Official Title of Study:

A Randomized, Head-to-head, Single-blind Study to Compare the Response to Treatment With Subcutaneous Abatacept vs Adalimumab, on Background Methotrexate, in Adults With Early, Seropositive Rheumatoid Arthritis Who Have "Shared Epitope" HLA Class II Risk Alleles and Have an Inadequate Response to Methotrexate

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CLINICAL PROTOCOL IM101863

A Randomized, Head-to-head, Single-blind Study to Compare the Response to Treatment with Subcutaneous Abatacept vs Adalimumab, on Background Methotrexate, in Adults with Early, Seropositive Rheumatoid Arthritis Who Have "Shared Epitope" HLA Class II Risk Alleles and Have an Inadequate Response to Methotrexate

Short Title: Abatacept vs Adalimumab in Early, Seropositive, and SE-positive RA

Protocol Amendment Number: 01

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DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Protocol Amendment 01	26-Feb-2021	Removed pharmacokinetics and immunogenicity assessments, removed Krebs von den Lungen-6 testing, and clarified country-specific requirements.
Original Protocol	29-Jan-2021	Not applicable

OVERALL RATIONALE FOR PROTOCOL AMENDMENT 01:

The primary reasons for these changes are to remove pharmacokinetics (PK) and immunogenicity (IMG) assessments, remove Krebs von den Lungen-6 (KL-6) testing, and clarify country-specific requirements.

This protocol amendment applies to all participants.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 2: Schedule of Activities; Section 7.1: Treatments Administered; Section 9.5: Pharmacokinetics and Immunogenicity (and all subsections); Section 9.8.3: Additional Research Collection; Section 10.2: Populations for Analyses; Section 10.3.2: Safety Analyses; Section 10.3.3.1: PK Analyses	Removed all language related to PK and IMG assessments.	Given that the PK and IMG of abatacept have been studied extensively in this rheumatoid arthritis (RA) population (ie, methotrexate-inadequate responders) in addition to the broader RA population, PK and IMG assessments can be omitted from the study.
Section 2: Schedule of Activities; Section 9.4.7: Clinical Safety Laboratory Assessments	The following updates were made: • Removed KL-6 testing. • Removed (1 to 3) β-D glucan testing.	These changes were made for the following reasons: • KL-6 testing is no longer applicable. • Country-specific (1 to 3) β-D glucan testing is now included in Appendix 16.
[redacted]		

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Appendix 16: Country-specific Requirements/Differences	The following updates were made: • Removed country-specific differences related to human immunodeficiency virus and hepatitis. • Removed Norway from list of countries. • For Japan: – Updated differences for (1 to 3) β-D glucan testing. – Added differences related to hepatitis B testing. – Added differences related to self-administration training. – Removed differences for contraceptive guidance.	Clarified country-specific requirements/differences.
All	Minor formatting and typographical corrections.	Changes are minor, and therefore have not been summarized.

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1 SYNOPSIS

Protocol Title: A Randomized, Head-to-head, Single-blind Study to Compare the Response to Treatment with Subcutaneous Abatacept vs Adalimumab, on Background Methotrexate, in Adults with Early, Seropositive Rheumatoid Arthritis Who Have "Shared Epitope" HLA Class II Risk Alleles and Have an Inadequate Response to Methotrexate

Short Title: Abatacept vs Adalimumab in Early, Seropositive, and SE-positive RA

Study Phase: 3

Rationale:

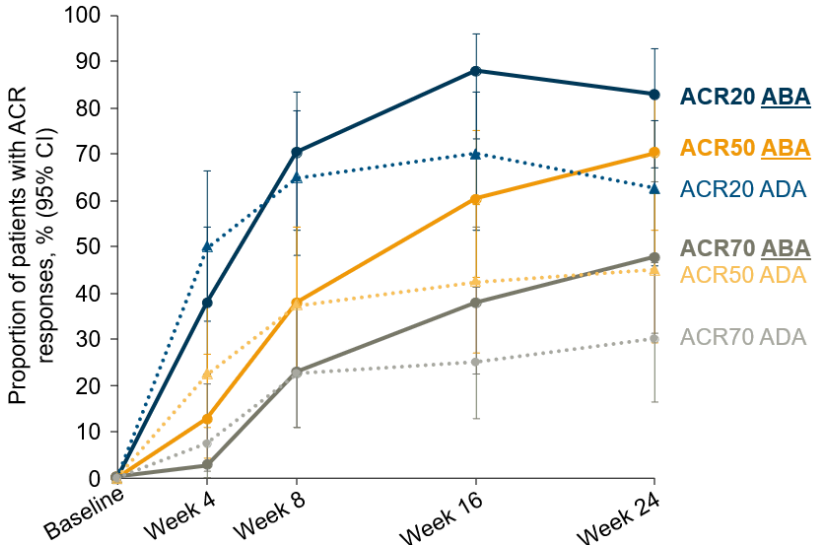
Available data sources describing the use of abatacept for the treatment of rheumatoid arthritis (RA) show that a subset of RA patients have characteristics that may predict a better response to abatacept than to treatment with tumor necrosis factor (TNF) inhibitor. These characteristics are: 1) early disease duration; 2) high titers of anti-citrullinated protein antibodies (ACPA) and rheumatoid factor (RF; dual seropositivity); 3) inadequate response to initial treatment with methotrexate (MTX; methotrexate inadequate responders [MTX-IR]); and 4) presence of the “shared epitope” (SE). Together, these characteristics appear to comprise a predictive response profile for enhanced clinical response with abatacept therapy. This study will test whether this predictive response profile will lead to better clinical outcomes for treatment with abatacept in this patient population compared with treatment with adalimumab.

Analyses of several prior Bristol-Myers Squibb (BMS) randomized, controlled trials (RCTs) of abatacept for the treatment of RA and external real-world clinical data suggested that RA patients early in their disease course who had high titers of ACPA demonstrated higher, differential benefit from abatacept therapy. In the Abatacept vs adaliMumab comParison in bioLogic-naivE RA participants with background methotrexate (AMPLE) study (IM101235; ClinicalTrials.gov: NCT00929864), baseline anti-cyclic citrullinated peptide (anti-CCP-2) positivity was associated with a better response to both abatacept and adalimumab; however, participants with the highest anti-CCP-2 antibody concentrations (1060-4894 IU/mL) had better clinical response with abatacept but not with adalimumab. Similarly, in the Assessing Very Early Rheumatoid Arthritis Treatment (AVERT; IM101226; ClinicalTrials.gov: NCT01142726) study, a higher proportion of anti-CCP-2-positive (anti-CCP-2+) vs anti-CCP-2-negative (anti-CCP-2-) participants achieved remission after 1 year of treatment with abatacept with background MTX. In a United States (US)-based clinical practice setting, greater efficacy was seen with abatacept, but not TNF inhibitors, in anti-CCP-2+ vs anti-CCP-2- patients with RA. In a meta-analysis of 19 studies, anti-CCP-2 positivity was associated with better European League Against Rheumatism (EULAR) responses in patients with RA receiving abatacept but not in those receiving a TNF inhibitor.

To further explore this early seropositive population and identify any novel characteristics that could confirm or further refine an RA subpopulation with differential benefit from treatment with abatacept over adalimumab, BMS executed the IM101567 study (Early AMPLE; ClinicalTrials.gov: NCT02557100). This was a mechanistic, head-to-head study between abatacept and adalimumab, designed to study a population of RA participants enriched for

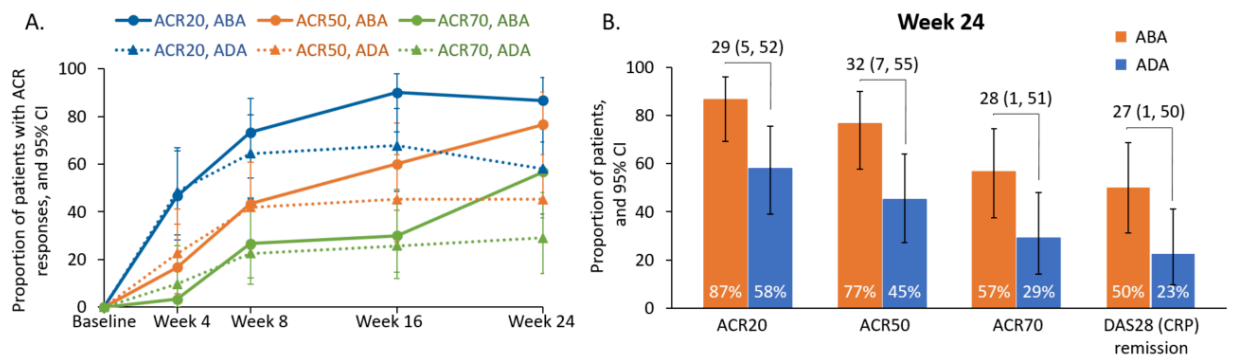
abatacept differential responders. These adult RA participants were characterized by: a) ≤ 12 months of disease symptoms; b) seropositivity for both RF and ACPA (≥ 3× upper limit of normal [ULN]); and c) moderate-to-severe RA (American College of Rheumatology [ACR]/EULAR 2010 criteria, and Disease Activity Score 28-joint count calculated using C-reactive protein [DAS28-CRP] ≥ 3.2) in spite of at least 3 months of therapy with methotrexate (MTX-IR). Eighty participants were randomized 1:1 to subcutaneous (SC) abatacept 125 mg weekly or SC adalimumab 40 mg every 2 weeks (both with stable, background oral MTX weekly) for 24 weeks. Higher ACR responses were seen with abatacept vs adalimumab after 24 weeks of treatment, supporting prior findings that early seropositive RA patients should respond better to abatacept (see Figure 1-1). To further refine the abatacept-response group, BMS prospectively explored the relationship between clinical efficacy to abatacept or adalimumab and the presence of a genetic marker known as the SE. The SE is encoded by a group of human leukocyte antigen Class II histocompatibility antigen, DRB2 beta chain (*HLA-DRB1*) alleles with shared homology in the beta chain (HLA-DRB1) at positions 70-74. The SE is a genetic marker of risk associated with earlier-onset, ACPA-positive (ACPA+), destructive RA and is present in 70-80% of ACPA+ RA patients. Seventy-five percent of Early AMPLE randomized participants were SE-positive (SE+) and showed even higher differential ACR response to abatacept compared with adalimumab (see Figure 1-2), suggesting that the differential benefit to therapy with abatacept in this population is driven by the SE+ participant subgroup. The current study, IM101863, aims to confirm the findings from Early AMPLE and other studies by demonstrating the superiority in efficacy of abatacept compared with adalimumab in a population of RA patients characterized by early disease, MTX-IR, and seropositivity (RF-positive [RF+] and ACPA+) and expressing SE HLA Class II risk alleles (ie, SE+).

Figure 1-1: Proportion of Patients with ACR Responses Over Time During the Single-blind Treatment Period (as-treated analysis IM101567)



Abbreviations: ABA, abatacept; ACR, American College of Rheumatology; ACR20/50/70, 20%/50%/70% improvement in American College of Rheumatology criteria; ADA, adalimumab; CI, confidence interval.
Note: Missing values were imputed as nonresponders. Error bars represent 95% CI.

Figure 1-2: Proportion of SE+ Patients with (A) ACR Responses Over Time and (B) Week 24 ACR Responses and DAS28-CRP Remission by Treatment Group (as-treated analysis IM101567)



Abbreviations: ABA, abatacept; ACR20/50/70, 20%/50%/70% improvement in American College of Rheumatology criteria; ADA, adalimumab; CI, confidence interval; DAS28-CRP, Disease Activity Score 28 joint count calculated using C-reactive protein; SE, shared epitope.

Note: ABA, n = 30; ADA, n = 31. DAS28-CRP remission was defined as DAS28-CRP < 2.6. Patients with missing data for efficacy parameters at Week 24 were imputed as nonresponders. Values above bars show estimate of difference (95% CI) for ABA vs ADA.

Study Population:

Adults (≥ 18 years old) who have early RA, defined as symptoms of RA (pain, stiffness, or joint swelling) for no more than 12 months prior to screening and satisfy the ACR/EULAR 2010 criteria for the classification of RA at some point during the 12-month period prior to signing the informed consent form (ICF). Participants who have had a single isolated episode of palindromic symptoms that occurred less than 2 years prior to enrollment are still eligible. Participants must have a second-generation anti-CCP-2 test result that is greater than 3× ULN and be RF+ at screening according to central laboratory testing. The anti-CCP-2 test is commonly used in the clinic to measure ACPA, and the 3× ULN cutoff in the anti-CCP-2 central laboratory test ensures a stable positive ACPA profile. Participants must have a DAS28-CRP of at least 3.2 at screening and have at least 3 tender and at least 3 swollen joints (excluding distal interphalangeals) at screening and at randomization. [redacted]

Eligible participants must have been treated with MTX for at least 12 weeks prior to randomization with a stable dose of oral or parenteral MTX for at least 4 weeks prior to randomization (ie, MTX-IR). The stable dose of oral or parenteral MTX should be the maximum tolerated oral or parenteral dose (15 mg to 25 mg per week). Participants may enroll with MTX doses < 15 mg/week but ≥ 7.5 mg/week if intolerance to higher doses has been documented and the dose of oral or parenteral MTX is stable for 4 weeks prior to randomization. Participants in Japan may also enroll at doses between 7.5 and 15 mg per week at the discretion of the investigator. Participants must be naive to prior therapy with other disease-modifying antirheumatic drugs (DMARDs), except brief exposure to either sulfasalazine or hydroxychloroquine.

Table 1-1: Objectives and Endpoints

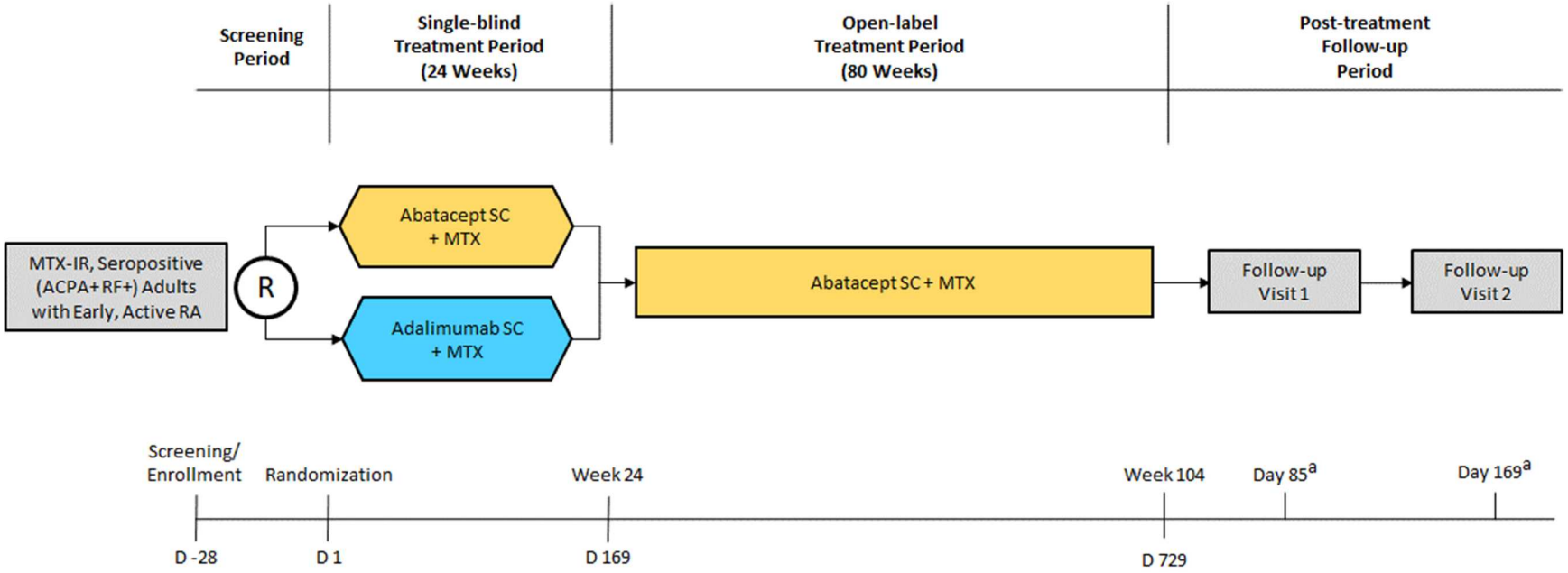
Objective	Endpoint
Primary	
• To demonstrate the superiority in efficacy of abatacept compared with adalimumab, both on background MTX, in achieving clinical response (ACR50) at Week 24, in early, seropositive (RF+ and ACPA+) RA patients with the SE HLA Class II risk alleles (ie, SE+).	• Proportion of SE+ participants meeting ACR50 response at Week 24
Key Secondary	
• To compare the efficacy of abatacept with adalimumab, both on background MTX, in achieving clinical remission criteria (DAS28-CRP remission) at Week 24 in early, seropositive RA patients with the SE HLA Class II risk alleles (ie, SE+).	• Proportion of SE+ participants achieving DAS28-CRP remission (DAS28-CRP < 2.6) at Week 24
• To compare the efficacy of abatacept with adalimumab, both on background MTX, in achieving clinical response (ACR50) at Week 24 in the whole study population of early, seropositive RA patients.	• Proportion of whole study population participants meeting ACR50 response at Week 24
• To compare the efficacy of abatacept with adalimumab, both on background MTX, in achieving clinical remission criteria (CDAI remission) at Week 24 in early, seropositive RA patients with the SE HLA Class II risk alleles (ie, SE+).	• Proportion of SE+ participants achieving CDAI remission (CDAI ≤ 2.8) at Week 24
• To compare the efficacy of abatacept with adalimumab, both on background MTX, in achieving improvement in pain at Week 24 in early, seropositive RA patients with the SE HLA Class II risk alleles (ie, SE+).	• Mean change from baseline in SE+ participant-reported pain (VAS) at Week 24
Other Secondary	
• To determine the efficacy over time by treatment in early, seropositive RA patients (SE+ subset and whole population).	• Proportion of SE+ subset and whole population achieving ACR20/50/70 responses, DAS remission, CDAI remission, SDAI remission over the SBTP and OLTP; Mean changes from baseline in DAS28-CRP, CDAI, SDAI over the SBTP and OLTP; Mean changes from baseline in the 7 ACR core components over the SBTP and OLTP
• To determine the improvement in health-related quality of life over time by treatment in early, seropositive RA patients (SE+ subset and whole population).	• Mean change from baseline in SF-36 in SE+ subset and whole population at Week 24 and Week 104 (4 physical and 4 mental subscales and the physical component and mental component summary)

Abbreviations: +, positive; ACPA, anti-citrullinated protein antibodies; ACR20/50/70, 20%/50%/70% improvement in American College of Rheumatology criteria; CDAI, Clinical Disease Activity Index; DAS28-CRP, Disease Activity Score 28-joint count calculated using C-reactive protein; MTX, methotrexate; OLTP, Open-label Treatment Period; RA, rheumatoid arthritis; RF, rheumatoid factor; SBTP, Single-blind Treatment Period; SDAI, Simple Disease Activity Index; SE, shared epitope; SF-36, 36-item Short Form Survey; VAS, visual analog scale.

Overall Design:

See schematic below for study design (Figure 1-3).

Figure 1-3: Study Design Schematic



Abbreviations: ACPA+, anti-citrullinated protein antibody-positive; D, Day; MTX, methotrexate; MTX-IR, methotrexate inadequate responders; OLTP, Open-label Treatment Period; R, randomize; RA, rheumatoid arthritis; RF+, rheumatoid factor-positive; SBTP, Single-blind Treatment Period; SC, subcutaneous.

[a] In reference to Day 729 for participants who complete the OLTP or the day of last study treatment for participants who discontinue study treatment during the SBTP or OLTP.

Screening Period:

Eligibility will be based on specified inclusion and exclusion criteria, medical history, disease activity, and safety assessments. Randomization must occur within 28 days of signing the ICF. Participants that experience delays may extend the screening period to 42 days.

Single-blind Treatment Period: Day 1 - Week 24:

On Day 1, participants will begin the Single-blind Treatment Period (SBTP) and be randomized according to a computer-generated fixed-block randomization schedule. The site must complete the Tender (68)/Swollen (66) Joint Count to verify the final inclusion criteria (at least 3 tender and at least 3 swollen joints, excluding distal interphalangeals) prior to contacting Interactive Response Technology (IRT) for randomization. The site must also have the results of the genotyping for the SE from the central lab prior to randomization because participants will be stratified by SE status (positive/negative). Participants will be randomized to 1 of 2 parallel treatment arms in a 1:1 ratio:

1) Abatacept SC (125 mg) weekly with background stable MTX therapy
2) Adalimumab SC (40 mg) once every 2 weeks with background stable MTX therapy

Abatacept and adalimumab administration: On Day 1, participants and/or personal caregivers will be trained in self administration of SC injections using prefilled syringes.

Methotrexate: Participants must have been treated with MTX for at least 12 weeks prior to randomization with a stable dose of oral or parenteral MTX for at least 4 weeks prior to randomization. The stable dose of oral or parenteral MTX should be the maximum tolerated dose (minimum of 15 mg and maximum of 25 mg per week). A dose of MTX < 15 mg/week but ≥ 7.5 mg/week is permitted if intolerance to higher doses has been recorded in the source documents and the dose of oral or parenteral MTX is stable for 4 weeks prior to randomization. Participants in Japan may also enroll at doses between 7.5 and 15 mg per week at the discretion of the investigator.

Switching between routes of administration of MTX or dose adjustment for any reason other than toxicity is not permitted during the SBTP.

All participants must receive folic acid, folinic acid, or leucovorin according to the manufacturer's recommendations.

Open-label Treatment Period: Week 24 - Week 104:

At Week 24, all participants ongoing in the Open-label Treatment Period (OLTP) will receive abatacept 125 mg SC weekly for the duration of the treatment period:

1) Participants receiving abatacept SC (125 mg) weekly will continue to receive abatacept.
2) Participants receiving adalimumab SC (40 mg) will switch to abatacept SC (125 mg) weekly at Week 24.

3) Participants will continue to be treated with oral or parenteral MTX as described above. Adjustments in MTX dosing and route of administration is allowed at the investigator's discretion in the OLTP.
4) Participants not wishing to continue on open-label abatacept have the option of discontinuing treatment at the end of the SBTP and continuing to the Post-treatment Follow-up Period (PTFUP).

Post-treatment Follow-up Period:

There will be a PTFUP for safety assessments. This period will be required only for some participants based on how they will be treated after study completion or Early Termination. Participants who complete the treatment periods (ie, OLTP) or discontinue prior to completing the OLTP AND are not treated with post-study abatacept, regardless of the source, will need to complete the PTFUP. This will consist of 2 follow-up visits on Day 85 and Day 169 post cessation of investigational product. The PTFUP will begin on Day 729 for participants who complete the OLTP. The PTFUP will begin on the day of last study treatment for participants who discontinue study treatment during the SBTP or OLTP. Participants who complete the OLTP or discontinue at any time prior to completing the OLTP AND are treated with post-study abatacept, regardless of the source, will not need to complete the PTFUP.

Number of Participants: 300

It is anticipated that approximately 400 participants will be screened to treat 300 eligible participants with abatacept (n = 150) or adalimumab (n = 150) with background stable MTX therapy. [redacted]

Treatment Arms and Duration:

The study treatments for IM101863 are provided in Table 1-2.

Table 1-2: Study Treatment for IM101863

Medication	Potency	IP/Non-IMP
Abatacept SC injection	125 mg/prefilled syringe (125 mg/mL)	IP
Adalimumab SC injection	40 mg/prefilled syringe (40 mg/0.4 mL)	IP

Abbreviations: IMP, investigational medicinal product; IP, investigational product.

Data Monitoring Committee: Not applicable.

2 SCHEDULE OF ACTIVITIES

Table 2-1: Screening Procedural Outline (IM101863)

Procedure	Screening Visit[a]	Extended Screening Visit[b]	Notes
Eligibility Assessments			
Informed Consent	X		
Enroll Participant	X		Contact IRT for participant number. If participant does not meet eligibility criteria, contact IRT to screen fail participant.
Inclusion/Exclusion Criteria	X	X	
Medical History	X	X	
Safety Assessments			
Complete Physical Examination	X		Includes height and weight.
Targeted Physical Examination		X	See Section 9.4.1.
Vital Signs	X	X	Includes body temperature, and seated blood pressure and heart rate.
Prior and Concomitant Medication Use	X	X	
Serious Adverse Events Assessment	X	X	Causality assessments must be performed by a blinded Clinical Assessor.
Smoking History and Current Status	X		
TB Screening Test	X		See Section 9.4.5. TB testing (IFN-γ release assay or PPD) performed locally within 1 month prior to Screening will be accepted. A copy of the report must be filed in the participant binder.
Chest X-ray	X		Required only if the results of a chest x-ray performed within the 3 months prior to (re)enrollment are not available (see Section 9.4.2).
Laboratory Tests		Perform as noted below and any safety laboratory tests deemed necessary.	
Hematology (CBC)	X	X	See Table 9.4.7-1.
Blood Chemistry	X	X	See Table 9.4.7-1.
hsCRP	X	X	hsCRP falls under blood chemistry but will be tracked separately.
Urinalysis	X		See Table 9.4.7-1.

Table 2-1: Screening Procedural Outline (IM101863)

Procedure	Screening Visit[a]	Extended Screening Visit[b]	Notes
Hepatitis Screening	X		See Section 9.4.6 and Section 9.4.7 for details of testing for positive results and other guidance.
HIV	X		Performed only where required or local standard of care (see Section 9.4.7).
Urine Pregnancy Test	X	X	WOCBP only; serum test if needed (see Section 9.4.7). Performed locally.
FSH	X		As needed (see Section 9.4.7 and Appendix 4).
[redacted]			
Anti-CCP-2	X		See Section 9.8.
RF	X		See Section 9.8.
HLA-DRB1 Shared Epitope Alleles Testing	X		Result required for randomization. See Section 9.8.
Disease Assessments			
Tender (68)/Swollen (66) Joint Count	X	X	Must be performed by a blinded Clinical Assessor (see Section 9.1.2).
Participant Global Assessment of Disease Activity	X	X	See Appendix 5.

Abbreviations: anti-CCP-2, anti-cyclic citrullinated peptide-2; CBC, complete blood count; FSH, follicle-stimulating hormone; HIV, human immunodeficiency virus; HLA-DRB1, human leukocyte antigen Class II histocompatibility antigen, DRB1 beta chain; hsCRP, high-sensitivity C-reactive protein; IFN-γ, interferon gamma; IRT, Interactive Response Technology; PPD, purified protein derivative; RF, rheumatoid factor; TB, tuberculosis; WOCBP, women of childbearing potential.

[a] Randomization must occur within 28 days of signing the informed consent form. Participants who experience delays may extend the screening period to 42 days (see Section 6.4.1.2). Rescreening is allowed (see Section 6.4.1.3).

[b] Please see Section 6.4.1.2 (Extended Screening) for further information.

Table 2-2: On-treatment Procedural Outline (IM101863): Single-blind Treatment Period (SBTP)

Procedure	Day 1 (Rand.) Visit 1	Week 4 Visit 2 (± 3 days)	Week 8 Visit 3 (± 3 days)	Week 12 Visit 4 (± 3 days)	Week 16 Visit 5 (± 3 days)	Week 20 Visit 6 (± 3 days)	Week 24a/ ET Visit 7a (± 3 days)	Notes
		Day 29	Day 57	Day 85	Day 113	Day 141	Day 169 or ET	
Eligibility Assessments								
Inclusion/Exclusion Criteria	X							Review of inclusion/exclusion criteria that are relative to the Randomization day.
Tender (68)/Swollen (66) Joint Count	X							Must be performed by a blinded Clinical Assessor; to be performed prior to randomization (see Section 9.1.2).
Randomize Participant Using IRT	X							Contact of IRT is required to randomize the participant on Day 1 (see Section 7.2).
Safety Assessments								
Targeted Physical Examination	X	X	X	X	X	X	X	
Vital Signs	X	X	X	X	X	X	X	Body temperature, seated blood pressure, and heart rate.
Adverse Events Assessment	X	X	X	X	X	X	X	Causality assessments must be performed by a blinded Clinical Assessor.
Concomitant Medication Use	X	X	X	X	X	X	X	
Laboratory Tests								
Urine Pregnancy Test	X	X	X	X	X	X	X	WOCBP only; serum test if needed (see Section 9.4.7). Performed locally.
Hematology (CBC)	X	X	X		X		X	See Table 9.4.7-1.
Blood Chemistry	X	X	X	X	X	X	X	See Table 9.4.7-1.
hsCRP	X	X	X	X	X	X	X	

Table 2-2: On-treatment Procedural Outline (IM101863): Single-blind Treatment Period (SBTP)

Procedure	Day 1 (Rand.) Visit 1	Week 4 Visit 2 (± 3 days)	Week 8 Visit 3 (± 3 days)	Week 12 Visit 4 (± 3 days)	Week 16 Visit 5 (± 3 days)	Week 20 Visit 6 (± 3 days)	Week 24a/ ET Visit 7a (± 3 days)	Notes
		Day 29	Day 57	Day 85	Day 113	Day 141	Day 169 or ET	
[redacted]								
RF	X			X			X	See Section 9.8.
Anti-CCP-2	X			X			X	See Section 9.8.
[redacted]								
Efficacy Assessments								
Tender (68)/Swollen (66) Joint Count		X	X	X	X	X	X	Must be performed by a blinded Clinical Assessor (see Section 9.1.2).
Participant Assessment of Pain	X	X	X	X	X	X	X	See Appendix 6.
Participant Global Assessment of Disease Activity	X	X	X	X	X	X	X	See Appendix 5.
Physician Global Assessment of Disease Activity	X	X	X	X	X	X	X	Must be performed by a blinded Clinical Assessor (see Section 9.1.1 and Appendix 7).
Physical Function (HAQ-DI)	X	X	X	X	X	X	X	See Appendix 8.
Quality of Life Scale (SF-36)	X						X	See Appendix 9.

Table 2-2: On-treatment Procedural Outline (IM101863): Single-blind Treatment Period (SBTP)

Procedure	Day 1 (Rand.) Visit 1	Week 4 Visit 2 (± 3 days)	Week 8 Visit 3 (± 3 days)	Week 12 Visit 4 (± 3 days)	Week 16 Visit 5 (± 3 days)	Week 20 Visit 6 (± 3 days)	Week 24a/ ET Visit 7a (± 3 days)	Notes
		Day 29	Day 57	Day 85	Day 113	Day 141	Day 169 or ET	
Work Productivity and Activity (WPAI-RA v2)	X						X	See Appendix 10.
Fatigue (FACIT-F v4)	X			X			X	See Appendix 11.
Duration of Morning Stiffness	X			X			X	See Appendix 12.
Study Treatment								
Contact IRT	X	X	X	X	X	X		Contact of IRT is required to dispense medication at each office visit.
Dispense Study Treatment	X	X	X	X	X	X		
Self-injection and Diary Card Training	X							
Dispense Diary Cards	X	X	X	X	X	X		
Collect and Review Diary Cards		X	X	X	X	X	X	
Dosing of Weekly Abatacept/Every-2-weeks Adalimumab	X	X	X	X	X	X		Must be self-administered weekly (abatacept) or every 2 weeks (adalimumab) between visits (see Section 7.1).
Reconciliation of Abatacept or Adalimumab Monthly Kits		X	X	X	X	X	X	

Abbreviations: anti-CCP-2, anti-cyclic citrullinated peptide-2; CBC, complete blood count; [redacted] ET, early termination; FACIT-F, Functional Assessment of Chronic Illness Therapy - Fatigue; HAQ-DI, Health Assessment Questionnaire Disability Index; hsCRP, high-sensitivity C-reactive protein; IRT, Interactive Response Technology; OLTP, Open-label Treatment Period; [redacted] Rand., randomization; RF, rheumatoid factor; [redacted] SF-36, 36-item Short Form Survey; WOCBP, women of childbearing potential; WPAI-RA, Work Productivity and Activity Impairment Questionnaire - Rheumatoid Arthritis.

Table 2-3: On-treatment Procedural Outline (IM101863): Open-label Treatment Period (OLTP)

Procedure	Wk 24b V7b (± 3 Days)	Wk 28 V8 (± 7 Days)	Wk 32 V9 (± 7 Days)	Wk 36 V10 (± 7 Days)	Wk 40 V11 (± 7 Days)	Wk 44 V12 (± 7 Days)	Wk 48 V13 (± 7 Days)	Wk 52 V14 (± 7 Days)	Wk 60 V15 (± 7 Days)	Wk 68 V16 (± 7 Days)	Wk 76 V17 (± 7 Days)	Wk 84 V18 (± 7 Days)	Wk 92 V19 (± 7 Days)	Wk 104/ET V20 (± 7 Days)	Notes
	Day 169	Day 197	Day 225	Day 253	Day 281	Day 309	Day 337	Day 365	Day 421	Day 477	Day 533	Day 589	Day 645	Day 729	
Safety Assessments															
Targeted Physical Examination		X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital Signs		X	X	X	X	X	X	X	X	X	X	X	X	X	Body temperature, seated blood pressure, and heart rate.
Concomitant Medication Use		X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Events Assessment		X	X	X	X	X	X	X	X	X	X	X	X	X	Causality assessments must be performed by a blinded Clinical Assessor.
Laboratory Tests															
Urine Pregnancy Test		X	X	X	X	X	X	X	X	X	X	X	X	X	WOCBP only; serum test if needed (see Section 9.4.7). Performed locally.
Hematology (CBC)		X		X		X		X	X	X	X	X	X	X	
Blood Chemistry		X		X		X		X	X	X	X	X	X	X	
hsCRP		X	X	X	X	X	X	X	X	X	X	X	X	X	

Table 2-3: On-treatment Procedural Outline (IM101863): Open-label Treatment Period (OLTP)

Procedure	Wk 24b V7b (± 3 Days) Day 169	Wk 28 V8 (± 7 Days) Day 197	Wk 32 V9 (± 7 Days) Day 225	Wk 36 V10 (± 7 Days) Day 253	Wk 40 V11 (± 7 Days) Day 281	Wk 44 V12 (± 7 Days) Day 309	Wk 48 V13 (± 7 Days) Day 337	Wk 52 V14 (± 7 Days) Day 365	Wk 60 V15 (± 7 Days) Day 421	Wk 68 V16 (± 7 Days) Day 477	Wk 76 V17 (± 7 Days) Day 533	Wk 84 V18 (± 7 Days) Day 589	Wk 92 V19 (± 7 Days) Day 645	Wk 104/ET V20 (± 7 Days) Day 729	Notes
[redacted]															
RF				X				X						X	See Section 9.8.
Anti-CCP-2				X				X						X	See Section 9.8.
[redacted]															
Efficacy Assessments															
Tender (68)/Swollen (66) Joint Count		X	X	X	X	X	X	X	X	X	X	X	X	X	Must be performed by a blinded Clinical Assessor (see Section 9.1.2).
Participant Assessment of Pain		X	X	X	X	X	X	X	X	X	X	X	X	X	See Appendix 6.
Participant Global Assessment of Disease Activity		X	X	X	X	X	X	X	X	X	X	X	X	X	See Appendix 5.

Table 2-3: On-treatment Procedural Outline (IM101863): Open-label Treatment Period (OLTP)

Procedure	Wk 24b V7b (± 3 Days)	Wk 28 V8 (± 7 Days)	Wk 32 V9 (± 7 Days)	Wk 36 V10 (± 7 Days)	Wk 40 V11 (± 7 Days)	Wk 44 V12 (± 7 Days)	Wk 48 V13 (± 7 Days)	Wk 52 V14 (± 7 Days)	Wk 60 V15 (± 7 Days)	Wk 68 V16 (± 7 Days)	Wk 76 V17 (± 7 Days)	Wk 84 V18 (± 7 Days)	Wk 92 V19 (± 7 Days)	Wk 104/ET V20 (± 7 Days)	Notes
	Day 169	Day 197	Day 225	Day 253	Day 281	Day 309	Day 337	Day 365	Day 421	Day 477	Day 533	Day 589	Day 645	Day 729	
Physician Global Assessment of Disease Activity		X	X	X	X	X	X	X	X	X	X	X	X	X	Must be performed by a blinded Clinical Assessor (see Section 9.1.1 and to Appendix 7).
Physical Function (HAQ-DI)		X	X	X	X	X	X	X	X	X	X	X	X	X	See Appendix 8.
Quality of Life Scale (SF-36)								X						X	See Appendix 9.
Work Productivity and Activity (WPAI-RA v2)								X						X	See Appendix 10.
Fatigue (FACIT-F v4)								X						X	See Appendix 11.
Duration of Morning Stiffness								X						X	See Appendix 12.
Study Treatment Administration															
Contact IRT	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Contact of IRT is required to dispense medication at each office visit.
Dispense Diary Cards	X	X	X	X	X	X	X	X	X	X	X	X	X		
Collect and Review Diary Cards		X	X	X	X	X	X	X	X	X	X	X	X	X	

Table 2-3: On-treatment Procedural Outline (IM101863): Open-label Treatment Period (OLTP)

Procedure	Wk 24b V7b (± 3 Days)	Wk 28 V8 (± 7 Days)	Wk 32 V9 (± 7 Days)	Wk 36 V10 (± 7 Days)	Wk 40 V11 (± 7 Days)	Wk 44 V12 (± 7 Days)	Wk 48 V13 (± 7 Days)	Wk 52 V14 (± 7 Days)	Wk 60 V15 (± 7 Days)	Wk 68 V16 (± 7 Days)	Wk 76 V17 (± 7 Days)	Wk 84 V18 (± 7 Days)	Wk 92 V19 (± 7 Days)	Wk 104/ET V20 (± 7 Days)	Notes
	Day 169	Day 197	Day 225	Day 253	Day 281	Day 309	Day 337	Day 365	Day 421	Day 477	Day 533	Day 589	Day 645	Day 729	
Dispense Urine Pregnancy Kits for WOCBP for Home Use Every 4 Weeks								X	X	X	X	X	X		Not applicable if serum pregnancy testing is required per local regulations.
Dosing of Weekly Abatacept	X	X	X	X	X	X	X	X	X	X	X	X	X		Abatacept must be self-administered weekly between visits. See Section 7.1.
Dispense Abatacept Kits	X	X	X	X	X	X	X	X	X	X	X	X	X		See Section 7.2.
Reconciliation of Abatacept Kits		X	X	X	X	X	X	X	X	X	X	X	X	X	

Abbreviations: anti-CCP-2, anti-cyclic citrullinated peptide-2; CBC, complete blood count; ET, early termination; FACIT-F, Functional Assessment of Chronic Illness Therapy - Fatigue; HAQ-DI, Health Assessment Questionnaire Disability Index; hsCRP, high-sensitivity C-reactive protein; IRT, Interactive Response Technology; [redacted] RF, rheumatoid factor; [redacted] SF-36, 36-item Short Form Survey; V, Visit; Wk, Week; WOCBP, women of childbearing potential; WPAI-RA, Work Productivity and Activity Impairment Questionnaire - Rheumatoid Arthritis.

Table 2-4: Post-treatment Follow-up Period (PTFUP; IM101863)

Procedure	Week 12 FU V1 (± 10 days)[a] Day 85	Week 24 FU V2 (± 10 days)[a] Day 169	Notes
Safety Assessments			
Vital Signs	X	X	Body temperature, seated blood pressure, and heart rate.
Adverse Events Assessment	X	X	
Concomitant Medication Report	X	X	
Laboratory Assessments			
Urine Pregnancy Test	X	X	WOCBP only; serum test if needed (see Section 9.4.7). Performed locally.

Abbreviations: FU, Follow-up; OLTP, Open-label Treatment Period; PTFUP, Post-treatment Follow-up Period; SBTP, Single-blind Treatment Period; V, Visit; WOCBP, women of childbearing potential.

[a] Visits only apply to participants who complete the study at Day 729 or discontinue study treatment during the SBTP or OLTP AND are not treated with abatacept as a post-study drug. The first day of the PTFUP is Day 729 for participants who complete the OLTP or the day of last study treatment for participants who discontinue study treatment during the SBTP or OLTP. Participants who complete the OLTP or discontinue at any time prior to completing the OLTP AND are treated with post-study abatacept, regardless of the source, will not need to complete the PTFUP. The follow-up visit should ideally be an in-person visit. If this is not possible, a telephone follow-up visit will be performed to confirm the results of the urine pregnancy test as well as adverse event and concomitant medication review. Vital signs will not be collected as part of a telephone follow-up phone visit.

3 INTRODUCTION

Rheumatoid arthritis (RA) is the most common chronic inflammatory arthritis, affecting approximately 1% of the population worldwide.[1] It is a complex and progressive disease with several heterogeneous aspects, including clinical presentation, detectable serological biomarkers, genetic risk factors, and speed of disease progression.[2,3,4,5] Women are 2 to 3 times more likely to develop the disease as compared with men, with a peak incidence between the fourth and sixth decades of life.[6,7,8,9] The etiology of RA involves genetic and epigenetic components, as well as environmental stimuli, such as cigarette smoking, dust exposure, and the microbiome, which represents an "internal" environment.[10] The natural history of RA is characterized by joint destruction, impaired physical function, and poor health-related quality of life. Joint erosions can be seen within 6 months of disease onset in the majority of patients and occur more rapidly in the first year compared with later disease.[11] Radiographic evidence of joint damage can be difficult to detect in early RA but has been shown to progress in a linear manner after the first year, and there is little evidence that current therapies can reverse the structural damage once it occurs.[12]

The underlying pathophysiology of RA involves an interplay between the adaptive and innate immune systems. Several environmental and genetic factors are prominent risks for the development and clinical course of RA.[4] The role of genetics in RA was first identified by researchers who noted that lymphocytes from RA patients were less likely to stimulate lymphocytes from other unrelated RA patients in mixed lymphocyte cultures.[13] The genetic basis of this was later identified as being due to the high frequency of related human leukocyte antigen Class II histocompatibility antigen, DRB1 beta chain (*HLA-DRB1*) locus alleles among RA patients, a major histocompatibility complex Class II protein receptor. These *HLA-DRB1* alleles encode for a common amino acid motif in codon positions 70-74. Together these alleles are referred to as the shared epitope (SE), and they increase the risk of developing, and the severity of, RA.[14] While the specific *HLA-DRB1* risk allele present shows regional variability, they all share the same amino acid motif of the SE, indicating the SE is a genetic risk shared across human populations.[15]

Abnormalities in the cellular and humoral immune response in RA drive the production of autoantibodies (such as rheumatoid factor [RF] and anti-citrullinated protein antibodies [ACPA]) that define "seropositive" RA. Of all RA patients, approximately 70-90% are ACPA-positive (ACPA+), 60-80% are RF-positive (RF+), and ~70% are seropositive for both ACPA and RF.[3,16] Seropositivity drives a severe disease subtype of RA because autoantibodies such as ACPA and RF are directly involved in the inflammatory response that is a key driver of disease pathophysiology.[17] The presence of autoantibodies in RA is associated with increased disease activity, systemic manifestations, and joint damage.[17,18,19,20] One of the most significant genetic risk factors for ACPA+ RA is the SE, and 70-80% of ACPA+ RA patients are SE-positive (SE+; see Section 9.8.1 for definition of SE positivity).[4,21,22,23] At diagnosis, ACPA+ and ACPA-negative (ACPA-) RA patients have similar clinical presentations, but as they progress, ACPA+ patients experience more extensive radiological destruction.[24] As compared with ACPA

seropositivity, RF serostatus has a similar but less severe impact on progressive bone erosion.[5] Based on real-world data analysis of the Brigham and Women's Rheumatoid Arthritis Sequential Study (BRASS) registry, ACPA seropositivity is associated with reduced likelihood of disease remission.[25] In addition to articular disease, seropositivity is also associated with higher rates of developing various systemic manifestations, including lung involvement and cardiovascular disease, that contribute to increased morbidity and mortality of RA patients.[18,19,20,26,27,28,29,30,31,32] Consequently, seropositive RA is associated with a greater economic burden, as evidenced by a 46% higher RA-related cost as compared with seronegative RA, based on a retrospective analysis of United States (US) claims data.[33]

In general, treatment options for RA patients range from agents that provide symptomatic relief (eg, analgesics, nonsteroidal anti-inflammatory drugs [NSAIDs]), to corticosteroids and disease-modifying antirheumatic drugs [DMARDs] that affect long-term structural damage. The approach to RA treatment involves early intervention and progressive changes in therapy to improve signs and symptoms and to prevent long-term structural damage. Traditionally, patients who are early in the disease course initiate treatment with 1 or more conventional synthetic DMARDs (eg, methotrexate [MTX]). Early intervention appears to offer the best opportunity for achieving favorable outcomes, such as induction of clinical remission, prevention of long-term joint damage, and restoration of normal physical function in patients with early RA.[34,35,36,37,38,39] If there is an inadequate response to conventional synthetic DMARDs, these patients may be candidates for biologic therapy. The treatment paradigm for treating RA patients has been shifting to the early use of combination therapy with both conventional and biologic DMARDs, which has been shown to result in more favorable outcomes.[40]

Commercially available biologic agents for RA have been shown to improve the signs and symptoms of RA and decrease the progression of structural damage in patients who have had an inadequate response to at least 1 DMARD, and in patients with severe, active, and progressive disease not previously treated with DMARDs. Consistent with the principle of early treatment with combination therapy, use of these biologic agents is becoming increasingly frequent in patients with factors predictive of rapidly progressive disease, such as early radiographic erosion and positive autoantibodies, such as RF and ACPA, which have been shown to be predictive of severe erosive disease. Guidelines from organizations such as the French Society of Rheumatologists Working Group for Therapeutic Strategies for Rheumatoid Arthritis (Strategies Therapeutiques de la Polyarthrite Rhumatoıde [STPR]) and others, specifically recommend the very early use of biologic therapy in patients with poor prognostic factors, taking into account the benefit-risk profile of the different therapeutic options.

Tumor necrosis factor (TNF) antagonists, which are the most commonly prescribed biologics for RA, have demonstrated consistent and favorable benefit-risk profiles; however, many patients do not achieve an adequate response or complete control of inflammation. In those who do achieve a response, prolonged maintenance of response is difficult. In addition, there are important safety concerns associated with TNF antagonists and other biologic agents. As clinical practice shifts to the earlier use of biologics, it is anticipated that patients will be treated with biologic therapies for

a longer duration over the course of their disease. As such, the availability of a treatment option with prolonged maintenance of efficacy and a favorable long-term safety profile, such as abatacept, would be highly desirable for these patients.

Abatacept is a selective costimulation modulator that blocks the interaction between cluster of differentiation (CD) 80/CD86 on antigen-presenting cells and CD28 on T cells.[41] This interaction provides a key signal necessary for full activation of T cells. Activated T cells play an important role in the pathogenesis of RA, especially early in the disease process, by participating in the autoimmune cascade that leads to joint inflammation and destruction. It is hypothesized that autoreactive T cells may be central to this process by producing proinflammatory cytokines and providing help to B cells, leading to the production of autoantibodies, which in turn contribute to downstream inflammatory events, including the recruitment of neutrophils, elaboration of cytokines such as TNF-alpha, synovitis, and ultimately joint destruction.[42] By inhibiting CD28-mediated immune activation, abatacept blocks antigen recognition and modulates the immune response to decrease T-cell activation and antibody production. Therefore, abatacept interferes with a step hypothesized to be early in the pathogenesis of RA.

Intravenously (IV) administered abatacept was first approved in the US for the treatment of moderate-to-severe RA in adults in Dec-2005. Since then, IV abatacept has received marketing approval for the treatment of adult RA in many other countries, including the European Union (EU), Japan, Latin America, and other countries.[41]

The subcutaneous (SC) formulation of abatacept was first approved in the US for the treatment of moderate-to-severe RA in adults in Jul-2011. Abatacept SC has subsequently received marketing approval for the treatment of adult RA in the EU and other regions of the world.[41]

The IM101235 (Abatacept vs adaliMumab comParison in bioLogic-naivE RA participants with background methotrexate [AMPLE]; ClinicalTrials.gov: NCT00929864)[43] study compared the efficacy of abatacept (125 mg weekly) and TNF-alpha blockade (adalimumab, 40 mg biweekly), both in combination with MTX, in adult participants with RA for 5 or fewer years who had an inadequate response to MTX (methotrexate inadequate responders [MTX-IR]) but who were naive to a biologic DMARDs. The primary endpoint was met, demonstrating that abatacept was noninferior to adalimumab based on the proportion of participants who achieved a 20% improvement in American College of Rheumatology criteria (ACR20) at 1 year. In addition, ACR20 response rates in both treatment groups increased comparably over the 12-month treatment period.

The IM101567 (Early AMPLE; ClinicalTrials.gov: NCT02557100)[44] trial was a mechanistic head-to-head study assessing changes in the immune profile with abatacept (125 mg weekly) and TNF-alpha blockade (adalimumab, 40 mg biweekly), both in combination with MTX, in 80 adult participants with early RA (symptoms for ≤ 12 months) who had an inadequate response to MTX. Although this exploratory study did not have any primary or secondary endpoints, numerically higher American College of Rheumatology (ACR) responses were seen with abatacept vs adalimumab after 24 weeks of treatment. The study also prospectively explored the relationship

between clinical efficacy and the presence of *HLA-DRB1* risk alleles (ie, SE). The vast majority of participants randomized in the Early AMPLE study were SE+ and showed higher differential efficacy (ACR responses and Disease Activity Score 28-joint count calculated using C-reactive protein [DAS28-CRP] remission) to abatacept vs adalimumab compared with the overall population, indicating that the differential benefit to therapy with abatacept in this population is driven by the SE+ patient subgroup.

In order to confirm the exploratory observations in Early AMPLE relating to abatacept efficacy in SE+ participants, IM101863 aims to demonstrate the superiority in efficacy of abatacept compared with adalimumab in a population of RA participants characterized by early disease, MTX-IR, and seropositivity (RF+ and ACPA+) and expressing SE HLA Class II risk alleles (ie, SE+).

3.1 Study Rationale

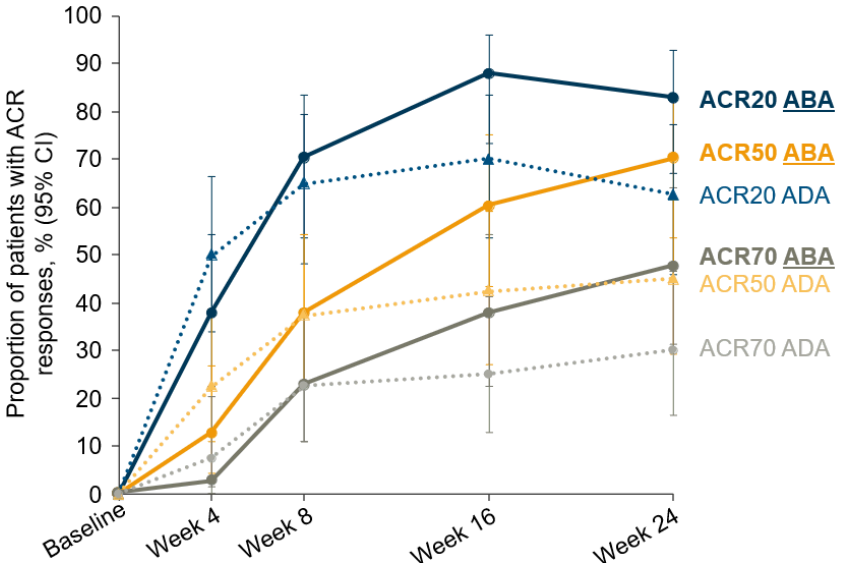
Available data sources describing the use of abatacept for the treatment of RA show that a subset of RA patients have characteristics that may predict a better response to abatacept than to treatment with TNF inhibitor.[44,45,46,47] These characteristics are: 1) early disease duration; 2) high titers of ACPA and RF (dual seropositivity); 3) inadequate response to initial treatment with MTX (MTX-IR); and 4) presence of the SE. Together, these characteristics appear to comprise a predictive response profile for enhanced clinical response with abatacept therapy. This study will test whether this predictive response profile will lead to better clinical outcomes for treatment with abatacept in this patient population compared with treatment with adalimumab.

Analyses of several prior Bristol-Myers Squibb (BMS) randomized, controlled trials (RCTs) of abatacept for the treatment of RA and external real-world clinical data suggested that RA patients early in their disease course who had high titers of ACPA demonstrated higher, differential benefit from abatacept therapy.[45,46,47,48] In the AMPLE study (IM101235; ClinicalTrials.gov: NCT00929864), baseline anti-cyclic citrullinated peptide-2 (anti-CCP-2) positivity was associated with a better response to both abatacept and adalimumab; however, participants with the highest anti-CCP-2 antibody concentrations (1060-4894 IU/mL) had better clinical response with abatacept but not with adalimumab.[45] Similarly, in the Assessing Very Early Rheumatoid Arthritis Treatment (AVERT; IM101226; ClinicalTrials.gov: NCT01142726) study, a higher proportion of anti-CCP-2-positive (anti-CCP-2+) vs anti-CCP-2-negative (anti-CCP-2-) participants achieved remission after 1 year of treatment with abatacept with background MTX.[48] In a US-based clinical practice setting, greater efficacy was seen with abatacept, but not TNF inhibitors, in anti-CCP-2+ vs anti-CCP-2- patients with RA.[46] In a meta-analysis of 19 studies, anti-CCP-2 positivity was associated with better European League Against Rheumatism (EULAR) responses in patients with RA receiving abatacept but not in those receiving a TNF inhibitor.[47]

To further explore this early seropositive population and identify any novel characteristics that could confirm or further refine an RA subpopulation with differential benefit from treatment with abatacept over adalimumab, BMS executed the IM101567 study (Early AMPLE; ClinicalTrials.gov: NCT02557100).[44] This was a mechanistic, head-to-head study between abatacept and adalimumab, designed to study a population of RA participants enriched for

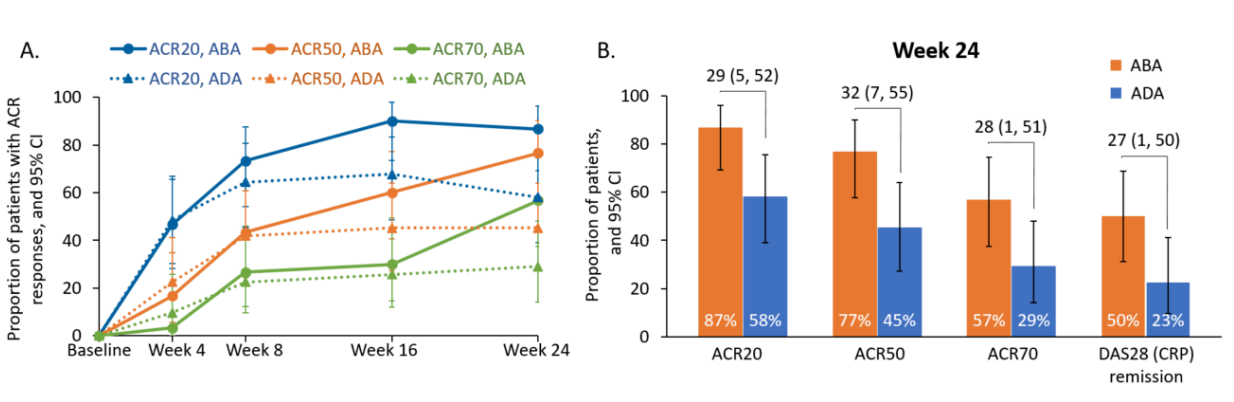
abatacept differential responders. These adult RA participants were characterized by: a) ≤ 12 months of disease symptoms; b) seropositivity for both RF and ACPA (≥ 3× upper limit of normal [ULN]); and c) moderate-to-severe RA (ACR/EULAR 2010 criteria and DAS28-CRP ≥ 3.2) in spite of at least 3 months of therapy with MTX (MTX-IR). Eighty participants were randomized 1:1 to SC abatacept 125 mg weekly or SC adalimumab 40 mg every 2 weeks (both with stable, background oral MTX weekly) for 24 weeks. Higher ACR responses were seen with abatacept vs adalimumab after 24 weeks of treatment, supporting prior findings that early seropositive RA patients should respond better to abatacept (see Figure 3.1-1). To further refine the abatacept-response group, BMS prospectively explored the relationship between clinical efficacy to abatacept or adalimumab and the presence of a genetic marker known as the SE. The SE is encoded by a group of *HLA-DRB1* alleles with shared homology in the beta chain at positions 70-74. The SE is a genetic marker of risk, associated with earlier-onset, ACPA+, destructive RA, and is present in 70-80% of ACPA+ RA patients. Seventy-five percent of Early AMPLE randomized participants were SE+ and showed even higher differential ACR response to abatacept compared with adalimumab (see Figure 3.1-2), suggesting that the differential benefit to therapy with abatacept in this population is driven by the SE+ patient subgroup. The current study, IM101863, aims to confirm the findings from the Early AMPLE and other studies by demonstrating the superiority in efficacy of abatacept compared with adalimumab in a population of RA patients characterized by early disease, MTX-IR, and seropositivity (RF+ and ACPA+) and expressing SE HLA Class II risk alleles (ie, SE+).

Figure 3.1-1: Proportion of Patients with ACR Responses Over Time During the Single-blind Treatment Period (as-treated analysis IM101567)



Abbreviations: ABA, abatacept; ACR, American College of Rheumatology; ACR20/50/70, 20%/50%/70% improvement in American College of Rheumatology criteria; ADA, adalimumab; CI, confidence interval.
Note: Missing values were imputed as nonresponders. Error bars represent 95% CI.

Figure 3.1-2: Proportion of SE+ Patients with (A) ACR Responses Over Time and (B) Week 24 ACR Responses and DAS28-CRP Remission by Treatment Group (as-treated analysis IM101567)



Abbreviations: ABA, abatacept; ACR20/50/70, 20%/50%/70% improvement in American College of Rheumatology criteria; ADA, adalimumab; CI, confidence interval; DAS28-CRP, Disease Activity Score 28-joint count calculated using C-reactive protein; SE, shared epitope.

Note: ABA, n = 30; ADA, n = 31. DAS28-CRP remission was defined as DAS28-CRP < 2.6. Patients with missing data for efficacy parameters at Week 24 were imputed as nonresponders. Values above bars show estimate of difference (95% CI) for ABA vs ADA.

3.2 Background

3.2.1 Abatacept Mechanism of Action

Abatacept is a recombinant fusion protein consisting of the extracellular domain of human cytotoxic T-lymphocyte-associated protein 4 (CTLA4) and a fragment of the Fc domain of human immunoglobulin (Ig) G1. Abatacept is the only member of a class of agents termed "selective costimulation modulators."

Effective T-cell activation involves a combination of 2 signals.[49] Starting with antigen presentation by an HLA Class II molecule, the first signal is the recognition by the T-cell receptor of an antigen presented by an antigen-presenting cell (APC) on its surface HLA molecule. The second costimulatory signal is from the interaction of CD28 on the T cell with CD80 or CD86 on the APC surface. A costimulatory signal is required for the full activation of naive T cells and may be required for the survival of autoimmune effector T cells. The SE, which is one of the strongest genetic risk factors for earlier-onset, ACPA+, erosive RA, is encoded by a group of *HLA-DRB1* alleles and comprises a small portion of the antigen-binding groove of the HLA molecule. HLA-DRB1 molecules with the SE have a higher affinity for citrullinated peptides, and thus may have increased binding and presentation of these citrullinated peptides. This SE-driven increase in the presentation of citrullinated self-peptides could lead to increase activation of autoreactive T cells.[21,49] Activated autoreactive T cells subsequently lead to increased autoreactive B-cell activation and ACPA production.[50] Indeed, RA patients who have the SE HLA risk alleles have higher levels of serum anti-CCP-2 (common laboratory assay used to measure ACPA).

Abatacept is a selective costimulation modulator that blocks the interaction between the costimulatory molecules CD80/CD86 and their receptor (CD28) that provides a key signal necessary for full activation of immune cells such as T cells. By inhibiting CD28-mediated immune activation upstream of inflammatory cytokines, such as TNF, abatacept blocks antigen recognition and modulates the immune response to decrease T-cell activation and antibody production. Activated T cells play an important role in the pathogenesis of RA, especially early in the disease process, by amplifying the inflammatory cascade that leads to joint inflammation and destruction. By inhibiting CD28-mediated T-cell activation upstream of inflammatory cytokines (eg, TNF), abatacept utilizes a unique mechanism of action that offers significant therapeutic benefit to patients with inflammatory arthritis by specifically modifying key underlying disease pathophysiology early in the cascade through autoantigen recognition blockade.

Adalimumab is a recombinant human IgG1 monoclonal antibody specific for the human TNF. Adalimumab binds specifically to TNF-alpha and blocks its interaction with the cell-surface TNF receptor p55 and p75. Adalimumab also lyses surface TNF-expressing cells in vitro in the presence of complement.[51]

IV-administered abatacept was first approved in the US for the treatment of moderate-to-severe RA in adults in Dec-2005. Since then, IV abatacept has received marketing approval for the treatment of adult RA in many other countries, including the EU, Canada, Australia, and Japan. IV abatacept was also approved in the US for the treatment of moderately-to-severely active juvenile idiopathic arthritis (JIA) in pediatric patients 6 years of age or older in Apr-2008. In addition, IV abatacept has received marketing approval for the treatment of JIA in several other countries, including the EU, Canada, and Australia.

The SC formulation of abatacept was first approved in the US for the treatment of moderate-to-severe RA in adults in Jul-2011. Abatacept SC has subsequently received marketing approval for the treatment of adult RA in the EU, Japan, and other regions of the world.

A detailed description of the chemistry, pharmacology, efficacy, and safety of abatacept is provided in the Investigator's Brochure (IB).[41]

3.2.2 Efficacy

Abatacept has an established benefit of improving signs and symptoms and halting progression of radiographic damage in patients with RA. This includes both seronegative and seropositive patients; patients with the full range of prior therapy, from naive to biologic DMARD failure; and disease duration from early to late disease. However, based on the mechanism of action of abatacept, which includes modulating the activation of autoreactive immune cells, participants with early RA would be expected to have a greater likelihood of achieving clinical remission. This was demonstrated in several studies in early RA that serve as a proof of concept that early intervention with abatacept may induce clinical remission in a substantial number of patients.

In the IM101023 study (Abatacept study to Gauge Remission and joint damage progression in MTX-naive patients with Early Erosive rheumatoid arthritis [AGREE]; ClinicalTrials.gov:

NCT00122382),[52] treatment with IV abatacept in participants with moderate-to-severe early RA (diagnosis within prior 2 years) who were MTX-naive, were seropositive for anti-CCP-2 antibodies or RF, and had erosions on imaging resulted in sustained rates of low disease activity. During the first year of the study, 41.4% of participants on abatacept plus MTX achieved Disease Activity Score (DAS)-defined remission (DAS28 < 2.6) compared with 23.3% on MTX alone. Of the participants who completed Year 2 of the study, 55.2% of participants treated with abatacept plus MTX achieved DAS28 < 2.6 compared with 26.9% on MTX alone. Of those participants who switched from MTX treatment alone to abatacept plus MTX at 1 year, 44.5% achieved DAS28 < 2.6 at 2 years.

In the IM101046 study (ADJUST; ClinicalTrials.gov: NCT00124449),[53] a population with earlier disease was targeted. In participants with a diagnosis of undifferentiated arthritis who satisfied 1 but no more than 3 classification criteria for RA (1987 classification) and who had less than 18 months of symptoms, had current active synovitis, and were positive for anti-CCP-2 antibodies, abatacept monotherapy demonstrated a therapeutic response over 6 months, which continued after drug discontinuation for another 6 months. Treatment with abatacept delayed progression to diagnosis of RA compared with the placebo control arm, which was left untreated. The placebo arm also developed more joint damage, as evidenced by radiographic evaluation and magnetic resonance imaging (MRI).

In the IM101235 study (AMPLE; ClinicalTrials.gov: NCT00929864),[43] RA patients treated with abatacept or adalimumab, on background of MTX therapy, demonstrated similar improvement across all efficacy outcomes over 2 years of treatment.[54] In a post-hoc analysis, the subset of participants enrolled in AMPLE with early, rapidly progressive disease (defined as ≤ 6 months' disease duration; seropositive for RF and/or ACPAs and had ≥ 1 radiographic erosion) were compared for efficacy outcomes.[55] When comparing abatacept with adalimumab, over 2 years of treatment, the adjusted mean change in DAS28-CRP from baseline at Day 365 was -2.58 (95% confidence interval [CI] -2.99 to -2.17) vs -1.68 (95% CI -2.10 to -1.25) and in Health Assessment Questionnaire Disability Index (HAQ-DI) from baseline at Day 365 was -0.70 (95% CI -0.90 to -0.51) vs -0.50 (95% CI -0.71 to -0.30), respectively. In this subset of RA patients with early, seropositive disease, abatacept appears to be more efficacious than adalimumab.

In another post-hoc analysis of the AMPLE study, study participants were tested for baseline anti-CCP-2 levels.[45] CCP-2 is a routine clinical assay for assessing ACPAs. Participants were divided according to CCP-2 concentrations in quartiles. Patients in the higher quartiles, especially Q4, had a better clinical response to abatacept than to adalimumab, independent of any other clinical characteristics. Here also, seropositivity and magnitude of this auto-antibody response was associated with better response to abatacept therapy.

The IM101567 trial (Early AMPLE; ClinicalTrials.gov: NCT02557100) was a mechanistic head-to-head study assessing changes in the immune profile with abatacept (125 mg weekly) and TNF-alpha blockade (adalimumab, 40 mg biweekly), both in combination with MTX, in 80 adult participants with early RA (symptoms for ≤ 12 months) who had an inadequate response to

MTX.[44] Numerically higher ACR responses were seen with abatacept vs adalimumab after 24 weeks of treatment; 50% improvement in ACR (ACR50) estimate of difference % was 25 (95% CI 2 to 46; see Figure 3.1-1). The vast majority (76%) of participants randomized in the Early AMPLE study were SE+ and showed higher differential efficacy to abatacept vs adalimumab compared with the overall population (estimate of difference % for ACR50 was 32 [95% CI 7 to 55] and for DAS28-CRP was 27 [95% CI 1 to 50]; see Figure 3.1-2).

Taken together, these previous studies provide evidence for the concept that abatacept may have differential benefits in patients who are MTX-IR with early seropositive RA, including inhibition of radiographic progression, and may enable higher rates of remission. The presence of the genetics encoding for the SE may further predict robust abatacept response.

Abatacept has been studied in RA patients with a variety of prior DMARD exposure. The understanding of the possible role that a novel therapeutic agent may have in the RA treatment paradigm has evolved to include its utility in populations based on prior DMARD experience. As a general concept, this can be organized into 3 categories: 1) before any DMARD use (ie, DMARD-naive); 2) after conventional synthetic DMARD use (usually MTX); and 3) after biologic DMARD (usually TNF inhibitors). This concept has been one of the core concepts in treatment guidelines since the emergence of novel targeted therapies.[56,57] The underlying rationale is to understand DMARD treatment choice by taking into account both acceptable safety and likelihood of response. What has not been well understood is what determines why some patients will respond well to one DMARD and not another. Clearly, stochastic effects could be at play, but evidence suggests underlying disease heterogeneity (including genetic variation) may be mostly responsible. Having a suboptimal response to initial therapy with MTX may therefore be understood as much a marker of the underlying pathomechanism. Work by Stuhlmüller et al. suggests that such an effect underlies an inadequate response to MTX.[58] RA patients naive to DMARD therapy, in whom analysis of whole blood transcriptomic showed a preponderance of transcripts for T- and B-lymphocytes, were less likely to respond to MTX. HLA-DRB4-positive (ie, SE+) patients with a prominent adaptive immune response profile were also more likely to be MTX-IR. This suggests that an MTX-IR designation is not random but may be a core marker of underlying disease pathogenesis, with impact on responsiveness to DMARD treatment.[58] The active comparator for the current study is adalimumab, which also has proven efficacy for improving the signs and symptoms of RA and is approved for the treatment of RA.[51]

3.2.3 Safety

Abatacept treatment in RA has an acceptable safety profile regarding serious infections, malignancies, and autoimmune reactions. The Phase 2/3 clinical program included participants from 5 core studies that, combined with 3 other studies, comprise more than 10,000 patient-years of exposure. The main identified risks of abatacept therapy are infections (primarily bacterial) and slightly increased risk of infusion reactions (for the IV formulation) compared with placebo. Autoimmune events (primarily psoriasis) have been noted. Malignancies are not increased in abatacept-treated participants compared with placebo-treated participants. The IB provides additional details on the information discussed in this section.[41]

The potential safety concerns associated with the use of adalimumab have been well described in the prescribing information.[51] Specifically, some of the safety events that have been noted include cases of serious and opportunistic infections, including invasive fungal infections; hepatitis B reactivation; anaphylaxis or serious allergic reactions; exacerbation or new onset of demyelinating disease; worsening or new onset of heart failure; and malignancies. These events are well recognized and managed by treating physicians through a combination of patient selection (eg, exclusion of high-risk patients), preventive screening (eg, chest x-ray, purified protein derivative [PPD] testing), and close observation during therapy. This study will aim to utilize investigators with prior experience using biologic DMARDs in the care of patients with RA.

3.2.4 Abatacept and COVID-19

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel enveloped ribonucleic acid (RNA) beta-coronavirus that is the etiological agent of coronavirus disease 2019 (COVID-19). COVID-19 produced a high incidence of mortality and morbidity and has been declared a pandemic by the World Health Organization (WHO).

Abatacept has been studied in human clinical trials for over 15 years. Based on the review of safety data relevant to viral infections from clinical studies and post-marketing experience, there is no current evidence suggesting increased risk of viral respiratory illnesses, severe or otherwise, associated with abatacept use that would warrant avoiding use of abatacept. Currently available information from published literature, active clinical studies, or post-marketing surveillance about acute infection with SARS-CoV-2 in patients receiving abatacept is limited. While poor outcomes have been reported, most reports suggest that good outcomes are likely.

Of note, abatacept is being proposed as a therapy that can modulate an ongoing/emerging dysregulated immune response considered to be driving the progression of disease severity in COVID-19. Abatacept is not a therapy for neutralizing cytokines but for preventing further activation (eg, CD4+ T cells, B cells, macrophages) and production of cytokines and interrupting the feedforward pathological process. Two studies evaluating abatacept in the treatment of hospitalized COVID-19 patients are ongoing (ClinicalTrials.gov Identifier: NCT04472494 and NCT04593940).

Due to ongoing community transmission of SARS-CoV-2, study execution will be carefully managed through participant and site selection, infection control recommendations, appropriate SARS-CoV-2 vaccination upon availability, close observation of COVID-19-related adverse events (AEs)/serious adverse events (SAEs) [redacted].

3.3 Benefit/Risk Assessment

RA is an autoimmune disorder that can lead to progressive joint destruction, deformity, significant physical disability, and poor quality of life. The standard of care is to use DMARDs; however, which, when, and how has evolved significantly with the emergence of modern targeted therapies. Treatment guidelines consider both efficacy and safety in their recommendation.[56,57] Both

abatacept and adalimumab have well-established benefit-risk profiles in the treatment of RA patients and are included in current treatment guidelines. This benefit-risk is in part dependent on following established screening and ongoing safety monitoring. This protocol will follow these established processes.

In order to minimize the overall risk to participants, this protocol has inclusion and exclusion criteria appropriate to the population and proposed treatments (see Section 6 [Study Population]). Exclusionary screening tests will be used to identify latent tuberculosis (TB), viral hepatitis, risk factors/age-specific screening, medical history, and specific follow-up safety assessments will be performed. Women of childbearing potential (WOCBP) will be required to use highly effective contraception and to comply with pregnancy testing throughout this study. In addition, AEs and SAEs will be reviewed on an ongoing basis by the Clinical Trial Physician/Medical Monitor and pharmacovigilance group to look for trends and any safety issues.

There is no current evidence suggesting increased risk of viral respiratory illnesses, severe or otherwise, associated with abatacept. The potential benefit of abatacept in the treatment of COVID-19, and therefore its potential utility, is being studied in 2 ongoing studies. No concerns for adalimumab has been reported. The impact of COVID-19-associated risk will still be carefully monitored during the trial. Country and site selection will include assessment of specific barriers to safe recruitment. The current understanding of the risk associated with COVID-19 and the use of abatacept or adalimumab does not appear to alter the benefit-risk assessment.

Currently, clinicians do not have an evidence-based method of choosing the most efficacious targeted therapies for any given RA patient. This trial will test whether a set of clinical and laboratory parameters can identify patients who are more likely to respond to abatacept therapy, both in frequency and magnitude, than adalimumab. To achieve an earlier and more profound clinical outcome will prevent joint damage that cannot be reversed and minimize impact on quality of life and work productivity for these patients. This will further improve the benefit-risk assessment by minimizing suboptimal therapy that nonetheless has risk.

Potential benefits: Abatacept has demonstrated consistent and statistically robust effects on all primary and secondary endpoints in RA efficacy trials. Based on the data from IM101023,[52] IM101046,[53] and IM101226,[59] the use of abatacept (in combination with MTX) in early RA has the potential to induce remission in a large proportion of patients. Finally, very early use of effective therapy may curtail or even halt radiographic progression of disease, which could lead to long-term joint protection.

Potential risks: The clinical safety profile of abatacept in RA is well established. The Phase 2/3 clinical program includes patients from 5 core studies that, combined with other studies, have 24,000 patient-years of abatacept exposure. Clinical studies of abatacept provide extensive experience characterizing the safety and efficacy/effectiveness of abatacept. Abatacept was first approved in 2005. Since that time, there have been an estimated 763,109 patient-years of exposure to abatacept in the marketplace. Post-marketing reports have not altered the favorable benefit-risk profile for abatacept, and its safety profile remains generally similar to that established during the clinical trials.

Abatacept treatment in RA has an acceptable safety profile regarding serious infections, malignancies, and autoimmune reactions that are usually a concern with agents acting on the immune system. The main identified risks of abatacept therapy are infections (primarily bacterial) and slightly increased risk of infusion reactions vs placebo. The overall frequency of infections was slightly increased in the abatacept-treated population, but the severity, treatment, and outcome of these infections was similar to those treated with placebo. Serious viral, fungal, or mycobacterial infections were uncommon. The risks of autoimmune disorders and malignancies are not increased in abatacept-treated participants vs placebo-treated participants.

In the IM101023[52] and IM101226[59] studies, the combination of abatacept and MTX administered IV or SC was generally safe and well tolerated in MTX-naive participants with early RA and was similar to MTX alone. The overall proportion of AEs was similar in both groups. Infections, mainly upper respiratory tract infections, were among the most frequent AEs and were generally mild. There were no reports of opportunistic infections. There was 1 case of pancreatic cancer in the active group. Autoimmune diseases were infrequent in both treatment groups, and the infusions were well tolerated. Similar to IM101023, in the IM101046 study, the safety of abatacept monotherapy was unremarkable. The latest IB provides details on the information discussed in this section.[41]

More detailed information about the known and expected benefits and risks and reasonably anticipated AEs of abatacept and adalimumab may be found in their respective Prescribing Information.[51,60]

4 OBJECTIVES AND ENDPOINTS

Table 4-1: Objectives and Endpoints

Objective	Endpoint
Primary	
• To demonstrate the superiority in efficacy of abatacept compared with adalimumab, both on background MTX, in achieving clinical response (ACR50) at Week 24, in early, seropositive (RF+ and ACPA+) RA patients with the SE HLA Class II risk alleles (ie, SE+).	• Proportion of SE+ participants meeting ACR50 response at Week 24
Key Secondary	
• To compare the efficacy of abatacept with adalimumab, both on background MTX, in achieving clinical remission criteria (DAS28-CRP remission) at Week 24 in early, seropositive RA patients with the SE HLA Class II risk alleles (ie, SE+).	• Proportion of SE+ participants achieving DAS28-CRP remission (DAS28-CRP < 2.6) at Week 24
• To compare the efficacy of abatacept with adalimumab, both on background MTX, in achieving clinical response (ACR50) at Week 24 in the whole study population of early, seropositive RA patients.	• Proportion of whole study population participants meeting ACR50 response at Week 24

Table 4-1: Objectives and Endpoints

Objective	Endpoint
• To compare the efficacy of abatacept with adalimumab, both on background MTX, in achieving clinical remission criteria (CDAI remission) at Week 24 in early, seropositive RA patients with the SE HLA Class II risk alleles (ie, SE+).	• Proportion of SE+ participants achieving CDAI remission (CDAI ≤ 2.8) at Week 24
• To compare the efficacy of abatacept with adalimumab, both on background MTX, in achieving improvement in pain at Week 24 in early, seropositive RA patients with the SE HLA Class II risk alleles (ie, SE+).	• Mean change from baseline in SE+ participant-reported pain (VAS) at Week 24
Other Secondary	
• To determine the efficacy over time by treatment in early, seropositive RA patients (SE+ subset and whole population).	• Proportion of SE+ subset and whole population achieving ACR20/50/70 responses, DAS remission, CDAI remission, SDAI remission over the SBTP and OLTP; mean changes from baseline in DAS28-CRP, CDAI, SDAI over the SBTP and OLTP; mean changes from baseline in the 7 ACR core components over the SBTP and OLTP
• To determine the improvement in health-related quality of life over time by treatment in early, seropositive RA patients (SE+ subset and whole population).	• Mean change from baseline in SF-36 in SE+ subset and whole population at Week 24 and Week 104 (4 physical and 4 mental subscales and the physical component and mental component summary)
Exploratory	
• To assess improvement in work and productivity over time.	• Mean change from baseline in WPAI-RA score at Week 24 and Week 104
• To assess improvement of fatigue over time.	• Mean change from baseline in FACIT-F score at Week 24 and Week 104
• To assess improvement in duration of morning stiffness over time.	• Mean change from baseline in duration of morning stiffness at Week 24 and Week 104
• To assess/explore biomarkers, including: – Serum proteins – Genetic risk alleles [redacted]	• [redacted] autoantibodies • Target gene (eg, HLA-DRB1, [redacted]) [redacted]

Abbreviations: +, positive; ACPA, anti-citrullinated protein antibodies; ACR20/50/70, 20%/50%/70% improvement in American College of Rheumatology criteria; CDAI, Clinical Disease Activity Index; [redacted] DAS, disease activity score; DAS28-CRP, Disease Activity Score 28-joint count calculated using C-reactive protein; FACIT-F, Functional Assessment of Chronic Illness Therapy - Fatigue; HLA-DRB1, human leukocyte antigen Class II histocompatibility antigen; MTX, methotrexate; OLTP, Open-label Treatment Period; [redacted] RA, rheumatoid arthritis; RF, rheumatoid factor; [redacted] SBTP, Single-blind Treatment Period; SDAI, Simple Disease Activity Index; SE, shared epitope; SE+, shared epitope-positive; SF-36, 36-item Short Form Survey; VAS, visual analog scale; WPAI-RA, Work Productivity and Activity Impairment Questionnaire - Rheumatoid Arthritis.

5 STUDY DESIGN

5.1 Overall Design

This is a randomized, single-blind, multicenter, global Phase 3 study. The head-to-head study is designed to evaluate the superiority in efficacy of abatacept compared with adalimumab in a population of RA patients who have early disease and are MTX-IR, seropositive (RF+ and ACPA+), and expressing SE HLA Class II risk alleles (ie, SE+).

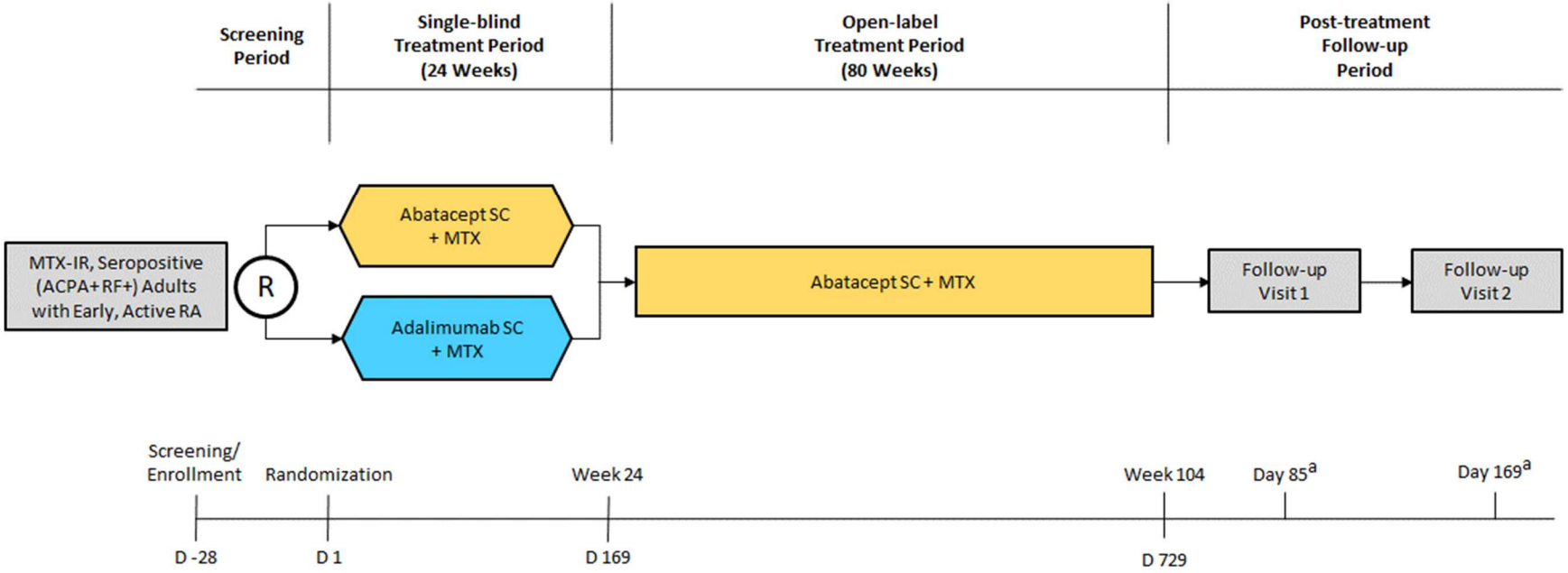
Eligible participants will include adults (≥ 18 years old) who have early RA, defined as symptoms of RA (pain, stiffness, or joint swelling) for no more than 12 months prior to screening, and satisfy the ACR/EULAR 2010 criteria for the classification of RA at some point during the 12-month period prior to signing the informed consent form (ICF). Participants who had a single isolated episode of palindromic symptoms that occurred less than 2 years prior to enrollment are still eligible. Participants must have a second-generation anti-CCP-2 test result that is greater than 3× ULN and be RF+ at screening according to central laboratory testing. The anti-CCP-2 test is commonly used in the clinic to measure ACPA, and the 3× ULN cutoff in the anti-CCP-2 central laboratory test ensures a stable positive ACPA profile. Participants must have a DAS28-CRP of at least 3.2 at screening and have at least 3 tender and at least 3 swollen joints (excluding distal interphalangeals) at screening and at randomization. [redacted]

Eligible participants must have been treated with MTX for at least 12 weeks prior to randomization with a stable dose of oral or parenteral MTX for at least 4 weeks prior to randomization (ie, MTX-IR). The stable dose of oral or parenteral MTX should be the maximum tolerated oral or parenteral dose (expected doses from 15 mg to 25 mg per week; see Section 7.1.3). Participants may enroll with MTX doses < 15 mg/week but ≥ 7.5 mg/week if intolerance to higher doses has been documented and the dose of oral or parenteral MTX is stable for 4 weeks prior to randomization. Participants in Japan may also enroll at doses between 7.5 and 15 mg per week at the discretion of the investigator. Participants must be naive to prior therapy with other DMARDs, except brief exposure to either sulfasalazine or hydroxychloroquine. See Section 6 (Study Population, Inclusion/Exclusion Criteria) for additional details.

The study is divided into 4 periods: Screening Period, Single-blind Treatment Period (SBTP) from Day 1 to Week 24, Open-label Treatment Period (OLTP) from Week 24 to Week 104, and Post-treatment Follow-up Period (PTFUP).

The study design schematic is presented in Figure 5.1-1.

Figure 5.1-1: Study Design Schematic



Abbreviations: ACPA+, anti-citrullinated protein antibody-positive; D, Day; MTX, methotrexate; MTX-IR, methotrexate inadequate responders; OLTP, Open-label Treatment Period; R, randomize; RA, rheumatoid arthritis; RF+, rheumatoid factor-positive; SBTP, Single-blind Treatment Period; SC, subcutaneous.

[a] In reference to Day 729 for participants who complete the OLTP or the day of last study treatment for participants who discontinue study treatment during the SBTP or OLTP.

5.1.1 Screening Period

Eligibility will be based on specified inclusion and exclusion criteria, medical history, disease activity, and safety assessments. Randomization must occur within 28 days of signing the ICF. Participants that experience delays may extend the screening period to 42 days (see Section 6.4.1.2). Rescreening is allowed (see Section 6.4.1.3).

5.1.2 Treatment Period

5.1.2.1 Single-blind Treatment Period: Day 1 - Week 24

On Day 1, participants will begin the SBTP and be randomized according to a computer-generated fixed-block randomization schedule. The site must complete the Tender (68)/Swollen (66) Joint Count to verify the final inclusion criteria (at least 3 tender and at least 3 swollen joints, excluding distal interphalangeals) prior to contacting Interactive Response Technology (IRT) for randomization. The site must also have the results of the genotyping for the SE from the central lab prior to randomization because participants will be stratified by SE status (positive or negative). Participants will be randomized to 1 of 2 parallel treatment arms in a 1:1 ratio:

1) Abatacept SC (125 mg) weekly with background stable MTX therapy
2) Adalimumab SC (40 mg) once every 2 weeks with background stable MTX therapy

Abatacept and adalimumab administration: On Day 1, participants and/or personal caregivers will be trained in self-administration of SC injections using prefilled syringes.

Methotrexate: Participants must have been treated with MTX for at least 12 weeks prior to randomization with a stable dose of oral or parenteral MTX for at least 4 weeks prior to randomization. The stable dose of oral or parenteral MTX should be the maximum tolerated dose (minimum of 15 mg and maximum of 25 mg per week). A dose of MTX < 15 mg/week but ≥ 7.5 mg/week is permitted if intolerance to higher doses has been recorded in the source documents and the dose of oral or parenteral MTX is stable for 4 weeks prior to randomization. Participants in Japan may also enroll at doses between 7.5 and 15 mg per week at the discretion of the investigator. For complete details of MTX use, see Section 7.1.3.

5.1.2.2 Open-label Treatment Period: Week 24 - Week 104

At Week 24, all participants ongoing in the OLTP will receive abatacept 125 mg SC weekly for the duration of the treatment period:

1) Participants receiving abatacept SC (125 mg) weekly will continue to receive abatacept.
2) Participants receiving adalimumab SC (40 mg) will switch to abatacept SC (125 mg) weekly at Week 24.
3) Participants will continue to be treated with oral or parenteral MTX as described above.
4) Participants not wishing to continue on open-label abatacept have the option of discontinuing treatment at the end of the SBTP and continuing to the PTFUP.

5.1.3 Post-treatment Follow-up Period

There will be a PTFUP for safety assessments. This period will be required only for some participants based on how they will be treated after study completion or Early Termination (ET). Participants who complete the treatment periods (ie, OLTP) or discontinue prior to completing the OLTP AND are not treated with post-study abatacept, regardless of the source, will need to complete the PTFUP. This will consist of 2 follow-up visits on Day 85 and Day 169 post cessation of investigational product (IP; see Table 2-4). The PTFUP will begin on Day 729 for participants who complete the OLTP. The PTFUP will begin on the day of last study treatment for participants who discontinue study treatment during the SBTP or OLTP. Participants who complete the OLTP or discontinue at any time prior to completing the OLTP AND are treated with post-study abatacept, regardless of the source, will not need to complete the PTFUP.

5.1.4 Data Monitoring Committee and Other External Committees

5.1.4.1 Data Monitoring Committee

Not applicable.

5.1.4.2 Study Steering Committee

A Study Steering Committee (SSC) will be established to obtain scientific guidance and advice on the protocol and conduct of the study. Detailed information can be found in the SSC Charter.

5.2 Number of Participants

It is anticipated that approximately 400 participants will be screened to treat 300 eligible participants with abatacept (n = 150) or adalimumab (n = 150) with background stable MTX therapy. [redacted] See Section 10.1 (Sample Size Determination) for additional details.

5.3 End of Study Definition

The start of the trial is defined as first visit for first participant screened. End of trial is defined as last visit or scheduled procedure shown in Section 2 (Schedule of Activities) for the last participant. Study completion is defined as the final date on which data for the primary endpoint were or are expected to be collected, if this is not the same.

5.4 Scientific Rationale for Study Design

5.4.1 Rationale for Population Profile

Taking together the prior study results described in Section 3 (Introduction) as well as the association of the SE with ACPA[61] and the immunopathogenesis of RA, it is reasonable to hypothesize that seropositive, SE+ patients with early RA may respond better to a T-cell costimulatory modulator, such as abatacept, than to a TNF-alpha inhibitor, such as adalimumab, due to their different mechanisms of action. Abatacept is a selective costimulation modulator that blocks the interaction between CD80/CD86 on APCs and CD28 on T cells. Relative to adalimumab, abatacept interferes more directly with T-cell activation and the continued breaking of immune tolerance in SE+ patients, as evidenced by the increased production of ACPAs.[61]

Consistent with this hypothesis, in a retrospective Japanese observational study, clinical efficacy of abatacept was significantly higher in SE+ vs SE- patients.[62] Moreover, SE positivity was predictive of response to treatment with abatacept, but not tocilizumab, which inhibits the interleukin (IL)-6 pathway.[63]

Because this study aims to demonstrate more definitively the higher abatacept vs adalimumab efficacy observed in IM101567, the study population will be aligned with the RA population enrolled in IM101567. Further, the primary endpoint and several key secondary endpoint analyses will be focused on the SE+ subgroup because this appears to define a more refined patient profile that is enriched for abatacept responders.

Participants in this study should have had symptoms of RA for 12 months or less prior to screening. Symptoms of RA are defined as signs and symptoms of synovitis (pain, swelling, tenderness) of joints commonly affected by RA. All participants must be seropositive for both RF and ACPA (measured with an anti-CCP-2 test that is > 3× ULN, which is considered high-level positive according to the 2010 ACR/EULAR RA classification criteria). Participants must have a DAS28-CRP ≥ 3.2 at screening in order to align with the population studied in the IM101235 and IM101567 trials comparing abatacept plus MTX with adalimumab plus MTX. [redacted]

5.4.2 Rationale for Choice of Endpoints

The primary endpoint of this study will be ACR50 at Week 24 in the SE+ subgroup. In IM101567, within the overall population, ACR50 estimate of difference between the abatacept and adalimumab showed the largest differential benefit (25), and the 95% CIs did not cross zero.[44] Moreover, the driver of this differential efficacy was the SE+ subgroup, because within the SE+ subgroup, the ACR50 estimate of difference between the abatacept and adalimumab was even larger (32), and the 95% CIs again did not cross zero. Because this study is aimed at replicating this observation of differential abatacept efficacy, the primary endpoint will be ACR50 at Week 24 in the SE+ population.

The list of key secondary efficacy endpoints and their hierarchical ordering is based on the magnitude of treatment differences observed in the IM101567 study.

5.4.3 Rationale for Timing of Endpoints

Because this study aims to recapitulate the abatacept vs adalimumab efficacy observed in IM101567[44] at Week 24, the duration of the SBTP, and therefore the timing of the primary analysis for this study, will also be performed at Week 24.

With the trend for clinical practice shifting to the earlier use of biologics, it is anticipated that patients will be treated with biologic therapies for a longer duration over the course of their disease. As such, the availability of a treatment option with prolonged maintenance of efficacy and a favorable long-term safety profile, such as abatacept, would be highly desirable for these patients.

Therefore, the OLTP will have a longer duration (80 weeks) as compared with IM101567 (24 weeks).

5.4.4 Rationale for Choice of Comparator Arm

The active comparator in this study is adalimumab, a recombinant human IgG1 monoclonal antibody specific for the human TNF. Adalimumab is approved for use in the treatment of RA. Because this study aims to confirm the higher efficacy of abatacept vs adalimumab observed in IM101567,[44] the dose of adalimumab will remain the same as that in IM101567; however, instead of the 40 mg/0.8 mL formulation of adalimumab, the choice of comparator for this study will be the citrate-free formulation of adalimumab (40 mg/0.4 mL [smaller volume]) in the prefilled syringe presentation that has a smaller-gauge needle than the 40 mg/0.8 mL forumlation.[51] In a randomized crossover comparison study of participants withRA, the citrate-free 40 mg/0.4 mL adalimumab formulation was associated with less injection site-related pain than the 40 mg/0.8 mL adalimumab formulation, with a tolerability and safety profile consistent with 40 mg/0.8 mL adalimumab.[64]

Participants will receive background MTX in both study arms. MTX is a cornerstone in the treatment of RA. Based on the IM101023 study,[52] the addition of abatacept to MTX is superior to MTX alone in inducing DAS-defined remission after a year of treatment in participants who have serologically positive early RA and are MTX-naive. In the control arm (initially treated with MTX alone), joint damage was more notable after the second year of open-label treatment (during which abatacept was added to MTX) than in the cohort that received combination therapy from the beginning of the study. In addition, the safety profile of the combination was similar to MTX alone.

5.4.5 Rationale for Switching

In IM101567,[44] participants in the adalimumab arm were required to undergo a 6-week washout period prior to receiving the first dose of open-label abatacept. The primary reason for this washout was to enable comparative immune biomarker analysis of these 2 biologic DMARDs with distinct mechanisms of action. Notably, based on the ARRIVE study, there is no safety-related concern with administering abatacept following treatment with a TNF inhibitor agent, including adalimumab, without a washout period.[65] Therefore, in IM101863, where the objective is focused on demonstrating differential efficacy, there is no requirement for an adalimumab washout before starting open-label abatacept.

5.5 Justification for Dose

The doses of abatacept and adalimumab will be the same as those used in IM101567.[44] The selected SC doses of both abatacept and adalimumab are the globally approved doses for the treatment of RA in patients receiving MTX.

6 STUDY POPULATION

For entry into the study, the following criteria MUST be met.

6.1 Inclusion Criteria

1) Signed Written Informed Consent

a) Participant is willing to participate in the study and has signed the ICF.

2) Type of Participant and Target Disease Characteristics

a) Participants have early RA, defined as symptoms of RA that started ≤ 12 months prior to screening and satisfied the ACR/EULAR 2010 criteria for the classification of RA (Appendix 13) at some point during the 12-month period. Participants who had a single isolated episode of palindromic symptoms that occurred less than 2 years prior to enrollment are still eligible.

b) Participants will have the *HLA-DRB1* alleles genotyped during screening and will be identified as carrying at least 1 copy of the SE alleles or not. The list of alleles comprising the SE are listed in Section 9.8.1. [redacted]

c) Participants must be naive to any targeted (biologic or nonbiologic) DMARDs.

d) Participants must be naive to conventional synthetic DMARDs other than MTX.

e) Participants must be naive to investigational therapies for RA.

f) Participants must have been treated with MTX for at least 12 weeks, with a stable dose of oral or parenteral MTX for at least 4 weeks prior to randomization. Participants must randomize on the maximum tolerated dose of oral or parenteral MTX (minimum of 15 mg and maximum of 25 mg per week). Participants may enroll with MTX doses < 15 mg/week but ≥ 7.5 mg/week if intolerance to higher doses has been documented and the dose of oral or parenteral MTX is stable for 4 weeks prior to randomization. Participants in Japan may also enroll at doses between 7.5 and 15 mg per week at the discretion of the investigator.

[redacted]

h) Participants must have at least a DAS28-CRP ≥ 3.2 (Appendix 14, Appendix 15) at screening.

i) Participants must have currently at least 3 tender and at least 3 swollen joints (excluding distal interphalangeals) at screening and at randomization.

j) Participants receiving oral corticosteroids must be on a stable dose and at the equivalent of ≤ 10 mg prednisone daily for at least 4 weeks prior to randomization. Participants may not receive an intramuscular (IM), IV, or intra-articular administration of a corticosteroid within 4 weeks prior to randomization.

k) Participant Rescreening: This study permits the rescreening of a participant who has discontinued the study as a pretreatment failure (ie, participant has not been randomized/has not been treated)and still meets all inclusion/exclusion criteria. If rescreened, the participant must be re-consented. Participants can only be rescreened once.

3) Age and Reproductive Status

a) Female Participants

i) Females, ages ≥ 18 years or local age of majority.

ii) Women who are not of childbearing potential are exempt from contraceptive requirements.

iii) Women participants must have documented proof that they are not of childbearing potential.

iv) WOCBP must have a negative highly sensitive serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin [HCG]) within 24 hours prior to the start of study treatment.

(1) If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

v) Women must not be breastfeeding and must agree not to breastfeed during the study and for 100 days thereafter.

vi) Additional requirements for pregnancy testing during and after study intervention are located in Section 2, Schedule of Activities.

vii) The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

viii) WOCBP must agree to follow instructions for method(s) of contraception defined in Appendix 4 and as described below and included in the ICF.

ix) WOCBP are permitted to use hormonal contraception methods (as described in Appendix 4).

x) A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

(1) Is not a WOCBP

OR

(2) Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of < 1% per year), preferably with low user dependency (as described in Appendix 4) during the intervention period and for at least 70 days (5 half-lives of the study treatment), and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction for the same time period.

b) Male Participants

i) Males, ages ≥ 18 years or local age of majority.

ii) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception defined in Appendix 4 and as described below.

iii) Azoospermic males are not exempt from contraceptive requirements and will be required to always use a latex or other synthetic condom during any sexual activity (eg, vaginal, anal, oral) with WOCBP, even if the participant has undergone a successful vasectomy or if the partner is pregnant.

iv) Male participants will be required to always use a latex or other synthetic condom during any sexual activity (eg, vaginal, anal, oral) with WOCBP, even if the participants have undergone a successful vasectomy or if their partner is already pregnant or breastfeeding. Males should continue to use a condom during the intervention period and for at least 70 days (5 half-lives of the study treatment) after the last dose of study intervention.

v) Female partners of males participating in the study should be advised to use highly effective methods of contraception during the intervention period and for at least 70 days (5 half-lives of the study treatment) after the last dose of study intervention in the male participant.

vi) Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from sexual activity or use a male condom during any sexual activity (eg, vaginal, anal, oral), even if the participants have undergone a successful vasectomy, during the intervention period and for at least 70 days (5 half-lives of the study treatment) after the last dose of study intervention.

vii) Male participants must refrain from donating sperm during the intervention period and for at least 70 days (5 half-lives of the study treatment) after the last dose of study intervention.

viii) Breastfeeding partners should be advised to consult their health care providers about using appropriate highly effective contraception during the time the participant is required to use condoms.

Investigators shall counsel WOCBP, and male participants who are sexually active with WOCBP on the importance of pregnancy prevention, the implications of an unexpected pregnancy, and the potential of fetal toxicity occurring due to transmission of treatment, present in seminal fluid, to a developing fetus, even if the participant has undergone a successful vasectomy or if the partner is pregnant.

- The investigator shall evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.
- Local laws and regulations may require the use of alternative and/or additional contraception methods.

6.2 Exclusion Criteria

1) Medical Conditions

a) Women who are breastfeeding.

b) Participants with autoimmune disease other than RA (eg, psoriasis, systemic lupus erythematosus [SLE], vasculitis, seronegative spondyloarthritis, inflammatory bowel disease, Sjogren's syndrome) or currently active fibromyalgia.

c) Prior history of or current inflammatory joint disease other than RA (eg, psoriatic arthritis, gout, reactive arthritis, Lyme disease).

d) Participants at risk for TB defined as follows:

   i) Current clinical, radiographic, or laboratory evidence of active TB. Chest x-rays (posterioranterior and lateral) obtained within the 3 months prior to obtaining written informed consent will be permitted, but the images must be available and reviewed by the investigator. TB testing (interferon gamma [IFN-γ] release assay or PPD) performed in the past month prior to Screening will be accepted; however, a copy of the report must be placed in the participant binder.

   ii) A history of active TB: within the last 3 years, even if it was treated; > 3 years unless there is documentation that the prior anti-TB treatment was appropriate in duration and type.

   iii) Participants with a positive TB screening test (PPD or IFN-γ release assay) indicative of latent TB will not be eligible for the study unless they:

      (1) Have no evidence of current TB based on chest x-ray performed during the screening period and by history and physical exam; and

      (2) Are actively being treated for TB or the site has documentation of successful prior treatment of latent TB. Treatment regimens should be dictated by local guidelines, as long as the treatment dose and duration meet or exceed local Health Authority guidelines. If permitted by local guidelines regarding treatment with biologic medications, participants may be randomized prior to completion of treatment as long as they have completed at least 4 weeks of treatment and they have no evidence of current TB on chest x-ray at screening.

e) Participants with recent acute infection, defined as:

   i) Any acute infection within 60 days prior to randomization that required hospitalization or treatment with parenteral antibiotics.

   ii) Any acute infection within 30 days prior to randomization that required oral antimicrobial or antiviral therapy.

   iii) In the case of prior SARS-CoV-2 infection within 30 days prior to enrollment, symptoms must have completely resolved with no clinically significant sequelae that would indicate a higher risk of participation in the study. Investigators should consult with the Clinical Trial Physician the decision to randomize these participants.

f) Participants with history of chronic or recurrent bacterial infection (eg, chronic pyelonephritis, osteomyelitis, bronchiectasis).

g) Participants with any history of infection of a joint prosthesis or artificial joint.

h) Participants who have a history of systemic fungal infections (such as histoplasmosis, blastomycosis, or coccidiomycosis).

i) Participants with history of recurrent herpes zoster (more than 1 episode) or disseminated (more than 1 dermatome) herpes zoster or disseminated herpes simplex or ophthalmic zoster will be excluded. Symptoms of herpes zoster or herpes simplex must have resolved more than 60 days prior to screening. Participants with history of human immunodeficiency virus (HIV) infection or who test positive for HIV at screening.

j) Participants with history of primary immunodeficiency.

k) Participants who have a present malignancy or previous malignancy within the last 5 years prior to screening (except documented history of cured nonmetastatic squamous or basal cell skin carcinoma or cervical carcinoma in situ). Participants who had a screening procedure that is suspicious for malignancy and in whom the possibility of malignancy cannot be reasonably excluded following additional clinical, laboratory, or other diagnostic evaluations.

l) Current clinical findings or a history of a demyelinating disorder.

m) New York Heart Association (NYHA) Class III or IV heart failure.

n) Any previous or current medical conditions that are warnings against the use of TNF inhibitor agents.

o) Current clinical findings of severe, progressive, or uncontrolled renal, hepatic, hematological, gastrointestinal, pulmonary, psychiatric, cardiac, endocrine, neurological, or cerebral disease, including severe and uncontrolled infections, such as sepsis and opportunistic infections. Concomitant medical conditions that, in the opinion of the investigator, might place the participant at unacceptable risk for participation in this study.

p) Participants who have received any live vaccines within 3 months of the study drug administration or are scheduled to receive live vaccines during the study. Study participants should not be administered a live virus vaccine for a minimum of 3 months following the last dose of study medication. Participants who are in close contact with others who have received a live vaccine may be enrolled at the investigator's discretion.

q) Participants who have received live attenuated or replication-competent vector SARS-CoV-2 vaccines within 3 months of study enrollment.

r) Participants who have undergone a major surgical procedure within the 60 days prior to randomization.

s) Participants for whom 5 or more joints cannot be assessed for tenderness or swelling (ie, due to surgery, fusion, amputation, etc).

t) Participants with a history of (within 12 months of signing the ICF), or known current problems with, drug or alcohol abuse history or known cirrhosis, including alcoholic cirrhosis.

u) Participants who are impaired, incapacitated, or incapable of completing study-related assessments.

2) Prior/Concomitant Therapy

a) Participants who have had previous exposure to abatacept or adalimumab.

b) Participants who have had previous exposure to conventional synthetic DMARD other than MTX. Prior exposure to sulfasalazine or hydroxychloroquine for less than 6 weeks prior to randomization will be allowed.

c) Participants who have been exposed to any treatment with an approved or investigational biologic DMARD, including, but not limited to, infliximab, etanercept, anakinra, rituximab, tocilizumab, golimumab, and certolizumab, or an investigational or approved targeted synthetic DMARD, including, but not limited to, tofacitinib, baricitinib, upadacitinib, or filgotinib.

d) Participants who have received an IM, IV, or intra-articular administration of a corticosteroid within 4 weeks prior to randomization (Day 1).

e) Participants currently taking NSAIDs must have been on a stable dose, as assessed by the investigator, for at least 14 days prior to randomization.

3) Physical and Laboratory Test Findings

a) Hepatitis B surface antigen (HBsAg)-positive, or hepatitis B core antibody (HBcAb) positive participants with detectable hepatitis B viral deoxyribonucleic acid (DNA).

b) Hepatitis C antibody (HcAb)-positive participants with detectable hepatitis C viral RNA.

c) Hemoglobin (Hgb) < 8.5 g/dL.

d) White blood count (WBC) < 3,000/mm^3 (3× 10^9/L).

e) Platelets < 100,000/mm^3 (100× 10^9/L).

f) Serum creatinine > 2× ULN.

g) Serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2× ULN.

h) Evidence of active cardiac or pulmonary disease on chest x-rays.

i) Any test results that, in the opinion of the investigator, might place the participants at unacceptable risk for participation in this study.

4) Allergies and Adverse Drug Reaction

a) Hypersensitivity to 1 of the IPs and/or its excipients.

5) Other Exclusion Criteria

a) Prisoners or participants who are involuntarily incarcerated. (Note: under certain specific circumstances and only in countries where local regulations permit, a person who has been imprisoned may be included or permitted to continue as a participant. Strict conditions apply and BMS approval is required.)

b) Participants who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness.

Eligibility criteria for this study have been carefully considered to ensure the safety of the study participants and that the results of the study can be used. It is imperative that participants fully meet all eligibility criteria.

6.3 Lifestyle Restrictions

Not applicable. No restrictions are required.

6.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but who are not subsequently randomized in the study/included in the analysis population. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants; to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, as applicable; and to respond to queries from regulatory authorities. Minimal information includes date of consent, demography, screen failure details, eligibility criteria, and any SAEs.

6.4.1 Retesting During Screening or Lead-in Period

Participant Re-enrollment: This study permits the re-enrollment of a participant who has discontinued the study as a pretreatment failure (ie, participant has not been randomized/has not been treated). If re-enrolled, the participant must be re-consented. If the initial screen failure was due to a medical concern (eg, TB assessment), the site must notify the Clinical Trial Physician/Medical Monitor of the intent to rescreen, describe the cause of the initial screen failure and the resolution of the medical consent, and receive approval prior to proceeding. This communication must be documented in the study record.

All screening procedures are to be performed within 4 weeks of the randomization visit except as described below.

6.4.1.1 Retesting

Retesting of laboratory parameters and/or other assessments within any single Screening or Lead-in period will be permitted (in addition to any parameters that require a confirmatory value) for laboratory errors.

The most current result prior to Randomization is the value by which study inclusion will be assessed, as it represents the participant's most current, clinical state.

Laboratory parameters and/or assessments that are included in Table 2-1 may be repeated in an effort to find all possible well-qualified participants. Consultation with the Clinical Trial Physician/Medical Monitor may be needed to identify whether repeat testing of any particular parameter is clinically relevant.

6.4.1.2 Extended Screening

Participants who experience a delay in completing screening may extend the screening period to 42 days, as long as this delay was not due to an intercurrent significant medical illness such as an infection requiring hospitalization or administration of parenteral antibiotic agents. This extension is intended to address nonmedical issues or extended medical assessments (eg, acute infection or assessment of latent TB). For medical events, like initiation of treatment for latent TB, consideration should be given to screen failure with the expectation of rescreening after resolution and approval from the Clinical Trial Physician/Medical Monitor.

If screening is extended beyond 28 days, all screening procedures except IRT enrollment, height/weight, urinalysis, anti-CCP-2, RF, HLA-DRB1 SE alleles, chest x-ray, TB, hepatitis B

virus (HBV)/hepatitis C virus (HCV), and HIV testing, should be repeated prior to randomization, as noted in Table 2-1.

6.4.1.3 Rescreening

This study permits the rescreening of a participant who has discontinued the study as a pretreatment failure (ie, participant has not been randomized/has not been treated) and still meets all inclusion/exclusion criteria. If rescreened, the participant must be re-consented. A participant may be rescreened only once. Clinical Trial Physician/Medical Monitor approval is required for screen failures due to medical concerns, and rescreens are not permitted less than 28 days after signing the first ICF. The participant will need to sign a new ICF and be re-enrolled with a new participant number via the IRT. Chest x-ray and TB screening will not be repeated if they were performed within the last 3 months, and prior results must be added to the study record. SE genotyping will not be repeated, and results from prior testing should be added to the study record.

7 TREATMENT

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device intended to be administered to a study participant according to the study randomization or treatment allocation.

Study treatment includes both IP/investigational medicinal product (IMP) and non-IP/non-IMP, and can consist of the following (see Table 7-1):

IPs to be supplied by the Sponsor:

- Abatacept (BMS-188667)
- Adalimumab (citrate-free formulation in prefilled syringe)

Non-IPs (the Sponsor will not provide non-IPs):

- MTX
- Corticosteroids
- NSAIDs (including aspirin)
- Folic acid and/or folinic acid (leucovorin)

An IP, also known as IMP in some regions, is defined as a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) differently than the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

Other medications used as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, may be considered as non-IP.

Table 7-1: Study Treatments for IM101863

Product Description/ Class and Dosage Form	Potency	IP/ Non-IMP	Blinded or Open-label	Packaging/ Appearance	Storage Conditions (per label)
Abatacept Injection	125 mg/mL	IP	Open-label	Prefilled syringe	Refer to the label on the container.
Adalimumab Injection	40 mg/0.4 mL	IP	Open-label	Prefilled syringe	Refer to the label on the container.

Abbreviations: IMP, investigational medicinal product; IP, investigational product.

7.1 Treatments Administered

The selection and timing of dose for each participant is provided in Table 7.1-1.

Table 7.1-1: Selection and Timing of Dose

Study Treatment	Unit Dose Strength(s)/ Dosage Level(s)	Dosage Formulation Frequency of Administration	Route of Administration
Abatacept	125 mg	Weekly	SC injection
Adalimumab	40 mg	Once every 2 weeks	SC injection

Abbreviations: mg, milligram; SC, subcutaneous.

On "office visit" days, study medication should be administered AFTER all assessments have been completed.

7.1.1 Abatacept Treatment

On Day 1, participants will self-administer abatacept 125 mg SC from a prefilled syringe. On Day 8, participants will self-administer abatacept 125 mg SC. Thereafter, participants will self-administer abatacept 125 mg SC once every 7 days, up to and including Week 103 (Day 722).

Participants randomized to adalimumab will switch to abatacept 125 mg SC weekly at Week 24 (Day 169).

7.1.1.1 Abatacept Self-administration of Subcutaneous Injection

Each prefilled syringe contains 1 weekly dose of abatacept, 125 mg/mL. Participants will be trained to self-administer their weekly SC injection. Training should be performed by investigational personnel who are considered qualified trainers by the site principal investigator. A procedure guide will be provided by the Sponsor. The participant should be able to self-administer the SC injection between office visits or have an office-trained caregiver do so.

On office visit days, SC injections should be given AFTER all assessments are completed, including blood draws. If a caregiver is responsible for giving the injections, he or she should accompany the participant to office visits.

7.1.1.2 Abatacept Administration Window

SC injections of study medication may be administered ± 3 days around the target day. The last dose before each office visit should be administered at least 4 days before the scheduled visit date. If an SC injection is not given within the administration window, the next SC injection should be given on the next scheduled target administration day.

7.1.2 Adalimumab Treatment

Participants randomized to adalimumab will self-administer an initial dose of adalimumab 40 mg SC from a prefilled syringe on Day 1. On Day 15, participants will self-administer adalimumab 40 mg SC. Thereafter, participants will self-administer adalimumab 40 mg SC once every 14 days, up to and including Week 22 (Day 155).

Participants randomized to adalimumab will switch to abatacept 125 mg SC weekly at Week 24 and continue with the self-administration of abatacept 125 mg SC once every 7 days, up to and including Week 103.

Participants not wishing to continue on open-label abatacept have the option of discontinuing treatment at the end of the SBTP and proceeding to the PTFUP.

7.1.2.1 Adalimumab Self-administration of Subcutaneous Injection

Each prefilled syringe contains 1 biweekly dose of adalimumab, 40 mg/0.4 mL. Participants will be trained to self-administer their biweekly SC injection. Training should be performed by investigational personnel who are considered qualified trainers by the site principal investigator. A procedure guide will be provided by the Sponsor. The participant should be able to self-administer the SC injection between office visits or have an office-trained caregiver do so.

On office visit days, SC injections should be given AFTER all assessments are completed, including blood draws. If a caregiver is responsible for giving the injections, he or she should accompany the participant to office visits.

7.1.2.2 Adalimumab Administration Window

SC injections of study medication may be administered ± 7 days around the target day. The last dose before each office visit should be administered at least 7 days before the scheduled visit date. If an SC injection is not given within the administration window, the next SC injection should be given on the next scheduled target administration day.

7.1.3 Guidelines for Methotrexate

Participants must enroll on a stable dose of maximum tolerated oral or parenteral MTX (minimum of 15 mg and maximum of 25 mg per week) for at least 4 weeks prior to randomization.

Participants may enroll with MTX doses < 15 mg/week but ≥ 7.5 mg/week if intolerance to higher doses has been recorded in the source documents and the dose of oral or parenteral MTX is stable for 4 weeks prior to randomization. Participants in Japan may also enroll at doses between 7.5 and 15 mg per week at the discretion of the investigator.

All participants must be maintained on the enrollment MTX dose during the SBTP, unless toxicity or intolerability occurs during the course of the study. In that event, the dose may be reduced or held as medically necessary for AEs. However, MTX should be returned to the baseline dose as soon as possible, or to the maximally tolerated dose below the baseline dose, but not less than 7.5 mg/week for the duration of the study. MTX should be given orally or parenterally.

Switching between routes of administration of MTX or dose adjustment for any reason other than toxicity is not permitted during the SBTP. Adjustments in MTX dosing and route of administration are allowed at the investigator's discretion in the OLTP.

All participants must receive folic acid, folinic acid, or leucovorin according to the manufacturer's recommendations.

7.2 Method of Treatment Assignment

All participants will be centrally randomized using an IRT. Before the study is initiated, each user will receive log-in information and directions on how to access the IRT. Each participant will be assigned a unique participant number after signing the ICF. Participant numbers will be used on all participants' study information. Participant numbers will not be reassigned. The investigator or designee will register the participant for enrollment by following the enrollment procedures established by the Sponsor.

The following information is required for enrollment:

- Date that informed consent was obtained
- Year of birth
- Gender at birth

Once enrolled in IRT, enrolled participants who have met all eligibility criteria will be ready to be randomized through the IRT. The following information is required for participant randomization:

- Participant number
- Year of birth
- Gender at birth (female or male)
- SE status (positive or negative)

The exact procedures for using the IRT will be detailed in the IRT manual.

Study treatment will be dispensed at the study visits as listed in Section 2 (Schedule of Activities). Sufficient drug will be dispensed at each visit to cover treatment until the next scheduled visit. These will be in intervals of 4, 8, or 12 weeks according to the visit schedule.

7.3 Blinding

Double blinding of study drug, adalimumab vis-à-vis abatacept, is not feasible due to logistical barriers around repackaging adalimumab as well as the expected differences in injection-site reactions. Both of these together make effective blinding of the patients to the randomized drug assignment impractical and unsustainable. The nature and frequency of adalimumab-associated injection-site reactions make blinding investigators responsible for clinical care unsustainable under usual practices. It is possible, however, to preserve the objectivity of clinical assessments with the following strategy that has been designed to establish and maintain a single-blinded assessor for clinical endpoints throughout the study. This will require a minimum of 3 individuals: a blinded Clinical Assessor, an unblinded Study Research Coordinator, and an unblinded physician investigator/sub-investigator to complete/approve the case report form (CRF).

Clinical Assessors will be blinded to treatment allocation so as to preserve the objectivity of study-related assessments (tender and swollen joint count, Physician's Global Assessment of Disease Activity [PGA], AE causality assessment) and routine clinical care (laboratory result

review, medication adjustment). To preserve blinding, they must be shielded from treatment allocation throughout the entire study. This will be the responsibility of the Study/Research Coordinators who need not be blinded to treatment allocation. At the beginning of each study visit throughout the study duration, the participant should be reminded that the Clinical Assessor is blinded to treatment allocation and that care must be taken to prevent revealing treatment allocation. They should be instructed to:

- Not discuss study treatment by name
- Not discuss the color or use of the prefilled syringe
- Not discuss how often injections are performed
- Only discuss injection-site reactions of significant concern

To comply with requirements for CRF completion, a qualified physician who is an investigator or sub-investigator who is unblinded to study treatment assignment will be needed to promptly review, sign, and date the CRF.

The site should maintain 2 distinct sets of source documents: 1 set accessible to the unblinded site staff and 1 set for the blinded Clinical Assessor.

Care should be taken by the Study/Research Coordinator to retrieve any study treatment and sharps containers returned by the participant at the beginning of each visit to shield the assessor from inadvertent exposure to participant allocation. Similarly, study treatment dispensing should be done after blinded assessments. Both retrieval and dispensing of study treatment should be done in an area shielded from the blinded Clinical Assessor(s).

The joint count assessment should be performed after completion of the patient-reported outcomes (PROs), vital sign assessment, and AE assessment. The Clinical Assessor will similarly be reminded at the beginning of each study visit throughout the study duration that they are performing a blinded-assessment for the study and to not ask question or elicit comments that may reveal treatment allocation as outlined above. Every effort must be made to ensure the same evaluator(s) will complete the assessment for each participant. If the usual evaluator is not available, another trained evaluator blinded to study treatment allocation for the participant may perform the clinical assessment. In the event that no blinded evaluator is available during the study visit, blinded clinical assessment measures (tender and swollen joint counts and PGA) should not be reported.

In cases of accidental unblinding of blinded staff, contact the Clinical Trial Physician/Medical Monitor and ensure every attempt is made to preserve the blind. The purpose of this is to review options to continue blinded assessments and review site processes to prevent additional unblinding.

7.4 Dosage Modification

7.4.1 Dose Modifications for Abatacept

7.4.1.1 Dose Modifications for Abatacept in the Absence of Adverse Events

Participants should complete their scheduled SC injections as described above. Participants who miss the dose window (± 3 days) should skip the SC injection and wait until the next targeted administration day.

7.4.1.2 Dose Modifications for Abatacept Due to Adverse Events

If abnormal laboratory test results or clinical AEs indicate toxicity that, in the judgment of the investigator, could place the participant at risk, study drug administration should be interrupted. If drug interruption exceeds 14 days, the investigator should notify the Sponsor's Clinical Trial Physician/Medical Monitor. Participants may receive further study medication treatment only if full resolution of the AE or abnormal laboratory finding is documented. **Under no circumstances should the dose of study drug be altered due to an AE.**

7.4.2 Dose Modifications for Adalimumab

7.4.2.1 Dose Modifications for Adalimumab in the Absence of Adverse Events

Participants should complete their scheduled SC injections as described above. Participants who miss the dose window (± 7 days) should skip the SC injection and wait until the next targeted administration day.

7.4.2.2 Dose Modifications for Adalimumab Due to Adverse Events

If abnormal laboratory test results or clinical AEs indicate toxicity that, in the judgment of the investigator, could place the participant at risk, study drug administration should be interrupted. If drug interruption exceeds 14 days, the investigator should notify the Sponsor's Clinical Trial Physician/Medical Monitor. Participants may receive further study medication treatment only if full resolution of the AE or abnormal laboratory finding is documented. **Under no circumstances should the dose of study drug be altered due to an AE.**

7.5 Preparation/Handling/Storage/Accountability

The IP should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that IP is only dispensed to study participants. The IP must be dispensed only from official study sites by authorized personnel according to local regulations.

The product storage manager should ensure that the study treatment is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by BMS. If concerns regarding the quality or appearance of the study treatment arise, the study treatment should not be dispensed and contact BMS immediately.

Study treatment not supplied by BMS will be stored in accordance with the package insert.

IP documentation (whether supplied by BMS or not) must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage,

administration and, as applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents, administration sets).

7.5.1 Retained Samples for Bioavailability/Bioequivalence/Biocomparability

Not applicable.

7.6 Treatment Compliance

All participants are expected to receive study therapy as outlined in the protocol. Participants will use diary cards to document self-injection of study drug between office visits. Permitted dose modifications are described in Section 7.4. Conditions under which therapy must be discontinued due to noncompliance are outlined in Section 8.1.

7.7 Concomitant Therapy

7.7.1 Prohibited and/or Restricted Treatments

7.7.1.1 Prohibited Treatment During the Treatment Period

- Conventional synthetic DMARDs other than methotrexate (including, but not limited to, sulfasalazine, leflunomide, hydroxychloroquine, chloroquine)
- Targeted synthetic DMARDs (including, but not limited to, tofacitinib, baricitinib, upadacitinib, or filgotinib)
- Adrenal corticotropic hormone (ACTH)
- Oral or parenteral gold
- Quinacrine or other related antimalarials
- D-penicillamine
- Azathioprine
- Oral cyclosporine
- Nimesulide
- Minocycline
- Sirolimus
- Everolimus
- Tacrolimus
- Mycophenolate mofetil (MPA)
- 6-mercaptopurine
- All investigational or approved targeted (biologic or nonbiologic) RA therapies other than abatacept and adalimumab (including, but not limited to, tocilizumab, etanercept, anakinra, infliximab, rituximab, etc.)
- Use of any investigational drug other than study medication
- Any prohibited concomitant medication listed in the current Humira® (adalimumab) or Orencia® (abatacept) prescribing information[51,60]
- Intra-articular injections of hyaluronic acid
- Immunoabsorption (ie, Prosorba®) column or cholestyramine

- Administration of a live vaccine (FluMist®; measles, mumps, rubella [MMR]; yellow fever; etc.)

7.7.1.2 Restricted Treatments During the Treatment Period

Methotrexate:

For complete details on MTX use, see Section 7.1.3, Guidelines for Methotrexate.

Corticosteroids for Treatment of RA Symptoms:

All participants who are receiving oral corticosteroids must continue to receive the dose being administered at the time of signing the ICF throughout the 24-week controlled SBTP (this dose may not exceed the equivalent of 10 mg of prednisone), except if a decrease in dose is necessitated by toxicity. IV and IM corticosteroid injections are not permitted during the study except to treat AEs. Use of parenteral corticosteroids to treat AEs should be limited to the lowest dose possible and not exceed 14 days. If treatment is to exceed 14 days during the 24-week controlled SBTP, contact the Clinical Trial Physician/Medical Monitor to discuss. After Week 24, corticosteroid taper is allowed if deemed appropriate. Tapers exceeding the equivalent rate of 1 mg of prednisone (or prednisone equivalent) a week is not recommended.

One instance of intra-articular glucocorticoids (no greater than 40 mg methylprednisolone or 40 mg of triamcinolone [or methylprednisolone or triamcinolone equivalent]) may be administered into 1 joint or divided into 2 joints. No intra-articular injections will be permitted within 42 days of the Week 24 visit. A joint that receives an intra-articular injection will be counted as "active" for the remainder of the study.

Inhaled corticosteroids for the treatment of asthma, chronic obstructive pulmonary disease (COPD), etc, are permitted, but the dose should remain stable throughout the study. Other nonparenteral corticosteroid formulations, such as topical corticosteroid use, are permitted.

Analgesics and NSAIDs:

- NSAIDs and analgesics (including topical NSAIDs) are not permitted within 12 hours before a joint assessment.
- NSAIDs doses should remain stable, as assessed by the investigator, with the exception of decreases being permitted due to related AEs, such as gastric toxicity, during the initial 24-week study period. After the initial 24-week study period, adjustment in NSAID use can be made at the discretion of the investigator.
- Analgesics
  - Acetaminophen (paracetamol)
    - Average dose of ≤ 3 g/day

- ♦ No single dose exceeding 1 g

  NOTE: combination products, including acetaminophen and narcotic analgesics (eg, acetaminophen with codeine phosphate, acetaminophen with propoxyphene napsylate, acetaminophen with oxycodone HCl, acetaminophen with hydrocodone bitartrate), are allowed provided the acetaminophen component dosage is accounted for in the maximum of 3 g/day.

- Narcotic analgesics must not exceed 30 mg/day of morphine or its equivalent.
- Tramadol, gabapentin, and pregabalin are allowed, but doses must be stable throughout Treatment Period.
- Acetylsalicylic acid is allowed in low doses (eg, ≤ 100 mg/day) for cardiovascular prophylaxis.
- Analgesics are not permitted within 12 hours before joint assessments.

- Short courses of NSAIDs and analgesics may be used to treat episodes of pain that are unrelated to arthritis, such as headache. Care should be taken to avoid taking these within 12 hours before a joint assessment.

7.7.2 Other Restrictions and Precautions

The prescribing label of all concomitant medications used as participant's background therapy should be evaluated by the investigator for continued administration during the participant's participation in this study (eg, known toxicities, drug-drug interactions). Participant eligibility and the decision to continue a participant in the study must take into consideration all precautions outlined in the locally approved labels for MTX, abatacept, and adalimumab.

7.7.2.1 Immunizations

Limited data are available on the effect of therapeutic vaccinations in participants receiving abatacept or adalimumab. All routine vaccinations should be administered prior to the study. SARS-CoV-2 vaccination, when available, is recommended prior to enrollment. If vaccination is performed near the expected enrollment date, delay enrollment until the vaccination series is completed and symptoms related to vaccination have resolved. If vaccination becomes available only after enrollment, vaccination can proceed at discretion of the investigator. These include genetic, protein-based, replication incompetent, or inactivated vaccine as approved by local authorities. All appropriate vaccination with non-live vaccines should be performed when appropriate based on local guidelines (eg, SARS-CoV-2 vaccine, seasonal influenza vaccine). Please contact the Clinical Trial Physician/Medical Monitor with any questions related to COVID-19 vaccines.

Due to the risk of infection, vaccination of participants with any live vaccine is absolutely contraindicated during the study drug treatment period of the study, as is the administration of live oral polio vaccine to household contacts. The Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) recommends that participants should not be administered a live virus vaccination for at least 3 months after discontinuing high-dose

corticosteroid therapy (defined as more than 20 mg of prednisone per day for more than 2 weeks). In view of the long half-life of abatacept and adalimumab, study participants should not be administered a live virus vaccine for a minimum of 3 months following the last dose of study medication.

7.7.2.2 Infectious Complications

Participants who develop significant infectious complications during the study should be treated appropriately, have study medication withheld, and be restarted only when clinically resolved and the investigator considers it appropriate

7.7.2.3 Management of Possible Acute Hypersensitivity Reactions

Hypersensitivity resulting in severe, acute allergic reactions may occur as a result of the protein nature of abatacept and adalimumab. As defined in a recent consensus statement,[66] anaphylaxis is highly likely if 2 or more of the following occur rapidly after administration of the study drug (minutes to several hours):

- Involvement of the skin-mucosal tissue (eg, generalized hives; itching or flushing; swollen lips, tongue, or uvula)
- Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia)
- Reduced blood pressure or associated symptoms (eg, hypotonia/collapse, syncope, incontinence)
- Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)

Sites must be appropriately prepared to handle medical emergencies such as severe hypersensitivity, including anaphylaxis. Participants must be rapidly assessed and stabilized at the site and transferred to an emergency facility as required. If participants experience symptoms of severe allergic reactions at home, he/she should be advised to seek immediate medical attention, including a visit to the local emergency facility, as needed. The site will provide emergency contact information to the participant. A blood sample for analysis of anti-abatacept antibodies should be obtained in case of a hypersensitivity reaction.

The decision whether to continue treatment with the study drug will be left to the medical judgment of the investigator. Care should be taken to treat any acute toxicity expeditiously should they occur. Adequate equipment and trained health care personnel should be available to handle medical emergencies when they occur at the site.

7.8 Treatment After the End of the Study

At the end of the OLTP, BMS will not continue to provide BMS-supplied study treatment to participants/investigators unless BMS chooses to extend the study. The investigator should ensure that the participant receives appropriate standard of care to treat the condition under study.

8 DISCONTINUATION CRITERIA

8.1 Discontinuation From Study Treatment

Participants MUST discontinue IP (and non-IP at the discretion of the investigator) for any of the following reasons:

- Use of prohibited medication. Hold IP and contact Clinical Trial Physician/Medical Monitor to discuss ongoing participation.
- Pregnancy
- Missed doses. If the participant meets any of the following criteria, the Clinical Trial Physician/Medical Monitor should be contacted to discuss ongoing participation:
  - Missed greater than 6 doses of abatacept OR greater than 3 doses of adalimumab for any reason during the initial 24-week study period.
  - Missed greater than 4 consecutive doses of abatacept OR greater than 2 consecutive doses of adalimumab for any reason between Week 8 and Week 24 of the study period.
- Participant's request to stop study treatment. Participants who request to discontinue study treatment will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by participant to provide this information.
- Any clinical AE, laboratory abnormality, or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the participant.
- Termination of the study by BMS.
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness. (Note: Under specific circumstances and only in countries where local regulations permit, a participant who has been imprisoned may be permitted to continue as a participant. Strict conditions apply and BMS approval is required.)

Refer to Section 2 (Schedule of Activities) for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that can be completed.

In the case of pregnancy, the investigator must immediately, within 24 hours of awareness of the pregnancy, notify the BMS Medical Monitor/designee of this event. In most cases, the study treatment will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant safety). Refer to Section 9.2.5 Pregnancy.

All participants who discontinue study treatment should comply with protocol-specified follow-up procedures as outlined in Section 2. The only exception to this requirement is when a participant withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If study treatment is discontinued prior to the participant's completion of the study, the reason for the discontinuation must be documented in the participant's medical records and entered on the appropriate CRF page.

8.1.1 Post Study Treatment Study Follow-up

Participants who discontinue study treatment may continue to be followed. Participants who withdraw consent (according to Section 8.2) or are lost to follow-up (according to Section 8.3) will not be followed in this study; all other participants will continue to be followed for collection of follow-up data as required and in line with Section 2 (Schedule of Activities).

8.2 Discontinuation From the Study

Participants who request to discontinue study treatment will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by participant to provide this information.

- Participants should notify the investigator of the decision to withdraw consent from future follow-up **in writing**, whenever possible.
- The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study treatment only or also from study procedures and/or post-treatment study follow-up, and entered on the appropriate CRF page.
- In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

8.3 Lost to Follow-up

- All reasonable efforts must be made to locate participants to determine and report their ongoing status. This includes follow-up with persons authorized by the participant.
- Lost to follow-up is defined by the inability to reach the participant after a minimum of **three** documented phone calls, faxes, or emails as well as lack of response by participant to one registered mail letter. All attempts should be documented in the participant's medical records.
- If it is determined that the participant has died, the site will use permissible local methods to obtain date and cause of death.
- If investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the participant's informed consent, then the investigator may use a Sponsor-retained, third-party representative to assist site staff with obtaining participant's contact information or other public vital status data necessary to complete the follow-up portion of the study.
- The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information.

- If after all attempts, the participant remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the participant's medical records.

9 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and timing are summarized in Section 2 (Schedule of Activities) and are recommended to be performed in the following order:

1) PRO questionnaires
2) AE collection
3) Vital signs
4) Joint assessments
5) Investigator assessments
6) Blood draws
7) Study drug administration

Additionally, please note the following:

- Protocol waivers or exemptions are not allowed.
- All immediate safety concerns must be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue treatment.
- Adherence to the study design requirements, including those specified in Section 2 (Schedule of Activities), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria before randomization. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of informed consent may be utilized for screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within the timeframe defined in Section 2 (Schedule of Activities).

9.1 Efficacy Assessments

Questionnaires and investigator/participant assessments will be completed prior to study drug administration.

9.1.1 Physician's Global Assessment

The PGA (Appendix 7) can be performed by the principal investigator or sub-investigator. The sub-investigator preferably should be a qualified physician or Doctor of Medicine (MD). Where permitted by local practice and guidelines, a qualified Doctor of Osteopathy (DO), Physician

Assistant (PA), or Nurse Practitioner (NP) may perform the PGA. The staff member performing the PGA needs to meet the definition of blinded Clinical Assessor (see Section 7.3).

9.1.2 Joint Count Assessments

The Joint Count Assessor may perform the PGA for the same participant. For both assessments, every effort should be made to ensure the same assessor is used for a given participant throughout the study. The staff member performing the joint count assessment needs to meet the definition of blinded Clinical Assessor (see Section 7.3).

Training and instruction on joint count assessments will be discussed at the Investigator's Meeting or at other trainings and workshops. Any assessors at a site who were not trained by a centralized BMS trainer should receive instruction by their site primary assessor who has undergone a standardized joint assessment training by BMS or by another Sponsor (if the training by another Sponsor is approved by the Clinical Trial Physician/Medical Monitor). The secondary assessor may conduct joint counts for the trial only after having performed satisfactorily at least 3 patient assessments under the supervision of the primary assessor. Additional information related to joint assessor training will be provided by the Sponsor or a delegate.

Joint Count Assessors should have appropriate medical credentials and/or should be individuals with appropriate scientific/medical background who are experienced in performing joint assessments for the Sponsor's Phase 3 RA studies. If the individual does not have medical credentials, documentation of their experience (preferably on a curriculum vitae) must be provided to the Sponsor's Trial Manager, and their eligibility as Joint Count Assessor must be confirmed by the Sponsor's Clinical Trial Physician/Medical Monitor before the individual's participation in the study as Joint Count Assessor.

Visits should be scheduled with the availability of the assessor taken into account. If the assessor is unable to complete the evaluation, then another qualified individual can take the place of the initial evaluator, as long as the restrictions described above are still met. The substitute evaluator will have also examined and reviewed the participant with the initial assessor to ensure consistency between participant evaluations.

9.1.3 Patient-reported Outcomes

Participants will complete the Global Assessment of Disease Activity (visual analog scale [VAS]; Appendix 5), Assessment of Pain (VAS; Appendix 6), and HAQ-DI (Appendix 8). Participants will also complete the 36-item Short Form Survey (SF-36; Appendix 9) measure of health-related quality of life, the Work Productivity and Activity Impairment Questionnaire - Rheumatoid Arthritis (WPAI-RA; Appendix 10), the Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F; Appendix 11), and morning stiffness (MS) duration questionnaire (Appendix 12).

Questionnaires should be completed by the participant prior to any procedures being performed at the visit, if possible. The forms should then be checked by site staff for completeness. If exceptional circumstances preclude the continued administration of measures using planned

modalities, then alternate administration methods may be required, including telephone administration by site staff.

The full scope of analysis will be outlined in the Statistical Analysis Plan (SAP).

9.1.3.1 36-item Short Form Survey

The SF-36 v2.0 (Appendix 9), which covers 8 health dimensions within 2 components, will be used to measure health-related quality of life.[67] This tool has been validated for use in RA patients.[68] It has been recommended by the Food and Drug Administration (FDA) for measuring broader effects of treatment on health-related quality of life in RA clinical studies.[69]

The physical component summary (PCS) of the SF-36 consists of these 4 subscales:

- Physical functioning
- Role-physical
- Bodily pain
- General health

The mental component summary (MCS) of the SF-36 consists of these 4 subscales:

- Vitality
- Social functioning
- Role-emotional
- Mental health

The 8 subscales will be scored using norm-based methods that have standardized the scores to a mean of 50 and a standard deviation of 10 in the general population. The scores range from 0 to 100, with a higher score indicating better quality of life. The 2 summary scores (PCS and MCS) will be calculated by taking a weighted linear combination of the 8 individual subscales.

9.1.3.2 Work Productivity and Activity

The WPAI-RA v2 (Appendix 10) completed by the participant will be used in this study to measure aspects of productivity and activity impairment over the previous 7 days. The WPAI-RA is a 6-item questionnaire that includes 2 visual analog scales: 1 for impact of disease on work and 1 for impact of disease on other daily activities.[70,71]

The WPAI-RA provides 4 types of scores:

1) Absenteeism (work time missed)
2) Presenteeism (impairment at work/reduced on-the-job effectiveness)
3) Work Productivity Loss (overall work impairment/absenteeism plus presenteeism)
4) Activity Impairment

9.1.3.3 Fatigue

Participant assessment of fatigue will be conducted using the FACIT-F Scale v4 (Appendix 11), a validated tool that measures the severity of fatigue over the past 7 days.[72] This participant-completed questionnaire consists of 13 items, with response options rated on a scale of 0 to 4. Instrument scoring yields a range from 0 to 52, with higher scores representing better participant status (less fatigue). A total score is calculated by summing the responses.

9.1.3.4 Morning Stiffness

Prolonged MS is a common symptom for inflammatory arthritis like RA.[73,74] In the past, it was used as part of the RA classification criteria.[75] While assessment of MS has been recommended as part of the PROs in RA because it is associated with functional disability and pain, there has never been a validated assessment tool. The recommended assessment is to measure MS duration from time of waking to time of maximal improvement, as reported by the participant. We will ascertain duration of MS duration (in minutes) in a PRO questionnaire (Appendix 12) from the time of waking up to the time to maximal improvement in the stiffness that was experienced over the last week.[73] For statistical analyses, MS duration will be analyzed as mean change from baseline in duration of MS and proportion of participants with change from baseline defined as none, mild (1-30 minutes), moderate (31-60 minutes), and severe (> 60 minutes) will be summarized.

9.1.4 Imaging Assessment for the Study

Not applicable.

9.2 Adverse Events

The definitions of an AE or SAE can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the participant to discontinue before completing the study.

Casualty assessments for AEs or SAEs must be performed by a blinded Clinical Assessor (see Section 7.3).

Contacts for SAE reporting specified in Appendix 3.

9.2.1 Time Period and Frequency for Collecting AE and SAE Information

All SAEs must be collected from the time of signing the consent, including those thought to be associated with protocol-specified procedures and within 56 days of discontinuation of dosing.

The investigator must report any SAE that occurs after these time periods and that is believed to be related to study treatment or protocol-specified procedure (eg, a follow-up skin biopsy).

- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the appropriate section of the CRF module.
- All SAEs will be recorded and reported to Sponsor or designee within 24 hours, as indicated in Appendix 3.
- The investigator will submit any updated SAE data to the Sponsor or designee within 24 hours of updated information being available.

Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify the Sponsor.

The method of evaluating and assessing causality of AEs and SAEs and the procedures for completing and reporting/transmitting SAE reports are provided in Appendix 3.

9.2.2 Method of Detecting AEs and SAEs

AEs can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a participant. Care should be taken not to introduce bias when collecting AE and/or SAEs. Inquiry about specific AEs should be guided by clinical judgement in the context of known AEs, when appropriate for the program or protocol.

9.2.3 Follow-up of AEs and SAEs

- Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Appendix 3).
- Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study treatment and for those present at the end of study treatment as appropriate.
- All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic). Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and nonserious AEs of special interest (malignancy, autoimmune diseases, injection-site reactions, and opportunistic infections) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the participant is lost to follow-up (as defined in Section 8.3).

Further information on follow-up procedures is given in Appendix 3.

9.2.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the Sponsor of SAEs is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a product under clinical investigation are met.

- An investigator who receives an investigator safety report describing SAEs or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will file it along with the IB and will notify the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), if appropriate, according to local requirements.

Sponsor or designee will be reporting AEs to regulatory authorities and ethics committees according to local applicable laws, including European Directive 2001/20/EC and FDA Code of Federal Regulations 21 CFR Parts 312 and 320. A suspected, unexpected serious adverse reaction (SUSAR) is a subset of SAEs and will be reported to the appropriate regulatory authorities and investigators following local and global guidelines and requirements.

9.2.5 Pregnancy

If, following initiation of the study treatment, it is subsequently discovered that a participant is pregnant or may have been pregnant at the time of study exposure, including during at least for 70 days (5 half-lives of the study treatment) after study product administration, the investigator must immediately notify the BMS Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to the BMS designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Appendix 3.

If the investigator determines a possible favorable benefit-risk ratio that warrants continuation of study treatment, or re-initiation of study treatment, a discussion between the investigator and the BMS Medical Monitor/designee must occur.

Protocol-required procedures for study discontinuation and follow-up must be performed on the participant.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information, must be reported on the Pregnancy Surveillance Form.

Any pregnancy that occurs in a female partner of a male study participant should be reported to the Sponsor or designee. In order for the Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an ICF for disclosure of this information. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

If any sexual activity (eg, vaginal, anal, oral) has occurred between a male participant and a pregnant partner(s) without the use of a condom during and at least for 70 days (5 half-lives of the study treatment) after study product administration, the information should be reported to the Sponsor or designee, even if the male participant has undergone a successful vasectomy.

In order for the Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner(s) must sign an ICF for disclosure of this information. Information on the pregnancy will be collected on the Pregnancy Surveillance Form.

9.2.6 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or SAE Report Form electronic, as appropriate. Paper forms are only intended as a back-up option when the electronic system is not functioning.

- Any laboratory test result that is clinically significant or meets the definition of an SAE.
- Any laboratory test result abnormality that required the participant to have study treatment discontinued or interrupted.
- Any laboratory test result abnormality that required the participant to receive specific corrective therapy.

It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (eg, anemia vs low hemoglobin value).

9.2.7 Potential Drug-induced Liver Injury (DILI)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential drug-induced liver injury (DILI) event. All occurrences of potential DILIs meeting the defined criteria must be reported as SAEs (see Section 9.2 and Appendix 3 for reporting details).

Potential DILI is defined as:

1) Aminotransaminase (AT; ALT or AST) elevation > 3× ULN

AND

2) Total bilirubin > 2× ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase),

AND

3) No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

9.2.8 COVID-19-related AEs/SAEs

During the study, special attention will be taken on COVID-19-related AEs/SAEs. In cases where SARS-CoV-2 infection occurs, study treatment should be held and care should be provided as guided by local practice. This protocol does not further offer guidance nor restrictions on the management of SARS-CoV-2 infections. Please consult with the study Medical Monitor regarding the decision to resume treatment with study drug.

COVID-19-related impact to the study will be captured in the general CRF pages and additional details for COVID-19 suspected or confirmed AEs/SAEs will be captured in specific clinical safety program (CSP) CRF pages.

9.2.9 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiogram, x-ray filming, any other potential safety assessment required or not required by protocol should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

9.3 Overdose

For this study, any dose of study treatment greater than the protocol-defined dose will be considered an overdose.

In the event of an overdose, the investigator should:

1) Closely monitor the participant for AEs/SAEs and laboratory abnormalities.
2) Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.
3) Notify the Clinical Trial Physician/Medical Monitor with a description of the event.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Clinical Trial Physician/Medical Monitor based on the clinical evaluation of the participant.

9.4 Safety

Planned time points for all safety assessments are listed in Section 2 (Schedule of Activities).

On Day 1, the results of all assessments must be reviewed to assure that eligibility requirements are met before contacting the Central Randomization System for the participant's randomization assignment.

Participants who terminate treatment early should complete the appropriate ET Visit and the PTFUP Visits. The ET Visit should be as soon as possible after the last dose of study medication.

All assessments should be performed or administered prior to study drug administration unless otherwise indicated.

Only data for the procedures and assessments specified in this protocol should be submitted to the Sponsor on a CRF. Additional procedures and assessments may be performed as part of standard of care; however, data for these assessments should remain in the participant's medical record and should not be provided to the Sponsor, unless specifically requested by the Sponsor.

9.4.1 Physical Examination

Physical examinations preferably should be performed by a qualified physician or MD. Where permitted by local practice and guidelines, a qualified DO, PA, or NP may perform the physical examination.

The complete physical examination should include examination of the general appearance, HEEN (head, eyes, ears, nose), throat, neck, heart, lungs, abdomen, lymph nodes, liver, spleen, extremities, skin, and neurologic, psychiatric, and musculoskeletal examination. Height and weight will be part of the complete physical examination and recorded at screening.

While the targeted physical examination may not be as comprehensive as the initial complete examination, key aspects of the targeted examination should evaluate important body systems clinically indicated. The targeted physical examination should include examination of the heart, lungs, and abdomen and may include other relevant body systems, such as the lymph nodes, liver, spleen, and breasts, at the discretion of the examiner.

A physical examination may note any changes in the participant's condition (body systems) since the last assessment and does not preclude examination of any other body systems as clinically indicated.

9.4.2 Chest X-ray

A posterior-anterior and lateral chest x-ray, performed during screening, is required for all participants unless performed within 3 months prior to obtaining written informed consent and documentation of the earlier x-ray is on file. Investigators must ensure that the results of the chest x-ray satisfy criteria for eligibility. The chest x-ray result will be recorded on the appropriate page of the CRF.

9.4.3 Physical Measurements

Weight and height are to be recorded at screening.

9.4.4 Vital Signs

Vital signs (seated blood pressure, heart rate, and temperature) will be recorded during every office visit and prior to dose administration, when applicable. Blood pressure and heart rate should be measured after the participant has been seated for at least 5 minutes.

9.4.5 TB Screening

A chest x-ray and physical examination are considered part of the process to assess a participant's eligibility. In addition to a chest x-ray that does not show any evidence or suspicion of active or latent TB, a tuberculin test will be performed and interpreted according to local country Health Authorities and/or Medical Society guidelines. Some guidelines have specific recommendations for participants who are to receive biologics or immunosuppressant therapies (eg, RA experience with biologic agents)[76,77] or who are immunocompromised and who have had prior Bacillus Calmette-Guérin (BCG) vaccination(s).[78,79] (For ex-US sites, local guidelines endorsed by medical societies on PPD testing in participants with RA being treated with biologics may also apply.) Tuberculin skin testing is not contraindicated for persons who have been vaccinated with BCG. An IFN-γ release assay (eg, QuantiFERON® Gold or Tspot/ELISpot) is an acceptable alternative when skin testing for TB (ie, PPD) is not appropriate, feasible, or based on preference. TB screening test may be performed by qualified personnel and/or by a qualified local laboratory. If a TB test has been performed within 4 weeks prior to informed consent and clear documentation is available, the test result may be used to screen for eligibility.

9.4.6 Viral Hepatitis Screening and Monitoring

Screening participants with serologic evidence of HBV infection (HBsAg-positive or anti-HBcAb-positive) are at risk for HBV reactivation if they receive immunosuppressive therapy,

such as adalimumab or abatacept. The risk increases with use of concomitant immunosuppressive drugs (eg, MTX). Risk is highest in participants who are HBsAg-positive. Reactivation in participants who are HBsAg-negative but anti-HBcAb-positive receiving immunosuppressive therapy (eg, MTX) is rare.[80] The American Association for the Study of Liver Diseases (AASLD) recommendations consider these patients to be at very low risk of HBV reactivation. HBV reactivation can be asymptomatic and have normal liver chemistries.[81]

Participants in this study will be screened for chronic or occult HBV infection with testing for HBsAg and anti-HBcAb-positive.[82] Participants positive for HBsAg will be excluded from this study. Participants positive for anti-HBcAb will have reflex testing for HBV DNA. Participants positive for anti-HBcAb and HBV DNA will be excluded from this study. Participants positive for anti-HBcAb but negative for HBV DNA (as defined by the lower limit of testing sensitivity) will be allowed to be randomized. These participants will be closely monitored for clinical and laboratory signs of HBV reactivation. HBV DNA testing should be performed on a monthly basis after initiation of treatment, for 6 months, along with review of liver chemistries. After 6 months, the interval and duration of surveillance should be decided at the investigator's discretion and in accordance with local guidelines. In the event of HBV reactivation, study treatment should be discontinued and local guidelines followed for management (eg, treatment with entecavir or tenofovir).

There is much less concern for worsening of untreated HCV infection with immunosuppressive treatment but participants with evidence of active HCV infection will be excluded from this trial. Participants will be tested for HCV antibody, and those positive will reflex to HCV RNA testing. Participants with detectable levels of HCV RNA will be excluded.

9.4.7 Clinical Safety Laboratory Assessments

Investigators must document their review of each laboratory safety report.

A list of the clinical laboratory assessments to be tested is provided below in Table 9.4.7-1. Assessments will be carried out as outlined in Section 2 (Schedule of Activities) by a central and/or local laboratory. Additional information on specific local requirements and laboratory guidelines is provided in Appendix 16 and Appendix 17.

Table 9.4.7-1: Clinical Safety Laboratory Assessments (Performed Centrally Unless Otherwise Stated)

Hematology	
Hemoglobin Hematocrit	Total leukocyte count, including differential Platelet count
Blood Chemistry	
Sodium Potassium Chloride Total protein Albumin Calcium Phosphorus Glucose	Creatinine BUN Total bilirubin ALT AST GGT Alkaline phosphatase hsCRP
Urinalysis	
pH, protein, glucose, blood Microscopic examination of the urine sediment if blood, protein, or glucose is positive on the dipstick.	
Serology (screening only)	
Hepatitis B surface antigen, hepatitis B core antibody. If positive, reflex HBV DNA testing must be performed.	
Hepatitis C antibody. If positive, reflex HCV RNA testing must be performed.	
HIV testing performed only where required or local standard of care (may be analyzed locally).	
Other Analyses	
TB screening: PPD or IFN-γ release assay (at screening only, may be analyzed locally); see Section 9.4.5.	
Pregnancy test for WOCBP only: urine pregnancy test, serum pregnancy test as needed.[a] (Performed locally.)	
FSH (as needed; refer to Appendix 4).	

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; DNA, deoxyribonucleic acid; FSH, follicle-stimulating hormone; GGT, gamma-glutamyltransferase; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IFN-γ, interferon gamma; hsCRP, high-sensitivity C-reactive protein; PPD, purified protein derivative; RNA, ribonucleic acid; WOCBP, women of childbearing potential.

[a] A serum test must be performed for confirmation of any positive urine test result. Urine tests can be processed locally and can be self-administered by the participant between office visits, if permitted by local regulations. If any female participant becomes pregnant, she will stop receiving study treatment immediately and enter the Post-treatment Follow-up Period (PTFUP). A pregnancy surveillance form will be completed and submitted to the Sponsor.

9.4.8 Imaging Safety Assessment

Not applicable.

9.5 Pharmacokinetics and Immunogenicity

Not applicable.

9.6 Pharmacodynamics

Not applicable.

9.7 Pharmacogenomics

Not applicable.

9.8 Biomarkers

9.8.1 HLA-DRB1 Shared Epitope Alleles

In this study, whole blood will be collected to assess SE alleles. The alleles considered to be part of the SE will include those with the following amino acid sequence in positions 70-74 and the respective alleles (see Table 9.8.1-1). Results of SE genotyping must be received prior to randomization.

Table 9.8.1-1: Shared Epitope-positive *HLA-DRB1* Alleles

AA 70-74 Sequence	*HLA-DRB1* Alleles
QKRAA	*04:01, *04:09, *04:13, *04:16, *04:21, *04:35, *04:66, *14:19, *14:21
QRRAA	*01:01, *01:02, *01:05, *04:04, *04:05, 04:08, *04:10, *04:19, *14:02, *14:06, *14:09, *14:13, *14:17, *14:20
RRRAA	*10:01

Abbreviations: AA, amino acid; HLA-DRB1, human leukocyte antigen Class II histocompatibility antigen, DRB1 beta chain.

[redacted]

[redacted]

Table 9.8.2-1: Biomarker Sampling Schedule (All Participants)

Study Day of Sample Collection[a]	[redacted]	anti-CCP-2 and RF	[redacted]	HLA-DRB1 Shared Epitope Allele
Screening		X		X
Day 1 Visit 1 (Randomization)		X		
Week 4 Visit 2 (Day 29)[c]				
Week 12 Visit 4 (Day 85)[c]		X		
Week 24/ET Visit 7a (Day 169)[c]		X		
Week 36 Visit 10 (Day 253)[d]		X		
Week 52 Visit 14 (Day 365)[d]		X		
Week 104/ET Visit 20 (Day 729)[d]		X		

Abbreviations: anti-CCP-2, anti-cyclic citrullinated peptide-2; [redacted] ET, early termination; HLA-DRB1, human leukocyte antigen Class II histocompatibility antigen, DRB1 beta chain; [redacted] Rand., randomization; RF, rheumatoid factor; [redacted]

[a] All biomarker sampling must take place prior to study drug administration.

[redacted]

[c] Samples can be collected ± 3 days from scheduled time point.

[d] Samples can be collected ± 7 days from scheduled time point.

9.8.2.1 Autoantibodies

Levels of autoantibodies (eg, anti-CCP-2 and RF) associated with RA will be collected and analyzed at the visits outlined in Table 9.8.2-1. The levels of other autoantibodies will be measured using serum biomarker samples collected at the visits outlined in Table 9.8.2-1. Additional exploratory autoantibody analyses, including but not limited to, anti-modified protein antibodies (AMPAs), ACPA isotypes, ACPA fine-specificities, and/or ACPA-glycosylation may be performed, if deemed relevant. Details for collection, processing, storing, and shipment of these samples will be provided in a separate Laboratory Manual.

[redacted]

9.8.3 Additional Research Collection

[redacted]

For All US Sites:

AR is required for all study participants, except where prohibited by IRBs/ethics committees, or academic/institutional requirements. Where 1 or more of these exceptions occurs, participation in the AR should be encouraged but will not be a condition of overall study participation.

- If the IRB/ethics committees and site agree to the mandatory AR retention and/or collection, then the study participant must agree to the mandatory AR as a requirement for inclusion in the study.
- If optional participation is permitted and approved, then the study participants may opt out of the AR retention and/or collection.

For Non-US Sites

AR is optional for all study participants, except where retention and/or collection is prohibited by local laws or regulations, ethics committees, or institutional requirements.

This collection for AR is intended to expand the translational research and development (R&D) capability at BMS, and will support as yet undefined research aims that will advance our understanding of disease and options for treatment. It may also be used to support Health Authority requests for analysis, and advancement of pharmacodiagnostic development to better target drugs to the right patients. This may also include genetic/genomic exploration aimed at exploring disease pathways, progression and response to treatment, etc.

Sample Collection and Storage

All requests for access to samples or data for AR will be vetted through a diverse committee of the study Sponsor's senior leaders in R&D (or designee) to ensure the research supports appropriate and well-defined scientific research activities.

[redacted]

[redacted]

The manager of these samples will ensure they are properly used throughout their usable life and will destroy the samples at the end of the scheduled storage period, no longer than fifteen (15) years after the end of the study or the maximum allowed by applicable law.

[redacted]

Samples will be stored in a coded fashion, and no researcher will have access to the key. The key is securely held by the investigator at the clinical site, so there is no direct ability for a researcher to connect a sample to a specific individual.

Further details of sample collection and processing will be provided to the site in the procedure manual.

[redacted]

9.8.4 Other Assessments

Not applicable.

9.9 Health Economics OR Medical Resource Utilization and Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters will not be specifically captured and evaluated as a primary part of this study.

10 STATISTICAL CONSIDERATIONS

10.1 Sample Size Determination

The planned sample size is approximately 150 participants per treatment group. Assuming that about 3/4 of the participants would be SE+, this would lead to approximately 112 SE+ participants per treatment group. [redacted]

[redacted]

[redacted]

To preserve an overall type I error rate of 5%, the primary endpoint and secondary efficacy endpoints will be assessed using a hierarchical testing approach. The hierarchy in secondary endpoints is determined by the order they are listed in Table 4-1 and is as follows:

1) Proportion of participants meeting ACR50 response at Week 24 in the SE+ subpopulation.
2) Proportion of participants achieving DAS28-CRP remission (< 2.6) at Week 24 in the SE+ subpopulation.
3) Proportion of participants meeting ACR50 response at Week 24 in the full study population.
4) Proportion of participants achieving Clinical Disease Activity Index (CDAI) remission (≤ 2.8) at Week 24 in the SE+ subpopulation.
5) Mean change from baseline in participant-reported pain at Week 24 in the SE+ subpopulation.

Each endpoint will be tested with a 2-sided alpha level of 5% if the endpoints at a higher level in the hierarchy are statistically significant. The testing will stop as soon as an endpoint is not statistically significant.

Assuming that the difference between treatment groups in the primary endpoint will be statistically significant, the samples size of 112 per arm will have [redacted] power to detect a difference in DAS28-CRP remission in SE+ population at Week 24 (Day 169) under the assumption of a response rate of [redacted] as observed in the SE+ subgroup in IM101567.

Assuming that both ACR50 and DAS28-CRP remission are statistically significantly different between the treatment groups in the SE+ population, there will be [redacted] power to detect a difference in ACR50 between the treatment groups in the entire population (SE+ and SE-) with a sample size of 150 per group and assuming response rates of [redacted] as in IM101567.

Assuming all endpoints higher in the hierarchy are statistically significantly different between the treatment groups, the sample size of 112 per arm will have [redacted] power to detect a difference in CDAI remission (≤ 2.8) at Week 24 if the underlying remission rate is [redacted] per treatment group as observed in the SE+ subgroup of IM101567.

Assuming all endpoints higher in the hierarchy are statistically significantly different between the treatment groups, a sample size of 112 per group will have [redacted] power to detect a difference

between the groups in mean change from baseline in participant-reported pain at Week 24. This assumes that the underlying mean change from baseline is [redacted] as observed in the SE+ subgroup of IM101567, with a common standard deviation of [redacted], using a 2-group t-test with 0.05 2-sided significance level.

10.2 Populations for Analyses

The populations for the purpose of analyses are defined in Table 10.2-1.

Table 10.2-1: Populations for Analyses

Population	Description
Enrolled	All participants who sign informed consent form.
Modified Intent-to-treat Analysis Population	All randomized participants who receive at least 1 dose of study medication. This population will exclude participants who are randomized, but not treated. Analyses using the mITT analysis population will group the participants according to the treatment group to which they are randomized. All efficacy analyses will use the mITT population.
Intent-to-treat Population	All randomized participants, also those who are never treated. Participants who were randomized and never treated and did not return for any assessments after discontinuation (ie, lost to follow-up or withdrew consent) will be excluded from the ITT analysis population. This population may be used for a sensitivity analysis of the primary endpoint. Analyses using the ITT analysis population will group the participants according to the treatment group to which they are randomized.
Per-protocol Analysis Population	All randomized participants who receive at least 1 dose of study medication, excluding the participants with relevant protocol deviations. Relevant protocol deviations are those that potentially may impact the primary efficacy outcome. The criteria for relevant protocol deviations will be defined in the SAP. Analyses using the PP analysis population will group the participants according to the treatment group to which they are randomized.
As-treated Analysis Population	All participants who receive at least 1 dose of study medication. Analyses using the as-treated analysis population will group the participants on an as-randomized basis unless a participant received the incorrect medication for the entire period of treatment. In that case, the participant will be analyzed in the treatment group associated with the incorrect medication they received ("as-treated"). The as-treated analysis population will be used for safety analyses of the SBTP.
Cumulative Abatacept Population	All randomized participants who receive at least 1 dose of abatacept during the SBTP and/or the OLTP. All participants of the as-treated population will be included, except for participants treated with adalimumab in the SBTP who never entered the OLTP.
Subgroup of SE+ Participants	The subgroup of participants that are SE+ at baseline.

Abbreviations: ITT, intent-to-treat; mITT, modified intent-to-treat; OLTP, Open-label Treatment Period; PP, per-protocol; SBTP, Single-blind Treatment Period; SC, subcutaneous; SE+, shared epitope-positive.

10.3 Statistical Analyses

A description of the participant population will be included in a clinical study report, including subgroups of age, gender, and race. Demography and baseline disease characteristics will be presented by randomized treatment group and overall for the intent-to-treat (ITT) population. Continuous variables such as age and weight will be summarized using means, standard deviations, median, and ranges. Categorical variables such as gender, race, and region, will be summarized using frequencies.

10.3.1 Efficacy Analyses

Hierarchical testing of the primary and key secondary endpoints, as described in Section 10.1, will be applied. P-values will be presented for the treatment comparisons of the primary and key secondary endpoints. Statistical analysis methods for efficacy analyses are provided in Table 10.3.1-1.

Table 10.3.1-1: Efficacy Statistical Analyses

Endpoint	Statistical Analysis Methods
Proportions	The binary efficacy endpoints (eg, the proportion of participants meeting ACR50 response at Week 24) will be analyzed with a logistic regression including treatment in the model. The OR along with its 95% CI will be provided. A missing responder value at Day 169 due to discontinuation or for other reasons will be imputed as a nonresponder. For analysis of variables in the overall population (SE+ and SE-), the stratification variable SE +/- will also be included as a factor in logistic regression model. For analysis of proportions that are based on a cutoff value of continuous variable (eg, remission defined as DAS28-CRP < 2.6) for which a corresponding value is measured at baseline (baseline DAS28-CRP measurement), the analysis model will also include the continuous baseline covariate.
Mean Change From Baseline	Mean changes from baseline in continuous variables will be analyzed using a longitudinal repeated measures analysis. The model will include the fixed categorical effects of treatment, day (is a windowed time point), stratification variable SE +/- (as appropriate), treatment-by-day interaction, and covariate of corresponding baseline and baseline-by-day interaction. An unstructured covariance matrix will be used to represent the correlation of the repeated measures within each participant. The parameter estimations will be based on the assumption of data being MAR and using the method of REML. The difference in adjusted LSMEANS between abatacept and adalimumab at the primary time point, Week 24, and corresponding 95% CI will be provided. For the key secondary variable of mean change from baseline at Week 24, the P-value will be based on the longitudinal model.
[redacted]	

Abbreviations: ACR50, 50% improvement in American College of Rheumatology criteria; CI, confidence interval; LSMEANS, least-squared means; DAS28-CRP, Disease Activity Score 28-joint count calculated using C-reactive protein; MAR, missing at random; OR, odds ratio; REML, restricted maximum likelihood; SAP, Statistical Analysis Plan; SE-, shared epitope; SE+, shared epitope-positive.

Details of the efficacy analysis during the OLTP will be provided in the SAP.

10.3.2 Safety Analyses

The proportion (%) of participants with AEs, deaths, SAEs, AEs of special interest, and AEs leading to discontinuation and of participants with laboratory marked abnormalities will be provided by treatment group. Summaries for the SBTP will include events from the start of study treatment up to start of the OLTP for participants continuing in the OLTP or up to last dosing date +56 days for participants discontinuing during the SBTP using the as-treated analysis population. AEs of special interest are infections, malignancies, autoimmune disorders, and injection-site reactions. Summaries for the cumulative abatacept period will include safety events with onset on or after the first day of abatacept treatment in the study up to 56 days after the last abatacept treatment in the study using the cumulative abatacept population.

10.3.3 Other Analyses

[redacted]

10.3.3.2 Patient-reported Outcomes Analyses

For the individual components of the SF-36, WPAI-RA, and FACIT-F and duration of MS, changes from baseline will be summarized by treatment, and 95% CI for the treatment differences in changes from baseline will be constructed.

10.3.4 Interim Analyses

Not applicable.

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[redacted]

12 APPENDICES

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
+	positive
AA	amino acid
AASLD	American Association for the Study of Liver Diseases
ABA	abatacept
ADA	adalimumab
AE	adverse event
ACIP	Advisory Committee on Immunization Practices
ACPA	anti-citrullinated protein antibodies
ACPA-	anti-citrullinated protein antibodies-negative
ACPA+	anti-citrullinated protein antibody-positive
ACR	American College of Rheumatology
ACR20	20% improvement in American College of Rheumatology criteria
ACR50	50% improvement in American College of Rheumatology criteria
ACR70	70% improvement in American College of Rheumatology criteria
ACTH	adrenal corticotropic hormone
AGREE	Abatacept study to Gauge Remission and joint damage progression in MTX-naive patients with Early Erosive rheumatoid arthritis
ALT	alanine aminotransferase
[redacted]	
AMPLE	Abatacept vs adaliMumab comParison in bioLogic-naivE RA participants with background methotrexate
anti-CCP-2	anti-cyclic citrullinated peptide-2
anti-CCP-2-	anti-cyclic citrullinated peptide-2-negative
anti-CCP-2+	anti-cyclic citrullinated peptide-2-positive
APC	antigen-presenting cell
AR	additional research
AST	aspartate aminotransferase
AT	aminotransaminase
AVERT	Assessing Very Early Rheumatoid Arthritis Treatment study
[redacted]	

Term	Definition
BCG	Bacillus Calmette-Guérin
BMS	Bristol-Myers Squibb
BRASS	Brigham and Women's Rheumatoid Arthritis Sequential Study
BUN	blood urea nitrogen
CBC	complete blood count
CD	cluster of differentiation
CDAI	Clinical Disease Activity Index
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	confidence interval
CONSORT	Consolidated Standards of Reporting Trials
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
CRF	case report form, paper or electronic
CRO	Contract Research Organization
CRP	C-reactive protein
CSP	clinical safety program
CTAg	Clinical Trial Agreement
CTLA4	cytotoxic T-lymphocyte-associated protein 4
[redacted]	
DAS	Disease Activity Score
DAS28-CRP	Disease Activity Score 28-joint count calculated using C-reactive protein
D	Day
DILI	drug-induced liver injury
DMARD	disease-modifying antirheumatic drug
DNA	deoxyribonucleic acid
DO	Doctor of Osteopathy
[redacted]	

Term	Definition
EDC	Electronic Data Capture
[redacted]	
ET	early termination
EULAR	European League Against Rheumatism
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FACIT-F	Functional Assessment of Chronic Illness Therapy - Fatigue
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
FU	follow-up
GCP	Good Clinical Practice
GGT	gamma-glutamyltransferase
HAQ-DI	Health Assessment Questionnaire Disability Index
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HcAb	hepatitis antibody
HBV	hepatitis B virus
HCG	human chorionic gonadotropin
HCV	hepatitis C virus
HEEN	head, eyes, ears, nose
Hgb	hemoglobin
HIV	human immunodeficiency virus
HLA-DRB1	human leukocyte antigen Class II histocompatibility antigen, DRB1 beta chain
hr	hours
hsCRP	high-sensitivity C-reactive protein
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation

Term	Definition
IEC	Independent Ethics Committee
IFN-γ	interferon gamma
Ig	immunoglobulin
IL	interleukin
IM	intramuscular
IMG	immunogenicity
IMP	investigational medicinal product
IND	Investigational New Drug Exemption
IP	investigational product
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	intent-to-treat
IV	intravenous(ly)
JIA	juvenile idiopathic arthritis
LSMEANS	least-squared means
MAR	missing at random
MCID	minimal clinically important difference
MCS	mental component summary
MD	Doctor of Medicine
min	minutes
mITT	modified intent-to-treat
MMR	measles, mumps, rubella
MPA	mycophenolate mofetil
[redacted]	
MRI	magnetic resonance imaging
MS	morning stiffness
MTX	methotrexate
MTX-IR	methotrexate inadequate responders
NCT	national clinical trial number
NP	Nurse Practitioner

Term	Definition
NSAID	nonsteroidal anti-inflammatory drug
NYHA	New York Heart Association
OLTP	Open-label Treatment Period
OR	odds ratio
PA	Physician Assistant
[redacted]	
PCS	physical component summary
PEF	peak expiratory flow
PGA	Physician's Global Assessment of Disease Activity
PK	pharmacokinetics
PP	per-protocol
PPD	purified protein derivative
PRO	patient-reported outcome
PTFUP	Post-treatment Follow-up Period
[redacted]	
R	randomize
R&D	research and development
RA	rheumatoid arthritis
Rand.	randomization
[redacted]	
RCT	randomized, controlled trial
REML	restrictive maximum likelihood
RF	rheumatoid factor
RF+	rheumatoid factor-positive
RNA	ribonucleic acid
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBTP	Single-blind Treatment Period
SC	subcutaneous

Term	Definition
SDAI	Simple Disease Activity Index
SE	shared epitope
SE-	shared epitope-negative
SE+	shared epitope-positive
SF-36	36-item Short Form Survey
[redacted]	
SLE	systemic lupus erythematosus
SOP	Standard Operating Procedures
STPR	Strategies Therapeutiques de la Polyarthrite Rhumatoıde
SSC	Study Steering Committee
SUSAR	suspected, unexpected serious adverse reaction
TB	tuberculosis
TNF	tumor necrosis factor
ULN	upper limit of normal
US	United States
V	Visit
VAS	visual analog scale
WBC	white blood cell
WHO	World Health Organization
Wk	Week
WNOCBP	women **not** of childbearing potential
WOCBP	women of childbearing potential
WPAI-RA	Work Productivity and Activity Impairment Questionnaire - Rheumatoid Arthritis

APPENDIX 2 STUDY GOVERNANCE CONSIDERATIONS

The term 'Participant' is used in the protocol to refer to a person who has consented to participate in the clinical research study. The term 'Subject' used in the CRF is intended to refer to a person (participant) who has consented to participate in the clinical research study.

REGULATORY AND ETHICAL CONSIDERATIONS

GOOD CLINICAL PRACTICE

This study will be conducted in accordance with:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines Good Clinical Practice (GCP),
- as defined by the International Council on Harmonisation (ICH),
- in accordance with the ethical principles underlying European Union Directive 2001/20/EC,
- United States Code of Federal Regulations, Title 21, Part 50 (21CFR50), and
- applicable local requirements.

The study will be conducted in compliance with the protocol. The protocol and any amendments and the participant informed consent will receive approval/favorable opinion by Institutional Review Board/Independent Ethics Committee (IRB/IEC), and regulatory authorities according to applicable local regulations prior to initiation of the study.

All potential serious breaches must be reported to the Sponsor or designee immediately. A potential serious breach is defined as a Quality Issue (eg, protocol deviation, etc) that is likely to affect, to a significant degree one or more of the following: (1) the physical, safety or mental integrity of one or more subjects/participants; (2) the scientific value of the trial (eg, reliability and robustness of generated data). Items (1) or (2) can be associated with either GCP Regulation(s) or Trial protocol(s).

Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (eg, loss of medical licensure, debarment).

INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, participant recruitment materials (eg, advertisements), and any other written information to be provided to subjects/participants. The investigator or BMS should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling information to be provided to subjects/participants and any updates.

The investigator, Sponsor, or designee should provide the IRB/IEC with reports, updates, and other information (eg, expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

COMPLIANCE WITH THE PROTOCOL AND PROTOCOL REVISIONS

The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion of an amendment from the IRB/IEC (and if applicable, also by local health authority) except where necessary to eliminate an immediate hazard(s) to study subjects/participants.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining relevant approval/favorable opinion(s) the deviation or change will be submitted, as soon as possible to:

- IRB/IEC
- Regulatory Authority(ies), if applicable by local regulations (per national requirements)

Documentation of approval/favorable opinion signed by the chairperson or designee of the IRB(s)/IEC(s) and if applicable, also by local health authority must be sent to BMS.

If an amendment substantially alters the study design or increases the potential risk to the participant: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects/participants currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects/participants prior to enrollment.

If the revision is done via an administrative letter, investigators must inform their IRB(s)/IEC(s).

FINANCIAL DISCLOSURE

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

INFORMED CONSENT PROCESS

Investigators must ensure that subjects/participants are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

In situations where consent cannot be given by subjects/participants, their legally acceptable representatives (as per country guidelines) are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which the participant volunteers to participate.

Sponsor or designee will provide the investigator with an appropriate (ie, Global or Local) sample informed consent form which will include all elements required by ICH, GCP, and applicable regulatory requirements. The sample informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

Investigators must:

- Provide a copy of the consent form and written information about the study in the language in which the participant is most proficient prior to clinical study participation. The language must be non-technical and easily understood.
- Allow time necessary for participant or participant's legally acceptable representative to inquire about the details of the study.
- Obtain an informed consent signed and personally dated by the participant or the participant's legally acceptable representative and by the person who conducted the informed consent discussion.
- Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects/participants, prior to the beginning of the study, and after any revisions are completed for new information.

If informed consent is initially given by a participant's legally acceptable representative or legal guardian, and the participant subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the participant.

Revise the informed consent whenever important new information becomes available that is relevant to the participant's consent. The investigator, or a person designated by the investigator, should fully inform the participant or the participant's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the participant's willingness to continue participation in the study. This communication should be documented.

The confidentiality of records that could identify subjects/participants must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the subjects'/participants' signed ICF and, in the US, the subjects'/participants' signed HIPAA Authorization.

The consent form must also include a statement that BMS and regulatory authorities have direct access to participant records.

The rights, safety, and well-being of the study subjects/participants are the most important considerations and should prevail over interests of science and society.

SOURCE DOCUMENTS

The investigator is responsible for ensuring that the source data are accurate, legible, contemporaneous, original, and attributable, whether the data are hand-written on paper or entered electronically. If source data are created (first entered), modified, maintained, archived, retrieved, or transmitted electronically via computerized systems (and/or any other kind of electronic

devices) as part of regulated clinical trial activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical/health records (EMRs/EHRs), adverse event tracking/reporting, protocol required assessments, and/or drug accountability records).

When paper records from such systems are used in place of electronic format to perform regulated activities, such paper records should be certified copies. A certified copy consists of a copy of original information that has been verified, as indicated by a dated signature, as an exact copy having all of the same attributes and information as the original.

STUDY TREATMENT RECORDS

Records for study treatments (whether supplied by BMS, its vendors, or the site) must substantiate study treatment integrity and traceability from receipt, preparation, administration, and through destruction or return. Records must be made available for review at the request of BMS/designee or a Health Authority.

If	Then
Supplied by BMS (or its vendors):	Records or logs must comply with applicable regulations and guidelines and should include: • amount received and placed in storage area • amount currently in storage area • label identification number or batch number • amount dispensed to and returned by each participant, including unique participant identifiers • amount transferred to another area/site for dispensing or storage • nonstudy disposition (eg, lost, wasted) • amount destroyed at study site, if applicable • amount returned to BMS • retain samples for bioavailability/bioequivalence/biocomparability, if applicable • dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.

If	Then
Sourced by site, and not supplied by BMS or its vendors (examples include IP sourced from the sites stock or commercial supply, or a specialty pharmacy)	The investigator or designee accepts responsibility for documenting traceability and study treatment integrity in accordance with requirements applicable under law and the SOPs/standards of the sourcing pharmacy.

BMS or designee will provide forms to facilitate inventory control if the investigational site does not have an established system that meets these requirements.

CASE REPORT FORMS

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data that are derived from source documents and reported on the CRF must be consistent with the source documents or the discrepancies must be explained. Additional clinical information may be collected and analyzed in an effort to enhance understanding of product safety. CRFs may be requested for AEs and/or laboratory abnormalities that are reported or identified during the course of the study.

For sites using the Sponsor or designee electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the electronic SAE form and Pregnancy Surveillance form, respectively. If electronic SAE form is not available, a paper SAE form can be used.

The confidentiality of records that could identify subjects/participants must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

The completed CRF, SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a sub-investigator and who is delegated this task on the Delegation of Authority Form. Sub-investigators in Japan may not be delegated the CRF approval task. The investigator must retain a copy of the CRFs including records of the changes and corrections.

Each individual electronically signing electronic CRFs must meet Sponsor or designee training requirements and must only access the BMS electronic data capture tool using the unique user account provided by Sponsor or designee. User accounts are not to be shared or reassigned to other individuals.

MONITORING

Sponsor or designee representatives will review data centrally to identify potential issues to determine a schedule of on-site visits for targeted review of study records.

Representatives of BMS must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable. Certain CRF pages and/or electronic files may serve as the source documents.

In addition, the study may be evaluated by Sponsor or designee internal auditors and government inspectors who must be allowed access to CRFs, source documents, other study files, and study facilities. BMS audit reports will be kept confidential.

The investigator must notify BMS promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to Sponsor or designee.

RECORDS RETENTION

The investigator (or head of the study site in Japan) must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by BMS or designee, whichever is longer. The investigator (or head of the study site in Japan) must contact BMS prior to destroying any records associated with the study.

BMS or designee will notify the investigator (or head of the study site in Japan) when the study records are no longer needed.

If the investigator withdraws from the study (eg, relocation, retirement), the records shall be transferred to a mutually agreed upon designee (eg, another investigator, study site, IRB). Notice of such transfer will be given in writing to BMS or designee.

RETURN OF STUDY TREATMENT

For this study, study treatments (those supplied by BMS, a vendor or sourced by the investigator) such as partially used study treatment containers, vials and syringes may be destroyed on site.

If	Then
Study treatments supplied by BMS (including its vendors)	Any unused study treatments supplied by BMS can only be destroyed after being inspected and reconciled by the responsible Study Monitor unless study treatments containers must be immediately destroyed as required for safety, or to meet local regulations (eg, cytotoxics or biologics). If study treatments will be returned, the return will be arranged by the responsible Study Monitor.

If	Then
Study treatments sourced by site, not supplied by BMS (or its vendors) (examples include study treatments sourced from the sites stock or commercial supply, or a specialty pharmacy)	It is the investigator's or designee's responsibility to dispose of all containers according to the institutional guidelines and procedures.

It is the investigator's or designee's responsibility to arrange for disposal, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept. The following minimal standards must be met:

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's SOPs and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal (ie, incinerator, licensed sanitary landfill, or licensed waste disposal vendor) must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period.

It is the investigator's or designee's responsibility to arrange for disposal of all empty containers.

If conditions for destruction cannot be met the responsible Study Monitor will make arrangements for return of study treatments provided by BMS (or its vendors). Destruction of non-study treatments sourced by the site, not supplied by BMS, is solely the responsibility of the investigator or designee.

CLINICAL STUDY REPORT

A Signatory Investigator must be selected to sign the clinical study report.

For each CSR related to this protocol, the following criteria will be used to select the signatory Investigator:

- External Principal Investigator designated at protocol development
- National Coordinating Investigator
- Study Steering Committee chair or their designee
- Subject recruitment (eg, among the top quartile of enrollers)
- Involvement in trial design

- Regional representation (eg, among top quartile of enrollers from a specified region or country)
- Other criteria (as determined by the study team)

SCIENTIFIC PUBLICATIONS

The data collected during this study are confidential and proprietary to Sponsor or designee. Any publications or abstracts arising from this study must adhere to the publication requirements set forth in the clinical trial agreement (CTAg) governing (study site or investigator) participation in the study. These requirements include, but are not limited to, submitting proposed publications to Sponsor or designee at the earliest practicable time prior to submission or presentation and otherwise within the time period set forth in the CTAg.

Scientific Publications (such as abstracts, congress podium presentations and posters, and manuscripts) of the study results will be a collaborative effort between the study Sponsor and the external authors. No public presentation or publication of any interim results may be made by any principal investigator, sub-investigator, or any other member of the study staff without the prior written consent of the Sponsor.

Authorship of publications at BMS is aligned with the criteria of the International Committee of Medical Journal Editors (ICMJE, www.icmje.org). Authorship selection is based upon significant contributions to the study (ie, ICMJE criterion #1). Authors must meet all 4 ICMJE criteria for authorship:

1) Substantial intellectual contribution to the conception or design of the work; or the acquisition of data (ie, evaluable subjects/participants with quality data), analysis, or interpretation of data for the work (eg, problem solving, advice, evaluation, insights and conclusion); AND
2) Drafting the work or revising it critically for important intellectual content; AND
3) Final approval of the version to be published; AND
4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Those who make the most significant contributions, as defined above, will be considered by BMS for authorship of the primary publication. Sub-investigators will generally not be considered for authorship in the primary publication. Geographic representation will also be considered.

Authors will be listed by order of significant contributions (highest to lowest), with the exception of the last author. Authors in first and last position have provided the most significant contributions to the work.

For secondary analyses and related publications, author list and author order may vary from primary to reflect additional contributions.

APPENDIX 3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP AND REPORTING

ADVERSE EVENTS

Adverse Event Definition:

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a clinical investigation participant administered study treatment and that does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of study treatment, whether or not considered related to the study treatment.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or results from other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Note that abnormal lab tests or other safety assessments should only be reported as AEs if the final diagnosis is not available. Once the final diagnosis is known, the reported term should be updated to be the diagnosis.
- Exacerbation of a chronic or intermittent pre-existing condition, including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration, even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose, as a verbatim term (as reported by the investigator), should not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae and should specify "intentional overdose" as the verbatim term

Events NOT Meeting the AE Definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

DEFINITION OF SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

SERIOUS ADVERSE EVENTS

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:
Results in death
Is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
Requires inpatient hospitalization or causes prolongation of existing hospitalization (see NOTE below) NOTE: The following hospitalizations are not considered SAEs in BMS clinical studies: • a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event) • elective surgery, planned prior to signing consent • admissions as per protocol for a planned medical/surgical procedure • routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy) • medical/surgical admission other than to remedy ill health and planned prior to entry into the study; appropriate documentation is required in these cases • admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason) • admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)
Results in persistent or significant disability/incapacity
Is a congenital anomaly/birth defect
Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the participant or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization. Potential drug induced liver injury (DILI) is also considered an important medical event. (See Section 9.2.7 for the definition of potential DILI.)

Pregnancy and potential drug induced liver injury (DILI) must follow the same transmission timing and processes to BMS as used for SAEs (see Section 9.2.5 for reporting pregnancies).

Any component of a study endpoint that is considered related to study therapy should be reported as SAE (eg, death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported).

EVALUATING AES AND SAES

Assessment of Intensity

The intensity of AEs is determined by a physician and will use the following levels:

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort, and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.

Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs
If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports must include the same investigator term(s) initially reported.) If an ongoing SAE changes in its intensity or relationship to study treatment or if new information becomes available, the SAE report must be updated and submitted within 24 hours to BMS (or designee) using the same procedure used for transmitting the initial SAE report. All SAEs must be followed to resolution or stabilization.

REPORTING OF SAES TO SPONSOR OR DESIGNEE

- SAEs, whether related or not related to study treatment, and pregnancies must be reported to BMS (or designee) immediately within 24 hours of awareness of the event.
- SAEs must be recorded on the SAE Report Form.
  - The required method for SAE data reporting is through the eCRF.
  - The paper SAE Report Form is only intended as a back-up option when the electronic data capture (EDC) system is unavailable/not functioning for transmission of the eCRF to BMS (or designee).
    - In this case, the paper form is transmitted via email or confirmed facsimile (fax) transmission
    - When paper forms are used, the original paper forms are to remain on site
- Pregnancies must be recorded on a paper Pregnancy Surveillance Form and transmitted via email or confirmed facsimile (fax) transmission

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

SAE Telephone Contact (required for SAE and pregnancy reporting): Refer to Contact Information list

APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Women in the following categories are not considered WOCBP

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle stimulating hormone (FSH) level > 40 mIU/mL to confirm menopause.

Note: Females treated with hormone replacement therapy (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. The duration of the washout period below are suggested guidelines and the investigators should use their judgement in checking serum FSH levels.

- 1 week minimum for vaginal hormonal products (rings, creams, gels)
- 4 week minimum for transdermal products
- 8 week minimum for oral products

Other parenteral products may require washout periods as long as 6 months. If the serum FSH level is > 40 mIU/ml at any time during the washout period, the woman can be considered postmenopausal.

End of Relevant Systemic Exposure

- End of relevant systemic exposure is the time point where the IMP or any active major metabolites has decreased to a concentration that is no longer considered to be relevant for human teratogenicity or fetotoxicity. This should be evaluated in context of safety margins from the no-observed adverse effect level (NOAEL) or the time required for 5 half-lives of the IMP to pass.

METHODS OF CONTRACEPTION

Local laws and regulations may require use of alternative and/or additional contraception methods.

Highly Effective Contraceptive Methods That Are <u>User Dependent</u> *Failure rate of < 1% per year when used consistently and correctly.*[a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation and/or implantation (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol.)[b] – oral (birth control pills) – intravaginal (vaginal birth control suppositories, rings, creams, gels) – transdermal • Combined (estrogen-and progestogen-containing) hormonal contraception must begin at least 30 days prior to initiation of study therapy
• Progestogen-only hormonal contraception associated with inhibition of ovulation (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol.)[b] – oral – injectable • Progestogen-only hormonal contraception must begin at least 30 days prior to initiation of study therapy
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation and/or implantation (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol.)[b] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol.)[b,c] • Bilateral tubal occlusion
• Vasectomized partner – For WOCPB: Having a vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.

– For male participants: A vasectomy is a highly effective contraception method provided that the participant is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. • Male participants will be required to always use a latex or other synthetic condom during any sexual activity (eg, vaginal, anal, oral) with WOCBP; even if the participants have undergone a successful vasectomy or if their partner is already pregnant or breastfeeding.
• Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.* • Continuous abstinence must begin at least 30 days prior to initiation of study therapy • It is not necessary to use any other method of contraception when complete abstinence is elected • WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in Section 2 • Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence • Periodic abstinence (including but not limited to calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception for this study
NOTES: [a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies. [b] Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the IMP and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized. [c] Intrauterine hormone releasing systems are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness.

Less Than Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of > 1% per year when used consistently and correctly.*
• Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously • Diaphragm with spermicide • Cervical cap with spermicide • Vaginal Sponge with spermicide • Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action (This method of contraception cannot be used by WOCBP participants in studies where hormonal contraception is prohibited.)
Unacceptable Methods of Contraception
• Periodic abstinence (calendar, symptothermal, post-ovulation methods) • Withdrawal (coitus interruptus). • Spermicide only • Lactation amenorrhea method (LAM)

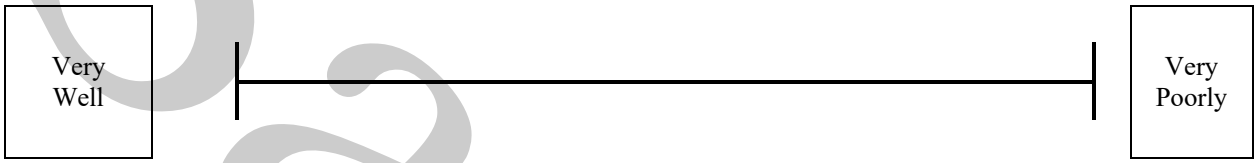
COLLECTION OF PREGNANCY INFORMATION

Guidance for collection of Pregnancy Information and outcome of pregnancy on the Pregnancy Surveillance Form is provided in Section 9.2.5 and the Appendix for Adverse Events and Serious Adverse Events Definitions and procedures for Evaluating, Follow-up and Reporting.

APPENDIX 5 AMERICAN COLLEGE OF RHEUMATOLOGY SUBJECT ASSESSMENT OF DISEASE ACTIVITY VISUAL ASSESSMENT SCALE

Measure with a metric ruler. Line on Case Report Form is exactly 10 cm long. Scores should be recorded in millimeter format. DO NOT USE THIS APPENDIX AS SOURCE DOCUMENT OR CASE REPORT FORM.

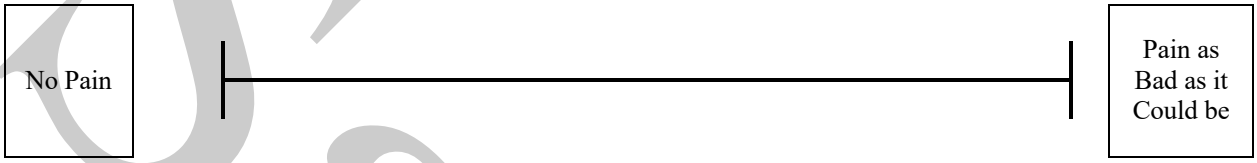
Considering all the ways in which illness and health conditions may affect you at this time, please make a mark below to show how you are doing.



APPENDIX 6 AMERICAN COLLEGE OF RHEUMATOLOGY SUBJECT ASSESSMENT OF PAIN VISUAL ASSESSMENT SCALE

Measure with a metric ruler. Line on Case Report Form is exactly 10 cm long. Scores should be recorded in millimeter format. DO NOT USE THIS APPENDIX AS SOURCE DOCUMENT OR CASE REPORT FORM.

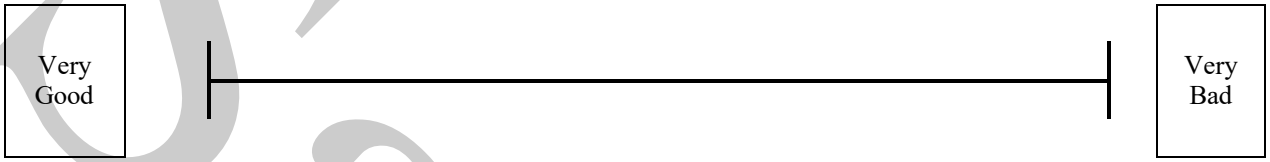
How much pain have you had because of your condition over the past week? Place a mark on the line below to indicate how severely your pain has been:



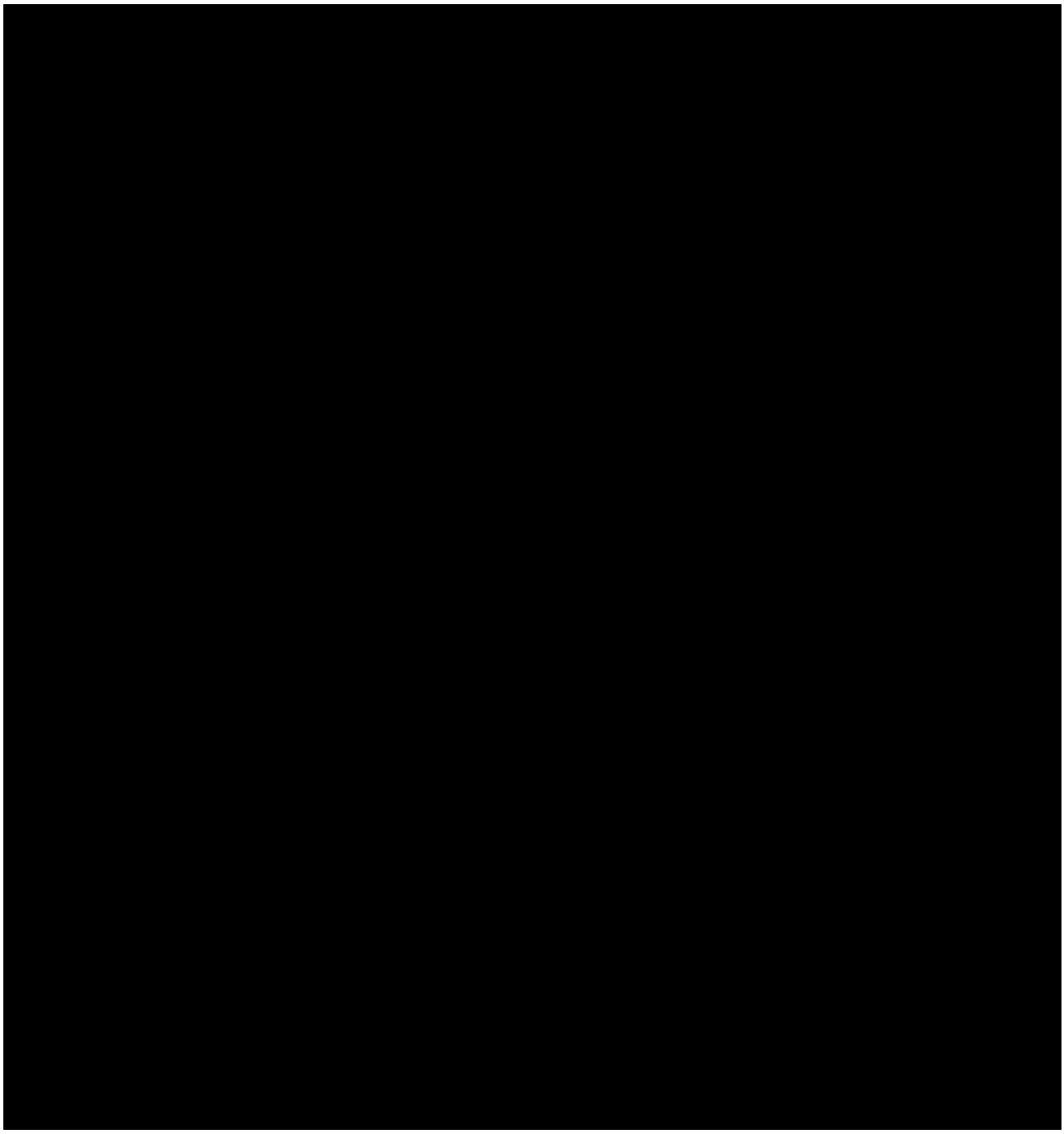
APPENDIX 7 AMERICAN COLLEGE OF RHEUMATOLOGY PHYSICIAN GLOBAL ASSESSMENT OF DISEASE ACTIVITY VISUAL ASSESSMENT SCALE

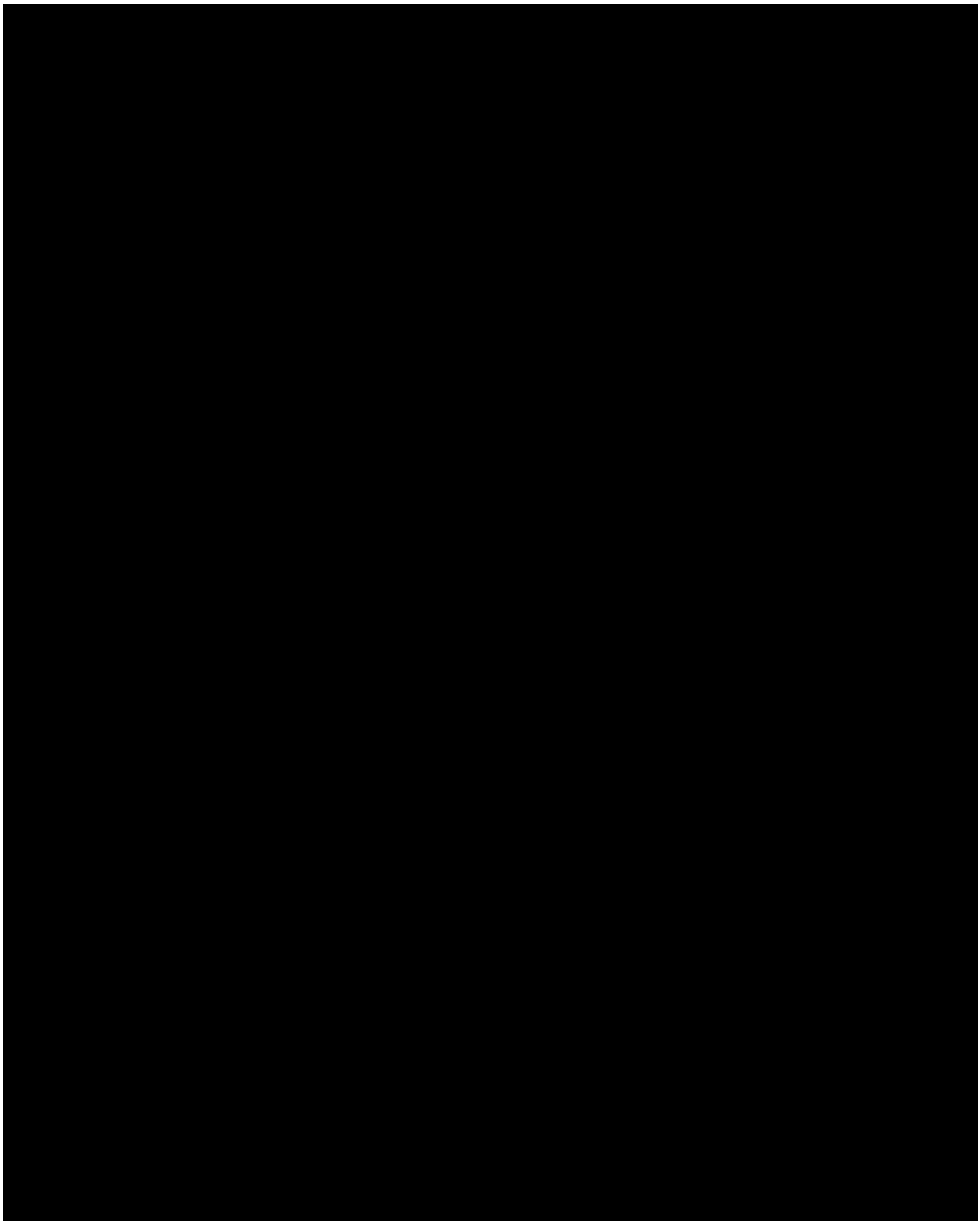
Measure with a metric ruler. Line on Case Report Form is exactly 10 cm long. Scores should be recorded in millimeter format. DO NOT USE THIS APPENDIX AS SOURCE DOCUMENT OR CASE REPORT FORM.

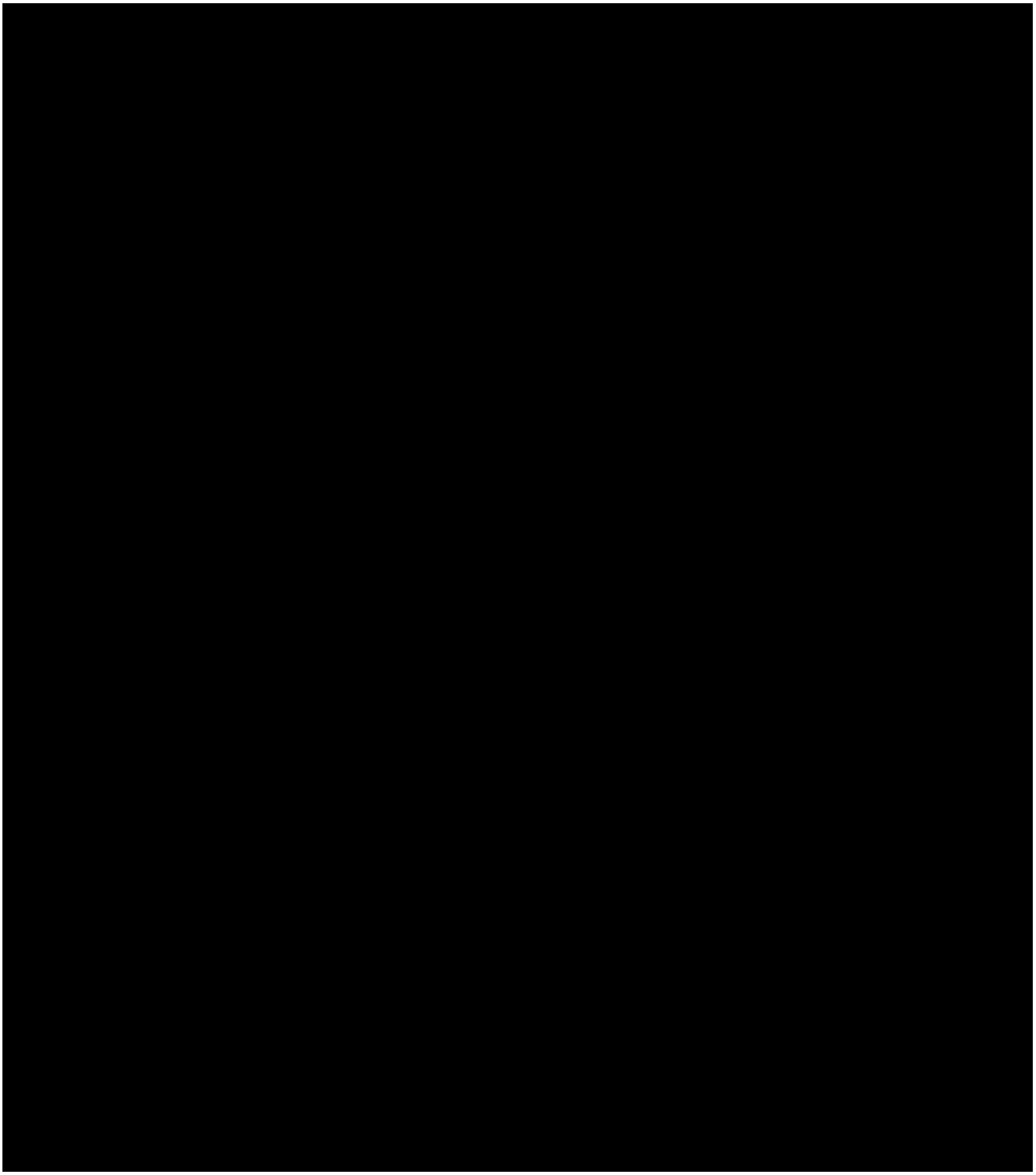
What is the disease activity independent of the participant's self-assessment?



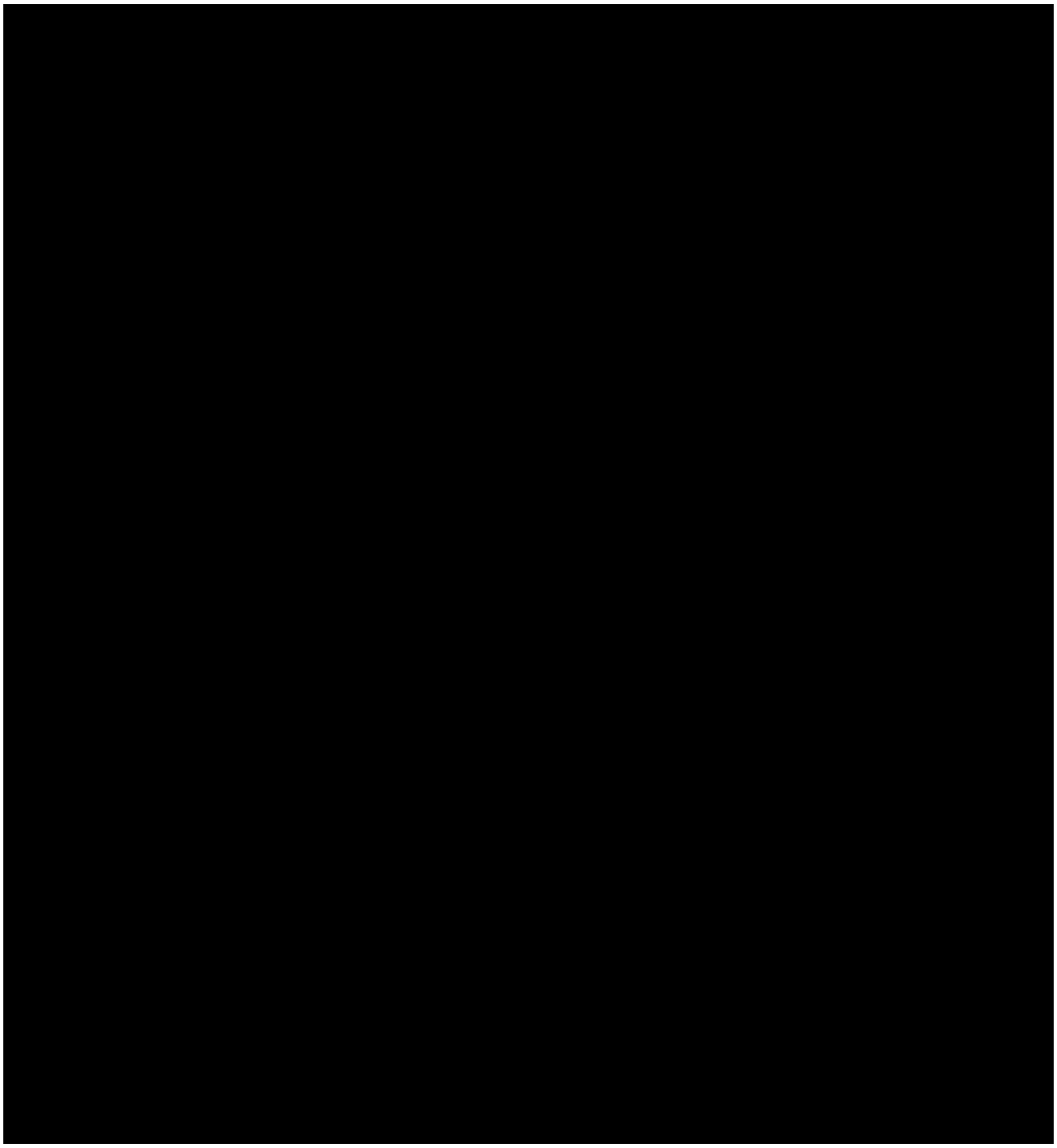
APPENDIX 8 AMERICAN COLLEGE OF RHEUMATOLOGY SUBJECT ASSESSMENT OF PHYSICAL FUNCTION SCALE: HEALTH ASSESSMENT QUESTIONNAIRE (HAQ)

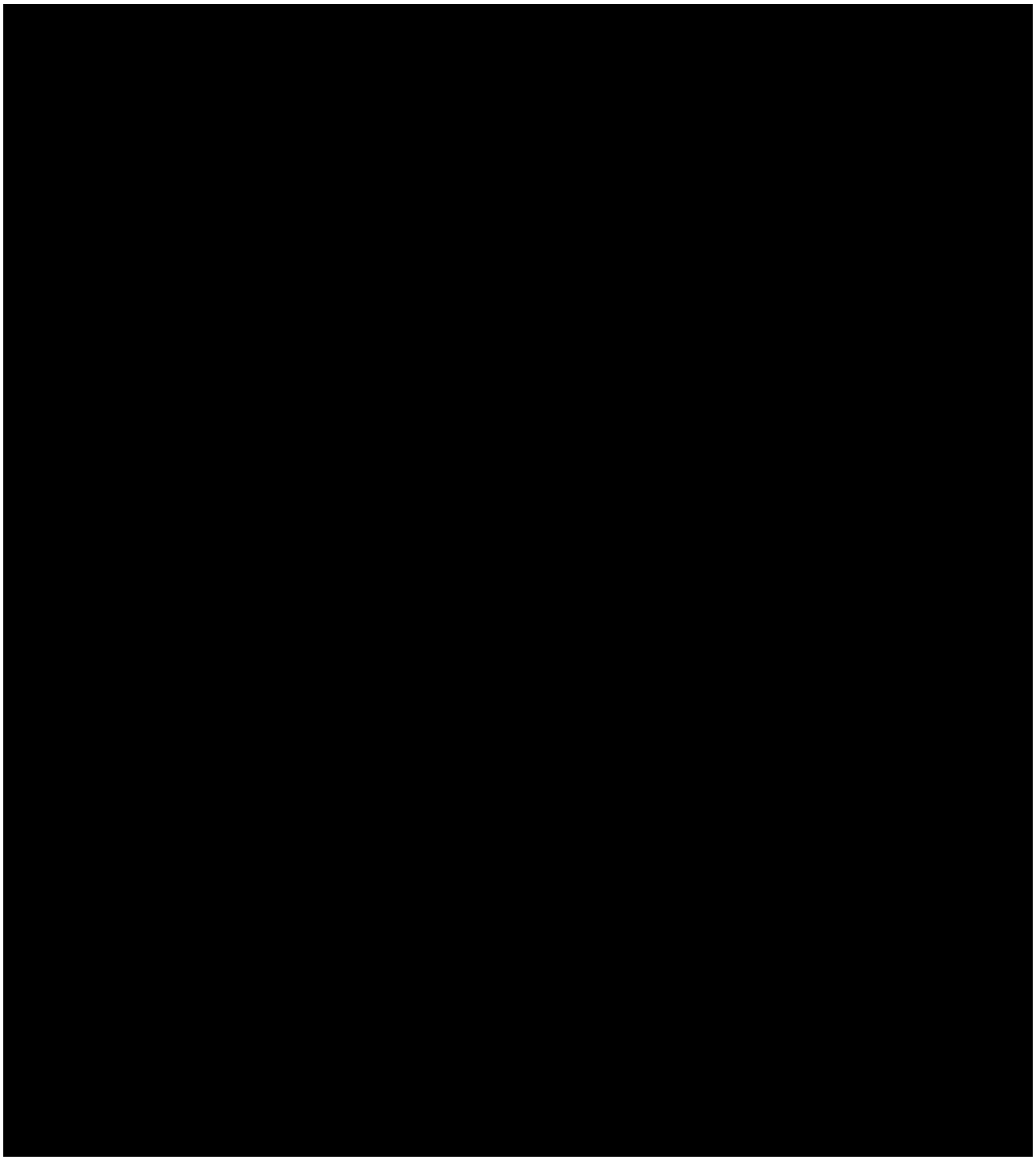


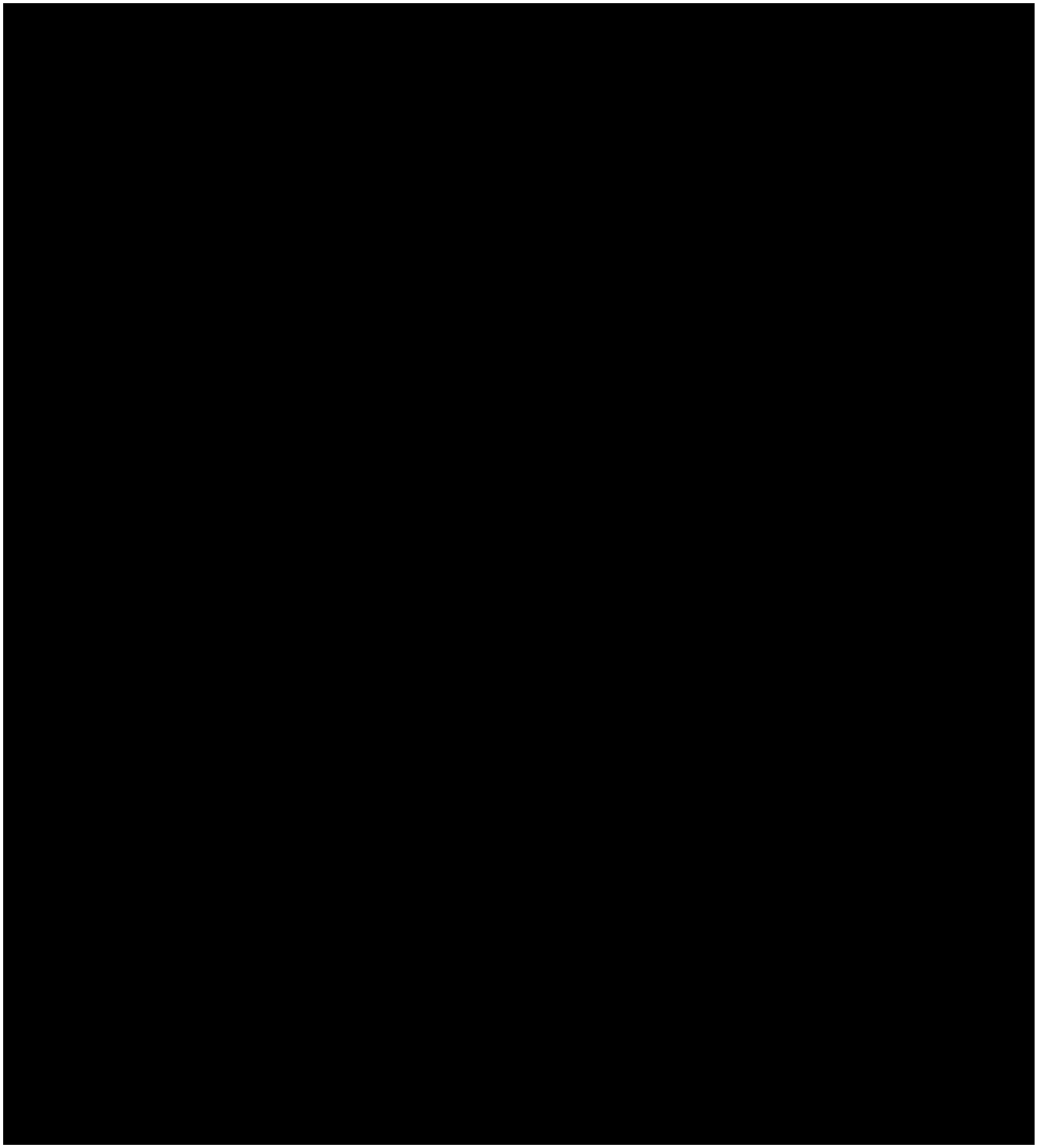


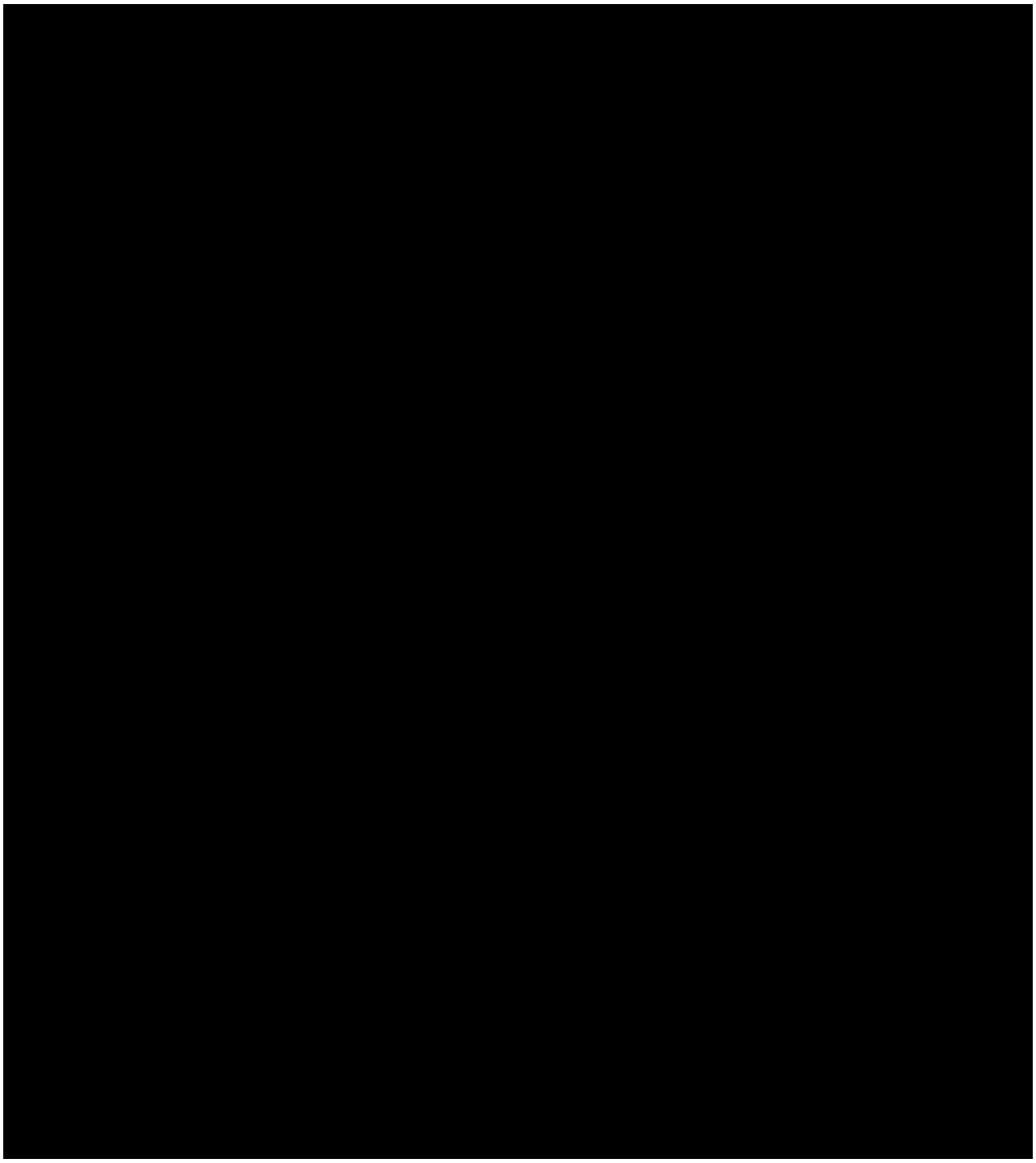


APPENDIX 9 SF-36 V2.0

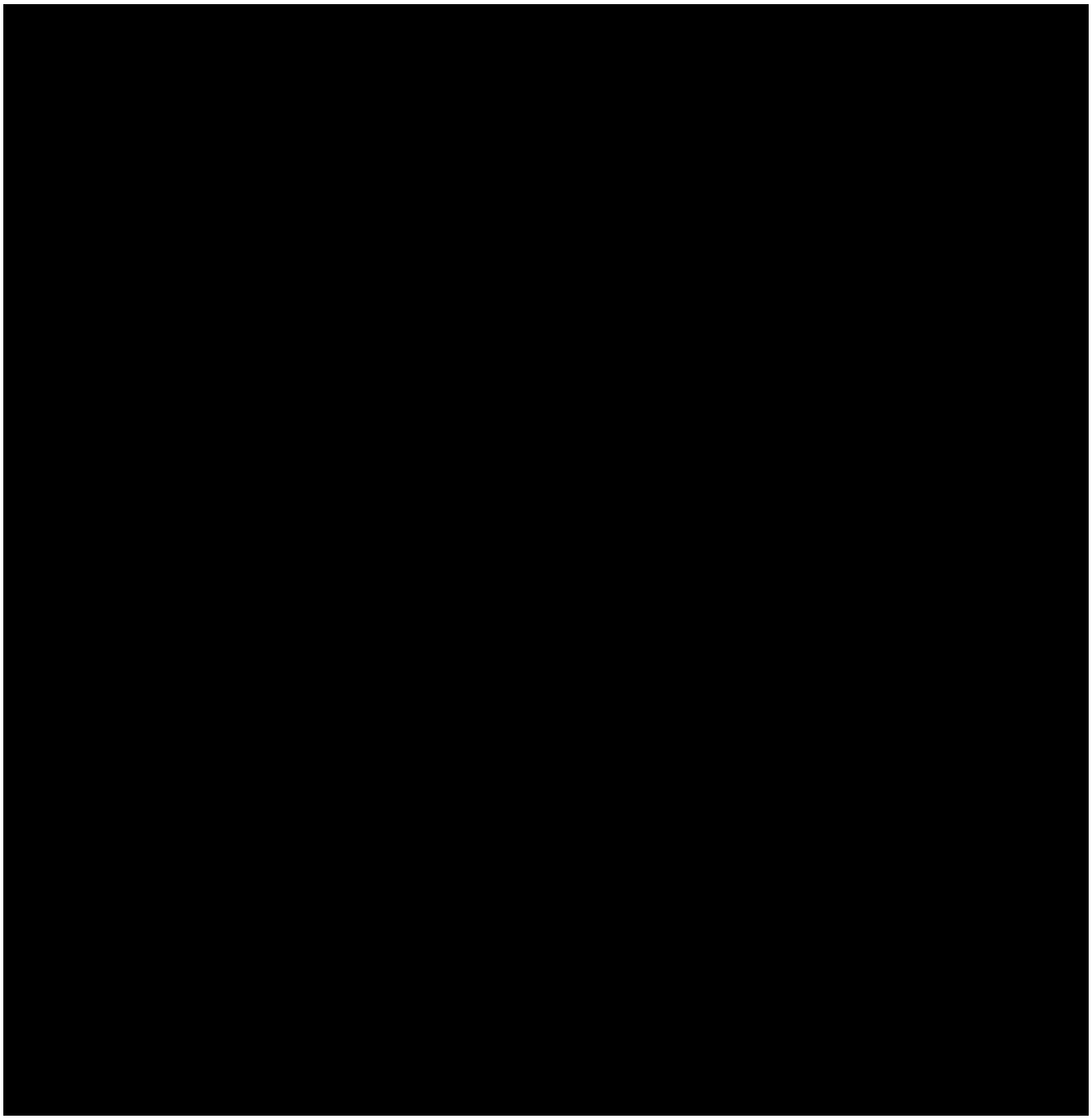


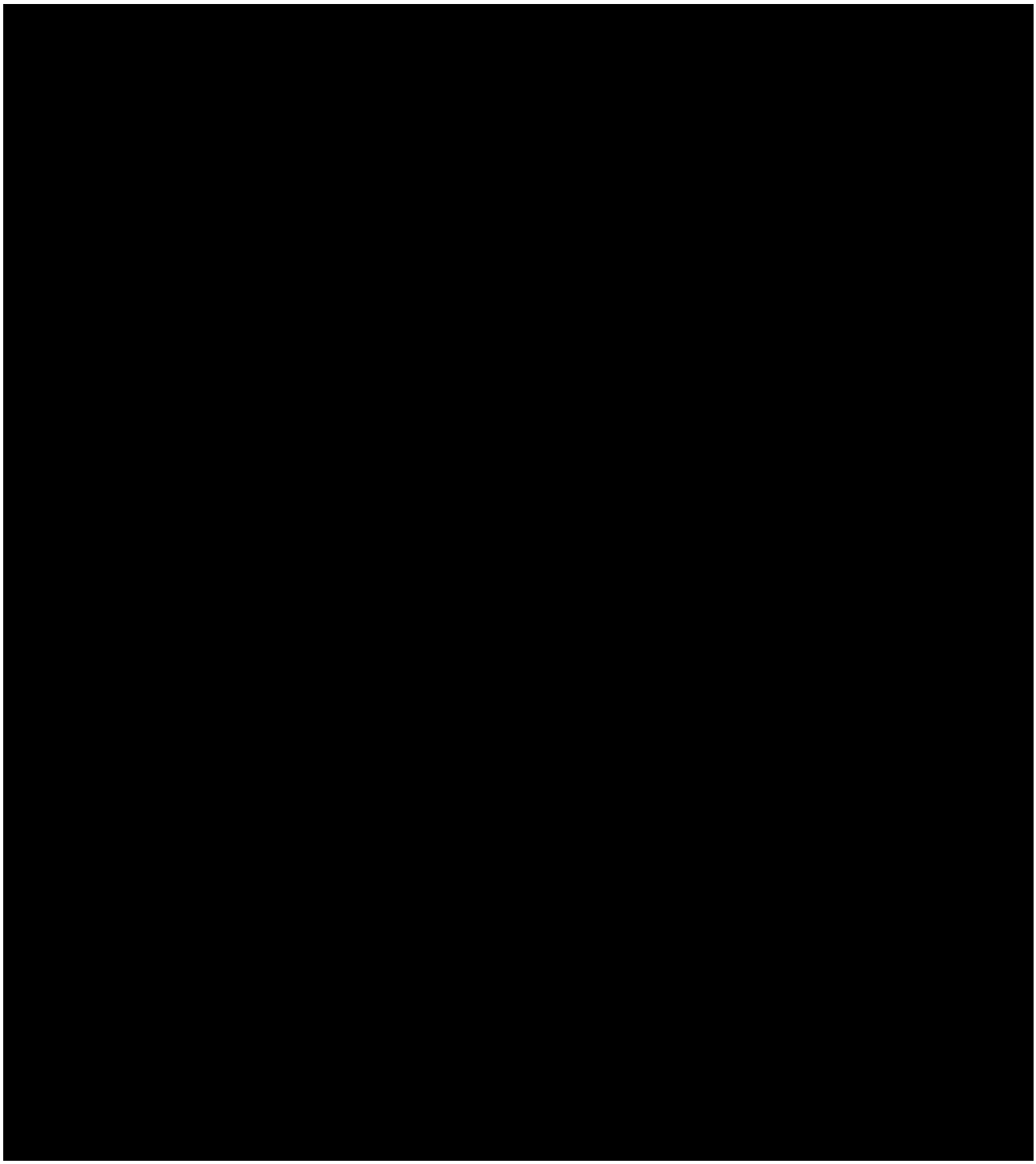




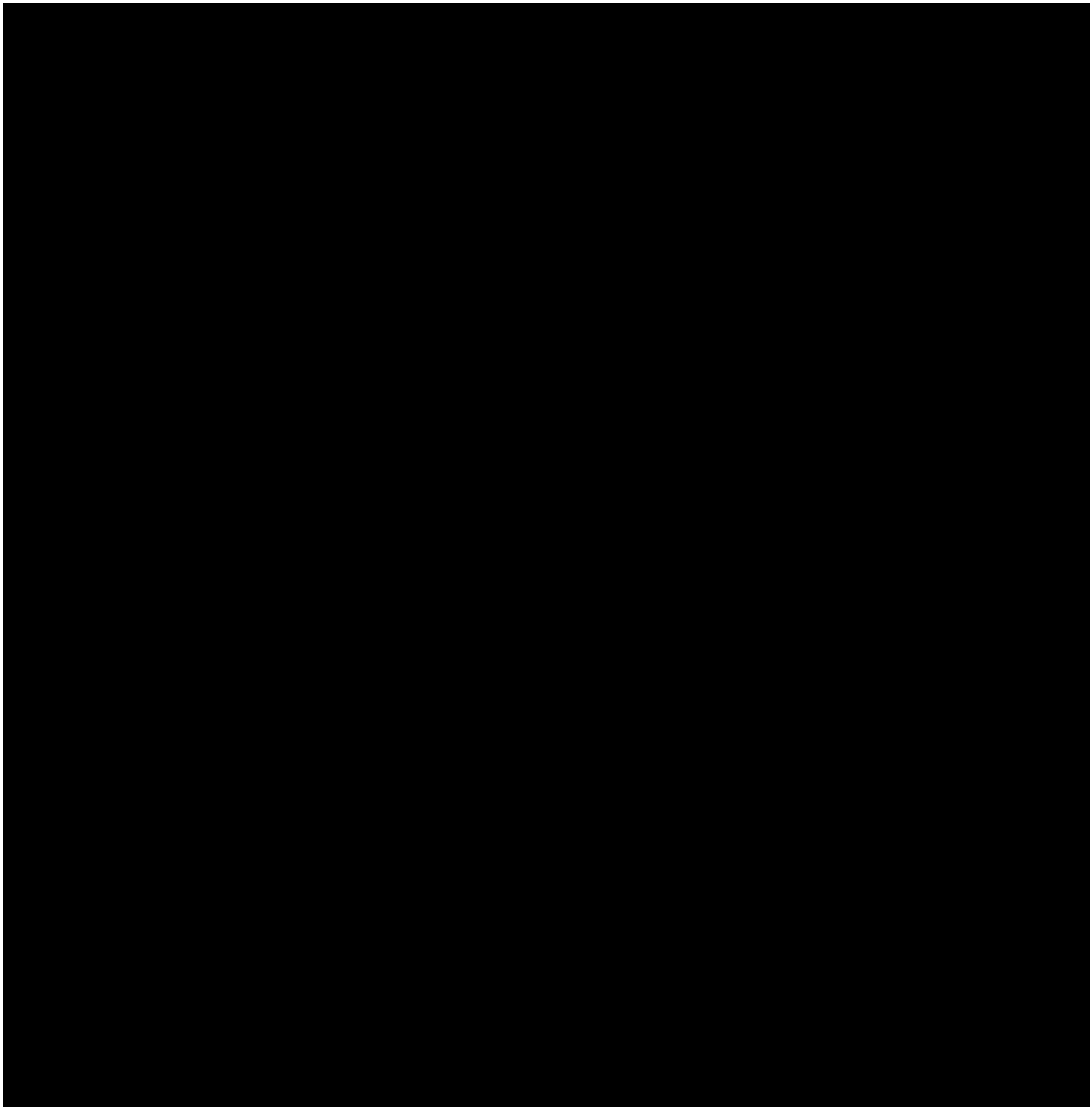


APPENDIX 10 WORK PRODUCTIVITY AND ACTIVITY IMPAIRMENT QUESTIONNAIRE-RHEUMATOID ARTHRITIS, V2.0 (WPAI-RA)

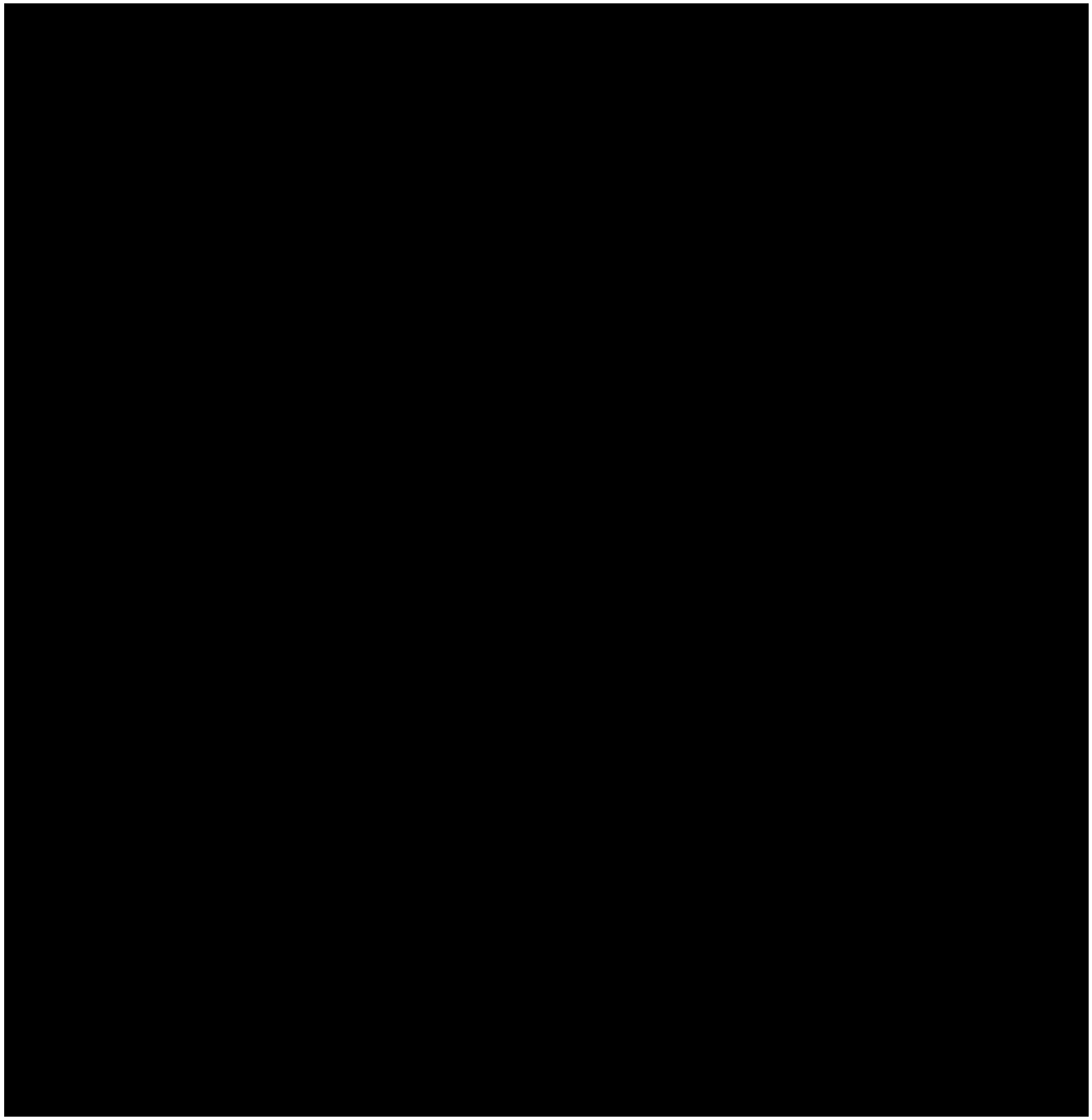




APPENDIX 11 FUNCTIONAL ASSESSMENT OF CHRONIC ILLNESS THERAPY (FACIT) - FATIGUE



APPENDIX 12 MORNING STIFFNESS DURATION



APPENDIX 13 2010 ACR-EULAR CLASSIFICATION CRITERIA FOR RHEUMATOID ARTHRITIS

The target population (Who should be tested)? Patients who:

1. have at least 1 joint with definite clinical synovitis (swelling)
2. with the synovitis not better explained by another disease

Classification criteria for RA (score-based algorithm: add score of categories A - D; a score of ≥6/10 is needed for classification of a patient as having definite RA.

A. Joint involvement	
1 large joint	0
2-10 large joints	1
1-3 small joints (with or without involvement of large joints)	2
4-10 small joints (with or without involvement of large joints)	3
>10 joints (at least 1 small joint)	5
B. Serology (at least 1 test result is needed for classification)	
Negative RF *and* negative ACPA	0
Low-positive RF *or* low-positive ACPA	2
High-positive RF *or* high-positive ACPA	3
C. Acute-phase reactants (at least 1 test result is needed for classification)	
Normal CRP *and* normal ESR	0
Abnormal CRP *or* abnormal ESR	1
D. Duration of symptoms	
<6 weeks	0
≥6 weeks	1

APPENDIX 14 RA DISEASE ACTIVITY DEFINITIONS

American College of Rheumatology Core Data Set

ACR core data set component	Validated Measurement Tool
Tender joint count	Standardized 68 joint count
Swollen joint count	Standardized 66 joint count
Subject global assessment of pain	A 0-100mm visual analog scale
Subject global assessment of disease activity	A 0-100mm visual analog scale
Physician global assessment of disease activity	A 0-100mm visual analog scale
Subject assessment of physical function	Health Assessment Questionnaire (HAQ)
Acute phase reactant value	ESR (Westergren) and C-reactive protein

The ACR 20, ACR 50, or ACR 70 definition of improvement is a 20%, 50%, or 70% improvement, respectively, over baseline in tender and swollen joint counts (#1 and #2) and a 20%, 50%, or 70% improvement, respectively, in 3 of the 5 remaining core data set measures (components #3 to #7).

Disease Activity Index (DAS)28-CRP is calculated using the following formula:

DAS28-CRP(4) = 0.56*sqrt(TJC28) + 0.28*sqrt(SJC28) + 0.36*ln(CRP+1) + 0.014*GH + 0.96

where t28 = number of painful joints from 28 joints, sw28 = number of swollen joints from 28 joints, CRP = c-reactive protein in mg/L, and GH = general health or patient's global assessment of disease activity on a 100 mm VAS

Simple Disease Activity Index (SDAI) is calculated using the following formula:

TJC + SJC + PGA + MDGA + CRP

Clinical Disease Activity Index (CDAI) is calculated using the following formula:

TJC + SJC + PGA + MDGA

(TJC = number of painful joints from 28 joints, SJC = number of swollen joints from 28 joints, PGA = patient global assessment on a visual analog scale 0-10 cm, MDGA = physician global assessment on a visual analog scale 0-10 cm, and CRP = c-reactive protein in mg/dL)

Boolean Remission is defined as:

Tender joint count ≤ 1, Swollen joint count ≤ 1, CRP ≤ 1 mg/dL, patient global assessment ≤ 1 (on 0 to 10 VAS scale).

APPENDIX 15 JOINT COUNT ASSESSMENT COMPONENTS FOR DAS28 (RIGHT AND LEFT SIDE)

Shoulder
Elbow
Wrist
MCP1
MCP2
MCP3
MCP4
MCP5
PIP1
PIP2
PIP3
PIP4
PIP5
Knee

APPENDIX 16 COUNTRY-SPECIFIC REQUIREMENTS/DIFFERENCES

Country/Location Requirement	Original Language/ Section Number	Country-specific Language or Differences
France, Germany, Czech Republic, UK	Section 8.1: Discontinuation from Study Treatment	Second paragraph following bulleted text modified to read: "In the case of pregnancy, the investigator must immediately notify the BMS Medical Monitor/designee of this event. In most cases, the study treatment will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant safety). Please call the BMS Medical Monitor within 24 hours of awareness of the pregnancy."
France/Italy		Add to discontinuation criteria bullets an item for discontinuation due to product inefficacy.
France		Add to discontinuation criteria bullets an item for discontinuation due to severe infection.
Sweden	Section 9: Study Assessments and Procedures	All assessments must be performed by a qualified physician.
Japan	Table 2-1: Screening Procedural Outline (IM101863)	Add the following test at Screening: (1 to 3) β-D glucan.
	Section 6.2: Exclusion Criteria	Add the following text as criterion 3) j): "Participants who are (1 to 3) β-D glucan positive."
	Section 9.4: Safety	Add subsection for Fungal Testing, with the following text: "The (1 to 3) β-D glucan test will be performed at the Screening visit."
	Table 9.4.7-1: Clinical Safety Laboratory Assessments	Add (1 to 3) β-D glucan.
	Table 2-1: Screening Procedural Outline (IM101863)	Add the following test at Screening: hepatitis B surface antibody (HBsAb).
	Section 6.2: Exclusion Criteria	Replace current text for criterion 3) a) with the following text: "Hepatitis B surface antigen (HBsAg)-positive participants are excluded from the study. Participants who are HBsAg negative but positive for hepatitis B surface antibody (HBsAb) or hepatitis B core antibody (HBcAb) must also be tested for quantitative hepatitis B virus (HBV) DNA. Participants with detectable levels as specified by local guidance are excluded from the study."

Country/Location Requirement	Original Language/ Section Number	Country-specific Language or Differences
Japan (continued)	Section 9.4.6: Viral Hepatitis Screening and Monitoring	Add the following text: "Participants who are positive for anti-HBsAb but negative for HBV DNA (as defined by the lower limit of testing sensitivity) will be allowed to be randomized. These participants will be closely monitored for clinical and laboratory signs of HBV reactivation. HBV DNA testing should be performed on a monthly basis after initiation of treatment, for 6 months, along with review of liver chemistries. After 6 months, the interval and duration of surveillance should be decided at the investigator's discretion and in accordance with local guidelines."
	Table 9.4.7-1: Clinical Safety Laboratory Assessments	Add HBsAb.
	Section 7.1.1.1: Abatacept Self-administration of Subcutaneous Injection	Add the following text: "Additional self-administration training for participants is allowed to be extended until Week 4. Training should be performed by unblinded study site personnel qualified in teaching patients about administration of medication in prefilled syringes. The site needs to ensure that any additional training visits do not imperil maintenance of the blind at the site (ie, shielding treatment allocation from blinded site study personnel)."
	Section 7.1.2.1: Adalimumab Self-administration of Subcutaneous Injection	Add the following text: "Additional self-administration training for participants is allowed to be extended until Week 4. Training should be performed by unblinded study site personnel qualified in teaching patients about administration of medication in prefilled syringes. The site needs to ensure that any additional training visits do not imperil maintenance of the blind at the site (ie, shielding treatment allocation from blinded site study personnel)."
	Section 9.2.9: Other Safety Considerations	Add the following text: "Malfunction of the prefilled syringes containing study treatment should be reported to the Sponsor via designated CRF. SAEs or events that could lead to an SAE that occurred as a result of the malfunction should be reported to the Sponsor within 24 hours of awareness of the event."

Abbreviations: BMS, Bristol-Myers Squibb Company; CRF, case report form; DNA, deoxyribonucleic acid; HBcAb, hepatitis B core antibody; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; SAE, serious adverse event; UK, United Kingdom.

APPENDIX 17 LABORATORY GUIDELINES: PATIENT STUDIES (REVISED AUGUST 13, 1999)

Laboratory test results, which meet these criteria, and the investigator feels is clinically relevant should be described on the Adverse Event Form. Those which are judged to be SERIOUS events require the completion of a Serious Adverse Event Form (see Section 9.2).

[NOTE: LLN = lower limit of normal; ULN = upper limit of normal.]

albumin - <0.9xLLN or if pretreatment value is <LLN, <0.75x pretreatment

alkaline phosphatase - >2 x ULN; or if pretreatment >ULN, 3x pretreatment value

basophils (%) - >3% if 0-1% pretreatment, >3x pretreatment value if pretreatment >1%

bilirubin

a) direct - >1.5x ULN, or if pretreatment above ULN, >2x pretreatment

b) total - >2x upper limit of normal, or if pretreatment above ULN, >4 x pretreatment value

blasts - >0

blood urea nitrogen (BUN) - >2x pretreatment

calcium - <0.8x LLN or >1.2x ULN; <0.75x pretreatment if pretreatment below LLN, or >1.25x pretreatment if pretreatment above ULN; >ULN if <LLN pretreatment, or <LLN if >ULN pretreatment

chloride - <0.9x LLN or >1.1x ULN; or <0.9x pretreatment if pretreatment below LLN, or >1.1x pretreatment if pretreatment above ULN; >ULN if <LLN pretreatment, or <LLN if >ULN pretreatment

creatinine - >1.5x pretreatment value

eosinophils (%) - >3x pretreatment and > 8% if pretreatment normal; if pretreatment >ULN, >3 x pretreatment

erythrocytes - <0.75x pretreatment value

glucose - <0.8x LLN or >1.5x ULN; if pretreatment <LLN then <0.8x pretreatment; if pretreatment >ULN then >2x pretreatment; <LLN if >ULN pretreatment, or >ULN if <LLN pretreatment

hematocrit - <0.75x pretreatment

hemoglobin - >3 g/dL decrease from pretreatment value

lactic dehydrogenase (LDH) - >1.5x ULN; if pretreatment value is above ULN, >3x pretreatment value

leukocyte (WBC) count - <0.75 x LLN or >1.25x ULN; <0.8x pretreatment if pretreatment <LLN or >1.2x pretreatment if pretreatment >ULN; >ULN if pretreatment <LLN or <LLN if >ULN pretreatment

lymphocytes (%) - <0.5x LLN or >2.0 x ULN, or <0.5x pretreatment if below LLN pretreatment; >2.0x pretreatment if above ULN pretreatment. >ULN if <LLN pretreatment, or <LLN if >ULN pretreatment

monocytes (%) - >2x ULN; >2x pretreatment if pretreatment above ULN

neutrophil count (neutrophils+bands) - <0.67x pretreatment if pretreatment <1000/mm^3; otherwise, <1000/mm^3.

phosphate - <0.75 x LLN or >1.25x ULN; <0.67x pretreatment value if below LLN pretreatment, or >1.33x pretreatment if above ULN pretreatment; >ULN if <LLN pretreatment, or <LLN if >ULN pretreatment

platelet count - <0.67x LLN or >1.5 x ULN; if below normal pretreatment, <0.5x pretreatment value and <100,000/mm^3

potassium - <0.9x LLN or >1.1x ULN; <0.9x pretreatment if pretreatment below LLN, or >1.1x pretreatment if pretreatment above ULN; >ULN if <LLN pretreatment, or <LLN if >ULN pretreatment

protein, total - <0.9x LLN or >1.1x ULN; <0.9 x pretreatment if below LLN pretreatment, or >1.1x ULN if above ULN pretreatment; >ULN if <LLN pretreatment, or <LLN if >ULN pretreatment

SGOT and SGPT (ASAT and ALAT) - >3 x upper limit of normal; if pretreatment above ULN, >4x pretreatment value

sodium - <0.95x LLN or >1.05x ULN; <0.95x pretreatment if below LLN pretreatment, >1.05x pretreatment if above ULN pretreatment; >ULN if <LLN pretreatment, or <LLN if >ULN pretreatment

uric acid - >1.5x ULN; if pretreatment above ULN, >2x pretreatment value

urinalysis

a) urinary protein - >1 gram/24 hours and 2x pretreatment value
b) urinary RBC - >5/HPF or, >4x pretreatment if pretreatment value 5/HPF
c) urinary WBC - >5/HPF or, >4x pretreatment if 5/HPF pretreatment
d) creatinine clearance (glomerular filtration rate) - <0.67x pretreatment value
e) urine dipstick measurements: Protein, blood, sugar, and acetone- 2+, or if 1+pretreatment, 2x pretreatment. Do not evaluate protein if quantitative protein determination done

stool hemoccult - positive if negative pretreatment