locally) after the last dose of study drug. After Week 14 for Study 1 (bDMARD-IR AS) and after Week 52 for Study 2 (nr-axSpA), if a live vaccine must be administered during participation, study drug must be held for at least 14 days prior to the vaccination and at least 30 days after the vaccination (or longer if required locally). Live vaccinations are prohibited during re-treatment in the Remission-Withdrawal Period.

If the live herpes zoster vaccine is to be administered and there is no known history of primary varicella (chicken pox), preexisting immunity to varicella should be confirmed with Ab testing at or prior to Screening and prior to administration of the herpes zoster vaccine. If screening varicella Ab testing is negative, the live herpes zoster vaccine should not be administered.

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Examples of live vaccines include, but are not limited to, the following:

- Monovalent live influenza A (H1N1) (intranasal);
- Seasonal trivalent live influenza (intranasal);
- Zostavax (herpes zoster, live attenuated);
- Rotavirus;
- Varicella (chicken pox);
- Measles-mumps-rubella or measles-mumps-rubella-varicella;
- Oral polio vaccine;
- Smallpox;
- Yellow fever;
- Bacille Calmette-Guérin;
- Typhoid (oral).

Administration of inactivated (non-live) vaccines is permitted prior to or during each study according to local practice guidelines. Examples of common vaccines that are inactivated, toxoid, or biosynthetic include, but are not limited to, injectable influenza vaccine, pneumococcal, Shingrix (zoster vaccine, recombinant, adjuvanted), and pertussis (Tdap) vaccines.

Strong CYP3A Inhibitors or Inducers

Systemic use of known strong CYP3A inhibitors (includes over-the-counter or prescription medicines, vitamins and/or herbal supplements) is not permitted from Screening through the end of study drug administration and use of strong CYP3A inducers is not permitted from 30 days prior to study drug administration through the end of study drug administration. Table 1 includes examples of commonly used strong CYP3A inhibitors and inducers. In addition, herbal therapies and other traditional medicines with unknown effects on CYP3A are not permitted from Screening through the end of study drug administration.

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Table 1. Examples of Commonly Used Strong CYP3A Inhibitors and Inducers

Strong CYP3A Inhibitors	Strong CYP3A Inducers
Boceprevir Cobicistat Clarithromycin Conivaptan Grapefruit (fruit or juice) Indinavir Itraconazole Ketoconazole Lopinavir/Ritonavir Mibefradil Nefazodone Nelfinavir Posaconazole Ritonavir Saquinavir Telaprevir Telithromycin Troleandomycin Voriconazole	Avasimibe Carbamazepine Phenytoin Rifampin Rifapentine St. John's Wort

For subjects enrolled in the Remission-Withdrawal Period, use of strong CYP3A inhibitors or inducers are prohibited while taking study drug.

Opiates

High potency opiates are not permitted during the study (i.e., Double-Blind Period and Open-Label Extension Period and Remission-Withdrawal Period), and subjects must have discontinued use at least 14 days prior to the first dose of study drug. High-potency opiates include but are not limited to:

- oxycodone;
- oxymorphone;
- fentanyl;
- levorphanol;
- buprenorphine;
- methadone;
- hydromorphone;
- morphine;
- meperidine.

Combination of acetaminophen/paracetamol and codeine or combination of acetaminophen/paracetamol and hydrocodone are allowed.

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Elective and Emergency Surgeries

For elective and emergency surgeries, the following rules will apply:

- If the subject must undergo emergency surgery, study drug should be interrupted at the time of the surgery. After emergency surgery, allow reintroduction of study drug once the physician has examined the surgical site and determined that it has healed and there is no sign of infection.
- Elective surgery, and interruption of study drug for such a surgery, will not be allowed for Study 1 (bDMARD-IR) and Study 2 (nr-axSpA) until after the primary endpoint visit at Week 14 for the respective study has been completed. For Study 1 and Study 2, if the subject undergoes elective surgery, the study drug should be interrupted at least 1 week prior to the planned surgery. Allow reintroduction of study drug once the physician has examined the surgical site and determined that it has healed and there is no sign of infection.

5.4 Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins and/or herbal supplements) that the subject is receiving at the time of Screening, and/or receives during a study, must be recorded along with the reason for use, date(s) of administration including start and end dates, and dosage information including dose, route, and frequency on the appropriate electronic case report form (eCRF). Also, medications taken for axSpA since date of diagnosis (based on subject recollection and available medical records) should be entered into the appropriate eCRF inclusive of the dates of first and last dose, maximum dosage taken, and route of administration.

Allowed Therapies:

Methotrexate, sulfasalazine (SSZ), hydroxychloroquine, chloroquine, or leflunomide are allowed during each study, but subjects must be on a stable dose of MTX (≤ 25 mg/week) or SSZ (≤ 3 g/day) or hydroxychloroquine (≤ 400 mg/day) or chloroquine (≤ 400 mg/day) or leflunomide (≤ 20 mg/day) for at least 28 days prior to the Baseline Visit. A combination of up to 2 background csDMARDs is allowed EXCEPT the combination of MTX and leflunomide. For Study 1, subjects should stay on their stable background csDMARD therapy until after their Week 24 Visit unless the subject meets the rescue criterion at Week 24, at which time they may add or modify background csDMARD therapy as outlined in the Addition or Modification of Medication for axSpA subsection below. For Study 2, subjects should stay on their stable background csDMARD therapy until after their Week 52 Visit unless the subject meets the rescue criterion between Week 24 and Week 52, at which time they may add or modify background csDMARD therapy as outlined in the Addition or Modification of Medication for axSpA subsection below. At any time in Study 1 and Study 2, the csDMARD dose may be decreased for safety reasons.

Oral corticosteroids are allowed during each study, but subjects must be on a stable dose of prednisone (≤ 10 mg/day) or oral corticosteroid equivalent for at least 14 days prior to the Baseline Visit. See Section 5.3 for short-term use (≤ 10 days) of corticosteroids for conditions that are not related to axSpA.

NSAIDs, tramadol, combination of acetaminophen/paracetamol and codeine or combination of acetaminophen/paracetamol and hydrocodone, and/or non-opioid analgesics are allowed during each study, but subjects must be on stable dose(s) for at least 14 days prior to the Baseline Visit.

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For subjects on concomitant NSAID therapy, the NSAID eCRF should be completed.

Until at least Week 24 in Study 1 or at least until Week 52 in Study 2, subjects should continue on their stable doses of NSAIDs, tramadol, combination acetaminophen/paracetamol and codeine or combination or acetaminophen/paracetamol and hydrocodone, and/or non-opioid analgesics; oral corticosteroids (equivalent to prednisone ≤ 10 mg/day); or inhaled corticosteroids. At any time, the dose of NSAIDs, tramadol, combination of acetaminophen/paracetamol and codeine or combination of acetaminophen/paracetamol and hydrocodone, and/or non-opioid analgesics, or oral corticosteroids may be decreased or interrupted for safety reasons.

- If taking any of the above on a scheduled basis, they should continue to take them as they did at study entry with no change in dose or frequency, including on study visit days, until at least Week 24 in Study 1 or at least until Week 52 in Study 2 unless the subject meets the rescue criterion between Week 24 and Week 52.
- If not taking any of the above at Baseline, these must not be initiated except where permitted by protocol.
- If taking any of the above at Baseline on an as-needed basis (PRN), they should continue to use them for the same reason and same dose each time but they should not be taken within 24 hours prior to any study visit to avoid bias in outcome measurements.

For Study 1, one intra-articular corticosteroid injection for a peripheral joint will be allowed up to the Week 14 Visit; however, the joint injection should be avoided within 21 days prior to the Week 14 Visit to avoid confounding effects of systemic absorption of intra-articular corticosteroids. Starting at Week 14 (after Week 14 assessments have been performed) and thereafter, peripheral intra-articular, trigger point or tender point, intra-bursa, and intra-tendon sheath injections of corticosteroids are allowed at the Investigator's discretion (dosage and frequency per standard of care). Once a peripheral joint is injected, it will be considered not evaluable/assessable ("NA") during the 90 days following injection.

For Study 2, one intra-articular corticosteroid injection for a peripheral joint will be allowed up to the Week 14 Visit; however, the joint injection should be avoided within 21 days prior to the Week 14 Visit to avoid confounding effects of systemic absorption of intra-articular corticosteroids. Starting at Week 14 (after Week 14 assessments have been performed) and thereafter, peripheral intra-articular, trigger point or tender point, intra-bursa, and intra-tendon sheath injections of corticosteroids are allowed at the Investigator's discretion (dosage and frequency per standard of care); however, joint injections should be avoided within 21 days prior to the Week 52 Visit. Once a peripheral joint is injected, it will be considered "NA" during the 90 days following injection.

During the Remission-Withdrawal Period peripheral intra-articular, trigger point or tender point, intra-bursa, and intra-tendon sheath injections of corticosteroids are allowed at the Investigator's discretion (dosage and frequency per standard of care); however, joint injections should be avoided within 21 days prior to the next Visit.

See Section 5.3 for permitted vaccines.

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Any questions regarding concomitant or prior therapy should be raised to the AbbVie Therapeutic Area Medical Director (TA MD)/AbbVie emergency contact. Information regarding potential drug interactions with upadacitinib can be located in the upadacitinib Investigator's Brochure.[30]

Addition or Modification of Medication for axSpA

Study 1 (bDMARD-IR AS):

Rescue Therapy:

After visit assessments have been performed at Week 24, subjects who do not achieve [redacted] response [redacted] should add or modify any of the following background axSpA medications per local label (Figure 2):

- NSAIDs, acetaminophen/paracetamol, low potency opioid medications (tramadol or combination of acetaminophen/paracetamol and codeine or combination of acetaminophen/paracetamol and hydrocodone); and/or
- MTX, SSZ, hydroxychloroquine, chloroquine, leflunomide, apremilast (concomitant use of up to 2 csDMARDs except the combination of MTX and leflunomide); and/or
- Prednisone (≤ 10 mg/day) (or oral corticosteroid equivalent) and/or a corticosteroid burst with no more than 3 consecutive days of systemic corticosteroids (including intramuscular and intravenous injections) (maximum dose of 0.5 mg/kg/day of prednisone or its equivalent).

Investigator or site staff will determine the subjects' ASAS20 response based on the values presented in the data capture systems.

After Week 24 (e.g., at Week 32 through Week 104 visits), addition or modification of background axSpA medications listed above can be made per Investigator judgment regardless of the disease activity status (Figure 2).

If rescue therapy is escalated to targeted biologic therapies including but not limited to a TNF inhibitor or IL-17 inhibitor (refer to Section 5.3), then study drug treatment must be permanently discontinued prior to initiation of the bDMARD therapy for safety reasons (refer to Section 5.5).

Disease Activity Criteria for Permanent Study Drug Discontinuation:

At Week 32 and through Week 104, subjects without [redacted] response at [redacted] scheduled visits will be permanently discontinued from study drug treatment (e.g., Week 24 and Week 32 with discontinuation at Week 32; or at Week 40 and Week 52 with discontinuation at Week 52), unless an alternative etiology exists to influence the individual domains of the ASAS20 response criteria (such as trauma, injury, or infection affecting the subject's ability to accurately perform pain, function, or global self-assessments of axial SpA disease activity) as documented by the Investigator (Figure 2).

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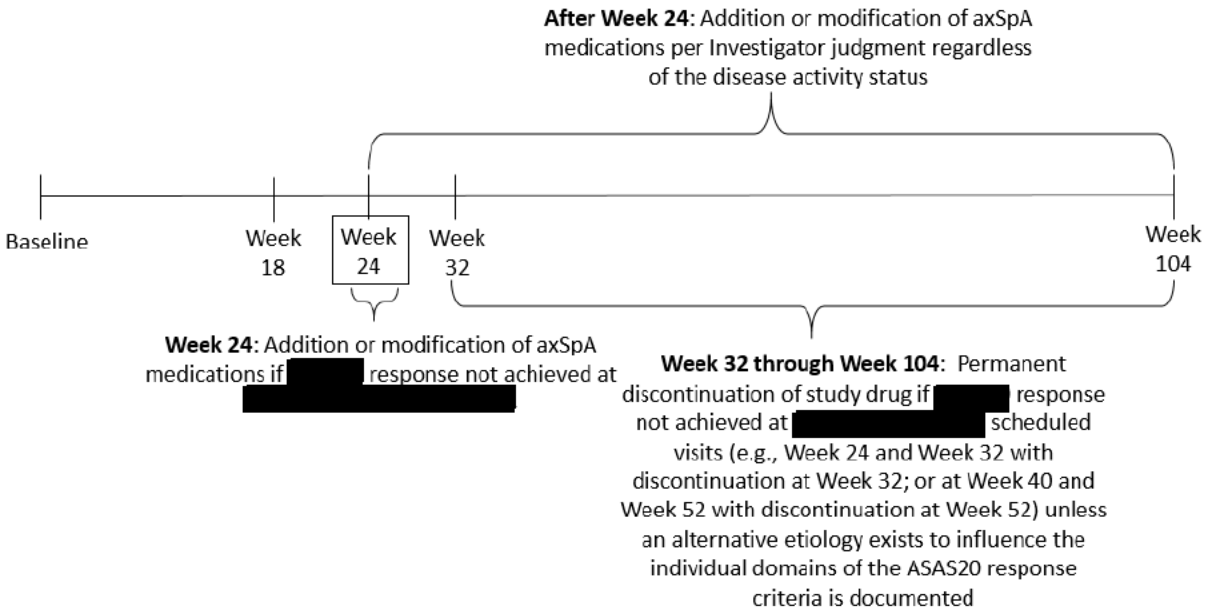
Figure 2. Study 1 (bDMARD-IR AS): Rescue Therapy and Permanent Study Drug Discontinuation Parameters



Study 2 (nr-axSpA):

Rescue Therapy:

After visit assessments have been performed at Week 24 and through Week 52, subjects who do not achieve an [redacted] response at [redacted] scheduled visits should be rescued with standard of care (e.g., Week 18 and Week 24 with rescue at Week 24; or Week 32 and Week 40 with rescue at Week 40) as follows (Figure 3):

1. Add or modify any of the following background axSpA medications listed below per standard of care (per local label) **without** initiation of a bDMARD:
   - NSAIDs, acetaminophen/paracetamol, low potency opioid medications (tramadol or combination of acetaminophen/paracetamol and codeine or combination of acetaminophen/paracetamol and hydrocodone); and/or
   - MTX, SSZ, hydroxychloroquine, chloroquine, leflunomide, apremilast (concomitant use of up to 2 csDMARDs except the combination of MTX and leflunomide); and/or
   - Prednisone (≤ 10 mg/day) (or oral corticosteroid equivalent) and/or a corticosteroid burst with no more than 3 consecutive days of systemic corticosteroids (including intramuscular and intravenous injections) (maximum dose of 0.5 mg/kg/day of prednisone or its equivalent).
   - Subjects may continue concomitant use of study drug if background medications remain within allowed parameters (refer to Section 5.4, Allowed Therapies).

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OR

2. Modify axSpA medications per standard of care (per local label) **with** initiation of a bDMARD:
   - TNF inhibitor or IL-17 inhibitor.
   - Subjects must permanently discontinue study drug prior to initiation of the bDMARD therapy for safety reasons (refer to Section 5.3 and Section 5.5).

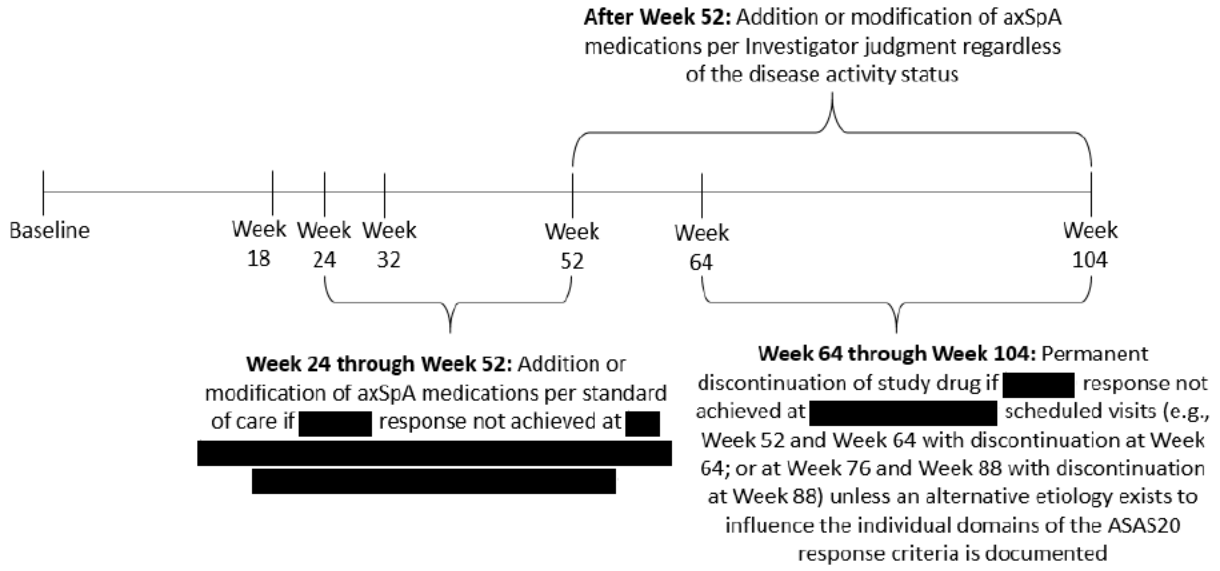
Investigator or site staff will determine the subjects' ASAS20 response based on the values presented in the data capture systems.

After Week 52 (e.g., at Week 64 through Week 104 visits), addition or modification of axSpA medications listed above can be made per Investigator judgment regardless of the disease activity status (Figure 3).

Disease Activity Criteria for Permanent Study Drug Discontinuation:

At Week 64 and through Week 104, subjects without an [redacted] response at [redacted] scheduled visits will be permanently discontinued from study drug treatment (e.g., Week 52 and Week 64 with discontinuation at Week 64; or at Week 76 and Week 88 with discontinuation at Week 88), unless an alternative etiology exists to influence the individual domains of the ASAS20 response criteria (such as trauma, injury, or infection affecting the subject's ability to accurately perform pain, function, or global self-assessments of axial SpA disease activity) as documented by the Investigator (Figure 3).

Figure 3. Study 2 (nr-axSpA): Rescue Therapy and Permanent Study Drug Discontinuation Parameters



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Background Medication During Remission-Withdrawal Period:

Starting at Week 104, subjects entering the Remission-Withdrawal Period, should keep their axSpA-related background medication stable.

COVID-19 Pandemic-Related Vaccination Guidance

Given the ongoing COVID-19 pandemic, selected non-live vaccines (e.g., mRNA, non-replicating viral vector, protein subunit, etc.) to prevent SARS-CoV-2 infection may be administered during screening or the treatment period, as long as components of the vaccine are not contraindicated.

The decision to receive a locally available vaccine should be based on local guidance and an individual discussion between the treating physician and the subject.

The potential impact of upadacitinib on SARS-CoV-2 vaccination is unknown. Therefore, study drug should be administered as follows:

- The first dose of upadacitinib during the Remission-Withdrawal Period, when possible, is preferred not to be given within ± 7 days from the SARS-CoV-2 vaccine administration.

Note: The above guidance applies to all SARS-CoV-2 vaccine doses given as part of the complete treatment course.

These recommendations may be subject to change based on the evolving knowledge around the use of SARS-CoV-2 vaccines in patients with axSpA and as more data are collected in real-world scenarios and clinical trials.

Any SARS-CoV-2 vaccine information must be documented on the COVID-19 vaccine eCRF. Refer to the Operations Manual for instructions on reporting any adverse events associated with the COVID-19 vaccine (Appendix G).

5.5 Withdrawal of Subjects and Discontinuation of Study

AbbVie may terminate Study 1 and/or Study 2 and/or the Remission-Withdrawal Period prematurely, either in its entirety or at any site. Study 1 and/or Study 2 and/or the Remission-Withdrawal Period will be discontinued or terminated in case of an unacceptable risk, any relevant toxicity, or a negative change in the benefit:risk assessment. This might include the occurrence of AEs with a character, severity, or frequency that is new in comparison to the existing risk profile. In addition, data deriving from other clinical trials or toxicological studies which negatively influence the benefit:risk assessment might cause discontinuation or termination of a study. The Investigator may also stop a study at his/her site if he/she has safety concerns. If AbbVie terminates a study for safety reasons, AbbVie will promptly notify the Investigator. Advance notice is not required by either party if a study is stopped due to safety concerns.

Subjects can request to be discontinued from participating in a study at any time for any reason. The Investigator may discontinue any subject's participation at any time for any reason. The AbbVie TA MD/Scientific Director may mandate individual subject discontinuation from study drug in case of safety concern.

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For each study, subjects must have study drug discontinued immediately if any of the following occur:

- The subject requests withdrawal from the study.
- The Investigator believes it is in the best interest of the subject.
- Abnormal laboratory results or AEs that either meet the criteria for discontinuation of study drug as stated in Section 6.2 or as determined by the Investigator or the AbbVie TA MD, that rule out safe continuation of the study drug.
- Serious infections (e.g., sepsis) which cannot be adequately controlled by anti-infective treatment or would put the subject at risk for continuation of the study drug.
- Subject is non-compliant with TB prophylaxis (if applicable) or develops active TB at any time during the study.
- Malignancy, except for localized NMSC or carcinoma in-situ of the cervix.
- Subject develops a GI perforation (defined as acute, spontaneous perforation of the GI tract that requires inpatient medical care or urgent surgical intervention other than appendicitis or mechanical injury). See also Section 6.2 Toxicity Management.
- Confirmed diagnosis of deep vein thrombosis, pulmonary embolism or non-cardiac, non-neurologic arterial thrombosis.
- The subject becomes pregnant while on study drug.
- Eligibility criteria violation was noted after the subject started study drug, when continuation of the study drug would place the subject at risk.
- Introduction of prohibited medications or dosages when continuation of the study drug would place the subject at risk.
- Subject is significantly non-compliant with study procedures, which would put the subject at risk for continued participation in the trial.
- For Study 1 (bDMARD-IR AS), at Week 32 and through Week 104, subjects without [redacted] response at [redacted] scheduled visits will be permanently discontinued from study drug treatment (e.g., Week 24 and Week 32 with discontinuation at Week 32; or at Week 40 and Week 52 with discontinuation at Week 52), unless an alternative etiology exists to influence the individual domains of the ASAS20 response criteria (such as trauma, injury, or infection affecting the subject's ability to accurately perform pain, function, or global self-assessments of axial SpA disease activity) as documented by the Investigator.
- For Study 2 (nr-axSpA), at Week 64 and through Week 104, subjects without [redacted] response at [redacted] scheduled visits will be permanently discontinued from study drug treatment (e.g., Week 52 and Week 64 with discontinuation at Week 64; or at Week 76 and Week 88 with discontinuation at Week 88), unless an alternative etiology exists to influence the individual domains of the ASAS20 response criteria (such as trauma, injury, or infection affecting the subject's ability to accurately perform pain, function, or global self-assessments of axial SpA disease activity) as documented by the Investigator.

Additional requirements related to abnormal laboratory values and selected AESIs are located in Section 6.2.

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5.6 Follow-Up for Subject Withdrawal from Study

Discontinuation of Study Drug and Continuation of Study Participation

If a subject prematurely discontinues study drug, the procedures outlined for a Premature Discontinuation Visit (PD Visit) should be completed as soon as possible, preferably within 2 weeks, and preferably prior to initiation of another therapy. To minimize missing data for efficacy and safety assessments, subjects who prematurely discontinue study drug treatment should continue to be followed for all regularly scheduled visits as outlined in the Activity Schedule (Appendix D) and adhere to all study procedures except for dispensing study drug, PK sample collection, and blood sample collection for optional biomarker research studies, unless subjects have decided to discontinue study participation entirely (withdrawal of informed consent). In addition, all efficacy-driven criteria for addition or modification of background medications and study drug discontinuation no longer apply. If at any point a subject no longer wants to provide assessments (withdrawal of informed consent) following discontinuation of study drug, a second PD Visit is not required. Subjects should be advised on the continued scientific importance of their data even if they discontinue treatment with study drug early. Following discontinuation of study drug, the subject should be treated in accordance with the Investigator's best clinical judgment irrespective of whether the subject decides to continue participation in a study.

Premature Discontinuation of Study (Withdrawal of Informed Consent)

If a subject prematurely discontinues study participation (withdrawal of informed consent), the procedures outlined for the PD Visit should be completed as soon as possible, preferably within 2 weeks, and preferably prior to initiation of another therapy. In addition, if subject is willing, a 30-day F/U Visit (or phone call) after the last dose of study drug may be completed to determine the status of any ongoing AEs/SAEs or the occurrence of any new AEs/SAEs.

For subjects to be considered lost to follow-up, reasonable attempts must be made to obtain information on the subject's final status. At a minimum, 2 telephone calls must be made and 1 certified letter must be sent and documented in the subject's source documentation.

5.7 Study Drug

Study drug will be taken orally QD, beginning on Day 1 (Baseline), and should be taken at approximately the same time each day, with or without food. Subjects will be instructed to return all drug containers (even if empty) to the study site personnel at each study visit; study site personnel will document compliance.

Subjects will continue their disease-related concomitant medications therapy as allowed per protocol. AbbVie will not supply any disease-related concomitant medication therapy taken during the course of each study.

AbbVie will supply upadacitinib and matching upadacitinib placebo.

All study drug investigational product must be stored at controlled room temperature (15° to 25°C/59° to 77°F). Study drug will be packaged in quantities sufficient to accommodate study design.

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Each kit will be labeled per local requirements and this label must remain affixed to the kit. Upon receipt, study drug should be stored as specified on the label and kept in a secure location. Each kit will contain a unique kit number. This kit number is assigned to a subject via interactive response technology (IRT) and encodes the appropriate study drug to be dispensed at the subject's corresponding study visit. All blank spaces on the label will be completed by the site staff prior to dispensing to subjects. Study drug will only be used for the conduct of the study.

The individual study drug information is presented in Table 2.

Table 2. Description of Study Drug

Investigational Product	Mode of Administration	Dosage Form	Strength	Blinded or Open Label	Frequency	Manufacturer
Upadacitinib (ABT-494)	Oral	Film-coated tablets	15 mg	Blinded for Double-Blind Period; unblinded for Open-Label Extension Period[a]	QD	AbbVie
Placebo for upadacitinib (ABT-494)	Oral	Film-coated tablets	Not applicable	Blinded for Double-Blind Period[a]	QD	AbbVie

a. For Study 1 and Study 2, study sites and subjects will remain blinded to the Double-Blind Period treatment assignments for the duration of the respective study.

If a subject is unable to come to the study site to pick up their study drug due to COVID-19, a direct-to-patient (DTP), study drug shipment can be made from the study site to the subject if allowed by local regulations. AbbVie will submit any required notifications to the regulatory authority as applicable. Refer to the Operations Manual in Appendix G for details on DTP shipment of study drug.

5.8 Randomization/Drug Assignment and Blinding

All subjects will be assigned a unique identification number by the IRT at the screening visit. For subjects who re-screen, the screening number assigned by the IRT at the initial screening visit should be used. The IRT will assign a randomization number that will encode the subject's treatment group assignment according to the randomization schedule generated by the statistics department at AbbVie. In the Double-Blind Period, subjects will be randomized in a 1:1 ratio to 1 of 2 treatment groups:

Study 1 (bDMARD-IR AS):

- Group 1: Upadacitinib 15 mg QD (N = 193)
- Group 2: Placebo QD (N = 193)

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Study 2 (nr-axSpA):

- Group 1: Upadacitinib 15 mg QD (N = 152)
- Group 2: Placebo QD (N = 152)

In Study 1 (bDMARD-IR AS), randomization will be stratified by hsCRP (≤ ULN versus > ULN) collected at Screening Visit, the class of the prior bDMARD use (1 TNF inhibitor, 1 IL-17 inhibitor, and "other"), and geographic region (US/Canada versus Rest of the World excluding Japan and China). The "other" category of prior bDMARD use includes exposure to 2 bDMARDs and cannot exceed 30% of subjects. Japan and China will each have a separate randomization schedule stratified by hsCRP (≤ ULN versus > ULN) collected at Screening Visit.

In Study 2 (nr-axSpA), randomization will be stratified by MRI and screening hsCRP status (MRI+/hsCRP > ULN, MRI+/hsCRP ≤ ULN, and MRI–/hsCRP > ULN) and exposure to bDMARDs (yes versus no). At least 20%, but not exceeding 35% of subjects with prior exposure to a bDMARD will be enrolled in Study 2. Japan and China will each have a separate randomization schedule stratified by MRI and screening hsCRP status (MRI+/hsCRP > ULN, MRI+/hsCRP ≤ ULN, and MRI–/hsCRP > ULN).

Subjects in the placebo group will be switched to upadacitinib 15 mg QD at Week 14 in the Open-Label Extension Period for Study 1 (bDMARD-IR AS) and Week 52 in the Open-Label Extension Period for Study 2 (nr-axSpA).

All AbbVie personnel with direct oversight of the conduct and management of the trial (with the exception of AbbVie Drug Supply Management Team), the Investigator, study site personnel, and the subject will remain blinded to each subject's treatment until the Week 14 primary analysis for Study 1 (bDMARD-IR AS). For Study 2 (nr-axSpA), all AbbVie personnel with direct oversight of the conduct and management of the trial (with the exception of AbbVie Drug Supply Management Team) will remain blinded to each subject's treatment until the Week 14 primary analysis, while the Investigator, study site personnel, and the subject will remain blinded to each subject's treatment until after all subjects have completed the Week 52 visit or have prematurely discontinued prior to Week 52. For Study 1 and Study 2, sites and subjects will remain blinded to the Double-Blind Period treatment assignments for the duration of the respective study. To maintain the blind, the upadacitinib tablets and placebo tablets provided for each study will be identical in appearance. The IRT will provide access to unblinded subject treatment information in the case of a medical emergency.

In the event of a medical emergency that requires unblinding of the study drug assignment, the Investigator is requested to contact the AbbVie TA MD prior to breaking the blind. However, if an urgent therapeutic intervention is necessary which warrants breaking the blind prior to contacting the AbbVie TA MD, the Investigator can directly access the IRT system to break the blind without AbbVie notification or agreement. Unblinding is available in the IRT system via the Unblind Subject transaction, which is available only to the Investigator. If the IRT system is unavailable, unblinding may occur by contacting the technical support of the IRT vendor via either phone (preferred) or email (support@endpointclinical.com). For country-specific phone numbers, please see the following website: http://www.endpointclinical.com/helpdesk/.

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In the event that the blind is broken before notification to the AbbVie TA MD, we request that the AbbVie TA MD be notified within 24 hours of the blind being broken. The date and reason that the blind was broken must be conveyed to AbbVie and recorded on appropriate eCRF.

5.9 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol except when necessary to eliminate an immediate hazard to study subjects. The Investigator is responsible for complying with all protocol requirements, written instructions, and applicable laws regarding protocol deviations. If a protocol deviation occurs (or is identified including those that may be due to the COVID-19 pandemic), the Investigator is responsible for notifying IEC/IRB, regulatory authorities (as applicable), and AbbVie.

5.10 TB Testing/TB Prophylaxis

All subjects must be evaluated for TB at Screening and annually. The results of the TB screening must be interpreted in the context of the subject's epidemiology, history, exam findings, etc., and it is the responsibility of the Investigator to determine if a subject has previous, active, or latent TB.

At Screening, all subjects will be assessed for evidence of increased risk for TB by a risk assessment questionnaire and tested for TB infection as described below. The site staff will complete the TB risk assessment questionnaire in its entirety (Part I and Part II) and enter the data into the appropriate eCRF. The TB risk assessment questionnaire will be completed annually (Part I only) for all subjects, regardless of TB test results.

Subjects with a negative TB test and CXR not suggestive of active TB may be enrolled. Subjects with history of active TB may be enrolled if it has been adequately treated with no evidence of current active TB; subjects with inadequate documentation of treatment should be cleared by a TB specialist prior to enrollment.

Subjects with a positive TB test must be assessed for evidence of active TB versus latent TB, including signs and symptoms and CXR. Subjects with latent TB (positive TB test with no signs or symptoms and a CXR not suggestive of active TB) may be enrolled after initiation of TB prophylaxis (see below).

Subjects with evidence of active TB must not be enrolled.

TB Testing:

- The QuantiFERON-TB Gold Plus test should be performed at Screening on all subjects unless the subject is considered to be TB test positive prior to Screening. The purified protein derivative (tuberculin) (PPD) Skin Test (also known as TB Skin test or Mantoux test) should only be utilized when the QuantiFERON-TB Gold Plus test is not possible or if both tests are required per local guidelines.
- If a subject had a QuantiFERON-TB Gold Plus test within 90 days prior to Screening and source documentation is available, TB testing does not need to be performed by the central laboratory at Screening provided nothing has changed in the subject's medical history to warrant a repeat test.

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- For subjects with only a negative PPD Skin Test available within 90 days prior to Screening, a QuantiFERON-TB Gold Plus test is required at Screening. If the QuantiFERON-TB Gold Plus test is not possible and source documentation is available, the PPD Skin Test does not need to be repeated provided nothing has changed in the subject's medical history to warrant a repeat test.
- For regions that require both PPD and QuantiFERON-TB Gold Plus testing, both will be performed. If either PPD or QuantiFERON-TB Gold Plus is positive, the TB test is considered positive.
- Subjects with documentation of prior positive result of QuantiFERON-TB Gold Plus test and/or PPD Skin Test and/or history of latent or active TB are not required to repeat a TB test at Screening or during a study and should be considered TB test positive.
    - If TB testing is done at Screening for subjects with a prior positive TB test and a positive result is reported, the subject is considered TB test positive.
    - If TB testing is done at Screening in subjects considered at low risk for TB as described below and a negative or indeterminate result is reported, the procedure for "Interpretation of a positive TB test in low risk subjects" should be followed OR either prior or concomitant treatment for latent TB is required.
    - If TB testing is done for subjects with a prior positive TB test at the annual evaluation, repeated TB prophylaxis is not required for a positive result unless indicated by the subject's medical history.
- Subjects without history of active or latent TB and having a negative TB test result at Screening or the most recent evaluation will undergo annual TB testing by QuantiFERON-TB Gold Plus Test and/or PPD Skin Test.
- If a site has the capacity to perform both PPD and QuantiFERON-TB Gold Plus Test, and local guidelines require only one test to be performed, then the QuantiFERON-TB Gold Plus Test is the preferred test. At a site with capacity to perform both tests, whatever TB test method (i.e., PPD or QuantiFERON-TB Gold Plus Test or other Interferon Gamma Release Assay [IGRA]) was performed at screening, then the subject should have their annual TB test performed with the same test method.
- If performed, the PPD Skin Test should be read by a licensed healthcare professional between 48 and 72 hours after administration. A subject who does not return within 72 hours will need to be rescheduled for another skin test. The reaction will be measured in millimeters (mm) of induration and induration ≥ 5 mm is considered a positive reaction. The absence of induration will be recorded as "0 mm" and not "negative."
- Subjects who have an ulcerating reaction to PPD in the past should not be re-exposed and the PPD should be considered positive and do not require subsequent testing with either PPD or QuantiFERON-TB Gold Plus.
- If the QuantiFERON-TB Gold Plus test is indeterminate, then the Investigator should perform a local QuantiFERON-TB Gold Plus test (or through the central laboratory if not locally available) to rule out a positive test result. If testing remains indeterminate or is positive, then the subject is considered to be positive for the purpose of the study. If the testing result is negative, then the subject is considered to be negative.

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- Interpretation of a positive TB test in low risk subjects: In cases where the QuantiFERON-TB Gold Plus test by the central laboratory is positive and the Investigator considers the subject at low risk for TB (i.e., no risk factors identified using the Part I and Part II questions of the TB risk assessment questionnaire at Screening or Part I questions annually) and has no clinical suspicion of TB, the Investigator may perform a local QuantiFERON-TB Gold Plus test (or repeat testing through the central laboratory if not locally available) to confirm the positive test result. If the repeat testing result is negative, the Investigator may consider the test to be negative based on his/her clinical judgment; if the repeat testing result is positive or indeterminate, the test is considered positive.
- An equivalent IGRA (such as T-SPOT TB test) may be substituted for the QuantiFERON-TB Gold Plus.
- TB test(s) results will be retained at the site as the original source documentation.

If an annual TB test is newly positive (seroconversion), a CXR needs to be performed as soon as possible to aid in distinguishing active versus latent TB and subsequent annual TB follow-up tests are not required. For subjects with seroconversion on an annual TB test, if a CXR cannot be done due to the COVID-19 pandemic, the Investigator should contact the AbbVie TA MD to determine if the subject may continue on study drug. CXR should be performed as soon as restrictions allow at the study site or local hospital/facility.

If the subject is experiencing signs or symptoms suspicious for TB or something has changed in the subject's medical history to warrant investigation and a repeat test before the next scheduled annual TB re-test, the case (including the TB test results) should be discussed with the AbbVie TA MD.

TB prophylaxis:

Note: Rifampicin and Rifapentine are not allowed for TB prophylaxis while on study drug.

At Screening, if the subject has evidence of latent TB infection, prophylactic treatment with isoniazid must be initiated at least 2 weeks prior to administration of study drug (or per local guidelines, whichever is longer). If receiving isoniazid prophylaxis during a study, at least 6 months must be completed; however, the full course of prophylaxis does not need to be completed prior to the first dose of study drug.

Subjects with a prior history of active or latent TB that have documented completion of a full course of anti-TB therapy will be allowed to enter a study provided nothing has changed in the subject's medical history to warrant repeat treatment. Prior to the study, a full course of latent TB prophylaxis may be achieved with at least 4 months of rifampin, at least 6 months of isoniazid, or at least 3 months of combination rifapentine and isoniazid. For subjects with completion of a full course of anti-TB therapy, but insufficient documentation, the Investigator should consult with the AbbVie TA MD.

During a study, subjects with new evidence of latent TB must initiate prophylactic treatment with isoniazid immediately and complete at least 6 months of prophylaxis. Study drug should not be withheld. Two to 4 weeks later, the subject should be re-evaluated (unscheduled visit) for signs and symptoms as well as laboratory assessment of toxicity to TB prophylaxis.

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At Screening, newly diagnosed latent TB should be entered in the TB Screening eCRF; prior history of latent or active TB should be entered into the medical history eCRF. Any positive TB test after the subject has started a study should be reported as an AE of latent TB or active TB (as applicable). Newly initiated prophylactic treatment and prior therapy should be captured in the concomitant/prior medications eCRF as appropriate.

6 SAFETY CONSIDERATIONS

6.1 Complaints and Adverse Events

Complaints

A complaint is any written, electronic, or oral communication that alleges deficiencies related to the physical characteristics, identity, quality, purity, potency, durability, reliability, safety, effectiveness, or performance of a product/device. Complaints associated with any component of this investigational product must be reported to AbbVie.

Product Complaint

A product complaint is any complaint related to the drug component of the product.

For a product this may include, but is not limited to, damaged/broken product or packaging, product appearance whose color/markings do not match the labeling, labeling discrepancies/inadequacies in the labeling/instructions (e.g., printing illegible), missing components/product, or packaging issues.

Product complaints concerning the investigational product must be reported to AbbVie within 24 hours of the study site's knowledge of the event. Product complaints occurring during each study will be followed up to a satisfactory conclusion.

Medical Complaints/Adverse Events and Serious Adverse Events

An AE is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product.

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal.

The Investigators will monitor each subject for clinical and laboratory evidence of AEs on a routine basis throughout each study. All AEs will be followed to a satisfactory conclusion. Laboratory abnormalities and changes in vital signs are considered to be AEs only if they result in discontinuation from the study drug, necessitate therapeutic medical intervention, and/or if the investigator considers them to be AEs.

An elective surgery/procedure scheduled to occur during a study will not be considered an AE if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure has been

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pre-planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during a study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an AE.

If an AE, whether associated with study drug or not, meets any of the following criteria, it is to be reported to AbbVie or contract research organization (as appropriate) as an SAE within 24 hours of the site being made aware of the SAE (refer to the Reporting Adverse Events and Intercurrent Illnesses section of the operations manual for reporting details and contact information):

Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the Investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization or Prolongation of Hospitalization	An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living (ADL) of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

All AEs reported from the time of study drug administration until 30 days after discontinuation of study drug administration will be collected, whether solicited or spontaneously reported by the subject. In addition, SAEs and protocol-related nonserious AEs will be collected from the time the subject signs the study-specific informed consent.

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AbbVie will be responsible for SUSAR reporting for the Investigational Medicinal Product (IMP) in accordance with global and local requirements. An adverse reaction implies at least a reasonable possibility of a causal relationship between a suspected medicinal product and an AE. An adverse reaction, in contrast to an AE, is characterized by the fact that a causal relationship between a medicinal product and an occurrence is suspected. A 'suspected' serious adverse reaction refers to individual SAE case reports from clinical trials where a causal relationship between the SAE and the IMP was suspected by either the Sponsor or the Investigator, is not listed is the applicable Reference Safety Information, and meets one of the following serious criteria: results in death, is life-threatening, requires hospitalization or prolongation of an existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect. All individually reported serious adverse reactions are considered suspected.

AEs will be monitored throughout each study to identify any of special interest that may indicate a trend or risk to subjects.

Adverse Events of Special Interest

The following AESIs will be monitored during each study:

- Serious infections
- Opportunistic infections
- Herpes Zoster
- Active TB
- Malignancy (all types)
- Adjudicated GI perforations
- Anemia
- Neutropenia
- Lymphopenia
- Renal dysfunction
- Hepatic disorder
- Adjudicated cardiovascular events (e.g., major adverse cardiac events)
- Adjudicated embolic and thrombotic events (non-cardiac, non-central nervous system)

Cardiovascular Adjudication Committee

An independent committee of physician experts in cardiovascular adjudication will be utilized to assess potential cardiovascular, cerebrovascular, embolic, and thrombotic AEs in a blinded manner as defined by the CAC charter. The CAC charter will be prepared separate from the protocol and will describe the objective, scope, frequency, and triggers for data reviews.

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Adverse Event Severity and Relationship to Study Drug

The Investigators will rate the severity of each AE according to the National Cancer Institute CTCAE version 4.03, which can be accessed at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50.

If no grading criteria are provided for the reported event, then the event should be graded as follows:

Mild (Grade 1)	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Moderate (Grade 2)	Minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL (instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.)
Severe (Grade 3 – 5)	
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL (self care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden)
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death related to AE

The Investigator will use the following definitions to assess the relationship of the AE to the use of study drug:

Reasonable Possibility	After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is sufficient evidence (information) to suggest a causal relationship.
No Reasonable Possibility	After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is insufficient evidence (information) to suggest a causal relationship.

For causality assessments, events assessed as having a reasonable possibility of being related to the study drug will be considered "associated." Events assessed as having no reasonable possibility of being related to study drug will be considered "not associated." In addition, when the Investigator has not reported a causality or deemed it not assessable, AbbVie will consider the event associated.

If an Investigator's opinion of no reasonable possibility of being related to study drug is given, an Other cause of event must be provided by the Investigator for the SAE.

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Pregnancy

While not an AE, pregnancy in a study subject must be reported to AbbVie within 24 hours after the site becomes aware of the pregnancy. If a pregnancy occurs in a study subject, information regarding the pregnancy and the outcome will be collected.

Female subjects should avoid pregnancy throughout the course of the study, starting with the Screening Visit through 30 days after the last study drug administration. Results of a positive pregnancy test or confirmation of a pregnancy will be assessed starting with the Screening Visit through the final study visit.

Subjects who become pregnant during a study must be discontinued from study drug, but may remain in the study (see Section 5.5).

The pregnancy outcome of an elective or spontaneous abortion, stillbirth, or congenital anomaly is considered an SAE and must be reported to AbbVie within 24 hours of the site becoming aware of the event.

6.2 Toxicity Management

The toxicity management of the AEs including AESIs consists of safety monitoring (review of AEs on an ongoing basis, and periodic/ad hoc review of safety issues by an Independent Data Monitoring Committee), and, if applicable, interruption of study drug dosing with appropriate clinical management and/or discontinuation of the subjects from study drug. The management of specific AEs and laboratory parameters is described below.

For subjects who discontinue study drug but continue study participation and are on standard of care therapies or are enrolled in the Remission-Withdrawal Period prior to retreatment, these toxicity management requirements do not apply (including alerts from the central laboratory) and any intolerability to standard of care therapies should be managed by the prescribing physician.

Serious Infections: Study drug should be interrupted if a subject develops a serious infection. Study drug may be restarted once the infection has been successfully treated. Subjects who develop active TB must be permanently discontinued from study drug.

Herpes Zoster: If a subject develops herpes zoster, consider temporarily interrupting study drug until the episode resolves.

Gastrointestinal Perforation: Subjects presenting with the onset of signs or symptoms of a GI perforation should be evaluated promptly for early diagnosis and treatment. Subjects with acute, spontaneous perforation of the GI tract that requires inpatient medical care or urgent surgical intervention (except for appendicitis or mechanical injury) must be permanently discontinued from study drug.

Thrombosis Events: Subjects who develop symptoms of thrombosis should be promptly evaluated and treated appropriately. If the diagnosis of deep vein thrombosis, pulmonary embolism or non-cardiac, non-neurologic arterial thrombosis is confirmed, the subject must be discontinued from study drug.

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Malignancy: Subjects who develop malignancy other than NMSC or carcinoma in situ of the cervix must be permanently discontinued from study drug. Information including histopathological results should be queried for confirmation of the diagnosis. Periodic skin examination is recommended for patients who are at increased risk for skin cancer.

Muscle-related symptoms: If a subject experiences symptoms suggestive of myositis or rhabdomyolysis, consider checking CPK and aldolase with clinical management and/or study drug interruption as deemed appropriate by the treating physician.

COVID-19: Interrupt study drug in subjects with a confirmed diagnosis of COVID-19. Consider interrupting study drug in subjects with signs and/or symptoms and suspicion of COVID-19. The COVID-19 eCRF must be completed.

Management of Select Laboratory Abnormalities: For any given laboratory abnormality, the Investigator should assess the subject and apply the standard of care for medical evaluation and treatment following any local guidelines. Specific toxicity management guidelines for abnormal laboratory values are described in Table 3 and may require a supplemental eCRF to be completed. For subjects with ongoing laboratory abnormalities which require data entry into an eCRF, an additional eCRF related to subsequent laboratory abnormalities is only required if the subject has relevant changes in history (e.g., new onset signs or symptoms) or laboratory values which have returned to normal reference range or its Baseline value followed by subsequent laboratory abnormalities meeting toxicity guidelines (considered a new event). All abnormal laboratory tests that are considered clinically significant by the Investigator will be followed to a satisfactory resolution. If a repeat test is required per protocol, the repeat testing is to occur as soon as possible.

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Table 3. Specific Toxicity Management Guidelines for Abnormal Laboratory Values (for Study 1 and Study 2 and Remission-Withdrawal Period)

Laboratory Parameter	Toxicity Management Guideline
Hemoglobin	• If hemoglobin < 8 g/dL, interrupt study drug dosing and confirm by repeat testing with a new sample. • If hemoglobin decreases ≥ 3.0 g/dL from Baseline without an alternative etiology, interrupt study drug dosing and confirm by repeat testing with new sample. • If hemoglobin decreases ≥ 3.0 g/dL from Baseline and an alternative etiology is known or the hemoglobin value remains in the normal reference range, the subject may remain on study drug at the Investigator's discretion. • If confirmed, continue to withhold study drug until hemoglobin value returns to normal reference range or its Baseline value.
ANC	• If confirmed < 1000/µL by repeat testing with new sample, interrupt study drug dosing until ANC value returns to normal reference range or its Baseline value. • Interrupt study drug if confirmed < 500/µL by repeat testing with new sample. If value returns to normal reference range or its Baseline value, restarting study drug is allowed if there is an alternative etiology identified; documentation should include reason that rechallenge is expected to be safe for the subject. Study drug should be discontinued if no alternative etiology can be found.
ALC	• If confirmed < 500/µL by repeat testing with new sample, interrupt study drug dosing until ALC returns to normal reference range or its Baseline value.
Total WBC count	• If confirmed < 2000/µL by repeat testing with new sample, interrupt study drug dosing until WBC count returns to normal reference range or its Baseline value.

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Laboratory Parameter	Toxicity Management Guideline

AST or ALT	• Interrupt study drug if confirmed ALT or AST > 3 × ULN by repeat testing with new sample and either a total bilirubin > 2 × ULN or an international normalized ratio > 1.5.
	  • A separate blood sample for international normalized ratio (INR) testing will be needed to measure INR at the time of repeat testing for ALT or AST. A repeat test of INR is not needed for determination if above toxicity management criteria are met.
	• Interrupt study drug if confirmed ALT or AST > 3 × ULN by repeat testing with new sample along with new appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5% increase from Baseline).
	• Interrupt study drug if confirmed ALT or AST > 5 × ULN by repeat testing with new sample for more than 2 weeks.
	• If ALT or AST > 8 × ULN, interrupt study drug immediately, confirm by repeat testing with a new sample, and contact the TA MD.
	Subjects with HBc Ab+ (irrespective of hepatitis B surface antibody status) and negative HBV DNA PCR testing at Screening who develop the following laboratory findings should have HBV DNA PCR testing performed within 1 week (based on initial elevated value):
	• ALT > 5 × ULN OR
	• ALT or AST > 3 × ULN and either a total bilirubin > 2 × ULN or INR > 1.5 OR
	• ALT or AST > 3 × ULN along with clinical signs of possible hepatitis.
	  • A separate blood sample for HBV DNA PCR testing will be needed at the time of repeat testing for ALT or AST.
	A positive result for HBV DNA PCR testing will require immediate interruption of study drug (unless not acceptable by local practices) and a hepatologist consultation should occur within 1 week for recommendation regarding subsequent treatment.
	Subjects who meet any of the above criteria should be evaluated for an alternative etiology of the ALT or AST elevation and managed as medically appropriate. If applicable, the alternative etiology should be documented in the eCRF. If ALT or AST values return to the normal reference range or the Baseline value, study drug may be restarted. If restarting study drug, documentation should include reason that rechallenge is expected to be safe. If after clinically appropriate evaluation no alternative etiology for ALT or AST elevation is found or the ALT or AST elevation has not resolved or is not trending down toward normal, the subject should be discontinued from study drug.
	For any confirmed ALT or AST elevations > 3 ULN, complete the appropriate supplemental hepatic eCRF(s).

Serum Creatinine	• If serum creatinine is > 1.5 × the Baseline value and > ULN, repeat the test for serum creatinine (with subject in an euvolemic state) to confirm the results. If the results of the repeat testing still meet this criterion, then interrupt study drug and restart study drug once serum creatinine returns to ≤ 1.5 × Baseline value and ≤ ULN. For the above serum creatinine elevation scenarios, complete the supplemental renal eCRF.

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Ab = antibody; ALC = absolute lymphocyte count; ALT = alanine aminotransferase; ANC = Absolute neutrophil count; AST = aspartate transaminase; DNA = deoxyribonucleic acid; eCRF = electronic case report form; HBc Ab= hepatitis B core antibody; HBV = Hepatitis B virus; INR = international normalized ratio; PCR = polymerase chain reaction; TA MD = Therapeutic Area Medical Director; ULN = upper limit of normal; WBC = white blood cell

6.3 Data Monitoring Committee

For each study, an independent, external DMC will be established for periodic review of unblinded safety data and to alert AbbVie to possible safety concerns related to the conduct of the study to ensure subject safety. If necessary to ensure subject safety, the DMC will also be given access to selected efficacy data which will be specified in the DMC charter.

The DMC charter will describe the roles and responsibilities of the DMC members, frequency of data reviews, and relevant data to be assessed. Communications from the DMC to the Study Team will not contain information that could potentially unblind the team to subject treatment assignments.

7 STATISTICAL METHODS & DETERMINATION OF SAMPLE SIZE

7.1 Statistical and Analytical Plans

Study 1 (bDMARD-IR AS) and Study 2 (nr-axSpA) will be analyzed separately for global submission purposes. The AbbVie study team will be unblinded to perform the primary analysis and reporting for each study independently.

For Study 1 (bDMARD-IR AS), the database lock for the primary analysis will occur after all Study 1 subjects have completed the Week 14 visit or have prematurely discontinued prior to Week 14.

For Study 2 (nr-axSpA), the database lock for the primary analysis will occur after all Study 2 subjects have completed the Week 14 visit or have prematurely discontinued prior to Week 14.

The primary analysis for Study 1 and Study 2 will be conducted for the comparisons of the upadacitinib group versus the placebo group. The database lock dates may be different for Study 1 and Study 2. For Study 1 and Study 2, sites and subjects will remain blinded to the placebo-controlled period treatment assignments for the duration of the respective study.

Additional analyses will also be conducted for each study independently as follows:

- For Study 1 (bDMARD-IR AS), an analysis will be conducted when all subjects in the study have completed the Week 104 visit or have prematurely discontinued prior to Week 104. An additional analysis may be conducted for regulatory purposes after all subjects have completed the Week 52 visit or have prematurely discontinued prior to Week 52.
- For Study 2 (nr-axSpA), an analysis will be conducted after all subjects in the study have completed the Week 104 visit or have prematurely discontinued prior to Week 104. An additional analysis will be conducted for regulatory purposes after all subjects have completed the Week 52 visit or have prematurely discontinued prior to Week 52.

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Specific details of the statistical analyses will be described and fully documented in the Statistical Analysis Plan (SAP) for each study. For both studies, the SAP will be finalized prior to the Week 14 database lock of the study. The statistical analyses will be performed using SAS (SAS Institute Inc., Cary, North Carolina, USA).

7.2 Definition for Analysis Populations

The Full Analysis Set (FAS) includes all randomized subjects who received at least 1 dose of study drug. Subjects will be included in the analysis based on the treatment group as randomized. The FAS will be used for all efficacy and Baseline analyses.

The Per Protocol Analysis Set represents a subset of the FAS and consists of all FAS subjects who did not have any major protocol violations that impact primary efficacy analysis. The primary endpoint will be analyzed in the Per Protocol Analysis Set. The Per Protocol Analysis Set will be determined prior to the respective primary analysis database lock.

The Safety Analysis Set consists of all subjects who received at least 1 dose of study drug. For the Safety Analysis Set, subjects will be assigned to a treatment group based on the treatment actually received, regardless of the treatment randomized.

7.3 Statistical Analyses for Efficacy

All efficacy analyses will be carried out for each study independently.

Analysis of the efficacy endpoints for Study 1 and Study 2 will be conducted on the FAS based on randomized treatment group. Unless otherwise specified, comparisons will be between the upadacitinib group and the placebo group. For each study, the between group comparison will be conducted using a two-sided test at significance level $\alpha = 0.05$.

For binary endpoints, point estimate for the response rate and 95% confidence interval (CI) will be reported for each randomized treatment group. Point estimate, 95% CI, and p-value for treatment comparison between upadacitinib and placebo will also be reported.

For continuous endpoints, the means at specified visits, least square means, and 95% CI of change from Baseline will be reported for each randomized treatment group. The least square means of treatment difference and associated 95% CI and p-value for treatment comparison between upadacitinib and placebo will also be reported.

For primary and secondary binary endpoints, the primary analysis method will use the composite estimand framework; the supplementary analysis will use the treatment policy estimand framework. For secondary continuous endpoints, the primary analysis method will use the treatment policy estimand framework. Details are outlined below.

Primary Efficacy Analysis

For Study 1 (bDMARD-IR AS), the primary endpoint is ASAS40 response at Week 14. For Study 2 (nr-axSpA), the primary endpoint is ASAS40 response at Week 14. The primary efficacy analysis will use

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the composite estimand framework, where the Week 14 primary endpoint for both studies is defined as a composite endpoint that is achieved if a subject fulfills the following 2 components: 1) Remain in the study and on study drug through 14 weeks; and 2) Achieve an ASAS40 response at Week 14. Corresponding to this estimand, in the primary analysis, subjects who discontinue study drug prior to Week 14 will be treated as non-responders. Missing data due to COVID-19 will be imputed using Multiple Imputation and additional missing data due to other reasons will be treated as non-responders.

All subjects in the FAS will be included in the primary efficacy analysis. Comparison of the primary endpoint will be made between the upadacitinib group and the placebo group using the Cochran-Mantel-Haenszel (CMH) test adjusting for the main stratification factor. For Study 1 (bDMARD-IR AS), the main stratification factor is hsCRP level (≤ ULN versus > ULN). For Study 2 (nr-axSpA), the main stratification factor is MRI and hsCRP status (MRI+/hsCRP > ULN, MRI+/hsCRP ≤ ULN, and MRI–/hsCRP > ULN). Rubin's method will be used to combine the results from the multiple datasets generated by the Multiple Imputation. For both studies, the same respective analysis will be conducted on the Per Protocol Analysis Set as a supplementary analysis.

Corresponding to the composite estimand, a sensitivity analysis will be conducted. Subjects who discontinue study drug prior to Week 14 will be treated as non-responders. Additional missing data including those due to COVID-19 will also be treated as non-responders. The same CMH analysis as the primary analysis will be conducted.

In addition, the following supplementary analyses will be performed using the treatment policy estimand framework. The same CMH analysis as the primary analysis will be conducted including all data as observed, regardless of adherence to study drug, with subjects missing ASAS40 response treated as non-responders. Additional sensitivity analysis using Multiple Imputation may also be conducted to handle missing ASAS40 responses.

Secondary Efficacy Analysis

For binary endpoints, similar analyses as for the primary endpoint will be conducted on the FAS.

The primary analysis of continuous endpoints will use the treatment policy estimand framework, intending to assess the treatment effect regardless of adherence to study drug. All subjects in the FAS will be included for the analysis. Comparisons between the upadacitinib group and the placebo group will be performed using the Mixed Model for Repeated Measures (MMRM) with treatment group, visit, and treatment-by-visit interaction as fixed effects and the corresponding Baseline value and the main stratification factor as the covariates. The same main stratification factors as in the primary endpoint analyses will be used. The MMRM model includes all longitudinal data as observed for subjects in the FAS, regardless of adherence to study drug.

For multiplicity-controlled secondary continuous efficacy variables, additional sensitivity analysis will be conducted corresponding the treatment policy estimand, where missing data will be imputed using Multiple Imputation. The imputation model will include demographics variables and Baseline disease characteristics, as well as longitudinal response observed at any other visits. The analysis of covariance (ANCOVA) model will be performed on each of the multiple imputed datasets adjusting for treatment, main stratification factor, and Baseline value. The ANCOVA results from the multiple imputed datasets will be combined using the Rubin's method.

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Additional Efficacy Analyses

Additional efficacy variables will be summarized for all visits. For efficacy analysis of the placebo-controlled period (up to Week 14 in Study 1 [bDMARD-IR] and Week 52 in Study 2 [nr-axSpA]), similar statistical methods as for the primary and secondary endpoints will be used. For binary endpoints, comparisons between the upadacitinib group and the placebo group will be performed using the CMH test adjusting for the main stratification factor. Corresponding to the composite estimand, subjects who discontinue study drug or use rescue medication will be treated as non-responders for visits after study drug discontinuation or initiation of rescue medication. Missing data will be imputed similarly as for the primary endpoint. A sensitivity analysis will be conducted where all missing data are treated as non-responders. For continuous endpoints, comparisons between the upadacitinib group and the placebo group will be performed using the MMRM with treatment group, visit, and treatment-by-visit interaction as fixed effects and the corresponding Baseline value and the main stratification factor as the covariates. Handling of data observed after rescue will be further detailed in the SAP.

Long-term efficacy analysis will be performed similarly as described above, corresponding to the composite estimand for binary endpoints and the treatment policy estimand for continuous endpoints. For binary endpoints, supplementary analysis using the treatment policy estimand may also be conducted on all data as observed. For efficacy analysis beyond the placebo-controlled period (Week 14 in Study 1 [bDMARD-IR] and Week 52 in Study 2 [nr-axSpA]), no statistical comparison will be performed; descriptive statistics and 95% CIs will be provided. The analyses will be performed by randomized treatment sequence as described below:

1. Placebo → upadacitinib 15 mg QD
2. Upadacitinib 15 mg QD → upadacitinib 15 mg QD

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Subgroup Analysis for Efficacy

The analyses for the primary efficacy endpoint for Study 1 and Study 2 will also be performed in demographic subgroups, including age, gender, race, weight, body mass index, and geographical region, to assess the consistency of the treatment effect. Additional subgroup analyses based on Baseline disease characteristics and stratification factors will also be conducted. The treatment difference between the upadacitinib group and the placebo group will be presented with point estimate and 95% CI. No p-value will be provided for subgroup analysis.

7.4 Statistical Analyses for Safety

All safety analyses will be carried out for each study independently using the Safety Analysis Set for both the primary analysis and for the entire study. Analyses for Study 1 and Study 2 will be based on treatments the subjects actually received. Safety will be assessed by TEAEs, physical examination, laboratory assessments, and vital signs. The descriptive summary of subjects experiencing TEAEs by treatment group will be tabulated by the Medical Dictionary for Regulatory Activities primary system organ class and preferred term. In addition, summary of SAEs and TEAEs by severity and relationship to study drug as assessed by the Investigator will be provided. SAEs, severe TEAEs, or TEAEs that lead to premature study discontinuation will be listed. A similar summary will also be performed for AESIs.

The observed values for vital signs, physical examination, and clinical laboratory variables at each visit will be summarized. The number and percentage of subjects meeting the criteria for potentially clinically significant laboratory values will be summarized. Shift of laboratory values from Baseline to defined time points will be tabulated.

Missing safety data will not be imputed.

Analysis details will be specified in the SAP.

7.5 Interim Analysis

There are no interim analyses planned for efficacy endpoints. Information on the interim safety monitoring DMC is described in Section 6.3. A separate DMC charter will be prepared outside of the protocol and will describe the roles and responsibilities of the DMC members, frequency of data reviews, and relevant data to be assessed.

7.6 Multiplicity Adjustment and Overall Type I Error Control

All efficacy analyses including multiplicity adjustment will be carried out for Study 1 (bDMARD-IR AS) and Study 2 (nr-axSpA) separately. Study 1 and Study 2 will have its own hypothesis testing and overall type I error rate control at a level of 0.05 independently. Since all efficacy comparisons target superior efficacy from placebo, this is equivalent to a one-sided test at a level of 0.025.

A fixed sequence testing approach will be employed to control the familywise error rate at 0.05 level for the primary and multiplicity-controlled secondary endpoints. The test starts with the primary endpoint using two-sided $\alpha = 0.05$; significance can be claimed for a lower ranked endpoint only if the previous

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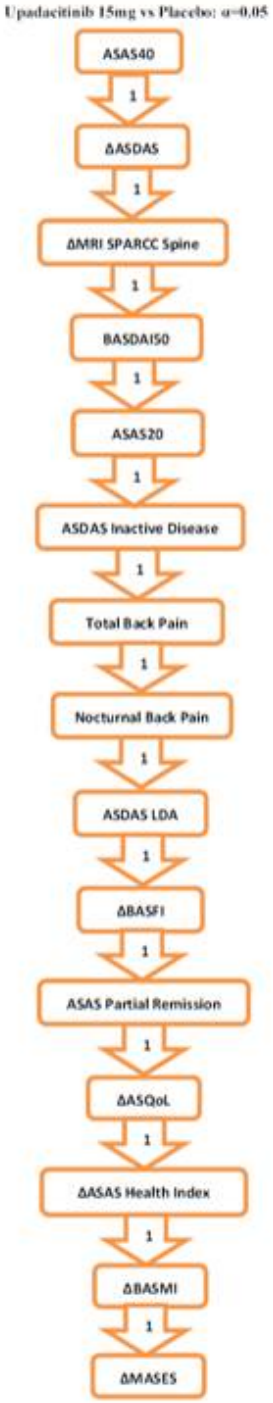
endpoints in the sequence meet the requirement of significance. The testing sequence for Study 1 (bDMARD-IR AS) is shown in Figure 4. The testing sequence for Study 2 (nr-axSpA) is shown in Figure 5.

Figure 4. Testing Sequence for Study 1 (bDMARD-IR AS)



Note: The primary endpoint and all multiplicity-controlled secondary endpoints will be assessed at Week 14.

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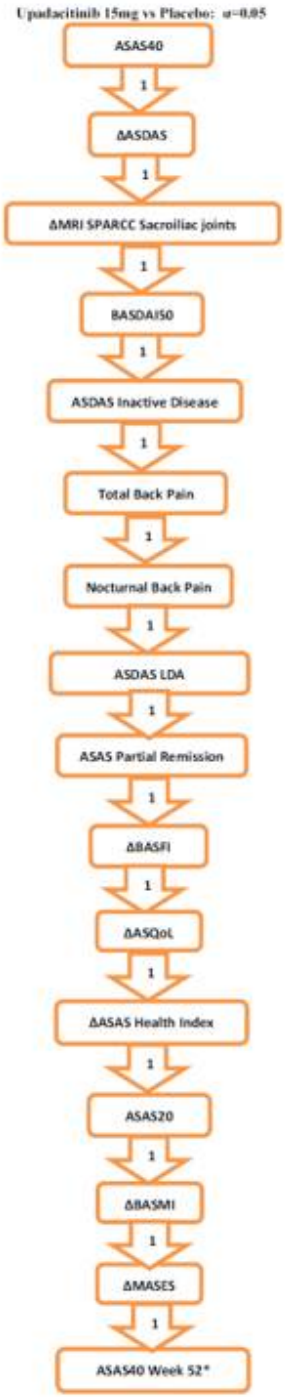
Figure 5. Testing Sequence for Study 2 (nr-axSpA)



* ASAS40 response at Week 52 is part of the testing sequence for EU/EMA regulatory purposes. For US/FDA regulatory purposes, the testing sequence stops at ΔMASES.

Note: The primary endpoint and multiplicity-controlled secondary endpoints will be assessed at Week 14 unless otherwise noted.

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7.7 Sample Size Determination

The sample size and power were calculated for Study 1 and Study 2 separately. Power and sample size calculations were performed at two-sided significance level of 0.05 and accounting for a 10% dropout rate for Week 14 endpoints.

Study 1 (bDMARD-IR AS)

The planned total sample size of 386 subjects for this study (with a 1:1 randomization ratio for placebo and upadacitinib 15 mg) provides at least 90% power for the primary endpoint ASAS40 response of upadacitinib 15 mg versus placebo using a two-sided Chi-square test at 0.05 level. For ASAS40, the assumed response rates for upadacitinib and placebo are 24% and 6%, respectively.[20,26,40] This sample size also provides 90% power for ASAS20, with assumed response rates for upadacitinib and placebo of 41% and 24%, respectively.

In addition, this sample size provides at least 80% power for several of the multiplicity-controlled secondary endpoints including change from Baseline in ASDAS, change from Baseline in MRI SPARCC score of spine, BASDAI 50 response, ASDAS ID, change from Baseline in Total Back Pain, change from Baseline in Nocturnal Back Pain, ASDAS LDA, change from Baseline in BASFI, and ASAS PR.[20,26,40]

Study 2 (nr-axSpA)

The planned total sample size of 304 for this study (with a 1:1 randomization ratio for placebo and upadacitinib 15 mg) provides at least 90% power for the primary endpoint ASAS40 response of upadacitinib 15 mg versus placebo using a two-sided Chi-square test at 0.05 level. For ASAS40 at Week 14, the assumed response rates for upadacitinib and placebo are 42% and 17%, respectively.[38,41,42,43]

In addition, this sample size provides at least 80% power for several of the multiplicity-controlled secondary endpoints including change from Baseline in ASDAS, change from Baseline in MRI score of SI joints, BASDAI 50 response, ASDAS ID, change from Baseline in Total Back Pain, change from Baseline in Nocturnal Back Pain, ASDAS LDA, ASAS PR, and Week 52 ASAS40 response (multiplicity-controlled for EU/EMA regulatory purposes).[38,41,43]

8 ETHICS

8.1 Independent Ethics Committee/Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the IEC/IRB for review and approval. Approval of both the protocol and the informed consent form(s) must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IEC/IRB before the changes are implemented to a study. In addition, all changes to the consent form(s) will be IEC/IRB approved.

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8.2 Ethical Conduct of the Study

Each study will be conducted in accordance with the protocol, operations manual, International Council for Harmonisation (ICH) guidelines, applicable regulations, and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki. Responsibilities of the Investigator are specified in Appendix B.

In cases of COVID-19 pandemic situations leading to difficulties in performing protocol-specified procedures, AbbVie will engage with study site personnel in efforts to ensure the safety of subjects, maintain protocol compliance, and minimize risks to the integrity of the study while trying to best manage subject continuity of care. This may include alternative methods for assessments (e.g., virtual site visits), alternative locations for data collection (e.g., use of a local laboratory instead of a central laboratory), and shipping investigational product and/or supplies DTP to ensure continuity of treatment where allowed. Refer to the operations manual for additional details. In all cases, these alternative measures must be allowed by local regulations and permitted by the IRB/IEC. Investigators should notify AbbVie if any urgent safety measures are taken to protect the subjects against any immediate hazard.

8.3 Subject Confidentiality

To protect subjects' confidentiality, all subjects and their associated samples will be assigned numerical study identifiers or "codes." No identifiable information will be provided to AbbVie.

During the COVID-19 pandemic, remote monitoring of data may be employed if allowed by the local regulatory authority, IRB/IEC, and the study site.

9 SOURCE DOCUMENTS AND CASE REPORT FORM COMPLETION

The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be attributable, legible, contemporaneous, original, accurate, and complete to ensure accurate interpretation of data. Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol, ICH Good Clinical Practice (GCP), and applicable local regulatory requirement(s). During the COVID-19 pandemic, remote data review and verification of data may be employed if allowed by the local regulatory authority, IRB/IEC, and the study site.

10 DATA QUALITY ASSURANCE

AbbVie will ensure that the clinical trial is conducted with a quality management system that will define quality tolerance limits in order to ensure human subject protection and reliability of study results. Data will be generated, documented, and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements.

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11 COMPLETION OF THE STUDY

For Study 1 and Study 2, the end-of-study is defined as the date of the last subject's last visit or the actual date of follow-up contact, whichever is later. The end-of-study, as it pertains to Study Protocol M19-944, is defined as the end-of-study for Study 1 or Study 2, whichever is later.

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APPENDIX A. STUDY SPECIFIC ABBREVIATIONS AND TERMS

Ab	antibody
AE(s)	adverse event(s)
ALT	alanine aminotransferase
AS	ankylosing spondylitis
ASAS	Assessment of SpondyloArthritis international Society
ASDAS	Ankylosing Spondylitis Disease Activity Score
ASQoL	Ankylosing Spondylitis Quality of Life
AST	aspartate transaminase
axSpA	axial spondyloarthritis
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
$BASMI_{lin}$	Linear Bath Ankylosing Spondylitis Metrology Index
bDMARD-IR	biologic disease-modifying antirheumatic drug inadequate responder(s)
bDMARDs	biologic disease-modifying antirheumatic drugs
CAC	Cardiovascular Adjudication Committee
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CRF	case report form
CRP	C-reactive protein
csDMARD(s)	conventional synthetic disease-modifying antirheumatic drug(s)
CXR	chest x-ray
CYP3A	cytochrome P450 3A isoform subfamily
DMC	Data Monitoring Committee
DTP	direct-to-patient
EC	Ethics Committee
eCRF	electronic case report form
EMA	European Medicines Agency
EQ-5D-5L	EuroQol 5 Dimensions 5 Levels Health State Instrument
EU	European Union
EudraCT	European Clinical Trials Database
FACIT-F	Functional Assessment of Chronic Illness Therapy-Fatigue
FDA	Food and Drug Administration

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GCP	Good Clinical Practice
GI	gastrointestinal
HI	Health Index
hsCRP	High sensitivity C-reactive protein
ICH	International Council for Harmonisation
ID	Inactive Disease
IEC	Independent Ethics Committee
IGRA	Interferon Gamma Release Assay
IL	interleukin
IRB	institutional review board
JAK	Janus kinase
KM	Kaplan-Meier
LDA	Low Disease Activity
MASES	Maastricht Ankylosing Spondylitis Enthesitis Score
Min	minimum
mm	millimeters
MMRM	Mixed Model for Repeated Measures
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
NA	not evaluable/assessable
nr-axSpA	non-radiographic axial spondyloarthritis
NSAID(s)	nonsteroidal anti-inflammatory drug(s)
NRS	numeric rating scale
PCR	polymerase chain reaction
PD Visit	Premature Discontinuation Visit
PED	Patient Experience Data
PGA	Physician's Global Assessment of Disease Activity
PK	pharmacokinetics
PPD	purified protein derivative (tuberculin)
PR	partial remission
PRO	patient-reported outcome
PsA	psoriatic arthritis
PtGA	Patient's Global Assessment of Disease Activity
QD	once daily

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QoL	quality of life
RA	rheumatoid arthritis
SAE	serious adverse event
SF-36	36-Item Short Form Health Survey
SI	sacroiliac
SJC	swollen joint count
SpA	spondyloarthritis
SPARCC	Spondyloarthritis Research Consortium of Canada
TA MD	Therapeutic Area Medical Director
TB	tuberculosis
TJC	tender joint count
TNF	tumor necrosis factor
ULN	upper limit of normal
US	United States
VAS	visual analogue scale

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APPENDIX B. RESPONSIBILITIES OF THE INVESTIGATOR

Protocol 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

Protocol Date: 12 July 2021

Clinical research studies sponsored by AbbVie are subject to the International Council for Harmonisation (ICH) Good Clinical Practices (GCP) and local regulations and guidelines governing the study at the site location. In signing the Investigator Agreement, the Investigator is agreeing to the following:

1. Conducting the study in accordance with ICH GCP, the applicable regulatory requirements, current protocol and operations manual, and making changes to a protocol only after notifying AbbVie and the appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC), except when necessary to protect the subject from immediate harm.
2. Personally conducting or supervising the described investigation(s).
3. Informing all subjects, or persons used as controls, that the drugs are being used for investigational purposes and complying with the requirements relating to informed consent and ethics committees (e.g., IEC or IRB) review and approval of the protocol and its amendments.
4. Reporting complaints that occur in the course of the investigation(s) to AbbVie.
5. Reading the information in the Investigator's Brochure/safety material provided, including the instructions for use and the potential risks and side effects of the investigational product(s).
6. Informing all associates, colleagues, and employees assisting in the conduct of the study about their obligations in meeting the above commitments.
7. Maintaining adequate and accurate records of the conduct of the study, making those records available for inspection by representatives of AbbVie and/or the appropriate regulatory agency, and retaining all study-related documents until notification from AbbVie.
8. Maintaining records demonstrating that an ethics committee reviewed and approved the initial clinical protocol and all of its amendments.
9. Reporting promptly, all changes in the research activity and all unanticipated problems involving risks to human subjects or others, to the appropriate individuals (e.g., Coordinating Investigator, Institution Director) and/or directly to the ethics committees and AbbVie.
10. Providing direct access to source data documents for study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s).

Signature of Principal Investigator	Date

Name of Principal Investigator (printed or typed)	

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APPENDIX C. LIST OF PROTOCOL SIGNATORIES

Name	Title	Functional Area
[redacted]		Immunology Clinical Development
		Immunology Clinical Development
		Clinical Program Development
		Data and Statistical Sciences
		Data and Statistical Sciences
		Clinical Pharmacology and Pharmacometrics
		Medical Writing

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APPENDIX D. ACTIVITY SCHEDULE

The following table shows the required activities across Screening and subsequent study visits. Activities are applicable for Study 1 and Study 2 unless specified. The individual activities are described in detail in the operations manual (Appendix G). Allowed modifications due to the COVID-19 pandemic are detailed within the operations manual.

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Study Activities Table (Applicable for Study 1 and Study 2 unless specified)

Activity	Screening	Baseline	Wk 1	Wk 2	Wk 4	Wk 8	Wk 12	Wk 14	Wk 18	Wk 24	Wk 32	Wk 40	Wk 52	Wk 64	Wk 76	Wk 88	Wk 104	Unscheduled Visit	PD Visit	30-Day F/U Visit OR Phone Call
		Day 1																		
INTERVIEWS & QUESTIONNAIRES																				
Subject information and informed consent	✓																✓ (Remission-Withdrawal Period only)			
Eligibility criteria	✓	✓															✓ (Remission-Withdrawal Period only)			
Medical history	✓	✓																		
Drug and alcohol history	✓																			
Prior/concomitant therapy	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Latent TB risk assessment questionnaire	✓												✓				✓			
Review and document pregnancy avoidance recommendations with females of childbearing potential	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
PRO																				
BASDAI, Total Back Pain, BASFI, PtGA, Patient's Global Assessment of Pain	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	
Nocturnal Back Pain		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	
ASQoL, SF-36		✓	✓		✓	✓		✓		✓		✓	✓				✓		✓	

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Activity	Screening	Baseline	Wk 1	Wk 2	Wk 4	Wk 8	Wk 12	Wk 14	Wk 18	Wk 24	Wk 32	Wk 40	Wk 52	Wk 64	Wk 76	Wk 88	Wk 104	Unscheduled Visit	PD Visit	30-Day F/U Visit OR Phone Call
		Day 1																		
ASAS HI		✓	✓	✓	✓	✓		✓		✓			✓				✓		✓	
FACIT – F		✓		✓				✓		✓		✓	✓				✓		✓	
EQ-5D-5L		✓		✓				✓		✓			✓				✓		✓	
WPAI		✓						✓		✓			✓				✓		✓	
PED questionnaire		✓																		
Subject diary		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
EXAM																				
Body weight	✓	✓			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Height		✓																		
Vital signs	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Physical exam	✓	✓						✓		✓			✓		✓		✓		✓	
MRI of spine and SI joints (prior to or at the scheduled visit)	✓							✓									✓		✓	
12-lead ECG (annually at Week 52 and Week 104 if required by country regulatory authorities)	✓												✓				✓		✓	
AE assessment	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Investigator assessments: TJC/SJC		✓						✓		✓			✓		✓		✓		✓	
Investigator assessments: $BASMI_{lin}$		✓						✓		✓			✓		✓		✓		✓	

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Activity	Screening	Baseline	Wk 1	Wk 2	Wk 4	Wk 8	Wk 12	Wk 14	Wk 18	Wk 24	Wk 32	Wk 40	Wk 52	Wk 64	Wk 76	Wk 88	Wk 104	Unscheduled Visit	PD Visit	30-Day F/U Visit OR Phone Call
		Day 1																		
Investigator assessments: MASES		✓			✓	✓		✓		✓			✓		✓		✓		✓	
Investigator assessments: PGA		✓	✓	✓	✓	✓	✓	✓		✓		✓	✓		✓		✓		✓	
Anteroposterior (AP) pelvis x-ray	✓																			
Lateral cervical and lumbar – spine x-ray	✓																✓		✓	
CXR (annually after Week 52 if annual TB test is newly positive [seroconversion])	✓												✓				✓			
Physical activity device dispensation (Study 1 [bDMARD-IR AS] only; except in countries where the digital health technology device is not available or is not allowed to be used in the study by the local regulatory authority) (device is to be worn through Week 14)		✓																		
Collection of physical activity device (Study 1 [bDMARD-IR AS] only; only applies to countries where the digital health technology device is approved)								✓												

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Activity	Screening	Baseline	Wk 1	Wk 2	Wk 4	Wk 8	Wk 12	Wk 14	Wk 18	Wk 24	Wk 32	Wk 40	Wk 52	Wk 64	Wk 76	Wk 88	Wk 104	Unscheduled Visit	PD Visit	30-Day F/U Visit OR Phone Call
		Day 1																		
Physical activity spinal range of motion tasks (Study 1 [bDMARD-IR AS] only; only applies to countries where the digital health technology device is approved)		✓	✓	✓	✓	✓	✓	✓												
[redacted]																				
LOCAL LAB																				
Urine pregnancy test (for all female subjects of childbearing potential)		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓
Dispense urine pregnancy tests for monthly home testing									✓	✓	✓	✓	✓	✓	✓	✓				
Erythrocyte sedimentation rate	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Beta-D-glucan (Japan only)	✓																			
CENTRAL LAB																				
FSH, HIV, HCV, serum pregnancy test	✓																			
hsCRP, clinical chemistry, hematology, urinalysis	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

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Activity	Screening	Baseline	Wk 1	Wk 2	Wk 4	Wk 8	Wk 12	Wk 14	Wk 18	Wk 24	Wk 32	Wk 40	Wk 52	Wk 64	Wk 76	Wk 88	Wk 104	Unscheduled Visit	PD Visit	30-Day F/U Visit OR Phone Call
		Day 1																		
TB test (QuantiFERON TB Gold test [or interferon gamma release assay equivalent such as T-SPOT test] and/or local PPD skin test, if required)	✓												✓				✓			
HBV (post-Baseline tests for subjects from Japan only)	✓						✓			✓	✓	✓	✓	✓	✓	✓	✓		✓	
HLA-B27		✓																		
Study 1 (bDMARD-IR AS) blood samples for upadacitinib PK assay (only in approximately 30% of subjects in select sites)				✓		✓	✓	✓											✓	
Study 2 (nr-axSpA) blood samples for upadacitinib PK assay (only in approximately 30% of subjects in select sites)				✓		✓		✓			✓		✓						✓	
Rx TREATMENT																				
Randomization/drug assignment		✓																		
Dispense study drug		✓			✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓		✓		
Dispense study drug (subjects entering open-label extension for applicable countries; see Appendix F)																	✓			

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Optional Biomarker Sample Activities Table (Applicable for Study 1 and Study 2)

Activity	Screening	Baseline	Wk 1	Wk 2	Wk 4	Wk 8	Wk 12	Wk 14	Wk 18	Wk 24	Wk 32	Wk 40	Wk 52	Wk 64	Wk 76	Wk 88	Wk 104	Unscheduled Visit	PD Visit	30-Day F/U Visit OR Phone Call
		Day 1																		
Study 1 (bDMARD-IR AS) blood: (DNA/RNA/serum/plasma)		✓		✓				✓												
Study 2 (nr-axSpA) blood: (DNA/RNA/serum/plasma)		✓		✓				✓					✓							

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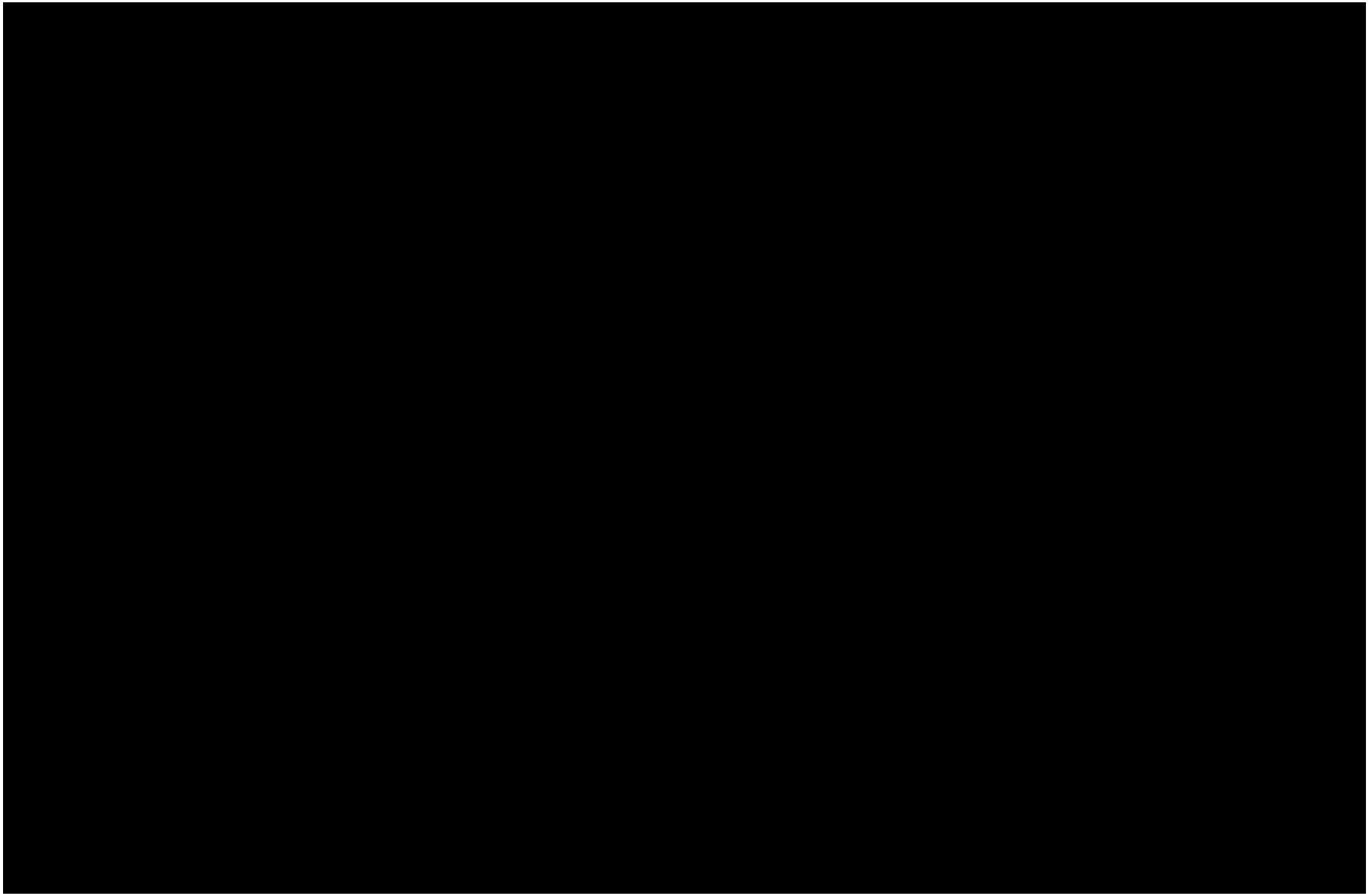

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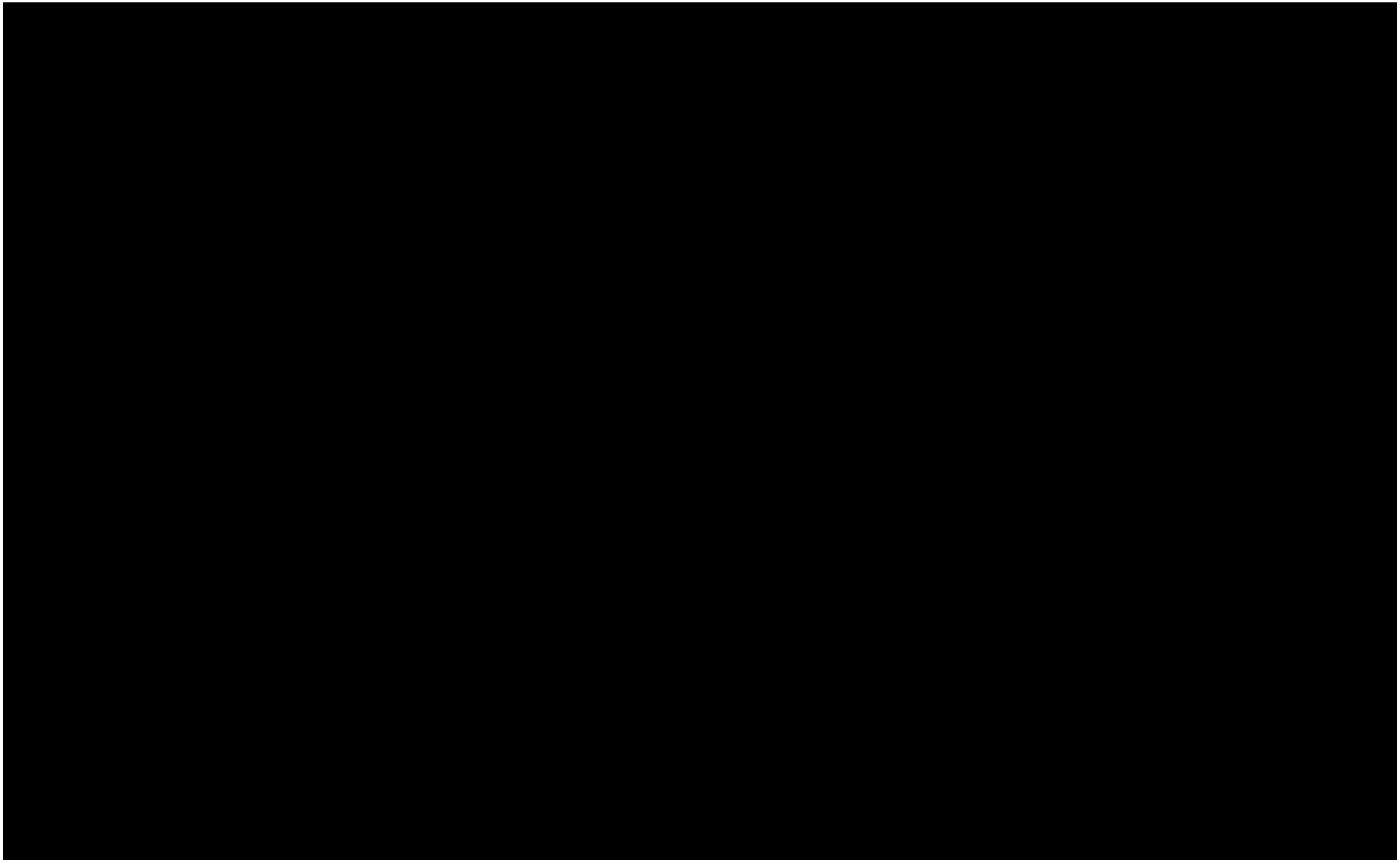

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APPENDIX E. PROTOCOL SUMMARY OF CHANGES

Protocol	Date
Version 1.0	23 August 2019
Version 2.0	13 September 2019
Version 3.0	01 February 2020
Administrative Change 1	06 March 2020
Version 4.0	29 December 2020
Version 4.1 (VHP Countries)	02 March 2021

The purpose of this Amendment is to incorporate the following changes:

Summary of Protocol Changes:

The rationale for the following changes was to include the Remission-Withdrawal Period in this study:

- Title page, Appendix G – Revised title of study.
- Section 3.1 – Added objective for the Remission-Withdrawal Period.
- Section 3.4 – Added an additional endpoint relating to the assessment of disease flare.
- Section 4.1 – Updated study design study schematic (Figure 1) to include a description of the Remission-Withdrawal Period.
- Section 4.1 – Updated study schematic (Figure 1) to include the Remission-Withdrawal Period.
- Section 5.1 – Added eligibility criteria for subjects who enter the Remission-Withdrawal Period.
- Section 5.3 – Added to include that concomitant biologic therapies and biosimilar versions of biologic drugs are prohibited during the Remission-Withdrawal Period.
- Section 5.3 – Added to include that initiation of additional systemic immunomodulating therapy for the treatment of axSpA is prohibited during the Remission-Withdrawal Period.
- Section 5.3 – Added to include that spinal/paraspinal and SI joint injection(s) or parenteral administration of corticosteroids (including intramuscular and intravenous injections) or prednisone (or oral corticosteroid equivalents) > 10 mg/day are not allowed during the Remission-Withdrawal Period.
- Section 5.3 – Added to include that investigational drugs are also prohibited during the Remission-Withdrawal Period.
- Section 5.3 – Added to include that live vaccinations are prohibited during re-treatment during the Remission-Withdrawal Period.
- Section 6.2 – Included the Remission-Withdrawal Period in the specific toxicity management guidelines for abnormal laboratory values in Table 3.

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- Section 7.3 – Added efficacy analysis during the Remission-Withdrawal Period.
- Appendix D – Specified that subject information, informed consent, and eligibility criteria at Week 104 in the main study is for the Remission-Withdrawal Period only.
- Appendix D – Added study activity tables for the Remission-Withdrawal Period.
- Appendix G – [redacted]
- Appendix G – [redacted]
- Appendix G – Added subject information, informed consent, and eligibility criteria at Week 104 for the Remission-Withdrawal Period only.
- Appendix G – Updated to include the Follow-Up Visit is not applicable for subjects who continue in the Remission-Withdrawal Period.
- Appendix G – Added study activities for the Remission-Withdrawal Period.
- Appendix G – Added guidance on assessing [redacted] during the Remission-Withdrawal Period.
- Appendix G – [redacted]
- Appendix G – Added that during the Remission-Withdrawal Period, unscheduled visit can be scheduled at any time to assess disease status (e.g., flare) and/or safety between scheduled visits, if needed.

The rationale for the following changes was to incorporate modifications due to the COVID-19 pandemic:

- Section 5.4 – Added guidance on COVID-19 pandemic-related vaccination.
- Section 5.7 – Included information on DTP study drug shipment and details on time limits for study drug interruption.
- Section 5.9 – Clarified that protocol deviations may include modifications due to COVID-19.
- Appendix G – Added guidance on the assessment of vital signs during the COVID-19 pandemic.
- Appendix G – Added guidance on reactions associated with the SARS-CoV-2 vaccine.

The rationale for the following changes was to update the statistical methods for handling of missing data and intercurrent events to address regulatory feedback:

- Section 7.3 – Clarified that for primary and secondary binary endpoints, the primary method will use the composite estimand framework. Added that the supplementary analysis will use the treatment policy estimand framework. Revised language to state that for secondary continuous endpoints, the primary method will use the treatment policy estimand framework.

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- Section 7.3 Primary Efficacy Analysis – Revised to state that missing data due to COVID-19 will be imputed using Multiple Imputation and additional missing data due to other reasons will be treated as non-responders.
- Section 7.3 Secondary Efficacy Analysis – Revised to state that the primary analysis of continuous endpoints will use the treatment policy estimand freamework, intending to assess the treatment effect regardless of adherence to study drug. Revised to state that the MMRM model included all longitudinal data as observed for subjects in the FAS, regardless of adherence to study drug. Removed information on supplementary analysis for continuous endpoints. For multiplicity-controlled secondary continuous efficacy variables, removed hypothetical estimand from additional sensitivity analysis.
- Section 7.3 Additional Efficacy Analysis – For missing data, revised statement to state that missing data will be imputed similarly as for the primary endpoint. Removed reference to hypothetical estimand. Replaced reference to hypothetical estimand to treatment policy estimand. Specified that for binary endpoints, supplementary analysis using the treatment policy estimand may also be conducted on all data as observed. Added that handling of data observed after rescue will be further detailed in the SAP.

Other protocol changes:

- Updated Section 1, Synopsis.

  Rationale: Revised to be consistent with Protocol Version 5.0 revisions**.**
- Section 2.1 – For Study M16-098, revised the duration from Week 14 to Week 64 for no new safety risks.

  Rationale: Updated background and rationale information based on more current study information.
- Section 2.1 – Added international treatment recommendations for axial SpA.

  Rationale: Updated to provide background information on study design.
- Section 5.3 – Added that for subjects enrolled in the Remission-Withdrawal Period, use of strong CYP3A inhibitors or inducers are not prohibited while off study drug. Added that high potency opiates are not permitted during the Remission-Withdrawal Period.

  Rationale: To provide guidance on handling of concomitant medication during Remission-Withdrawal Period.
- Section 5.4 – Added guidance on background medication during the Remission-Withdrawal Period.

  Rationale: To provide guidance on handling of concomitant medication during Remission-Withdrawal Period.
- Section 5.5 – Added that AbbVie may terminate the study prematurely, including the Remission-Withdrawal Period.

  Rationale: To clarify that the discontinuation criteria apply to Remission-Withdrawal Period.

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- Section 6.2 – Add that toxicity management requirements do not apply to subjects enrolled Remission-Withdrawal Period.

  Rationale: For subjects enrolled in the Remission-Withdrawal Period, the toxicity management criteria are only applicable if subjects take study drug.

- Section 3.3 and Section 7.6 (Figure 5) – Switched the ranking order of ASAS20 and BASFI for Study 2

  Rationale: Ranking order for ASAS20 and BASFI for Study 2 modified to align ranking with updated estimated statistical power based on emerging external literature data and clinical relevance.

- Section 7.3 – Removed reference to use of rescue in the primary analysis.

  Rationale: Use of rescue does not apply to Week 14 endpoints.

- Section 7.7 – Removed statement: This sample size also provides 90% power for ASAS20, with assumed response rates for upadacitinib and placebo of 59% and 36%, respectively. Removed change from Baseline in BASFI.

  Rationale: Ranking order for ASAS20 and BASFI for Study 2 modified to align ranking with updated estimated statistical power based on emerging external literature data and clinical relevance.

- Appendix D and Appendix G – Added that study drug will be dispensed at Week 104.

  Rationale: To accommodate subjects who enter the open-label extension for applicable countries.

- Appendix F – Added appendix to include information on the overall study design and plan for applicable countries in the open-label extension period.

  Rationale: To provide continued upadacitinib therapy for subjects in applicable countries to accommodate country-specific requests.

- Appendix G – Updated hsCRP to be performed by a local clinic/hospital/laboratory at Week 104.

  Rationale: To allow hsCRP to be tested locally if subjects cannot come to the site due to COVID-19 in order to assess remission status.

- Appendix G – Added footnote that pharmacodynamic (PD) samples should only be collected if PD occurs after the Double-Blind Period (Week 14 for Study 1 and Week 52 for Study 2).

  Rationale: To clarify that PD samples need to be collected if the subject discontinued after the Double-Blind Period.

In addition to the above modifications, this Amendment contains the following minor changes:

- Minor text edits as needed for consistency and clarity.
- Correct minor clerical errors for consistency throughout the protocol.
- Replaced Figure 4 with higher resolution figures.
- Added new references throughout the protocol.

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- Appendix C – Updated list of protocol signatures.
- Appendix G – Updated contact number and email address for safety concerns, and updated contact information for Protocol Deviations and Product Complaints

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APPENDIX F. OPEN-LABEL EXTENSION FOR APPLICABLE COUNTRIES

Directions for sites in countries that require continued study drug provision to accommodate country-specific needs is found throughout this appendix. Applicable countries include Belgium, Bulgaria, China, Czechia, France, Japan, Hungary, Mexico, Russia, Slovakia, Turkey, Korea, and New Zealand.

INVESTIGATIONAL PLAN

Overall Study Design and Plan (for additional details please review main Protocol)

- 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 [redacted]
- 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, which are at least 2 weeks apart, or an ASDAS (CRP) > 3.5 at one visit.
    - Subjects who flare during the Remission-Withdrawal Period will receive open-label upadacitinib 15 mg QD from the time of flare for 24 weeks (re-treatment) or until the date listed below for their respective country, whichever date is later.
    - Subjects who do not flare during the Remission-Withdrawal Period, will be followed without upadacitinib treatment until Week 152 at which point they will receive open label upadacitinib for the predefined time period, if Week 152 is before the date listed below for their respective country. If Week 152 is after the date listed below, the subject will complete the study at Week 152.
- Subjects who are not in remission at Week 104 can continue to receive open-label treatment with upadacitinib 15 mg QD for the following predefined time period per country:

Country	End of Study Date
Belgium	[redacted]
Bulgaria	
China	
Czechia	
France	
Hungary	

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Japan	[redacted]
Korea	
Mexico	
New Zealand	
Russia	
Slovakia	
Turkey	

Subjects will be evaluated for safety and tolerability of upadacitinib every 12 weeks until the end of the study. Subjects who remain active in this clinical trial 2 weeks prior to the end of study in each respective country should be contacted by the site to return for their final visit. Sites should complete the final visit by the date listed above for all the remaining active subjects.

Following country, local (if applicable) regulatory approval, and/or applicable local reimbursement approval of the study drug in a country, or at such time that development or pursuit of regulatory approval is discontinued, subjects should return to their next scheduled study visit as specified in the protocol. The dates listed above are an estimation, if regulatory approval, local reimbursement, or the decision to discontinue pursuit of regulatory approval occurs prior to the dates listed above, subjects should then be brought in for their termination visit based on the actual date. The final visit should be conducted in place of their regularly scheduled study visit. These subjects will be considered as having completed the study.

CONCOMITANT MEDICATION

For subjects who are not in remission at Week 104 and who receive open-label treatment with upadacitinib 15 mg QD after Week 104, addition or modification of axSpA medications can be made per Investigator judgment regardless of the disease activity status.

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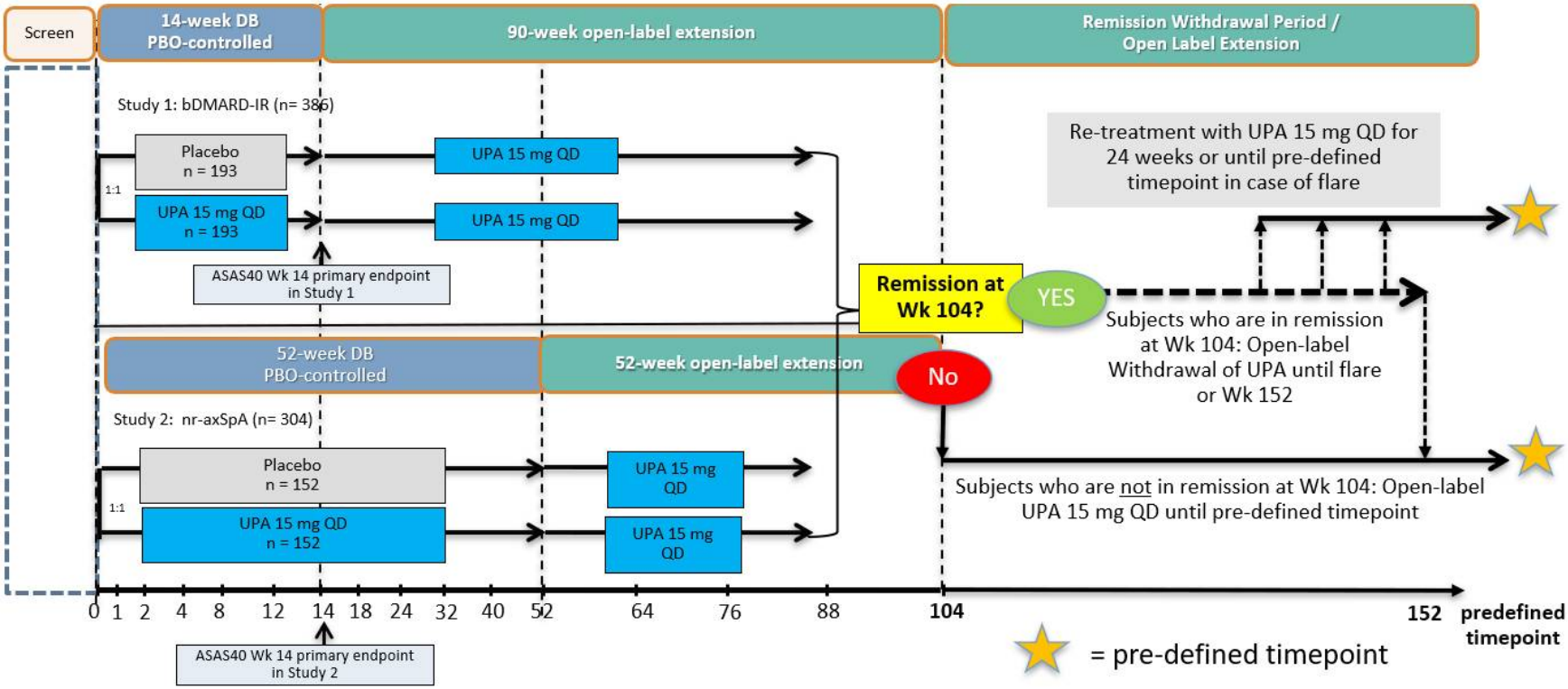
Figure 6. Study Schematic



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Study Activities Table After Week 104 for Specified Countries Listed Above

Activity	Every 12 weeks following Week 104 or completion of Remission-Withdrawal Period/Final Visit	Unscheduled Visit	30-Day F/U Visit OR Phone Call
INTERVIEWS & QUESTIONNAIRES			
Concomitant therapy	✓	✓	✓
Review and document pregnancy avoidance recommendations with females of childbearing potential	✓	✓	✓
Latent TB risk assessment questionnaire	✓ Annually		
EXAM			
Body weight	✓	✓	
Vital signs	✓	✓	
Physical Exam	✓	✓	
AE assessment	✓	✓	✓
LOCAL LAB			
Urine pregnancy test (for all female subjects of childbearing potential)	✓		
Dispense urine pregnancy tests for monthly home testing	✓		
CENTRAL LAB			
Clinical chemistry, hematology, urinalysis	✓	✓	
HBV (post-Baseline tests for subjects from Japan only)	✓		
TB test (QuantiFERON TB Gold test [or interferon gamma release assay equivalent such as T-SPOT test] and/or local PPD skin test, if required)	✓ Annually		
TREATMENT			
Dispense Study Drug	✓(excludes Final Visit)		

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