Official Title of Study:

A Randomized, Placebo-Controlled, Double-Blind, Multicenter Study to Assess the Efficacy and Safety of Branebrutinib Treatment in Subjects with Active Systemic Lupus Erythematosus or Primary Sjögren's Syndrome, or Branebrutinib Treatment Followed by Open-label Abatacept Treatment in Subjects with Active Rheumatoid Arthritis

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Clinical Protocol IM014029

A Randomized, Placebo-Controlled, Double-Blind, Multicenter Study to Assess the Efficacy and Safety of Branebrutinib Treatment in Subjects with Active Systemic Lupus Erythematosus or Primary Sjögren's Syndrome, or Branebrutinib Treatment Followed by Open-label Abatacept Treatment in Subjects with Active Rheumatoid Arthritis

Protocol Amendment 04

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DOCUMENT HISTORY

Document	Date of Issue	Approver(s)	Summary of Change
Protocol Amendment 04	01-Dec-2021	[redacted] Bristol Myers Squibb	Changed timing for primary endpoint and other efficacy, safety, PK, and PD analysis for the RA sub-protocol; included patient-reported outcome assessments as Additional endpoints in all 3 sub-protocols; updated unintentionally omitted changes in inclusion criteria in RA sub-protocol schema; added information from Administrative Letter 03, Administrative Letter 04 FR, and Administrative Letter 05; clarified PK and biomarker blood samples to be collected for abatacept and branebrutinib, respectively, at Week 24 in the RA sub-protocol [redacted]; corrected an inclusion criterion numbering error in the previous version of the RA sub-protocol; and removed unintentionally retained subject assessment of pain in Section 9.3.3 of the RA sub-protocol.
Revised Protocol 03	30-Mar-2021	[redacted] Bristol Myers Squibb	Removed Study Acknowledgment/Disclosure page; added number of subjects that have received at least 1 dose of branebrutinib; added section for study termination for unexpectedly unfavorable risk/benefit balance; added information/guidance related to SARS-CoV-2 infection/COVID-19 pandemic, including vaccines (also included for influenza), titers, serology, exploratory endpoints, and exclusion criteria; changed the maximum age of the study population; clarified CS requirements (SLE sub-protocol only); excluded subjects with diagnosis of antiphospholipid syndrome from SLE sub-protocol; clarified LTBI prestudy treatment requirements; deleted all references to legally acceptable/ authorized representative or legal guardian; clarified all instances in which branebrutinib may be discontinued permanently or temporarily at the discretion of the investigator/Medical Monitor; added blood pressure hypertension exclusion criterion; added information/exclusion criterion related to ECGs; removed cerivastatin from excluded/restricted medication; referenced inclusion criteria sections in Appendix 4 for specific requirements for male and female

Document	Date of Issue	Approver(s)	Summary of Change
			contraception; added optional post-hoc measurements/analysis/PK sample collection timing for concentrations of chronic medications that could be sensitive to modulation of CYP2C8/P-gp; extended duration after completion of IP dosing in which live vaccines are prohibited (SLE and pSS sub-protocols); clarified permitted and restricted medication usage requirements (SLE and pSS sub-protocols); clarified at which study visits the study drug is to be administered/dispensed at the site; added optional salivary/parotid gland biopsy analysis as exploratory endpoint (pSS sub-protocol); deleted Week 4 postdose PK sample collection for branebrutinib (RA sub-protocol); clarified the scheduling of EOT and Safety FU visits/ assessments required at premature treatment and/or study termination; updated required washout periods prior to randomization for antimalarial drugs; increased time interval between RA diagnosis and screening for study eligibility; clarified use of first screening MRI results for rescreening (RA sub-protocol); provided general window for abatacept administration during the open-label part of RA sub-protocol; rearranged subheadings/streamlined assessments in SoA tables/Efficacy Assessments section in all 3 sub-protocols; updated language and/or figures in clinical efficacy appendices; removed Subject-reported Pain Assessment appendix for RA; and added Physician Global Assessment of Disease Activity appendix for RA.
Revised Protocol 02a Argentina-Specific	17-Sep-2020	[redacted] Bristol Myers Squibb	Updated all sub-protocols in response to ANMAT review comments
Revised Protocol 02a France-Specific	08-Sep-2020	[redacted] Bristol Myers Squibb	Updated all sub-protocols in response to French CEC review comments
Revised Protocol 02b Germany-Specific	20-Aug-2020	[redacted]	Updated all sub-protocols in response to BfArM review comments

Document	Date of Issue	Approver(s)	Summary of Change
		[redacted] Bristol Myers Squibb	
Revised Protocol 02a Germany-Specific	24-Jun-2020	[redacted] Bristol Myers Squibb	Updated all sub-protocols in response to BfArM review comments
Revised Protocol 02a UK-Specific	17-Feb-2020	[redacted] Bristol Myers Squibb	Updated all sub-protocols in response to MHRA review comments
Revised Protocol 02 Global Global Protocol v2.0, Revised Protocol 2 Global_Final Approved	18-Dec-2019	[redacted] Bristol Myers Squibb [redacted] Bristol Myers Squibb	Updated RA sub-protocol to include omitted joint assessor instructions, Updated all sub-protocols to current BMS standards for reproductive status inclusion criteria
Global Amendment 1 Global Protocol v2.0, Revised Protocol 1 Global_Final Approved	07-Oct-2019	[redacted] Bristol Myers Squibb [redacted] Bristol Myers Squibb	Updated RA sub-protocol to exclude combination therapy of branebrutinib and abatacept, revised timing period for collection of nonserious AEs in all sub-protocols, updated and aligned branebrutinib PK sampling schedule in all sub-protocols to accommodate change in RA protocol design
Original Protocol (Version 2.0, submitted to FDA) Original Protocol v2.0_Final Approved	01-Jul-2019	[redacted] Bristol Myers Squibb [redacted] Bristol Myers Squibb	Minor editorial changes for consistency

Document	Date of Issue	Approver(s)	Summary of Change
Original Protocol (Version 1.0, not released)	24-Jun-2019	[redacted] Bristol Myers Squibb	Not applicable
Original Protocol v1.0_Final Approved		[redacted] Bristol Myers Squibb	

OVERALL RATIONALE FOR PROTOCOL AMENDMENT 04

The primary purpose of this Global Protocol Amendment is to change the timing for primary endpoint analysis in the rheumatoid arthritis (RA) sub-protocol to after all subjects have either completed Week 12 efficacy assessments or discontinued prior to Week 12, rather than waiting for all subjects to either complete Week 24 activities or discontinue prior to Week 24.

Key additions and clarifications include:

- Changing timing for primary endpoint and other efficacy, safety, PK, and PD analyses to after all subjects in the RA sub-protocol have completed Week 12 efficacy assessments or discontinued treatment/study prior to Week 12
- Including patient-reported outcome assessments as Additional endpoints in all 3 sub-protocols, as appropriate
- Updating unintentionally omitted changes in inclusion criteria in the RA sub-protocol schema to match protocol text
- Clarifying pharmacokinetic (PK) and biomarker blood samples to be collected for abatacept and branebrutinib, respectively, at Week 24 in the RA sub-protocol
- Adding information from Administrative Letter 03 (provided updated Appendix 7 figure for proper rendering in the published PDF version), Administrative Letter 04 France (clarified the days after randomization within which the initial magnetic resonance imaging screening may be used for rescreening, respectively), and Administrative Letter 05 (added unintentionally omitted biomarker blood samples to be collected for Bruton's tyrosine kinase occupancy from Week 0 to Week 12 in the RA sub-protocol and aligned SARS-CoV-2 serology collection at Week 12 in Table 8 with that in Table 2 of the RA sub-protocol)
- Correcting an inclusion criterion numbering error in the previous version of the RA sub-protocol
- Removed unintentionally retained subject assessment of pain in Section 9.3.3 of the RA sub-protocol

This protocol amendment will be implemented upon receiving all appropriate Agency and Institutional Review Board/Ethics Committee approvals.

All changes applied to the body were applied to the synopsis, as necessary, and synopsis changes are not included in the list below.

Only major additions and deletions are provided in this summary document, and all minor grammatical, formatting, rephrasing, stylistic changes, or clarifications, as well as reorganizational changes, are not included.

The rationales for changes to this Protocol Amendment are provided in the summary of key changes table, as shown below:

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 04

Section Number & Title	Description of Change	Brief Rationale
Section 1.4.6.3: Master Protocol: Analysis and Reporting Section RA 9.4.4 Analysis and Reporting	Changed timing for primary endpoint and other efficacy, safety, PK, and PD analysis to after all subjects in the RA sub-protocol have completed Week 12 efficacy assessments or discontinued treatment/study prior to Week 12, as opposed to waiting for all subjects to either complete Week 24 activities or discontinue prior to Week 24.	Results from the 12-week primary endpoint and other efficacy, safety, PK, and PD analysis is required for timely decision-making and planning of further branebrutinib development in RA. Performing this analysis prior to completion of the 12-week abatacept treatment period will not affect the scientific value of the study since (i) there are no data accruing for primary or secondary endpoints after Week 12, (ii) the abatacept treatment period from Week 12 to Week 24 is open-label and only supports "additional" and "exploratory" endpoints, and (iii) no change in study conduct will accrue from the results of the rescheduled 12-week primary endpoint analysis.
Section SLE 3: Objectives and Endpoints, SLE Table 3 Section SLE 9.3.3: Additional Endpoints Section pSS 3: Objectives and Endpoints, pSS Table 3 Section pSS 9.3.2: Additional Endpoints Section RA 3: Objectives and Endpoints, RA Table 4 Section RA 9.3.3: Additional Endpoints	To harmonize with text in Section 8 of each sub-protocol, patient-reported outcome (PRO) assessments were included as Additional endpoints in each sub-protocol objectives and endpoints table, as follows: SLE Sub-protocol Patient-Reported Outcomes Measurement Information System (PROMIS) Fatigue 6 a SLE Pain Numeric Rating Score (NRS) pSS Sub-protocol PROMIS Fatigue 6 a Physician Global Assessment and Subject Global Assessment NRS for Mouth and Eye Dryness RA Sub-protocol PROMIS Fatigue 6 a	PRO assessments were already included in the protocol to assess critical aspects of patient-reported quality of life and the data collected; however, these assessments were unintentionally omitted from the list of endpoints in each sub-protocol in previous protocol amendments. This error in the tables is corrected in this amendment. No changes were made to the actual endpoints being assessed in the protocol.
Section RA 1.2: Schema	Updated the RA sub-protocol schema (Section RA 1.2) to accurately reflect Inclusion Criterion 3h in Section RA 5.1: diagnosis of RA < 4 years before screening	The previous protocol amendment extended the time from diagnosis to screening from 2 years to 4 years. This was mistakenly not updated in the schema of Section RA 1.2, and is now corrected in this amendment.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 04

Section Number & Title	Description of Change	Brief Rationale
Section RA 1.3: Schedule of Activities, RA Table 2	[redacted]	Added due to unintentional omission of these blood sample collections in Revised Protocol 03 Global.
Section RA 5.1, 3) Type of Subject and Target Disease Characteristics: RA Sub-protocol	Changed repeated inclusion criterion 3)h) to 3)i) in the RA sub-protocol.	This corrects erroneous assignment of the same numbering "3)h)" to distinct inclusion criterion.
Section RA 5.4.1: Rescreening and Retesting During Screening Period Section RA 8.1.2.3: RA Magnetic Resonance Imaging (MRI) Scoring System	Revised from within 28 days of randomization to within 30 days of randomization for initial MRI performance date at Screening, should the subject require rescreening.	To incorporate changes in the RA sub-protocol from Administrative Letter 04 France.
Section RA 8.4.5: Clinical Safety Laboratory Assessments, RA Table 8,Other Analyses	Added SARS-CoV-2 serology collection at Week 12 in RA Table 8.	To align SARS-CoV-2 serology collection at Week 12 in RA Table 8 with that in RA Table 2.
Section RA 8.5.1: PK and Immunogenicity of Abatacept (Weeks 12 and Later), RA Table 10: PK and Immunogenicity Sampling Schedule for Abatacept Section RA 8.6: Biomarkers, RA Table 11: PD Sampling for Branebrutinib	Clarified that the PK and biomarker blood samples to be collected for abatacept and branebrutinib, respectively, at Week 24 in the RA sub-protocol are not to be collected predose.	Since abatacept and branebrutinib are not administered at Week 24 (last administration for both study treatments is at Week 20), these blood samples cannot be collected predose. Previously confusing language regarding “predose” has been deleted.
Section RA 9.3.3: Additional Endpoints	Removed subject assessment of pain in Section RA 9.3.3.	This assessment was removed throughout Revised Protocol 03 Global, but was unintentionally retained in Section RA 9.3.3, and is now removed in this amendment.
Appendix 7: British Isles Lupus Assessment Group (BILAG)-2004 Index	Updated appendix figure for proper rendering in the published PDF version.	To incorporate changes from Administrative Letter 03.

Please provide a copy to your Investigational Review Board/Ethics Committee, unless agreed otherwise with BMS.

MASTER TABLE OF CONTENTS

1 STUDY IM014029 MASTER PROTOCOL

1.1 Introduction: Role of Bruton's Tyrosine Kinase in Normal Immune Function and Dysregulation in the Pathogenesis of Autoimmunity

Bruton's tyrosine kinase (BTK) is a member of the Tec family of nonreceptor tyrosine kinases and is expressed in all hematopoietic cells, except T cells and terminally-differentiated plasma cells.[1] The underlying pathobiology of several immune-mediated diseases involves signaling pathways associated with BTK activation.

In B cells, BTK plays an essential role in mediating the B cell receptor (BCR) responses to autoantigens and pro-inflammatory signaling.[2] Regulation of BTK has also been shown to be important for B cell tolerance. Elevated expression of BTK has been associated with immune-mediated diseases in human and animal models, and BTK levels in B cells are correlated with autoantibody titers.[3, 4] In addition to the formation of autoantibodies, BTK plays a critical role in autoimmunity through antibody-independent mechanisms, including the activation of pro-inflammatory cytokines and chemokines, such as interleukin (IL)-6 and tumor necrosis factor (TNF)α. BTK also plays a role in signaling via the Fc gamma receptor (FcγR)IIa and FcγRIIIa receptors (low affinity activating receptors for immune complexes [ICs] containing immunoglobulin [Ig]G on myeloid and dendritic cells[5, 6, 7]) and low affinity activating receptors for immune complexes (ICs) containing immunoglobulin (Ig)G, which may play a critical role in the immunopathology of immune-mediated disorders.

BTK inhibition is expected to inhibit antigen-dependent B cell signaling and function without depleting B cells,[2] lead to decreases in IC-mediated production of pro-inflammatory cytokines, and reduce IC signaling to monocytic cells.[8, 9, 10, 11] Many of the processes targeted by BTK inhibition are shared key pathogenic molecular mechanisms of immune-mediated diseases.

BTK inhibitors (eg, ibrutinib, acalabrutinib) have already been approved for the treatment of hematological malignancies, including chronic lymphocytic leukemia and Waldenstrom's macroglobulinemia. One BTK inhibitor, ibrutinib, has a number of off-target activities; other more selective BTK inhibitors are currently being developed for treatment of immune-mediated diseases in which a more favorable adverse event (AE) profile is sought. There have already been successful Phase 2 studies with BTK inhibitors in diseases where antibody production plays an important role, such as pemphigus. Studies with BTK inhibitors are ongoing in rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), as well as in primary Sjögren's syndrome (pSS). For example, evobrutinib (EMD Serono Research and Development, Inc.) is being evaluated in both SLE and RA (refer to ClinicalTrials.gov evobrutinib in SLE [Identifier: NCT02975336] and evobrutinib in RA [Identifier: NCT03233230] for study details), and tirabrutinib (Gilead Sciences) is being evaluated in pSS (refer to ClinicalTrials.gov tirabrutinib in pSS [Identifier: NCT03100942] for study details).

Branebrutinib (BMS-986195) is an oral highly selective, irreversible covalent inhibitor of BTK. The effect of BTK inhibition on antigen-specific BCR-mediated B cell functions and IgG-containing IC signaling through Fcγ receptors in monocytic cells may provide benefit in the treatment of multiple immune-mediated disorders, including those to be evaluated in the current

proposed Master Protocol, Study IM014029. In addition, BTK plays a role in receptor activation of nuclear factor kappa-B (RANK)-dependent osteoclastogenesis, as well as IgE-containing signaling through the BTK-dependent receptor Fc epsilon receptor (FcεR)I in mast cells and basophils.

A detailed description of the chemistry, pharmacology, efficacy, and safety of branebrutinib is provided in the Investigator's Brochure (IB).[12] Due to the potent and highly selective inactivation of BTK and optimized pharmacokinetics (PK) of branebrutinib, the efficacious dose in humans is projected to be ≤ 10 mg/day; branebrutinib 9 mg has been selected as the dose that will be used in all 3 sub-protocols that will comprise this study.

1.2 Rationale for a Master Protocol for Three Immune-mediated Diseases with Shared Disease Mechanisms Including Dysregulation of BTK-Mediated Pathways: Systemic Lupus Erythematosus, Primary Sjögren's Syndrome, and Rheumatoid Arthritis

Traditional randomized clinical studies focus on a specific single disease type. However, the demarcations of named diseases are in most cases over a century old. This clinical study will use a 3-sub-protocol study design under a master protocol to evaluate the efficacy of branebrutinib on the basis of its potential shared mechanisms in 3 indications (SLE, pSS, and RA). Prospectively planned evaluation of primary endpoints will be carried out for each sub-protocol. Since each sub-protocol will enroll a small number of subjects to establish the proof of mechanism, the number of subjects treated will be minimized compared to a stand-alone study for each indication; however, composite safety data will be evaluated across all 3 sub-protocols, as well as within each sub-protocol.

The choice of a master protocol design to evaluate the safety and efficacy of branebrutinib in 3 separate disease states (SLE, pSS, and RA) is based primarily on several known overlapping features present in all 3 immune-mediated/autoantibody-mediated diseases, including dysregulation of BTK pathways, and it is possible that BTK inhibition could confer clinical benefits across these diseases. In addition, because the experience and available study populations in rheumatology clinics commonly cover all 3 of these indications, the master protocol design is likely to facilitate clinical site readiness, recruitment efficiency, accuracy in investigator assessments, understanding of common treatments, and the administration of study treatment across the sites. It is further expected that these logistical benefits will require fewer overall sites to complete the study, thereby supporting greater consistency in the evaluation of disease states and in testing the safety and efficacy of study treatment. Moreover, analysis of the study using a master protocol design will allow for a comparison of safety and efficacy (where feasible) across indications, in addition to composite views of safety, which can also provide important data on the impact of some shared concomitant treatments across indications. The fact that all subjects will receive the same dose of branebrutinib will also provide safety data from a larger population and will allow better representation of minority demographic variables to contribute to the analysis of safety and biomarkers.

In all sub-protocols, a placebo (PBO) control is included to allow the assessment of effects of treatment, both desired and adverse, to be appropriately attributed to the treatment received. The PBO control will also provide a basis for comparison of safety assessments.

In summary, the effect of BTK inhibition by branebrutinib on antigen-specific BCR-mediated B cell functions and IgG-containing IC signaling through Fcγ receptors on monocytic cells may provide benefit in the treatment of the immune-mediated/autoantibody-mediated diseases SLE, pSS, and RA. Additional effects on signaling through the BTK-dependent receptor FcεRI on mast cells and basophils, as well as RANK-dependent osteoclastogenesis, can also be evaluated.

1.2.1 Rationale for Sub-protocols

1.2.1.1 Rationale for the Sub-protocol in Systemic Lupus Erythematosus

Systemic lupus erythematosus is a systemic immune-mediated disease characterized by the production of autoantibodies to components of the cell that results in a diverse array of clinical manifestations including musculoskeletal, cutaneous, renal, constitutional, hematologic, neurologic, cardiovascular, and other vital organ involvement.

Current therapies for SLE are unsatisfactory. Patients with moderate to severe flares of SLE usually receive immunosuppressive drugs and corticosteroids (CSs), which must be used over many years, can only temporarily control SLE flares, and are associated with numerous toxicities. Adverse effects of CS use are serious and include increased risk of cardiovascular events, infections, osteoporosis, and many other morbidities. The goal in management of SLE is to achieve disease and symptom control while minimizing excessive immunosuppressive drug exposure and limiting CS exposure. Specific standard of care (SOC) treatments include antimalarials, immunosuppressants (especially azathioprine, mycophenolate, methotrexate [MTX], leflunomide, and tacrolimus), biologics including belimumab (approved in most countries), and other agents (generally prescribed off-label). The only Food and Drug Administration (FDA)-approved treatments for SLE are steroids, antimalarials, aspirin, and belimumab. Other SOC treatments were borrowed from other diseases and have not completed a scientifically rigorous approval process for patients with SLE. There remains an unmet need for novel, well-tolerated, orally administered therapies that can effectively modify the disease course and control symptoms, while minimizing CS and immunosuppressive drug exposure. In particular, treatment of this difficult disease will be improved when agents with clearly understood molecular targets are properly characterized with available technology to improve rationale for treatment selection and dosing.

Systemic lupus erythematosus is associated with the presence of autoreactive ICs that induce pathobiology through the action of Fcγ receptors. Other approaches to targeting B cells have been validated in lupus.[13] Preclinical models suggest IgG-IC-driven pathobiology, by activating Fcγ receptors, is key to perpetuating adaptive immunity, and may provide a promising approach to the treatment of patients with SLE.[14, 15] Basophils, when stimulated by autoreactive IgE through the BTK-dependent receptor FcεRI, have also been implicated in lupus nephritis,[16] and could have some relevance to other manifestations of SLE. Therefore, BTK inhibition may target pathogenic mechanisms of SLE on several levels.

The SLE sub-protocol in this study will help determine if branebrutinib is biologically active and whether it can demonstrate efficacy in the treatment of SLE patients with active disease despite SOC.

1.2.1.2 Rationale for the Sub-protocol in Primary Sjögren's Syndrome

Sjögren's syndrome is a chronic, systemic immune-mediated disease characterized by lymphocytic infiltration of salivary and lacrimal glands, systemic manifestations including renal, pulmonary, and neurological complications, and an increased incidence of lymphoma.[17] Damage to exocrine glands is slowly progressive, initially recognized as persistent dryness of the mouth and eyes due to functional impairment of the salivary and lacrimal glands. Over half of pSS subjects experience extraglandular symptoms, including overwhelming fatigue, arthralgias and myalgias, and Raynaud's phenomenon. pSS is also recognized frequently in patients with RA and SLE, underscoring clinical relationships that could have shared pathophysiologic features. pSS itself is heterogeneous, and not all patients exhibit all of the same symptoms.

In pSS, there is no currently approved treatment that targets the underlying immune pathology of the disease, indicating a clear unmet medical need in this patient population.

B and T cells play key roles in the pathobiology of pSS.[17] As evidenced by hypergammaglobulinemia, alterations in B cell subpopulations, ectopic germinal center-like structures in the affected glands, and increased risk of lymphoma, B cells are critical in driving the disease.[17] B cells produce autoantibodies such as anti-Ro/Sjögren's syndrome antigen A (SSA) and anti-La/Sjögren's syndrome antigen B (SSB), that both drive the amplification of type I interferon (IFN) production. B cells are also prominent at sites of inflammation in the glands, producing pro-inflammatory cytokines.[17] Within salivary glands, ectopic germinal center-like structures have been identified, which likely serve as primary sites for B cell/T cell interactions.[18] Moreover, B-lymphocyte stimulator (BlyS), which drives B cell proliferation and survival, has been shown to be elevated both in the serum and salivary glands of patients with pSS.[19, 20, 21] Recently, increased levels of BTK protein have been observed in circulating B cells of patients with pSS and appear to correlate with rheumatoid factor (RF) levels and parotid gland T cell infiltration.[4] Since BTK plays an essential role in the mediation of BCR response to autoantigen and pro-inflammatory signaling in B cells, BTK inhibition may address key pathogenic mechanisms of pSS.

1.2.1.3 Rationale for the Sub-protocol in Rheumatoid Arthritis

Rheumatoid arthritis is a chronic disease affecting 0.5 to 1.0% of the population in which diarthrodial (synovial) joints become inflamed, usually with a bilateral symmetric pattern, and with a high incidence of damage and disability.[22] RA is a systemic disease, and manifestations may include constitutional symptoms such as fatigue, fever and malaise, vasculitis, cardiovascular complications, ocular involvement, pulmonary interstitial disease, and widespread nodulosis. Patients with RA have a reduced life span which correlates with disease severity, and increased levels of cytokines such as TNF-α, IL-1 and IL-6, circulating ICs, RF, and anti-citrullinated protein antibodies (ACPAs).[23]

Despite recent progress in RA therapy with a number of approved targeted biologics in the United States (US) and Europe,[12] unmet medical needs remain.[24] First, many agents approved for RA exhibit significant safety concerns, including risk of tuberculosis (TB) and other serious infections, malignancies, and gastrointestinal perforation. Second, many patients are only partial responders to current available therapies, and true remission is achieved by only a minority of patients (< 10% in many series). Third, current treatments have toxicities that lead to frequent drug discontinuation. In addition, the destructive process of RA cannot be halted in all patients, and new drugs that reduce osteoclast-mediated bone loss and inflammation may offer unique benefits to patients with RA.[25]

ICs containing IgG play a critical role in the immunopathology of many immune-mediated disorders. In RA, ICs are present in the joints and act on synovial macrophages to drive the production of the cytokines, chemokines, and matrix metalloproteinases (MMPs) that are critical in mediating disease pathology. Expression of FcγRIIa and FcγRIIIa are increased in monocytes and macrophages of patients with RA,[26, 27, 28] and produce higher levels of TNFα and MMPs than healthy controls.[26]

Activating Fcγ receptors are also important in the activation of monocyte-derived dendritic cells.[29] Genome-wide association studies have shown FcγRIIIa to be associated with RA susceptibility,[30] and murine models of RA such as the collagen-induced arthritis (CIA) model have demonstrated a role for activating Fcγ receptors in disease pathogenesis.[31, 32] BTK is highly expressed in myeloid lineages and regulates signaling pathways leading from the binding of ICs to FcγRIIIa and FcγRIIa to expression of pro-inflammatory cytokines, chemokines, and cell adhesion molecules.[5, 6, 7, 33, 34] BTK also mediates FcγRI signaling in mast cells and basophils although the role of these pathways in RA is not well established. However, IgE ACPAs have been identified in patients with RA,[10] and the number of activated mast cells may be increased in synovial tissue and have been correlated with disease activity.[8, 9, 11] Thus, inhibition of BTK could have therapeutic benefit on a variety of immunopathogenic features of RA.

Lastly, BTK inhibition could potentially counter the bone damage in RA through its role in mediating RANK-dependent osteoclastogenesis.[35, 36]

The RA sub-protocol of this study will help determine if branebrutinib is biologically active and effective in the treatment of RA (see Section RA 4.4).

In addition, the safety and efficacy of switching from branebrutinib or PBO to abatacept (also named BMS-188667 and Orencia™; referred to hereafter as abatacept) will also be evaluated.

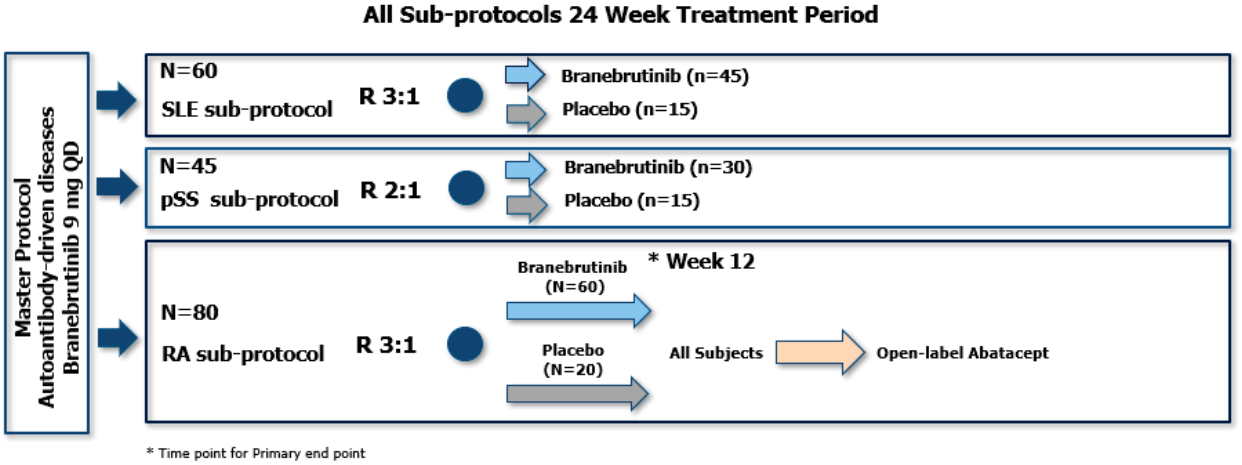
1.3 Master Protocol: Overall Research Hypothesis

The processes targeted by BTK inhibition are shared pathogenic molecular mechanisms of multiple immune-mediated diseases. Treatment with branebrutinib (BMS-986195), an oral, highly selective, irreversible inhibitor of BTK, may provide clinical benefit in the treatment of the immune-mediated diseases SLE, pSS, and RA.

1.4 Master Protocol Study Design

This Master Protocol with 3 sub-protocols is a double-blind, placebo-controlled multicenter study to assess the effect of branebrutinib (BMS-986195) treatment in subjects with SLE (SLE sub-protocol), pSS (pSS sub-protocol), and RA (RA sub-protocol). In the RA sub-protocol, the safety and efficacy of switching from branebrutinib or PBO to abatacept, which will be administered at a dose of 125 mg subcutaneously (SC), once weekly (QW), will also be evaluated. Enrollment in each sub-protocol will be concurrent.

Figure 1 Master Protocol Study Design



pSS = primary Sjögren's syndrome; QD = once daily; R = randomization ratio; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus

1.4.1 Master Protocol: Study Population

- The study population will include male and female subjects aged 18 (or age of majority) to 75 years inclusive at screening. Subjects must have active SLE, moderate to severe pSS, or moderate to severe adult-onset RA.
- Approximately 185 subjects will be randomized in the study (60 subjects in the SLE sub-protocol, 45 subjects in the pSS sub-protocol, and 80 subjects in the RA sub-protocol).
- For the SLE and pSS sub-protocols, there will be a 24-week double-blind placebo-controlled treatment period in which subjects will receive branebrutinib 9 mg or placebo once daily (QD). For the RA sub-protocol, there will be a 12-week double-blind PBO-controlled treatment period in which subjects will receive branebrutinib 9 mg or branebrutinib PBO, followed by an additional 12 weeks of treatment with open-label abatacept (Section 1.4.2).

1.4.2 Master Protocol: Study Treatment

Blinded treatment assignment will be conducted by randomization on Day 1 and managed by interactive response technology (IRT). Subjects will undergo screening evaluations to determine eligibility within 28 days prior to administration of study medication. After successfully meeting entry criteria and completing screening assessments, subjects in each

sub-protocol will be randomized in a blinded manner to branebrutinib or PBO treatment. Separate randomization schedules will be developed for each sub-protocol. Details of blinding and treatment assignment are provided in Section 6.0 of each sub-protocol. Subjects will be randomized to branebrutinib or PBO as follows:

  - SLE sub-protocol – 3:1 ratio of branebrutinib 9 mg to PBO QD
  - pSS sub-protocol – 2:1 ratio of branebrutinib 9 mg to PBO QD
  - RA sub-protocol – 3:1 ratio of branebrutinib 9 mg to PBO QD
- Randomization in the SLE sub-protocol will be stratified by immunosuppressant use (yes/no).
- Randomization in the pSS sub-protocol will be stratified by hydroxychloroquine (HCQ) use (yes/no).
- No stratification will be imposed in the RA sub-protocol.

1.4.3 Master Protocol: Independent Data Monitoring Committee

Safety monitoring, including laboratory monitoring, will be ongoing throughout the study, for subjects in all treatment arms, along with the employment of an Independent Data Monitoring Committee (DMC). The DMC will conduct at regular, prespecified intervals and on an ad hoc basis if warranted, safety review meetings throughout the study to ensure that the benefit and risks of study participation remain acceptable. Based on the DMC's assessment, recommendations of protocol modifications or other actions may occur, including but not limited to sample size adjustment, study modification, or discontinuation of the study or one or more of the sub-studies. In addition, hold of enrollment, pending more detailed assessment may be requested. For details, please refer to Sections SLE 4.1.1, pSS 4.1.1, and RA 4.1.1.

1.4.4 Master Protocol: Duration of Participation

- The duration of participation in the SLE and pSS sub-protocols will be approximately 32 weeks divided into the following periods: screening (up to 4 weeks [28 days]), double-blind PBO-controlled treatment for 24 weeks (Week 0 to Week 24) and follow-up (4 weeks).
- The duration of participation in the RA sub-protocol will be approximately 32 weeks divided into the following periods: screening (up to 4 weeks), double-blind PBO-controlled treatment for 12 weeks (Week 0 to Week 12), open-label abatacept treatment for an additional 12 weeks (all subjects; Week 12 to Week 24), and follow-up (4 weeks).

1.4.5 Master Protocol: Study Assessments

Efficacy and safety will be assessed throughout the study. Blood samples will be collected for PK and biomarker clinical laboratory assessments.

1.4.6 Master Protocol: Statistical Methods

1.4.6.1 General Methodology

Efficacy, safety, PK, and biomarker data will be combined and summarized across each sub-protocol for variables that are similar among the sub-protocols in addition to analyses provided

separately for each sub-protocol. Statistical methods will be similar to those specified in the sub-protocols.

1.4.6.2 Master Protocol: Interim Analysis

An interim analysis will be performed for future study planning at a time point after approximately 50% of the RA subjects have either completed Week 12 efficacy assessments or have discontinued prior to Week 12. The objective of this interim analysis will be to help in early planning for further clinical development of the compound. The study will not be stopped on the basis of any efficacy findings in the interim analysis, and there is no plan to modify the study design based on the results of this interim analysis. The results of this interim analysis will be reviewed by an unblinded development team that is independent of the study team responsible for the conduct of the study. The study team responsible for managing the study, including the Medical Monitors, will remain blinded to treatment assignment and will not have access to any unblinded interim analysis results or data until the study is completed and there is a final database lock and unblinding.

1.4.6.3 Master Protocol: Analysis and Reporting

After all subjects in the RA sub-protocol have completed Week 12 efficacy assessments or discontinued treatment/study prior to Week 12, an analysis of efficacy, safety, PK, and PD will be performed using data up to Week 12. The objective of this analysis will be to support early planning decisions on clinical development of the compound. After all subjects in a sub-protocol have finished the respective sub-protocol and the data have been locked for the sub-protocol, final analyses for that sub-protocol will be performed. Details of these analyses will be described in the statistical analysis plan (SAP).

The study team responsible for managing the study, including Medical Monitors, will remain blinded to treatment assignment and the results of safety analysis until full database lock and treatment unblinding has occurred. The data will be reported only after completion of all 3 sub-protocols.

1.4.7 Master Protocol: Justification for Dose

The selection of the branebrutinib dose and regimen to be assessed in this Master Protocol study was based on findings in the first-in-human (FIH) and nonclinical studies.

In the multiple ascending dose (MAD) panels (Part B) of the FIH study (Study IM014001), healthy subjects received branebrutinib solution once daily QD for 14 days at 4 dose levels (0.3, 1, 3, and 10 mg; n = 6 subjects per dose).[37] Increases in maximum observed plasma concentration (Cmax) and area under the plasma concentration-time curve (AUC) from the start to the end of the dosing period (AUC[TAU]) were approximately dose proportional within the dose levels tested. The mean half-life (T-HALF) was shorter than 2 hours across the dose range tested, indicating that branebrutinib was rapidly eliminated from the body. Consequently, as expected, accumulation at steady-state after multiple daily dosing was negligible.

Safety results were similar between branebrutinib 3 mg and 10 mg solution doses in Study IM014001. The drug was well-tolerated at both dose levels and most AEs observed were

similar in subjects receiving PBO and active treatment. The most common AEs included headache and upper respiratory tract infection. Based on the AUC in rats and dogs at the no-adverse-effect-level (NOAEL) after chronic daily administration (rat, 6 months; dog, 9 months), the safety multiple in humans after multiple doses of 10 mg is > 500×.[12] In the current study, the dose level of branebrutinib will be 9 mg; consistent with a good safety margin for humans participating in the study.

The dose for branebrutinib was selected based on the totality of data from multiple biomarkers obtained through post-hoc analysis from Study IM014001. The biomarkers evaluated were BTK occupancy by branebrutinib, inhibition of ex vivo stimulated cluster of differentiation (CD)69 expression, and plasma C-X-C motif chemokine ligand 13 (CXCL13) levels. The maximum occupancy reached ≥ 99% at branebrutinib doses of 1 mg and above (100%; maximum occupancy at doses ≥ 3 mg); however, the time to reach maximum occupancy was faster and maintained for a longer duration at 3 mg and 10 mg doses (solution formulation). The variability of the effect was lower for the higher dose of 10 mg. A similar result was obtained for CD69 inhibition, while the largest median inhibition in CD69 expression was observed at the branebrutinib 10 mg dose. The highest inhibition of plasma levels of CXCL13 was also obtained at the 10 mg dose level. Considering the higher variability and expression of BTK in patients with immune-mediated disorders,[4] the higher dose is expected to sustain more stable inhibition of BTK for optimal chronic treatment of a larger proportion of patients.

The comparison of exposure between the branebrutinib 10 mg solution formulation from Study IM014001 and the branebrutinib 9 mg capsule formulation (3 × 3 mg) from Day 1 Cycle 2 in Study IM014023 demonstrated comparable exposure for Cmax and AUC(TAU) with only slight delay in time to maximum concentration (Tmax) for capsule formulation. Thus, the use of 3 × 3 mg capsules of branebrutinib is expected to be equivalent to the 10 mg solution formulation in terms of exposure, safety, and pharmacodynamic (PD) effects.

The exposure for the 9 mg dose level is also much lower than the safety limit for exposure identified in preclinical studies. As previously mentioned, based on the AUC in rats at the NOAEL, the safety multiple in humans after multiple doses of 10 mg is > 500×.

In summary, the dose to evaluate PD response with optimal safety and best potential to detect an efficacy signal was chosen to be 9 mg branebrutinib administered as 3 × 3 mg capsules.

All RA subjects will receive open-label treatment with abatacept SC 125 mg administered QW in a prefilled syringe. This dose and regimen is approved for the treatment of patients with active RA and has demonstrated efficacy in Study IM101174 while maintaining steady-state trough concentration (Cminss) of 10 µg/mL and above, the exposure associated with near-maximal efficacy response in RA, in patients across all body weights.[38]

1.5 Master Protocol: Benefit/Risk Assessment

1.5.1 Branebrutinib

At this early stage in the development of branebrutinib for the treatment of immune-mediated disorders, assessments of benefit and risk rely on nonclinical data and data from ongoing and

completed Phase 1 studies in healthy volunteer subjects. As of the date of this protocol amendment, 143 subjects in the Phase 1 studies have received at least 1 dose of branebrutinib. The proposed 9 mg QD dosing regimen reflects implementation of appropriate safety margins (> 500× based on the AUC in rats and dogs at the NOAEL [20 mg/kg/day and 15 mg/kg/day in rats and dogs, respectively]) and is within the range of doses tested in the FIH study (Study IM014001[37]).

The effects of BTK inhibition by branebrutinib have been documented in pharmacology studies, and the potential for benefit in RA and SLE have been demonstrated by nonclinical studies using mouse models of RA and SLE. Branebrutinib demonstrated robust in vivo efficacy in CIA and collagen antibody-induced arthritis murine models of RA, protecting against clinically evident disease, histological joint damage, and bone mineral density loss. In both models, maximal efficacy was observed with ≥ 95% inactivation of BTK in vivo. Similarly, potent efficacy was observed in a mouse model (New Zealand Black and New Zealand White) of lupus-induced nephritis (see branebrutinib IB Section 4.1.1.2[12] for further details).

Findings in nonclinical toxicology studies were consistent with expectations based on the pharmacology of branebrutinib and included on-target PD effects such as decreases in B cells, suppression of keyhole limpet hemocyanin-specific IgM and IgG responses, and dose-related germinal center lymphoid depletion of minimal to moderate severity in the gut-associated lymphatic tissue.

Branebrutinib-related pancreatic toxicity was identified in oral Sprague-Dawley (SD) rat toxicity studies with up to 6 months of exposure.[39, 40, 41] Findings related to branebrutinib were noted at all doses, and were generally islet-centric (see the branebrutinib IB[12] for further details). These pancreatic lesions are similar to those observed with other BTK inhibitors and represent an exacerbation of an age-related pancreatic finding specific to rats.[42, 43, 44, 45] As such, these findings were considered nonadverse. The FDA has acknowledged that pancreatic lesions observed in rats treated with BTK inhibitors are unlikely to have relevance to the safety assessment for human subjects treated with this drug class.

With the exception of an unrelated serious adverse event (SAE) that was consistent with the subject's medical history, AEs in the FIH study (Study IM014001[37]) were mild to moderate, reversible, and consistent with expectations based on nonclinical experience.

Based upon nonclinical toxicology findings and the mechanism of action of the compound (immunosuppression), BMS has implemented additional assessments and risk mitigation approaches (including careful consideration of appropriate exclusion criteria and monitoring of subjects during and after dosing) in combination with conventional safety monitoring. In Parts A, B, C, and D of the FIH study,[37] there were no dose-related elevations of amylase, lipase, or fasting glucose; no decreases in white blood cells (WBCs) or Ig levels; and no clinically significant infections; however, this protocol continues to stipulate exclusion criteria (eg, assessment for latent TB infection [LTBI] and chronic viral infections) and clinical and laboratory monitoring to reduce the risk of infection.

Because of the slow return of BTK activity following the discontinuation of branebrutinib dosing (based on post-hoc analyses following Study IM014001; BTK occupancy was found to be between

10% and 30% with a steep downward trend following treatment with 10 mg branebrutinib for 2 weeks), the duration of postdose follow-up of 4 weeks was chosen to account for the time needed to recover BTK activity.

To minimize risk to participating subjects, this protocol has inclusion and exclusion criteria appropriate to the populations and proposed treatments, as well as frequent study visits for safety assessments. Blinded safety data will be reviewed on an ongoing basis by the BMS Medical Monitor and pharmacovigilance group to look for emerging safety trends or issues, and an independent external DMC will be in place for the duration of the study.

In order to provide active study treatment to subjects who may be receiving PBO treatment for a maximum of 24 weeks, subjects in the SLE and pSS sub-protocols will also receive protocol-defined SOC therapy for their primary disease. Although successful CS tapering for those taking ≥ 10 mg/day will be encouraged as appropriate, inability to taper or a requirement to increase the CS dose to protect a subject's safety or well-being will not be prohibited by the protocol. All subjects in the RA sub-protocol who may be receiving PBO treatment for a maximum of 12 weeks from Week 0 to Week 12 will also receive protocol-defined SOC therapy for their RA; all subjects will receive open-label abatacept from Week 12 to Week 24.

The risk for drug-drug interactions (DDIs) with branebrutinib has previously been assessed. The potential for clinically relevant DDIs of branebrutinib with substrates of a number of enzymes and transporters (cytochrome P450 [CYP]1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, and organic anion transporting polypeptide OATP1B1 and 1B3) is likely to be minimal based on the low projected therapeutic concentration (Cmax < 0.20 μM) and high serum protein binding.[46] Based on the results of Study IM014013 and in vitro studies, branebrutinib may affect the PK of drugs that are sensitive substrates of CYP2C8 and P-glycoprotein (P-gp) as a weak inhibitor. Therefore, until more knowledge is gained, drugs that are sensitive substrates of CYP2C8 and P-gp may be restricted or excluded based on their therapeutic window and metabolism.

In vivo studies to evaluate the developmental and reproductive effects of branebrutinib have shown developmental toxicity in rabbits (at an exposure multiple of 53× relative to the dose of 9 mg proposed for this study) that were associated with maternal mortality (IB Section 4.3.5[12]). At the NOAEL of 40 mg/kg/day, the safety margin was 16× compared to the human AUC at 10 mg MAD. Branebrutinib was not associated with maternal or developmental toxicity in pregnant rats at exposure multiples up to 437× (versus human AUC at 10 mg MAD). Based on the exposure safety multiple, there is minimal risk to women of childbearing potential (WOCBP). However, to ensure safety, the study will require WOCBP to use highly effective contraception, and pregnant women will not be enrolled in this study. It is not known whether branebrutinib passes into human milk. Therefore, breastfeeding women will also not be enrolled in this study. The DDI study with oral contraceptives (Study IM014023) demonstrated lack of PK interaction,[47] which ensures efficacy of hormonal contraception co-administered with branebrutinib.

1.5.2 Open-label Therapy with Abatacept after Week 12

Only the RA sub-protocol includes open-label treatment with abatacept starting at Week 12. Abatacept, a soluble fusion protein that consists of the extracellular domain of human CTLA-4 linked to the modified Fc (hinge, constant region heavy chain [C_H]2, and C_H3 domains) portion of human IgG1, is a selective co-stimulation modulator that inhibits T cell activation by binding to cluster of differentiation (CD)80 and CD86 molecules on antigen-presenting cells, thereby inhibiting interaction with CD28.

Abatacept is a biologic compound approved for the treatment of patients with active RA (see the abatacept IB[48] for properties and mechanisms of action of abatacept).

In clinical studies, abatacept demonstrated clear, consistent, and medically important benefit in the treatment of signs and symptoms of RA, improving physical function, reducing the progression of structural damage, and improving the quality of life in subjects with moderate to severe RA who were MTX-naïve, or were inadequate responders to MTX or anti-TNF therapies.[49]

With over 27,754 patient-years of abatacept exposure, clinical studies of abatacept provide extensive experience characterizing the safety and efficacy/effectiveness of abatacept.[49] Review of safety data from the ongoing long-term extensions of the clinical studies reveals a consistent safety profile for abatacept over time. However, there are inherent limitations to the assessment of infrequent AEs in clinical programs. Abatacept was first approved in 2005. Since that time, there have been an estimated 648,974 patient-years of exposure to abatacept in the marketplace. Postmarketing reports have not altered the favorable benefit-risk profile for abatacept and its safety profile remains generally similar to that established during the clinical studies. There remains limited information in patients with hepatic and renal impairment, combination therapy including other biologics, and use in elderly subjects.

Based on the clinical study experience in adults, the identified risks associated with the use of abatacept include infections (some of which may be serious or fatal), infusion-related reactions (IV only), and systemic injection reactions (SC only).[49] The main potential risks include the development of malignancies and immune-mediated disorders, but an increased risk of these types of events has not been observed. The rate of immunogenicity has generally been low, and there has not been an apparent effect on safety, efficacy, or PK.

With regard to the developmental and reproductive effects of abatacept, the study treatment has been shown to have no effects on male or female fertility in rats, no teratogenic effects in rats and rabbits at doses up to 200 mg/kg daily (29-fold higher than the human 10 mg/kg dose based on AUC in rats and rabbits), and no adverse effects in offspring of rats treated with abatacept during early gestation and throughout the lactation period at doses up to 45 mg/kg (threefold higher than the human 10 mg/kg dose based on AUC).[50] Alterations in immune function in female rats consisting of increase in the T cell-dependent antibody response and inflammation of the thyroid in female have been observed, but only at a dose of 200 mg/kg (11-fold higher than the human 10 mg/kg dose based on AUC). Evidence of thyroiditis has also been observed in adult rats treated with abatacept, but thyroiditis has not been observed in mice, monkeys, or humans treated with abatacept, and is not considered to be clinically relevant. Abatacept has also been shown to cross

the placenta in rats and rabbits. Because animal reproduction studies are not always predictive of human response, and because there are no adequate and well-controlled studies of abatacept use in pregnant women, pregnant and breastfeeding women will not be enrolled in this study, and WOCBP will be required to use protocol-specified highly effective contraceptive methods (APPENDIX 4).

Detailed information about the known and expected benefits and risks and reasonably anticipated AEs of branebrutinib and abatacept are provided in the branebrutinib IB[12] and the abatacept IB[48], respectively.

In summary, nonclinical data, clinical experience with branebrutinib in healthy subjects, ongoing clinical studies with other BTK inhibitors in RA, pSS, and SLE, and clinical experience with abatacept in RA, taken together with the design and study treatment doses selected for the current Phase 2a study indicate an overall favorable benefit/risk assessment for investigating branebrutinib in subjects with SLE, pSS, or RA, and treatment of branebrutinib followed by abatacept in subjects with RA.

1.5.3 Concomitant Medication Exclusions and Restrictions for All Sub-protocols

For concomitant medications exclusions and restrictions that apply to the SLE, pSS, and RA sub-protocols, see Table 1. This table lists concomitant medications that, if taken, may result in exclusions from the study or concomitant medication restrictions on use, irrespective of indication.

Based on vitro and in vivo studies, properties of branebrutinib exhibit weak inhibitory potential toward P-gp transporter and CYP2C8 enzyme. The drugs that may be administered in combination with branebrutinib for the specified and other possible underlying conditions were evaluated to determine their sensitivity for potential interactions. The evaluation was based on the metabolism of the concomitant medications, prescribing dose range and therapeutic window, and known information on interactions with P-gp and CYP2C8 inhibitors.

The strategy was to limit the upper dose so that possible weak interaction through P-gp and CYP2C8 (< 50% increase in bioavailability) would not result in exposure greater than the safe exposure established in patients.

Table 1 Concomitant Medications Requiring Exclusions from Study or Restrictions

Drug	Pathway	Typical Dose Range	Recommendations
Exclusions			
pioglitazone	CYP2C8	15 mg or 30 mg QD	Exclude subjects on this medication
repaglinide	CYP2C8	0.5 mg to 1 to 2 mg with each meal preprandially	Exclude subjects on this medication
tolvaptan	P-gp	45+15 mg, 60+30 mg, or 90+30 mg BID	Exclude subjects with autosomal dominant polycystic kidney disease or on tolvaptan

Table 1 Concomitant Medications Requiring Exclusions from Study or Restrictions

Drug	Pathway	Typical Dose Range	Recommendations
Restrictions			
ambrisentan	P-gp	5 to 10 mg QD	Dose up to 5 mg can be used
amitriptyline	P-gp	25 mg TID to 150 mg QD	Allowed dose up to 100 mg (SLE, RA) Exclude in pSS if taken within 4 weeks of randomization
aripiprazole	P-gp	10 to 15 mg/day	Allowed dose up to 10 mg QD
cevimeline	P-gp	30 mg TID	Allowed; monitor for hyperhidrosis as adverse effect of increased exposure
citalopram	P-gp	40 to 60 mg/day	Allowed dose up to 40 mg QD
clonazepam	P-gp	1.5 mg/day TID; 8 to 10 mg/day TID up to 20 mg/day	Allowed dose up to 10 mg/day
colchicine	P-gp	0.6 mg, prophylaxis – 1 tablet QD or BID, flares – 2 tablets	Dose up to 0.6 mg QD can be used
dabigatran etexilate	P-gp	110, 150, 220 mg BID	Dose up to 150 mg can be used
desipramine	P-gp	100, 200, 300 mg/day	Allowed dose up to 200 mg/day (SLE, RA) Exclude in pSS if taken within 4 weeks of randomization
desvenlafaxine	P-gp	50, 100, 200 mg/day	Allowed dose up to 100 mg QD
digoxin	P-gp	Injection 125 to 500 mcg, weight based; tablets 0.0625 mg, 0.125 mg, and 0.25 mg – 8 to 12 mcg/kg, loading 500 to 750 mcg, additional 125 to 375 mcg	For acute use only; exclude at baseline; limit highest dose and monitor trough concentrations; stop treatment with branebrutinib during treatment with digoxin and for 3 days afterwards
doxepin	P-gp	75 to 150 mg/day	Allowed dose up to 150 mg QD (SLE, RA) Exclude in pSS if taken within 4 weeks of randomization
escitalopram	P-gp	10 to 20 mg/day	Allowed dose up to 10 mg/day
fexofenadine	P-gp	60 and 120 mg; starting dose 60 mg QD, then 60 mg BID or 120 mg QD	Dose up to 60 mg QD can be used
hydroxychloroquine	P-gp	Strength 200 mg; 6.5 mg (salt form)/kg ideal (lean) body weight; 200 to 400 mg daily	Limit to maintenance dose 400 mg, no loading dose; measure PK at any time during the screening visit. The time at which the sample was taken will be recorded and the time the HCQ was self-administered will be recorded by the subject.

Table 1 Concomitant Medications Requiring Exclusions from Study or Restrictions

Drug	Pathway	Typical Dose Range	Recommendations
			HCQ concentration not to exceed 2.0 µg/mL at screening.
imipramine	P-gp	100, 200, 250 to 300 mg/day	Allowed dose up to 100 mg/day (SLE, RA) Exclude in pSS if taken within 4 weeks of randomization
minocycline	P-gp	100 mg or 200 mg initially, followed by 100 mg BID or 50 mg Q6h	Dose up to 100 mg BID can be used
mycophenolate mofetil	P-gp	1 to 1.5 g BID	Allowed in SLE, limit highest dose to 2 g/day (in subjects of African ancestry, 3 g/day is acceptable).
nortriptyline	P-gp	25 mg TID or QID, 100 to 150 mg/day	Allowed dose up to 100 mg/day (SLE, RA) Exclude in pSS if taken within 4 weeks of randomization
olanzapine	P-gp	5 to 20 mg/day	Allowed dose up to 10 mg/day
paroxetine	P-gp	10 to 60 mg/day	Allowed dose up to 40 mg/day
piroxicam	P-gp	20 mg, or 10 mg BID Then 10 to 20 mg QD	Dose up to 10 mg QD can be used
posaconazole	P-gp	Loading 300 to 400 mg BID, then 300 mg QD	Dose up to 300 mg QD can be used as maintenance dose, for acute infections stop using branebrutinib until dosing with posaconazole is discontinued
quetiapine	P-gp	50 to 800 mg/day	Allowed dose up to 600 mg/day (SLE, RA) Exclude in pSS if taken within 4 weeks of randomization
ranolazine	P-gp	500 mg to 1000 mg BID	Dose up to 500 mg BID can be used
rivaroxaban	P-gp	10 and 20 mg QD	Dose up to 10 mg QD can be used
rosiglitazone	CYP2C8	2, 4, 8 mg	Dose up to 4 mg can be used, monitor glucose closely
torasemide	CYP2C8	2.5 mg to 20 mg	Dose up to 10 mg can be used
trimipramine	P-gp	75 mg/day BID or TID to 150 mg/day in 25-mg increments	Allowed dose up to 150 mg/day (SLE, RA) Exclude in pSS if taken within 4 weeks of randomization
venlafaxine	P-gp	75 to 225 mg/day	Allowed dose up to 150 mg QD
vilazodone	P-gp	10 to 40 mg/day	Allowed dose up to 20 mg/day

BID = twice daily; CYP = cytochrome P450; ECG = electrocardiogram; P-gp = P-glycoprotein; PK = pharmacokinetic; Q6h = every 6 hours; QD = once daily; SLE = systemic lupus erythematosus; TID = 3 times daily.

1.5.4 Approach to SARS-CoV-2

Since initiation of this study, a global pandemic of coronavirus disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) has supervened. [51] Critical illness and mortality occur more frequently with COVID-19 than with infections by common respiratory viruses - with increased risk in the aged and those with certain comorbidities. [52, 53] The impact of rheumatologic diseases and their treatments on COVID-19-associated risk remains, at the time of this authoring, unclear.

The Sponsor is evaluating the risk-benefit profile of this study on an ongoing basis, and in particular, regarding (i) the risk-benefit profile of branebrutinib in the context of the COVID-19 pandemic, and (ii) vaccination against SARS-CoV-2.

1.5.4.1 Risk/Benefit Profile of Branebrutinib in the Context of the COVID-19 Pandemic

Risk from SARS-CoV-2 is intimately linked with the immune response following exposure. The immune system must control viral replication and cytopathology[54], while avoiding the exaggerated inflammation associated with severe COVID-19. [55] It is reasonable to hypothesize that BTK function may influence both these aspects of the response to SARS-CoV-2. BTK is central to activation, proliferation, and survival responses downstream of the B cell antigen receptor and other receptors on B cells and key myeloid cell types. Details of BTK signaling are summarized in Section 1.1 of this protocol, Section 2 of the IB, and references therein. Notably, however, signaling through BTK depends both on the latter's kinase activity, and on its "scaffolding" activity (ie, physical association with other proteins). [2, 56, 57]

Insights into the effect of deficiency in both BTK activities can be gained by observing COVID-19 outcomes in patients with X-linked agammaglobulinemia (XLA), a genetic immunodeficiency characterized by profound reductions in B cell counts and serum immunoglobulins caused by null mutations in BTK. XLA patients demonstrate high susceptibility to bacterial and some viral infections that is largely ameliorated by administration of intravenous immunoglobulin and prophylactic antibiotics. [58] Published cases of COVID-19 in XLA patients reveal disease courses ranging from mild disease [59] to nonlethal pneumonia. [60, 61, 62] While these reports are anecdotal, they do demonstrate that lifelong deficiency of BTK kinase and scaffolding activities does not preclude recovery from COVID-19. Moreover, susceptibility to COVID-19 in rheumatology patients treated with branebrutinib is plausibly lower than that of XLA patients because the former have: (i) intact BTK protein despite inhibition of kinase activity, (ii) fully-developed adaptive immunity with a lifetime of intact pretreatment BTK function, and (iii) normal B cell counts. A published description of 5 COVID-19 cases in Waldenstrom's macroglobulinemia patients chronically treated with full-dose ibrutinib demonstrated a mild infection course without need for hospitalization; a sixth patient chronically treated with low-dose ibrutinib had a more severe course but showed improvement temporally linked with increased dosage. [63] A cohort of 19 severely

affected COVID-19 patients without prior indication for BTK inhibitor therapy, who were treated acutely and experimentally with acalabrutinib, demonstrated reduced inflammatory measures, and outcomes no worse than expected given their disease severity. [64] Thus, publicly disclosed COVID-19 experiences in patients with XLA or receiving BTK inhibitors do not indicate increased risk of adverse COVID-19 outcomes associated with pharmacologic BTK inhibition. Furthermore, professional rheumatology organizations have not advocated prophylactic withdrawal of any class of rheumatologic treatment -- including immunosuppressants and Janus kinase (JAK) inhibitors. [65, 66] Indeed, elevated disease activity in RA and SLE is associated with greater susceptibility to serious infections in general [67, 68], while treatment with biologic or targeted DMARDs may be associated with reduced risk of COVID-19-associated hospitalization. [69]

Branebrutinib offers the potential for better disease control with acceptable safety, as discussed in Sections 1.1 and 1.5.3 of this protocol and in the IB. This, together with the currently available insight regarding BTK and COVID-19, supports the continued clinical evaluation of branebrutinib despite the pandemic. Individual investigators and each potential subject together should decide the appropriateness of study participation depending on the medical particulars of each subject, and the local COVID-19 situation. Because the understanding of COVID-19 risk and disease mechanisms is rapidly evolving, the Sponsor will monitor for emerging knowledge that might affect the risk-benefit profile of this study.

1.5.4.2 Vaccination Against SARS-CoV-2

Vaccines against SARS-CoV-2 are emerging rapidly on an emergency basis, though the degree of protection in patients with rheumatologic diseases with or without disease-modifying treatment remains unclear. Experience with influenza vaccination may be informative however, which strongly supports the protective effect of inactivated influenza vaccination in rheumatology patients taking DMARDs, such as methotrexate, anti-TNF agents, and others [70]. Furthermore, a small study indicates that hematology patients who are not heavily pretreated and are receiving ibrutinib can still mount clinically significant anti-influenza titers following vaccination with high-dose inactivated influenza vaccine. [71] This experience forms the basis for emerging professional rheumatologist guidance supporting SARS-CoV-2 vaccination for rheumatology patients receiving DMARDs. [72, 73, 74] As with general COVID-19 risk assessment, the management of SARS-CoV-2 vaccination in rheumatology patients is also rapidly evolving and is a focus of ongoing monitoring by the Sponsor.

Vaccination prior to enrollment in this study is encouraged; however, this may be difficult due to inconsistent vaccine availability and variable patient perception of the vaccines. Thus, this amended protocol permits vaccination, during study treatment, against SARS-CoV-2 and influenza using nonlive/nonreplicating vaccine types (Sub-protocol Sections SLE 6.7, pSS 6.7, and RA 6.7).

1.5.5 Study Termination for Unexpectedly Unfavorable Risk/Benefit Balance

The Sponsor will evaluate the risk/benefit profile of the study on an ongoing basis. This evaluation will be based on all available data – with particular attention to: (i) AEs or other safety trends in

this or any other clinical study of branebrutinib whose character, severity, and/or frequency suggest that subjects would be exposed to an unreasonable and significant risk of illness or injury; (ii) new nonclinical data suggesting unreasonable and significant risk of illness or injury.

If such evaluation suggests that the risk/benefit profile of the study (or one of its sub-protocols) has become unfavorable to subjects, the Sponsor will pause enrollment and/or dosing until further assessment of data, and interaction with the appropriate Health Authority(ies) can take place on potential actions. Such actions may include (but are not limited to) study continuation, substantial amendment, or termination of the entire study or any of its sub-protocols.

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Clinical Protocol IM014029:

SLE SUB-PROTOCOL

A Randomized, Placebo-Controlled, Double-Blind, Multicenter Study to Assess the Efficacy and Safety of Branebrutinib Treatment in Subjects with Active Systemic Lupus Erythematosus or Primary Sjögren's Syndrome, or Branebrutinib Treatment Followed by Open-label Abatacept Treatment in Subjects with Active Rheumatoid Arthritis

Protocol Amendment 04 SLE

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SLE 1 SUB-PROTOCOL SUMMARY

SLE 1.1 Synopsis

Protocol Title: A Randomized, Placebo-Controlled, Double-Blind, Multicenter Study to Assess the Efficacy and Safety of Branebrutinib Treatment in Subjects with Active Systemic Lupus Erythematosus or Primary Sjögren's Syndrome, or Branebrutinib Treatment Followed by Open-label Abatacept Treatment in Subjects with Active Rheumatoid Arthritis

Short Title:

Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of Branebrutinib in Systemic Lupus Erythematosus: SLE Sub-protocol

Study Phase:

Phase 2a

SLE Sub-protocol Rationale:

The Study IM014029 SLE sub-protocol is designed to evaluate the efficacy and safety of branebrutinib in addition to background disease therapy in the treatment of subjects with active SLE. Based on several underlying molecular mechanisms of SLE targeted by Bruton's tyrosine kinase (BTK) inhibition, this sub-protocol will test the hypothesis that branebrutinib may be effective in the treatment of patients with SLE.

Patients with moderate to severe flares of SLE usually receive immunosuppressive drugs and corticosteroids (CSs), antimalarials, immunosuppressants (especially azathioprine, mycophenolate, methotrexate [MTX], leflunomide, and tacrolimus), biologics including belimumab (approved in most countries), and other agents (generally prescribed off-label). The only FDA-approved treatments for SLE are steroids, antimalarials, aspirin, and belimumab. Other SOC treatments were borrowed from other diseases and have not completed a scientifically rigorous approval process for patients with SLE. These treatments temporarily control SLE flares and are associated with numerous toxicities. Adverse effects of CS use are serious and can include increased risk of cardiovascular events, infections, osteoporosis, and many other morbidities. The goal in the management of SLE is to achieve disease and symptom control while minimizing excessive immunosuppressive drug exposure and limiting CS exposure and treatment-related AEs. There remains an unmet need for novel, well-tolerated, orally administered therapies that can effectively modify the course and control symptoms, while minimizing CS and immunosuppressive drug exposure. In particular, treatment of this difficult disease will be improved when agents with clearly understood molecular targets are properly characterized with available technology to improve rationale for treatment selection and dosing. The SLE sub-protocol in this study will help determine if branebrutinib is biologically active and effective in the treatment of patients with active SLE despite receiving SOC treatments.

SLE Sub-protocol Study Population:

The study population will consist of male and female subjects aged 18 years (or age of majority) to 75 years inclusive at screening with active SLE.

SLE Sub-protocol Key Inclusion/Exclusion Criteria

a) Diagnosed with SLE, which meets the Systemic Lupus Erythematosus Internal Collaborating Clinics 2012 (SLICC 2012) classification criteria, ≥ 24 weeks before the screening visit

b) Modified Cutaneous Lupus Erythematosus Disease Area and Severity Index (mCLASI) activity score ≥ 10 (excluding mucous membrane ulcerations and diffuse non-inflammatory alopecia)

c) For subjects taking CS, the dose cannot exceed 40 mg/day prednisone or equivalent

d) Subjects with other immune-mediated diseases (eg, scleroderma, mixed connective tissue disease, multiple sclerosis, psoriasis, inflammatory bowel disease, etc) are excluded. Subjects with Type 1 autoimmune diabetes mellitus, thyroid autoimmune disease, or secondary Sjögren's syndrome are not excluded.

e) Subjects with drug-induced lupus, or active or unstable lupus activity in the neuropsychiatric body system, including but not limited to subjects with a British Isles Lupus Assessment Group (BILAG-2004) A grade are excluded, with the exception of subjects with mononeuritis multiplex and polyneuropathy, who are allowed with approval by the Medical Monitor or [redacted] Lupus Central Review Services.

f) Subjects with active, severe lupus nephritis (World Health Organization Class III or IV) that requires or may require treatment with cytotoxic agents or high-dose CS are excluded. Subjects with prior controlled renal disease with serum creatinine ≤ 2× upper limit of normal (ULN) and either residual proteinuria ≤ 3 g/day or a urine protein/creatinine ratio (UPCR) of ≤ 3 mg/mg or 339 mg/mmol are allowed. Stability of renal disease must be documented with at least 2 measurements of proteinuria or UPCR over the past 6 months or with 2 tests during the screening period at least 1 week apart and must be approved by the Medical Monitor.

g) Active fibromyalgia with pain symptoms or signs that would interfere with joint assessment or requiring adjustment in medication within the 3 months before screening to control symptoms; subjects with fibromyalgia that is well controlled on stable treatment may be included.

h) Elevated antinuclear antibodies (ANA) ≥ 1:80 or positive anti-double-stranded deoxyribonucleic acid (dsDNA) (excluding results in the equivocal range) or positive anti-Smith (Sm), as determined by the central laboratory at the screening visit, are required; if initial results for all of these are negative at screening such that a subject would be deemed a screen failure, then 1 retest will be allowed for subjects with a documented history of positive results.

i) Subjects hospitalized with PCR-proven or suspected COVID-19 infection (unless for quarantine/observation) within the 3 months prior to randomization, as well as any subjects with any sequelae of prior COVID-19 infection at screening, regardless of time since infection, are excluded.

SLE Sub-protocol Objectives and Endpoints:

Objective	Endpoint
SLE Sub-protocol	
Primary	
• To compare the efficacy of branebrutinib with PBO at Week 24 in the treatment of subjects with SLE	Proportion of subjects with: ≥ 50% decrease in mCLASI activity score in subjects with a baseline mCLASI score ≥ 10 **AND** CS (prednisone or equivalent) ≤ 10 mg/day at Week 20 and Week 24
Secondary/Additional	
• To compare the efficacy of branebrutinib with PBO at Week 24 in the treatment of subjects with SLE	**Secondary**: • Change from baseline in SLEDAI-2K score **Additional**: • Change from baseline in autoantibody titers (ANA, anti-dsDNA) • Change from baseline in C3, C4 • Change from baseline in hsCRP, ESR • Changes from baseline in PGA and SGA • Change from baseline in the EQ-5 D-5 L score • Change from baseline in PROMIS Fatigue 6 a • Change from baseline in SLE Pain NRS
• To compare the efficacy of branebrutinib with PBO on measures of global and organ-specific clinical responses at Week 24 in the treatment of subjects with SLE	**Secondary**: • BILAG-based Composite Lupus Assessment response **Additional**: • Change from baseline in the 40-joint count for tender, swollen, and tender + swollen joints in subjects with arthritis at baseline • Change from baseline in SDI
Safety	
• To compare the safety and tolerability of branebrutinib with PBO in subjects with SLE	• Number and proportion of subjects experiencing SAEs, AEs, and abnormalities in laboratory parameters, vital signs, and ECGs
Exploratory	
• Time to SLE flare, as measured by BILAG-2004 assessment • PK of branebrutinib and metabolites of clinical interest • [redacted]	

SLE Sub-protocol Objectives and Endpoints:

Objective	Endpoint
[redacted]	

[redacted]

AE = adverse event; ANA = antinuclear antibodies; [redacted]; BICLA = BILAG-based Composite Lupus Assessment; BILAG = British Isles Lupus Assessment Group; [redacted]; C = complement; CS = corticosteroid; [redacted] dsDNA = double-stranded deoxyribonucleic acid; ECG = electrocardiogram; EQ-5 D-5 L = Euro Quality of Life Five Dimensions Questionnaire: 5 Level version; ESR = erythrocyte sedimentation rate; hsCRP = high-sensitivity C-reactive protein; [redacted]; mCLASI = modified Cutaneous Lupus Erythematosus Disease Area and Severity Index; NRS = numeric rating score; PBO = placebo; PGA = Physician Global Assessment; PK = pharmacokinetic; PROMIS = Patient-Reported Outcomes Measurement Information System; [redacted]; SAE = serious adverse event; [redacted] SGA = Subject Global Assessment; SLE = systemic lupus erythematosus; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index– 2000; Sm = Smith; [redacted]

SLE Sub-protocol Overall Design:

- This is a double-blind, PBO-controlled Phase 2a sub-protocol to evaluate the effect of branebrutinib (BMS-986195) in subjects with active SLE. All subjects will continue background therapy for their primary disease within protocol-defined limits.
- Subjects will receive double-blind branebrutinib 9 mg or PBO treatment administered orally once daily (QD) for 24 weeks (Week 0 to Week 24).
- Treatment assignment will be conducted by randomization. Subjects will undergo screening evaluations to determine eligibility within 28 days prior to administration of study medication. Following the screening process, if eligible for study participation, subjects will be randomized in the SLE sub-protocol to receive branebrutinib or PBO treatment in a 3:1 ratio. Randomization will be stratified by immunosuppressant use (yes/no).

SLE Sub-protocol Number of Subjects:

It is expected that 60 subjects will be randomized in the SLE sub-protocol.

SLE Sub-protocol Duration:

The total duration of participation in the SLE sub-protocol is approximately 32 weeks and will be divided into the following periods: screening (up to 4 weeks), double-blind PBO-controlled treatment for 24 weeks (Week 0 to Week 24), and follow-up (4 weeks).

SLE Sub-protocol Study Treatment:

Study Drug for IM014029		
Medication	**Potency**	**IP/Non-IP**
Branebrutinib	9 mg QD, oral	IP
PBO	QD, oral	IP

IP = investigational product; PBO = placebo; QD = once daily

SLE Sub-protocol Statistical Methods:

Sample size is calculated based on the estimated effect size for the primary endpoint comparison between branebrutinib and PBO treatment groups. The primary endpoint for the SLE sub-protocol is a ≥ 50% decrease from baseline mCLASI activity score in subjects with a baseline mCLASI activity score ≥ 10, at Week 24 and CS (prednisone or equivalent) ≤ 10 mg/day at Week 20 and Week 24.

Estimates for PBO response rates, treatment differences, and common standard deviations were obtained from the published literature. Sample size justification is as follows:

Assuming a total sample size of 60 subjects randomized in a blinded fashion in a 3:1 ratio to branebrutinib (45 subjects) or PBO (15 subjects) and a treatment difference of 25% with a PBO response of 30% for mCLASI at Week 24, the 95% confidence interval (CI) is expected to exclude 0 (expected 95% CI based on a z-test = 2%, 56%).

Categorical data will be summarized by treatment group as frequency counts and percentages. Continuous data will be summarized by treatment group using n, mean, standard deviation, median, minimum, and maximum unless otherwise specified. Efficacy data will be summarized separately for each sub-protocol and with each sub-protocol combined for variables that are similar among the sub-protocols. The primary analysis for each sub-protocol will be performed after all subjects finish the study within a sub-protocol. There will be no alpha level adjustment for multiple endpoint testing.

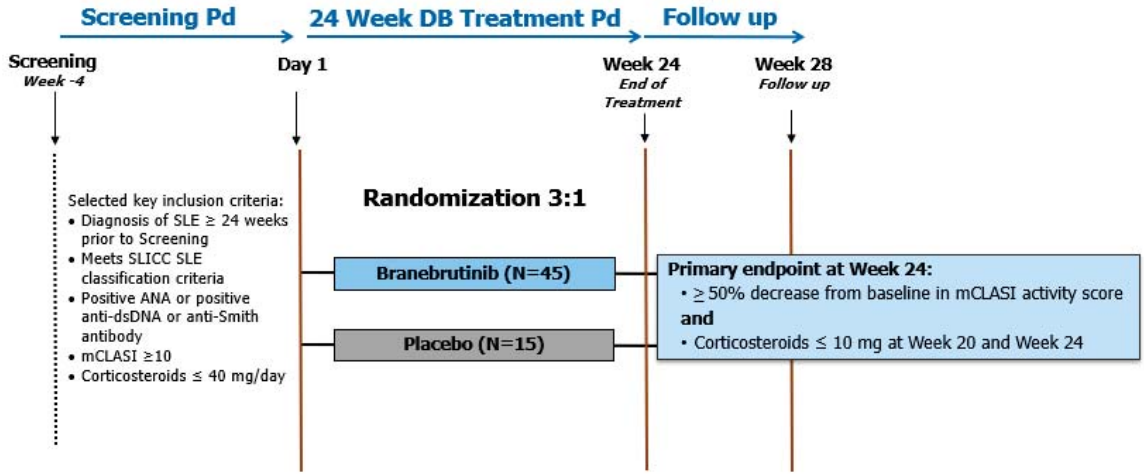
Response rates of branebrutinib compared to PBO for binary endpoints will be analyzed using a Cochran-Mantel-Haenzsel test stratified by immunosuppressant use (yes/no). The 95% CIs for each treatment group response rate and the difference in response rate for branebrutinib compared to PBO will be provided. If expected cell counts are not sufficient, then Fisher's exact test will be used. Logistic regression models for the primary endpoint may be used in supportive analyses to incorporate additional covariates of interest.

Continuous endpoints (change from baseline values) will be analyzed using analysis of covariance. The baseline value of the endpoint being tested will be added into the model as a covariate and immunosuppressant use (yes/no) and treatment as fixed effects. Treatment differences based on least-squares means and corresponding 2-sided 95% CIs will be provided for the difference between branebrutinib and PBO. Mixed model repeated measures (MMRM) analyses may be used in supportive analyses for continuous endpoints. Bayesian borrowing to utilize historical controls may also be performed as supportive analyses. Details will be provided in the SAP if needed.

Nonresponder imputation will be used for binary endpoints for subjects who discontinue study treatment early, start a protocol-prohibited medication/therapy prior to the specified timepoint, or otherwise have missing endpoint data for the specified timepoint. Missing data are addressed in these models and assumed to be missing at random.

Treatment-emergent AEs (TEAEs) and serious adverse events (SAEs) will be summarized using counts and percentages of subjects experiencing the event as well as the number of events by system organ class, preferred term, and treatment group. Physical examinations findings, vital signs, clinical laboratory test results, and electrocardiogram (ECG) test results will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) for continuous variables and frequency distributions (counts and percentages) for categorical variables. Safety data will be summarized separately for each sub-protocol and with all sub-protocols combined.

SLE 1.2 Schema



ANA = antinuclear antibodies; DB = double-blind; dsDNA = double-stranded deoxyribonucleic acid; mCLASI = modified Cutaneous Lupus Erythematosus Disease Area and Severity Index; Pd = period; SLE = systemic lupus erythematosus; SLICC = Systemic Lupus Erythematosus International Collaborating Clinics

Note: mCLASI ≥ 10 excludes mucous membrane ulcerations and diffuse noninflammatory alopecia.

SLE 1.3 Schedule of Activities

SLE Table 1 Screening Procedural Outline Branebrutinib Study IM014029

Procedure	Screening (V1)	Notes
Eligibility Assessments		
Informed Consent	X	A subject is considered enrolled only when a protocol-specific ICF is signed; this includes subjects at preselected clinical sites consenting to participate in extended PK sampling in addition to the sampling scheduled for all study subjects.
Enroll subject in the IRT system	X	
Inclusion/Exclusion Criteria	X	Includes: SLE diagnosis ≥ 24 weeks before screening based on SLICC 2012 classification criteria Elevated ANA (≥ 1:80) or positive anti-dsDNA or anti-Smith antibody mCLASI ≥10
SLE History, SLE-related Treatment	X	
General Medical History	X	
History of Tobacco Use	X	Nonsmoker, light, or heavy smoker.
Subject-reported Outcomes		
SGA	X	Collected on eCOA device; refer to Section SLE 8.1.2.1.
SLE Pain NRS	X	Collected on eCOA device; refer to Section SLE 8.1.2.4.
EQ-5 D-5 L	X	Collected on eCOA device; refer to Section SLE 8.1.2.3.
PROMIS-Fatigue 6 a	X	Collected on eCOA device; refer to Section SLE 8.1.2.2.
Safety Assessments		
Physical Examination (PE)	X	Complete PE.
Physical Assessments	X	
Vital Signs	X	Includes height (screening only) and weight, body Temperature (ear or oral), respiratory rate, seated BP, and seated heart rate. BP and heart rate should be measured after the subject has been sitting quietly for at least 5 minutes.
ECG	X	ECGs should be recorded after the subject has been supine for 5 to 10 minutes. Lab work must be done after the ECG.

SLE Table 1 Screening Procedural Outline Branebrutinib Study IM014029

Procedure	Screening (V1)	Notes
Chest Imaging (eg, Chest x-ray)	X	Chest imaging is required if not performed within 6 months of screening visit; copy of radiology report must be on file and reviewed by the investigator.
Prior and Concomitant Medication Use[a]	X	Includes prescription, over-the-counter medications, and herbal supplements. All concomitant medications to be reviewed by the Medical Monitor and clinical pharmacology asset lead.
SAE Assessment	X	All SAEs must be collected from the time of signing the consent, including those thought to be associated with protocol-specified procedures and within 30 days of discontinuation of dosing or subject's participation in the study if the last scheduled visit occurs at a later time.
Clinical Assessments		
SLICC 2012 criteria for SLE	X	Entered into EDC by site; refer to Section SLE 8.1.1.1.
BILAG-2004 Index	X	Entered into EDC by site; refer to Section SLE 8.1.1.3.
SLEDAI-2K	X	Entered into EDC by site; refer to Section SLE 8.1.1.6.
PGA	X	Entered into EDC by site; refer to Section SLE 8.1.1.8.
40-joint count	X	Entered into EDC by site; refer to Section SLE 8.1.1.9.
CLASI	X	Entered into EDC by site; refer to Section SLE 8.1.1.7.
Photography	X	All subjects will be photographed. See Photography Manual for details. Can be performed by site staff trained on study-specific requirements and delegated by PI accordingly.
Laboratory Tests		Includes blood and urine samples.
Hematology	X	CBC with differential.
Serum Chemistry Panel	X	Includes liver function testing.
Lipid Panel	X	Nonfasting.
Urinalysis	X	
HbA1c	X	If HbA1c ≥ 9 consult Medical Monitor.
TSH	X	If out of normal range (high or low), consult the Medical Monitor.
UPCR	X	
eGFR	X	

SLE Table 1 Screening Procedural Outline Branebrutinib Study IM014029

Procedure	Screening (V1)	Notes
ESR	X	Local laboratory assessment by site.
C3, C4	X	
HCQ concentration [b]	X	To be reviewed by the Medical Monitor and clinical pharmacology asset lead.
Coomb's test (direct)	X	**Only** if clinically indicated.
ANA	X	
anti-Smith	X	
anti-dsDNA	X	
Infectious Serology	X	Includes HCV antibody, HBsAg, HbsAb, HbcAb, and HIV antibodies.
TB Test (IGRA; eg, QuantiFERON®-TB Gold)	X	
Pregnancy Test (Serum or Urine)	X	WOCBP only. Must have negative pregnancy test within 24 hours prior to the start of treatment.
Follicle-stimulating hormone	X	For those women who require FSH to confirm menopausal status. See APPENDIX 4 for definition and Section SLE 5.1 for reproductive status inclusion criteria.
Breast and cervical cancer screening	X	Because most patients with SLE are young women, screening for cervical and breast cancer prior to randomization is encouraged as per local guidelines and investigator judgment.
Biomarker Assessments		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

ANA = antinuclear antibodies; [redacted] BILAG = British Isles Lupus Assessment Group; BP = blood pressure; C3, C4 = serum complement C3, C4; CBC = complete blood count; CS = corticosteroids (prednisone or equivalent); [redacted]; dsDNA = double-stranded DNA; eCOA = Electronic Clinical Outcome Assessment; EDC = RAVE electronic data capture; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; EQ-5 D-5 L = Euro Quality of Life Five Dimensions Questionnaire: 5 Level version;

ESR = erythrocyte sedimentation rate; FSH = follicle-stimulating hormone; HbA1c = hemoglobin A1c Test for Diabetes; HbcAb = hepatitis B core antibody; HbsAb = anti-hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HCQ = hydroxychloroquine; HCV = hepatitis C virus; HIV = human immunodeficiency virus; [redacted] ICF = informed consent form; IGRA = interferon gamma-release assay; [redacted]; IRT = interactive response technology; mCLASI = modified Cutaneous Lupus Erythematosus Disease Area and Severity Index; NRS = numeric rating score; MMP = matrix metalloproteinase; PK = pharmacokinetic; PGA = Physician Global Assessment; PI = principal investigator; PROMIS = Patient-reported Outcomes Measurement Information System; [redacted] SAE = serious adverse event; SGA = Subject Global Assessment SLE = systemic lupus erythematosus; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000; SLICC= Systemic Lupus Erythematosus International Collaborating Clinics; TB = tuberculosis; [redacted]; TSH = thyroid-stimulating hormone; UPCR = urine protein:creatinine ratio; WOCBP = women of childbearing potential

[a] For subjects receiving CS, the dose must be stable for 2 weeks before the screening visit (signing of the ICF) and throughout the screening period until randomization (for additional details, refer to Section SLE 8.1.1.10).

[b] For subjects taking HCQ concomitantly, a sample of whole blood will be drawn for HCQ PK analysis.

[redacted]

When multiple assessments are conducted at a single visit, the following is the order in which they should be performed:

1) Subject-reported Outcomes (eg, SGA, EQ-5 D-5 L, etc)
2) Safety assessments (eg, vitals, AEs)
3) Investigator-administered Assessments (eg, PGA, joint count, etc)
4) Laboratory tests (eg, safety laboratory tests, PK assessments, biomarker assessments)

SLE Table 2 Procedural Outline Branebrutinib Study IM014029 (Week 0 to Week 28)

Procedure	W0 D1 V2	W2 D15 (± 3 d) V3	W4 D29 (± 3 d) V4	W8 D57 (± 3 d) V5	W12 D85 (± 3 d) V6	W16 D113 (± 3 d) V7	W20 D141 (± 3 d) V8	W24 D169 (± 3 d) V9 (EOT) [a]	W28 D197 (± 3 d) V10 Safety FU	Notes
Subject-reported Outcomes										
SGA	X		X	X	X	X	X	X	X	Collected on eCOA device; refer to Section SLE 8.1.2.1.
SLE Pain NRS	X		X	X	X	X	X	X	X	Collected on eCOA device; refer to Section SLE 8.1.2.4.
EQ-5 D-5 L	X				X			X	X	Collected on eCOA device; refer to Section SLE 8.1.2.3.
PROMIS-Fatigue 6 a	X				X			X	X	Collected on eCOA device; refer to Section SLE 8.1.2.2.
Safety Assessments										
Complete Physical Examination	X								X	See Section SLE 8.4.1.
Targeted Physical Examination		X	X	X	X	X	X	X		See Section SLE 8.4.1.
Body Weight	X		X	X	X	X	X	X	X	
Vital Signs	X	X	X	X	X	X	X	X	X	Temperature (ear or oral), respiratory rate, seated BP, and seated heart rate; BP and heart rate should be measured after the subject has been resting quietly for at least 5 minutes.
ECG	X	X	X	X	X	X	X	X	X	ECGs should be recorded after the subject has been supine for 5 to 10 minutes. Lab work must be done after the ECG.

SLE Table 2 Procedural Outline Branebrutinib Study IM014029 (Week 0 to Week 28)

Procedure	W0 D1 V2	W2 D15 (± 3 d) V3	W4 D29 (± 3 d) V4	W8 D57 (± 3 d) V5	W12 D85 (± 3 d) V6	W16 D113 (± 3 d) V7	W20 D141 (± 3 d) V8	W24 D169 (± 3 d) V9 (EOT) [a]	W28 D197 (± 3 d) V10 Safety FU	Notes
Concomitant Medication Use [b]	X	X	X	X	X	X	X	X	X	Refer to Section SLE 6.7, SLE Table 1.
AE and SAE Assessment	X	X	X	X	X	X	X	X	X	Nonserious AEs must be collected from the time of the first dose of the study drug through the date of the follow-up or last visit.
Clinical Assessments										
SDI	X							X		Entered into EDC by site; refer to Section SLE 8.1.1.1.
BILAG-2004 Index	X		X	X	X	X	X	X	X	Entered into EDC by site; refer to Section SLE 8.1.1.3.
SLEDAI-2K	X		X	X	X	X	X	X	X	Entered into EDC by site; refer to Section SLE 8.1.1.6.
PGA	X		X	X	X	X	X	X	X	Entered into EDC by site; refer to Section SLE 8.1.1.8.
40-joint count	X		X	X	X	X	X	X	X	Entered into EDC by site; refer to Section SLE 8.1.1.9.
CLASI	X		X	X	X	X	X	X	X	Entered into EDC by site; refer to Section SLE 8.1.1.7.

SLE Table 2 Procedural Outline Branebrutinib Study IM014029 (Week 0 to Week 28)

Procedure	W0 D1 V2	W2 D15 (± 3 d) V3	W4 D29 (± 3 d) V4	W8 D57 (± 3 d) V5	W12 D85 (± 3 d) V6	W16 D113 (± 3 d) V7	W20 D141 (± 3 d) V8	W24 D169 (± 3 d) V9 (EOT) [a]	W28 D197 (± 3 d) V10 Safety FU	Notes
Assess suitability for CS taper [b]	X		X	X	X	X				(Refer to Section SLE 8.1.1.10). CS dose must remain stable from the Week 16 visit through the Week 24 visit.
Photography	X		X	X	X	X	X	X	X	All subjects will be photographed. See Photography Manual for details. Can be performed by site staff trained on study-specific requirements and delegated by PI accordingly.
Laboratory Tests										
Hematology	X	X	X	X	X	X	X	X	X	
Serum Chemistry Panel	X	X	X	X	X	X	X	X	X	
Lipid Panel (Fasting)	X		X	X	X	X	X	X	X	Fasting for at least 8 hours prior to collection.
Urinalysis	X	X	X	X	X	X	X	X	X	
HbA1c								X	X	
UPCR	X	X	X	X	X	X	X	X	X	
eGFR	X	X	X	X	X	X	X	X	X	
ESR	X	X	X	X	X	X	X	X	X	Local laboratory assessment by site.
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
HCQ concentration	X		X							Predose and 2 hours postdose; included with

SLE Table 2 Procedural Outline Branebrutinib Study IM014029 (Week 0 to Week 28)

Procedure	W0 D1 V2	W2 D15 (± 3 d) V3	W4 D29 (± 3 d) V4	W8 D57 (± 3 d) V5	W12 D85 (± 3 d) V6	W16 D113 (± 3 d) V7	W20 D141 (± 3 d) V8	W24 D169 (± 3 d) V9 (EOT) [a]	W28 D197 (± 3 d) V10 Safety FU	Notes
										concomitant medications PK (refer to Section SLE 8.5, SLE Table 8).
Coomb's test (direct)	X	X	X	X	X	X	X	X	X	**Only** if clinically indicated.
hsCRP	X	X	X	X	X	X	X	X	X	
[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Beta-2-microglobulin	X	X	X	X	X	X	X	X	X	
TBNK	X	X	X		X			X	X	
Anti-ds-DNA antibody	X		X	X	X	X	X	X	X	
[redacted], anti-Ro/SSA, anti-La/SSB, [redacted]; [redacted] ANA, [redacted]	X				X			X	X	
[redacted]	[redacted]		[redacted]		[redacted]	[redacted]		[redacted]	[redacted]	
Pregnancy Test (serum or urine)	X		X	X	X	X	X	X	X	WOCBP only. Must have negative pregnancy test within 24 hours prior to the start of treatment.
[redacted]	[redacted]							[redacted]		[redacted]

SLE Table 2 Procedural Outline Branebrutinib Study IM014029 (Week 0 to Week 28)

Procedure	W0 D1 V2	W2 D15 (± 3 d) V3	W4 D29 (± 3 d) V4	W8 D57 (± 3 d) V5	W12 D85 (± 3 d) V6	W16 D113 (± 3 d) V7	W20 D141 (± 3 d) V8	W24 D169 (± 3 d) V9 (EOT) [a]	W28 D197 (± 3 d) V10 Safety FU	Notes
PK Assessments										
Standard blood samples for the PK of branebrutinib [c]	X		X	X		X		X		Refer to Section SLE 8.5, SLE Table 8.
Blood samples at preselected sites for the PK of branebrutinib and metabolites [d]	X			X						Refer to Section SLE 8.5, SLE Table 8.
Blood samples for the PK assessment of concomitant medications [e]	X		X							Refer to Section SLE 8.5, SLE Table 8.
Biomarker Sampling										
[redacted]	[redacted]	[redacted]	[redacted]		[redacted]			[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]		[redacted]			[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
[redacted]					[redacted]					[redacted]
[redacted]	[redacted]	[redacted]	[redacted]		[redacted]			[redacted]	[redacted]	[redacted]

SLE Table 2 Procedural Outline Branebrutinib Study IM014029 (Week 0 to Week 28)

Procedure	W0 D1 V2	W2 D15 (± 3 d) V3	W4 D29 (± 3 d) V4	W8 D57 (± 3 d) V5	W12 D85 (± 3 d) V6	W16 D113 (± 3 d) V7	W20 D141 (± 3 d) V8	W24 D169 (± 3 d) V9 (EOT) [a]	W28 D197 (± 3 d) V10 Safety FU	Notes
[redacted]	[redacted]		[redacted]		[redacted]			[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		[redacted]		[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]		[redacted]			[redacted]	[redacted]	[redacted]
[redacted]	[redacted]							[redacted]		[redacted]
Study Treatment										
Randomize	X									
Dispense/Administer Study Treatment	X	X	X	X	X	X	X	X		Note: At Week 2 and Week 24, the subject is requested to bring IP to the site visit and IP is administered at the site; no new kit is dispensed at these visits.
Study Treatment Compliance		X	X	X	X	X	X	X	X [g]	

[redacted]; AE = adverse event; ANA = antinuclear antibodies; [redacted]; [redacted]; BILAG = British Isles Lupus Assessment Group; BP = blood pressure; [redacted]; C3, C4 = serum complement C3 and C4; CLASI = Cutaneous Lupus Erythematosus Disease Area and Severity Index; CS = corticosteroids; [redacted] D/d = day; DNA = deoxyribonucleic acid; dsDNA = double-stranded deoxyribonucleic acid; ECG = electrocardiogram; eCRF = electronic case report form; eGFR = estimated glomerular filtration rate; EOT = end of treatment; EQ-5 D-5 L = Euro Quality of Life Five Dimensions Questionnaire: 5-Level version; ESR = erythrocyte sedimentation rate; FU = Follow-up; HbA1c = Hemoglobin A1c; HCQ = hydroxychloroquine; hsCRP = high-sensitivity C-reactive protein; [redacted] Ig = immunoglobulin; [redacted]; IP = investigational product; MMP = matrix metalloproteinase; NRS = numeric rating score; PGA = Physician Global Assessment; PI = principal investigator; PK = pharmacokinetic; PROMIS = Patient-Reported Outcomes Measurement Information System; [redacted]; RF = rheumatoid factor; RNA = ribonucleic acid; [redacted]; [redacted] SAE = serious adverse event; SDI = SLICC/American College of Rheumatology Damage Index; SLE = systemic lupus erythematosus; SLEDAI 2K = Systemic Lupus Erythematosus Disease Activity Index 2000; SLICC = Systemic Lupus Erythematosus International Collaborating Clinics; Sm = Smith; SGA = Subject Global Assessment; -4 = Systemic Lupus Erythematosus Responder Index -4; SSA = Sjögren's syndrome

antigen A; SSB = Sjögren's syndrome antigen B; TBNK = T cells, B cells, natural killer cells; [redacted]; UPCR = urine protein:creatinine ratio; V = visit; W = Week; WOCBP = women of childbearing potential

[a] If the decision has been made for a subject to permanently discontinue treatment before the planned Week 24 visit (Section SLE 7.1.1), the subject should undergo a Week 24 EOT visit as specified in the Week 24 column of this table, followed by a Week 28 Safety FU visit, 4 weeks (±3 d) later, as specified in the Week 28 column of this table. The appropriate eCRF pages for the EOT and Safety FU visits should be completed accordingly.

[b] For subjects receiving CS (prednisone or equivalent), unless a reason for not tapering is documented, the investigator must assess the subject's suitability for, and implement, CS taper at each visit from Week 8 up to, but not including, Week 16 (Section SLE 8.1.1.10). CS dose must remain stable from the Week 16 visit through the Week 24 visit. CS dose reduction may be started any time after Day 1.

[c] Blood samples for the PK assessment of branebrutinib concentrations will be taken predose from all study subjects at Week 0 (Day 1), Week 4 (Day 29), Week 8 (Day 57), Week 16 (Day 113), and Week 24 (Day 169), and postdose at Week 0 (Day 1), Week 8 (Day 57), and Week 24 (Day 169) at approximately 0.5, 1, 2, and 4 hours after dosing.

[d] At preselected clinical sites only, blood samples for the PK assessment of branebrutinib and its metabolites concentrations will be taken predose at Week 8 (Day 57); and postdose at Week 0 (Day 1) and Week 8 (Day 57) at approximately 0.5, 1, 2, and 4 hours. In addition, samples will be taken postdose at 6 hours and from 8-10 hours (flexible window) and 10-12 hours (flexible window) on the same days. A PK sample will also be drawn at Week 0 (Day 2) at 24 hours after dosing (predose of branebrutinib on Day 2). (For these assessments, collected blood samples will be aliquoted into 2 tubes.)

[e] Blood samples for PK assessment of relevant concomitant medications that are sensitive substrates of CYP2C8 and other potentially relevant drug metabolizing enzymes and P-gp transporter may be measured post-hoc. For these concomitant medications, plasma samples will be collected predose and 2 hours postdose at Week 0 (Day 1) and Week 4 (Day 29). For subjects taking HCQ on-study, whole blood samples at predose and 2 hours postdose of branebrutinib on both Day 1 (Week 0) and Day 29 (Week 4) will be collected in addition for the assessment of HCQ level.

[redacted]

[g] Study treatment compliance is to be performed at Week 28 only if the subject's study participation has completed and the subject failed to return study drug at the prior visit.

When multiple assessments are conducted at a single visit, the following is the order in which they should be performed:

1. Subject-reported Outcomes (eg, SGA, EQ-5 D-5 L, etc)
2. Safety assessments (eg, vitals, AEs)
3. Investigator-administered Assessments (eg, PGA, joint count, etc)
4. Laboratory tests (eg, safety laboratory tests, PK assessments, biomarker assessments)
5. Treatment dosing

SLE 2 INTRODUCTION

An overall introduction to this protocol employing a master protocol design for 3 separate immune-mediated indications is provided in Master Protocol Section 1.2.

SLE 2.1 Background and Research Hypothesis

The IM014029 SLE sub-protocol is designed to evaluate the efficacy and safety of branebrutinib in subjects with active SLE, when added to background disease therapy within protocol-defined limits. Based on several key underlying molecular mechanisms of SLE targeted by BTK inhibition, the hypothesis will be tested that branebrutinib is effective in the treatment of SLE.

SLE is a systemic immune-mediated disease characterized by the production of autoantibodies to components of the cell that results in a diverse array of clinical manifestations including musculoskeletal, cutaneous, renal, constitutional, hematologic, neurologic, cardiovascular, and other vital organ involvement.

Patients with SLE are treated with immunosuppressive drugs and CS, antimalarials, biologics including belimumab, and other agents (generally prescribed off-label). These treatments temporarily reduce the signs and symptoms of SLE but do not prevent progression of organ damage and may be toxic, particularly with prolonged use. Adverse effects of CS use can be serious and can include increased risk of cardiovascular disease, infections, osteoporosis, and many other morbidities. The goal in the management of SLE is to achieve disease and symptom control while minimizing excessive immunosuppression, CS exposure, and treatment-related AEs. There remains an unmet need for novel, well-tolerated orally administered therapies that can be optimized to effectively modify the disease course and control symptoms, while minimizing CS exposure.

SLE is associated with the presence of autoreactive ICs that induce pathobiology through the action of Fcγ receptors. Preclinical models suggest that IgG-IC-driven activation of Fcγ receptors may be important in the pathology of SLE via B cell and myeloid cell modulation and relevant as an approach to treatment.[13] Basophils, when stimulated by autoreactive IgE through the BTK-dependent receptor FcεRI, might also be relevant to lupus nephritis.[16] Therefore, BTK inhibition may target several underlying molecular mechanisms of SLE, and it is on this basis that the BTK inhibitor branebrutinib will be tested.

The SLE sub-protocol in this study will help determine if branebrutinib is biologically active and effective in the treatment of patients with active SLE despite receiving SOC therapies.

SLE 2.1.1 Study Hypothesis

BTK plays a role in the pathology of SLE. The hypothesis to be tested is that treatment with branebrutinib 9 mg will have greater efficacy than PBO as assessed by mCLASI response, defined as a decrease of ≥ 50% from baseline mCLASI activity score, in subjects with a baseline mCLASI activity score ≥ 10, at Week 24.

SLE 2.2 Benefit/Risk Assessment

At this early stage in the development of branebrutinib for the treatment of immune-mediated disorders, assessments of benefit and risk rely on nonclinical data and data from completed Phase 1 studies in healthy volunteer subjects. The proposed 9 mg QD dosing regimen reflects implementation of appropriate safety margins (> 500× based on the AUC in rats and dogs at the NOAEL [20 mg/kg/day and 15 mg/kg/day in rats and dogs, respectively]) and is within the range of doses tested in the FIH study (Study IM014001[37]).

The effects of BTK inhibition by branebrutinib have been documented in pharmacology studies, and the potential for benefit in RA and SLE have been demonstrated by nonclinical studies using mouse models of RA and SLE. Branebrutinib demonstrated robust in vivo efficacy in CIA and collagen antibody-induced arthritis (CAIA) murine models of RA, protecting against clinically evident disease, histological joint damage, and bone mineral density loss. In both models, maximal efficacy was observed with ≥ 95% inactivation of BTK in vivo. Similarly, potent efficacy was observed in a mouse model (New Zealand Black and New Zealand White) of lupus-induced nephritis (see branebrutinib IB Section 4.1.1.2[12] for further details).

Findings in nonclinical toxicology studies were consistent with expectations based on the pharmacology of branebrutinib and included on-target PD effects such as decreases in B cells, suppression of keyhole limpet hemocyanin-specific IgM and IgG responses, and dose-related germinal center lymphoid depletion of minimal to moderate severity in the gut-associated lymphatic tissue.

Branebrutinib-related pancreatic toxicity was identified in oral SD rat toxicity studies with up to 6 months of exposure.[39, 40, 41] Findings related to branebrutinib were noted at all doses, and were generally islet-centric (see the branebrutinib IB[12] for further details). These pancreatic lesions are similar to those observed with other BTK inhibitors and represent an exacerbation of an age-related pancreatic finding specific to rats.[42, 43, 44, 45] As such, these findings were considered nonadverse. The FDA has acknowledged that pancreatic lesions observed in rats treated with BTK inhibitors are unlikely to have relevance to the safety assessment for human subjects treated with this drug class.

With the exception of an unrelated SAE that was consistent with the subject's medical history, AEs in the FIH study (Study IM014001[37]) were mild to moderate, reversible, and consistent with expectations based on nonclinical experience.

Based upon the mechanism of action of the compound (immunosuppression), BMS has implemented additional assessments and risk mitigation approaches (including careful consideration of appropriate exclusion criteria and monitoring of subjects during and after dosing) in combination with conventional safety monitoring. In Parts A, B, C, and D of the FIH study,[37] there were no dose-related elevations of amylase, lipase, or fasting glucose; no decreases in WBCs or Ig levels; and no clinically significant infections; however, this protocol continues to stipulate exclusion criteria (eg, assessment for LTBI and chronic viral infections) and clinical and laboratory monitoring to reduce the risk of infection.

Because of the slow return of BTK activity following the discontinuation of branebrutinib dosing (based on post-hoc analyses following Study IM014001), BTK occupancy was found to be between 10% and 30% with a steep downward trend following treatment with 10 mg branebrutinib for 2 weeks), the duration of postdose follow-up of 4 weeks was chosen to account for the time needed to recover BTK activity.

To minimize risk to participating subjects, this protocol has inclusion and exclusion criteria appropriate to the populations and proposed treatments, as well as frequent study visits for safety assessments. Blinded safety data will be reviewed on an ongoing basis by the BMS Medical Monitor and pharmacovigilance group to look for emerging safety trends or issues, and an independent external DMC will be in place for the duration of the study.

In order to provide active study treatment while receiving PBO treatment for a maximum of 24 weeks, subjects in the SLE sub-protocol will also receive protocol-defined SOC therapy for their primary disease. Although successful CS tapering for those taking ≥ 10 mg/day will be encouraged as appropriate, inability to taper or a requirement to increase the CS dose to protect a subject's safety or well-being will not be prohibited by the protocol.

The risk for drug-DDIs with branebrutinib has previously been assessed. The potential for clinically relevant DDIs of branebrutinib with substrates of a number of enzymes and transporters (cytochrome P450 [CYP]1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, and organic anion transporting polypeptide OATP1B1 and 1B3) is likely to be minimal based on the low projected therapeutic concentration (Cmax < 0.20 μM) and high serum protein binding.[46] Based on the results of Study IM014013 and in vitro studies, branebrutinib may affect the PK of drugs that are sensitive substrates of CYP2C8 and P-glycoprotein (P-gp) as a weak inhibitor. Therefore, until more knowledge is gained, drugs that are sensitive substrates of CYP2C8 and P-gp may be restricted or excluded based on their therapeutic window and metabolism.

In vivo studies to evaluate the developmental and reproductive effects of branebrutinib have shown developmental toxicity in rabbits (at an exposure multiple of 53× relative to the dose of 9 mg proposed for this study) that were associated with maternal mortality (IB Section 4.3.5[12]). At the NOAEL of 40 mg/kg/day, the safety margin was 16× compared to the human AUC at 10 mg MAD. Branebrutinib was not associated with maternal or developmental toxicity in pregnant rats at exposure multiples up to 437× (versus human AUC at 10 mg MAD). Based on the exposure safety multiple, there is minimal risk to WOCBP. However, to ensure safety, the study will require WOCBP to use highly effective contraception, and pregnant women will not be enrolled in this study. It is not known whether branebrutinib passes into human milk. Therefore, breastfeeding women will also not be enrolled in this study. The DDI study with oral contraceptives (Study IM014023) demonstrated lack of PK interaction,[47] which ensures efficacy of hormonal contraception co-administered with branebrutinib.

SLE 3 OBJECTIVES AND ENDPOINTS

SLE Table 3 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To compare the efficacy of branebrutinib with PBO at Week 24 in the treatment of subjects with SLE	Proportion of subjects with: ≥ 50% decrease in mCLASI activity score in subjects with a baseline mCLASI score ≥ 10 **AND** CS (prednisone or equivalent) ≤ 10 mg/day at Week 20 and Week 24
Secondary/Additional	
• To compare the efficacy of branebrutinib with PBO at Week 24 in the treatment of subjects with SLE	**Secondary**: • Change from baseline in SLEDAI-2K score **Additional**: • Change from baseline in autoantibody titers (ANA, anti-dsDNA) • Change from baseline in C3, C4 • Change from baseline in hsCRP, ESR • Changes from baseline in PGA and SGA • Change from baseline in the EQ-5 D-5 L score • Change from baseline in PROMIS Fatigue 6 a • Change from baseline in SLE Pain NRS
• To compare the efficacy of branebrutinib with PBO on measures of global and organ-specific clinical responses at Week 24 in the treatment of subjects with SLE	**Secondary**: • BICLA response **Additional**: • Change from baseline in the 40-joint count for tender, swollen, and tender + swollen joints in subjects with arthritis at baseline • Change from baseline in SDI
Safety	
• To compare the safety and tolerability of branebrutinib with PBO in subjects with SLE	• Number and proportion of subjects experiencing SAEs, AEs, and abnormalities in laboratory parameters, vital signs, and ECGs
Exploratory	
• Time to SLE flare, as measured by BILAG-2004 Index-defined SLE Flare • PK of branebrutinib and metabolites of clinical interest [redacted]	

SLE Table 3 Objectives and Endpoints

Objectives	Endpoints
• [redacted]	

[redacted]; AE = adverse event; ANA = antinuclear antibodies; [redacted] BICLA = BILAG-based Composite Lupus Assessment; BILAG = British Isles Lupus Assessment Group; [redacted] C = complement; CS = corticosteroid; [redacted] dsDNA = double-stranded deoxyribonucleic acid; ECG = electrocardiogram; EQ-5 D-5 L = Euro Quality of Life Five Dimensions Questionnaire: 5 Level version; ESR = erythrocyte sedimentation rate; hsCRP = high-sensitivity C-reactive protein; [redacted] mCLASI = modified Cutaneous Lupus Erythematosus Disease Area and Severity Index; NRS = numeric rating score; PBO = placebo; PGA = Physician Global Assessment; PK = pharmacokinetic; PROMIS = Patient-Reported Outcomes Measurement Information System; [redacted] SAE = serious adverse event; [redacted] SGA = Subject Global Assessment; SLE = systemic lupus erythematosus; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index– 2000; Sm = Smith; [redacted]

SLE 4 STUDY DESIGN

SLE 4.1 Overall Design

- This is a double-blind, PBO-controlled multicenter Phase 2a study to assess the effect of branebrutinib treatment in subjects with active SLE when added to background disease therapy within protocol-defined limits.
- Approximately 60 subjects will be randomized in the SLE sub-protocol. Sample size considerations are presented in Section SLE 9.1 Sample Size Determination.
- For the SLE sub-protocol, there will be a 24-week double-blind PBO-controlled treatment period during which subjects will receive branebrutinib 9 mg or PBO QD.
- Blinded treatment assignment will be conducted by randomization on Day 1 and managed by IRT. Subjects will undergo screening evaluation within 28 days prior to administration of study medication to determine eligibility. After successfully completing screening assessments, eligible subjects will be randomized in a blinded manner to receive branebrutinib 9 mg or PBO in a 3:1 ratio. Randomization will be stratified by immunosuppressant use (yes/no).
- The duration of participation in the SLE sub-protocol will be approximately 32 weeks divided into the following periods: screening (up to 4 weeks), double-blind PBO-controlled treatment for 24 weeks (Week 0 to Week 24), and follow-up (4 weeks).
- Efficacy and safety will be assessed throughout the study (see Section SLE 8.1 Efficacy Assessments, Section SLE 8.2 Adverse Events, and Section SLE 8.4 Safety for details of

assessments). Blood samples will be collected for PK and biomarker clinical laboratory assessments (see Section SLE 8.5 and [redacted] respectively, for details of assessments).

- An independent DMC will assess study findings on a periodic basis (Section SLE 4.1.1).

The study design schematic for the SLE sub-protocol is presented in Section SLE 1.2.

SLE 4.1.1 DMC and Other External Committees

To ensure the safety of study subjects, across all sub-protocols, an external independent DMC consisting of 2 experienced rheumatologists, an infectious disease clinician, and a statistician will be established for ongoing evaluation of safety assessments, AEs, and laboratory measurements. An independent reporting statistician not involved in the conduct of the study will be designated to provide the DMC with essential safety data unblinded to treatment during the study, if required.

The DMC will conduct at regular, prespecified intervals and on an ad hoc basis if warranted, safety review meetings throughout the study to ensure that the benefit and risks of study participation remain acceptable. Ad hoc meetings may be initiated by the DMC or by the Sponsor based on emerging new safety information. Based on the DMC's assessment, recommendations of protocol modifications or other actions may occur, including but not limited to sample size adjustment, study modification, or discontinuation of the study or one or more of the sub-studies. In addition, hold of enrollment, pending more detailed assessment may be requested.

Blinded Suspected, Unexpected Serious Adverse Reactions (SUSARs) will be sent to the DMC members on an ongoing basis. SAEs will be sent to the DMC on a monthly basis or on an ongoing basis as requested by the DMC.

The DMC will review safety data including but not limited to SAEs and adverse events of interest (AEIs). At the request of the DMC, designated personnel will provide further information on the medical assessment for a specific case.

The DMC may also consider external data from other branebrutinib studies that may be initiated in future or from novel scientific information that may be generated on branebrutinib or other BTK inhibitors.

Further details of DMC responsibilities, specific timing of safety reviews, content, and methods of data reports, authorities, processes, and procedures will be specified in the DMC charter.

SLE 4.2 Number of Subjects

It is expected that approximately 60 subjects will be randomized in the SLE sub-protocol. Details regarding sample size determination are provided in Section SLE 9.1.

SLE 4.3 End of Study Definition

The start of the study is defined as the date that the first subject signs the informed consent. End of the SLE sub-protocol is defined as the last visit of the last subject to complete the study or the final scheduled procedure shown in the Schedule of Activities (SoA; Section SLE 1.3). Study completion for the SLE sub-protocol is defined as the final date on which data for the primary

endpoint was or is expected to be collected, if this is not the same. The master protocol study will be reported only after the last endpoint has been analyzed for all 3 sub-protocols.

The total duration of study participation for subjects in the SLE sub-protocol is expected to be approximately 32 weeks.

SLE 4.4 Scientific Rationale for Study Design

(Please refer to Master Section 1.2 for rationale supporting the choice of a master protocol design to evaluate the safety and efficacy of branebrutinib in 3 immune-mediated/autoantibody-related diseases.)

The pathology of SLE involves several signaling events regulated by BTK, as described in Section SLE 2.1. It is therefore hypothesized that BTK inhibition will have clinical benefits in subjects with SLE.

In the SLE sub-protocol, all subjects will continue their existing therapies for SLE except for prohibited medications (see Section SLE 6.7.1). Rescue treatments are permitted as needed (with a few protocol-specified limitations; see Section SLE 6.7.2) for subject safety. A plan for CS tapering is included to allow subjects to use the lowest dose that meets their needs, consistent with SOC; however, doses are to be held stable for 8 weeks before the Week 24 assessments (primary efficacy endpoint).

A PBO control will be included in the SLE sub-protocol to allow the effects of treatment, both desired and adverse, to be appropriately compared against active treatment, with effort to minimize treatment period on PBO, as well as to allow continuation of certain background therapy within protocol-defined limits (see Section SLE 5.1, Inclusion criterion #4).

SLE 4.5 Justification for Dose

The selection of the branebrutinib dose and regimen to be assessed in this study was based on findings of the FIH and nonclinical studies.

In the MAD panels (Part B) of the FIH study (Study IM014001), healthy subjects received branebrutinib orally QD for 14 days at 4 dose levels (0.3, 1, 3, and 10 mg; n = 6 per dose).[37] Increases in Cmax and AUC(TAU) were approximately dose proportional within the dose levels tested. The mean T-HALF was shorter than 2 hours across the dose range tested, indicating that branebrutinib was rapidly eliminated from the body. Consequently, as expected, accumulation at steady-state after multiple daily dosing was negligible.

The safety between branebrutinib 3 mg and 10 mg doses in Study IM014001 demonstrated lack of dose effects on safety. The drug was well-tolerated at both dose levels with most AEs also observed for the subjects treated with PBO. The AEs mainly included headache and upper respiratory tract infection. Based on the AUC in rats at the NOAEL (61,900 ng•h/mL), the safety multiple in humans after multiple doses of 10 mg is > 500×.[12] In this study, the dose level of branebrutinib will be 9 mg; therefore, the safety margin is sufficient for humans participating in the study.

The dose for branebrutinib was selected based on data from biomarkers obtained in post-hoc analysis of Study IM014001. The biomarkers evaluated were BTK occupancy by branebrutinib, inhibition of ex vivo stimulated CD69 expression, and plasma CXCL13 levels. The maximum occupancy reached ≥ 99% at branebrutinib doses of 1 mg and above (100%; maximum occupancy at doses ≥ 3 mg); however, the time to reach maximum occupancy was faster and maintained for a longer duration at 3 mg and 10 mg doses (solution formulation). The variability of the effect was lower for the higher dose of 10 mg. A similar result was obtained for CD69 inhibition, while the largest median inhibition in CD69 expression was observed at the branebrutinib 10 mg dose. The highest inhibition of plasma levels of CXCL13 was also obtained at the 10 mg dose level. Considering the higher variability and expression of BTK in patients with immune-mediated disorders,[4] the higher dose is expected to sustain more stable inhibition of BTK for chronic treatment of heterogenous patients.

The comparison of exposure between the branebrutinib 10 mg solution formulation from Study IM014001 and the branebrutinib 9 mg capsule formulation (3 × 3 mg) from Day 1 Cycle 2 in Study IM014023 demonstrated comparable exposure for Cmax and AUC(TAU) with only slight delay in Tmax for capsule formulation. Thus, the use of 3 × 3 mg capsules of branebrutinib is expected to be equivalent to the 10 mg solution formulation in terms of exposure, safety, and PD effects considering the specifics of the patient population.

The exposure for this dose level is also much lower than the safety limit for exposure identified in preclinical studies; as previously mentioned, based on the AUC in rats at the NOAEL, the safety multiple in humans after multiple doses of 10 mg is > 500×.

In summary, the dose to evaluate the PD response with optimal safety and efficacy was chosen to be branebrutinib 9 mg administered as 3 × 3 mg capsules (details of treatment administration are provided in Section SLE 6.1).

SLE 5 STUDY POPULATION

Eligibility criteria for this sub-protocol have been carefully considered for the safety of the study subjects and to ensure that the results of the study can be interpreted. It is imperative that randomized subjects meet all eligibility criteria.

Screening evaluations must be completed and reviewed by the investigator to confirm whether potential subjects are eligible. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable. Subject eligibility will be reviewed and confirmed by the Medical Monitor or [redacted] Lupus Central Review Services prior to randomization.

SLE 5.1 Inclusion Criteria

In order to be eligible to participate in this SLE sub-protocol, an individual must meet all of the following criteria:

1) Signed Written Informed Consent: SLE Sub-protocol

a) Willing to participate in the study after completing all informed consent procedures and sign the informed consent form (ICF).

b) Willing and able to complete all study-specific procedures and visits.

2) Age and Reproductive Status: SLE Sub-protocol

a) **Not Applicable per Revised Protocol 02 -** Male and female patients, aged 18 (or age of majority) to 65 years, inclusive

b) **Not Applicable per Revised Protocol 02 -** WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of beta-human chorionic gonadotropin [β-HCG]) within 24 hours prior to the start of study treatment.

c) **Not Applicable per Revised Protocol 02 -** Women must not be breastfeeding.

d) **Not Applicable per Revised Protocol 02 -** WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study treatment(s) branebrutinib or PBO, 30 days before screening and 33 days posttreatment completion or longer based on country-specific label for other background therapy.

e) **Not Applicable per Revised Protocol 02 -** Male subjects who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception and fetal protection (APPENDIX 4) for the duration of treatment with study treatment(s) (branebrutinib or PBO) plus 33 days after the final dose of study treatment, or longer based on country-specific label for other background therapy. In addition, male subjects must be willing to refrain from sperm donation during this time.

f) **Not Applicable per Revised Protocol 02 -** WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements, and still must undergo pregnancy testing as described in this section.

Investigators shall counsel WOCBP, and male subjects 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 study drug, 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.

g) **Not Applicable per Revised Protocol 03** - Female Participants

h) **Not Applicable per Revised Protocol 03 -** Male Participants

i) Female Subjects

i) Females ages 18 years or local age of majority to 75 years, inclusive.

ii) Women who are not of childbearing potential are exempt from contraceptive requirements. Women subjects must have documented proof that they are not of childbearing potential.

iii) WOCBP must have a negative highly sensitive pregnancy test (minimum sensitivity 25 IU/L or equivalent units of 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.

iv) Additional requirements for pregnancy testing during and after study intervention are located in Section SLE 1.3, SoA

v) 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.

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

vii) WOCBP are permitted to use hormonal contraception methods (as described in APPENDIX 4).

viii) A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one 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, for at least 30 days before screening and at least 33 days posttreatment completion or longer based on country-specific label for other background therapy and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction for the same time period.

j) Male Subjects

i) Males ages 18 years or local age of majority to 75 years, inclusive

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 subjects 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 subjects 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 33 days after the last dose of study intervention or longer based on country-specific label for other background therapy.

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 33 days after the last dose of study intervention in the male participant or longer based on country-specific label for other background therapy.

vi) Male subjects 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 subjects have undergone a successful vasectomy, during the intervention period and for at least 33 days after the last dose of study intervention or longer based on country-specific label for other background therapy.

vii) Male subjects must refrain from donating sperm during the intervention period and for at least 33 days after the last dose of study intervention or longer based on country-specific label for other background therapy.

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

3) Type of Subject and Target Disease Characteristics: SLE Sub-protocol

a) **Not Applicable per Revised Protocol 03 -** Meets Systemic Lupus Erythematosus International Collaborating Clinics (SLICC) classification criteria for SLE and diagnosed with SLE ≥ 24 weeks before the screening visit.

b) **Not Applicable per Revised Protocol 03 -** Elevated antinuclear antibodies (ANA) ≥ 1:80 or positive (per central laboratory excluding results in the equivocal range) anti-double-stranded deoxyribonucleic acid (dsDNA) or positive anti-Sm, as determined by the central laboratory, at the screening visit; if initial results for any of these are negative at screening such that a subject would be deemed a screen failure, then 1 retest will be allowed for subjects with a documented history of positive results.

c) mCLASI activity score ≥ 10 (excluding mucous membrane ulcerations, and diffuse non-inflammatory alopecia)

d) **Not Applicable per Revised Protocol 03 -** CS (prednisone or equivalent) ≤ 40 mg/day

e) Meets SLICC 2012 classification criteria for SLE and diagnosed with SLE ≥ 24 weeks before the screening visit.

f) Elevated antinuclear antibodies (ANA) ≥ 1:80 or positive anti-double-stranded deoxyribonucleic acid (dsDNA) (excluding results in the equivocal range) or positive anti-Smith (Sm), as determined by the central laboratory at the screening visit; if initial results for all of these are negative at screening such that a subject would be deemed a screen failure, then 1 retest will be allowed for subjects with a documented history of positive results.

g) For subjects taking CS, the dose cannot exceed 40 mg/day prednisone or equivalent

4) Medications for Target Disease: SLE Sub-protocol

a) Requirements for subjects who are receiving chronic therapy with nonsteroidal anti-inflammatory drugs (NSAIDs; including marketed cyclooxygenase-2 inhibitors) are as follows; exceptions or changes may be possible with approval by the [redacted] Medical Monitor:

i. Doses must be stable for 14 days before the screening visit and must remain stable until randomization and throughout the study.

ii. No more than 1 oral NSAID may be used concurrently during the study and may be combined with topical NSAIDs.

iii. Use of 1 or more topical NSAIDs is permitted but must follow a stable regimen throughout the study.

b) **Not applicable per Revised Protocol 03 -** Standard of care that is allowed in this study must have been taken for ≥ 12 weeks before the screening visit and must be at a stable dose for ≥ 8 weeks before the screening visit and remain stable until randomization and throughout study participation. Details for specific medications are as follows:

Antimalarials: chloroquine, HCQ, or quinacrine; monotherapy is permitted. Also see exclusion criteria below regarding HCQ dose limitation and exclusionary screening HCQ levels. Patients on HCQ must have an ophthalmology assessment within 6 months prior to randomization, confirming no findings of HCQ induced retinal toxicity.

Immunosuppressants (combinations of these are NOT permitted):

i. Azathioprine (maximum 200 mg per day).

ii. 6-mercaptopurine (6-MP, maximum 1.5 mg/kg per day).

iii. MTX: Subjects are permitted to continue MTX provided that the dose is stable for ≥ 12 weeks prior to randomization and remains stable throughout the study. Decrease in dose or discontinuation is permitted for AEs or intolerance.

iv. Leflunomide (20 mg per day).

v. Mycophenolate mofetil/mycophenolic acid (MMF). Note: Subjects who are receiving MMF may participate in the study only if administered as a maintenance therapy and up to a maximum of 2 g/day (or equivalent); in subjects of African ancestry, 3 g/day (or equivalent) is acceptable.

vi. Dapsone (maximum 100 mg per day).

c) **Not applicable per Revised Protocol 03 -** CS (prednisone or equivalent) background therapy is permitted but not required. For subjects taking CS, the dose must be stable for ≥ 2 weeks before the screening visit, cannot exceed 40 mg/day at screening, and must remain stable until randomization. Further specifications are as follows:

- Topical and inhaled CS use is permitted but must follow a stable regimen throughout the study and cannot be used on an as-needed basis. Discontinuation of topical steroids should be allowed if lesions/rash resolve completely. Inhaled CS for nonlupus conditions will not count against the maximum CS dose.
    - Patients are ineligible if they received intramuscular (IM), intra-articular (IA), intrabursal, IV, and modified-release CS use within 4 weeks prior to randomization.

d) SOC that is allowed in this study must include at least one of the following:

Antimalarials, Immunosuppressants, or oral CS

Antimalarials and/or Immunosuppressants must have been taken for ≥ 12 weeks before the screening visit and must be at a stable dose for ≥ 8 weeks before the screening visit and remain stable until randomization and throughout study participation. Details for Antimalarials and/or Immunosuppressants are as follows:

- Antimalarials: chloroquine, HCQ, or quinacrine; monotherapy is permitted. Also see exclusion criteria below regarding HCQ dose limitation and exclusionary screening HCQ levels. Subjects on HCQ must have an ophthalmology assessment within

6 months prior to randomization, confirming no findings of HCQ induced retinal toxicity.

- Immunosuppressants (combinations of these are NOT permitted):
  - Azathioprine (maximum 200 mg per day).
  - 6-mercaptopurine (6-MP, maximum 1.5 mg/kg per day).
  - MTX: Subjects are permitted to continue MTX provided that the dose is stable for ≥ 12 weeks prior to randomization and remains stable throughout the study. Decrease in dose or discontinuation is permitted for AEs or intolerance.
  - Leflunomide (20 mg per day).
  - Mycophenolate mofetil/mycophenolic acid (MMF). Note: Subjects who are receiving MMF may participate in the study only if administered as a maintenance therapy and up to a maximum of 2 g/day (or equivalent); in subjects of African ancestry, 3 g/day (or equivalent) is acceptable.
  - Dapsone (maximum 100 mg per day).

e) CS (prednisone or equivalent), as follows:

- For subjects taking oral CS as monotherapy, CS must have been taken for ≥ 6 weeks prior to the screening visit at a dose ≥ 7.5 mg/day and ≤ 40 mg/day prednisone (or prednisone equivalent), must be at a stable dose for ≥ 2 weeks prior to the screening visit and remain stable until randomization.
- For subjects taking oral CS not as monotherapy, the CS dose must be stable for ≥ 2 weeks before the screening visit, cannot exceed 40 mg/day at screening, and must remain stable until randomization.
- Topical and inhaled CS use is permitted but must follow a stable regimen throughout the study and cannot be used on an as-needed basis. Discontinuation of topical steroids should be allowed if lesions/rash resolve completely. Inhaled CS for nonlupus conditions will not count against the maximum CS dose.
- Subjects are ineligible if they received IM, IA, intrabursal, IV, and modified-release CS use within 4 weeks prior to randomization.

5) Other Inclusion Criteria: SLE Sub-protocol

a) Subject re-enrollment (rescreening): This study permits the re-enrollment of a subject who has discontinued the study as a pretreatment (screening) failure (ie, subject has not been randomized/has not been treated). If re-enrolled, the subject must be re-consented.

SLE 5.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in the SLE sub-protocol:

1) General Medical Conditions and History: SLE Sub-protocol

a) Any major illness/condition or evidence of an unstable clinical condition (eg, renal, hepatic, hematologic, gastrointestinal, endocrine, pulmonary, immunologic, psychiatric) or local active infection/infectious illness that, in the investigator's judgment, will substantially increase the risk to the subject if he or she participates in the study.

b) Any major surgery within the last 30 days before the first dose of study treatment, or any surgery planned during the course of the study.

c) Cancer or history of cancer or lymphoproliferative disease (other than adequately treated cutaneous basal cell or squamous cell carcinoma with no evidence of recurrence within the previous 5 years), including pre-lymphoma (pseudolymphoma of the orbit and small intestine, lymphomatoid granulomatosis, angioimmunoblastic lymphadenopathy, and lymphoid interstitial pneumonitis).

d) Class III or IV congestive heart failure as defined by the New York Heart Association (NYHA) or any recent onset of heart failure resulting in NYHA Class III/IV symptoms

e) Acute coronary syndrome (eg, myocardial infarction, unstable angina pectoris) and/or any history of significant cerebrovascular disease within 24 weeks before the screening visit.

f) Current or recent (within 3 months before randomization) gastrointestinal disease, including gastrointestinal surgery, that could impact the absorption of study treatment.

g) **Not Applicable per Revised Protocol 03 -** Subjects with non-SLE concomitant illness that, in the opinion of the investigator, is likely to require additional systemic glucocorticosteroid therapy during the study (eg, asthma).

h) Significant blood loss (> 500 mL) or blood transfusion within 4 weeks before randomization.

i) Inability to tolerate oral medication.

j) Inability to tolerate venipuncture and/or inadequate venous access.

k) Recent (within 6 months before randomization) drug or alcohol abuse as defined by the Diagnostic Criteria for Drug and Alcohol Abuse in the Diagnostic and Statistical Manual of Mental Disorders 5 (DSM 5).

l) Any other sound medical, psychiatric, and/or social reason as determined by the investigator.

m) Subjects with a diagnosis of antiphospholipid antibody syndrome.

n) Any prior history of atrial fibrillation or flutter.

o) Subjects with non-SLE concomitant illness that, in the opinion of the investigator, is likely to require additional systemic CS therapy during the study (eg, asthma).

2) Findings Related to Possible Infection: SLE Sub-protocol

a) **Not Applicable per Revised Protocol 03 -** Any of the following TB criteria:

- History of active TB prior to screening visit, regardless of completion of adequate treatment.

- Signs or symptoms of active TB (eg, fever, cough, night sweats, and weight loss) during screening as judged by the investigator.
  - Any imaging of the chest (eg, chest x-ray, chest computed tomography [CT] scan) obtained during the screening period, or anytime within 6 months prior to screening, with documentation showing evidence of current active or old pulmonary TB
- LTBI defined as positive IFN gamma-release assay (IGRA), by QuantiFERON-TB Gold testing at screening, in the absence of clinical manifestations Note: Subject may be eligible if (i) there are no current signs or symptoms of active TB and (ii) the subject has received adequate documented treatment for LTBI within 5 years of screening.

  Note: An IGRA test that is indeterminate with no signs or symptoms of active TB must be retested for confirmation. If the second test is again indeterminate the subject will be excluded from the study. If the retest is positive, the subject should be treated as having LTBI. If the retest is negative, subject may be eligible provided no other exclusion criteria for TB are met.

b) Hepatitis C virus (HCV), hepatitis B virus (HBV), or human immunodeficiency virus (HIV) infection as demonstrated by a positive blood screen for HCV antibody confirmed by positive reflex HCV RNA test, hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HbcAb), or HIV-1 and -2 antibody. Subjects who have been vaccinated for hepatitis B (hepatitis B surface antibody [HbsAb]-positive) are not excluded.

   Note: Subjects who are newly found to be HIV-positive should be directed to appropriate follow-up care.

c) History of congenital or acquired immunodeficiency.

d) Known active infection, or any major episode of infection requiring hospitalization or treatment with parenteral (IM or IV) antimicrobial agents (eg, antibiotics, antiviral, antifungal, or antiparasitic agents) within 30 days of randomization, or completion of oral antimicrobial agents within 2 weeks of randomization.

e) Previous history of recurrent herpes zoster (more than 1 episode), disseminated herpes simplex, or influenza infection within 12 weeks before randomization or a history of disseminated/complicated herpes zoster infection (multidermatomal involvement, ophthalmic zoster, central nervous system involvement, or postherpetic neuralgia).

f) Chronic infection within 4 weeks of randomization (eg, pneumocystis, cytomegalovirus [CMV], invasive bacterial or fungal infections, or atypical mycobacteria).

g) Any of the following TB criteria:
   - History of active TB prior to screening visit, regardless of completion of adequate treatment.
   - Signs or symptoms of active TB (eg, fever, cough, night sweats, and weight loss) during screening as judged by the investigator.
     - Any imaging of the chest (eg, chest x-ray, chest CT scan) obtained during the screening period, or anytime within 6 months prior to screening, with documentation showing evidence of current active or old pulmonary TB.
   - LTBI defined as positive IGRA, by QuantiFERON-TB Gold testing at screening, in the absence of clinical manifestations. Note: Subject may be eligible if (i) there are no

current signs or symptoms of active TB and (ii) the subject has received adequate documented treatment for LTBI within 5 years of screening; this treatment must have been completed as defined by local guidance and documented in the subject study file. Incomplete or ongoing treatment is unacceptable.

Note: An IGRA test that is indeterminate with no signs or symptoms of active TB must be retested for confirmation. If the second test is again indeterminate, the subject will be excluded from the study, unless there is documentation of a local negative TB Spot test result. If the retest is positive, the subject should be treated as having LTBI. If the retest is negative, the subject may be eligible provided no other exclusion criteria for TB are met.

h) Subjects hospitalized with PCR-proven or suspected COVID-19 infection (unless for quarantine/observation) within the 3 months prior to randomization, as well as any subjects with any sequelae of prior COVID-19 infection at screening, regardless of time since infection.

3) Allergies and Adverse Drug Reaction: SLE Sub-protocol

a) History of allergy to BTK inhibitors or related compounds

b) History of any serious condition induced by drug allergy (such as anaphylaxis or hepatotoxicity)

4) Target Disease Exclusions/Exceptions: SLE Sub-protocol

a) **Not Applicable per Revised Protocol 03 -** Subjects with other immune-mediated diseases (eg, scleroderma, mixed connective tissue disease, multiple sclerosis, psoriasis, inflammatory bowel disease, etc) are excluded. Subjects with Type 1 autoimmune diabetes mellitus, thyroid autoimmune disease, antiphospholipid syndrome, or secondary Sjögren's syndrome are not excluded.

b) **Not Applicable per Revised Protocol 03 -** Subjects with drug-induced lupus, or active or unstable lupus neuropsychiatric manifestations, including but not limited to any condition defined by British Isles Lupus Assessment Group (BILAG) A criteria, are excluded, with the exception of subjects with mononeuritis multiplex and polyneuropathy, which are allowed with approval by the Medical Monitor or Lupus Central review Services [redacted]

c) **Not Applicable per Revised Protocol 03** - Subjects with active, severe lupus nephritis (World Health Organization Class III or IV) that requires or may require treatment with cytotoxic agents or high-dose CS are excluded. Subjects with prior controlled renal disease with serum creatinine $\geq 2\times$ upper limit of normal (ULN) and either residual proteinuria ≤ 3 g/day or a urine protein/creatinine ratio (UPCR) of ≤ 3 mg/mg or 339 mg/mmol are allowed. Stability of renal disease must be documented with at least 2 measurements of proteinuria or UPCR over the past 6 months or with 2 tests during the screening period at least 1 week apart and must be approved by the Medical Monitor.

d) Active fibromyalgia with pain symptoms or signs that would interfere with joint assessment or requiring adjustment in medication within the 3 months before screening to control symptoms. Subjects with fibromyalgia that is well controlled on stable treatment may otherwise be included.

e) Subjects with other immune-mediated diseases (eg, scleroderma, mixed connective tissue disease, multiple sclerosis, psoriasis, inflammatory bowel disease, etc) are excluded.

Subjects with Type 1 autoimmune diabetes mellitus, thyroid autoimmune disease, or secondary Sjögren's syndrome are not excluded.

f) Subjects with drug-induced lupus, or active or unstable lupus activity in the neuropsychiatric body system, including but not limited to those resulting in a British Isles Assessment Group (BILAG-2004) A grade are excluded, with the exception of subjects with mononeuritis multiplex and polyneuropathy, which are allowed with approval by the Medical Monitor or [redacted] Lupus Central Review Services.

g) Subjects with active, severe lupus nephritis (World Health Organization Class III or IV) that requires or may require treatment with cytotoxic agents or high-dose CS are excluded. Subjects with prior controlled renal disease with serum creatinine ≤ 2× ULN and either residual proteinuria ≤ 3 g/day or a UPCR of ≤ 3 mg/mg or 339 mg/mmol are allowed. Stability of renal disease must be documented with at least 2 measurements of proteinuria or UPCR over the past 6 months or with 2 tests during the screening period at least 1 week apart and must be approved by the Medical Monitor**.**

5) Prior/Concomitant Therapy: SLE Sub-protocol

a) Inability to comply with restrictions and prohibited treatments as listed in Section SLE 6.7 Concomitant Therapy; inability to comply with discontinuation requirements (Section SLE 7.1).

b) **Not applicable per Revised Protocol 03 -** Prior exposure to BTK inhibitors such as ibrutinib, acalabrutinib, or experimental drugs (eg, tirabrutinib, vecabrutinib, zanibrutinib, ARQ-531, GDC-0853, or others).

c) Other investigational agents must be discontinued at least 12 weeks or 5 half-lives before the screening visit, whichever is longer.

d) Exposure to JAK inhibitors such as tofacitinib, baricitinib, filgotinib, or upadacitinib within 8 weeks prior to randomization or during the study.

e) Required discontinuation periods for immunomodulatory drugs (eg, cyclosporine, tacrolimus, etc) or biologic drugs (including those specifically listed below) are provided in SLE Table 6. If a drug is not specifically listed, consult the [redacted] Medical Monitor for guidance. Usual discontinuation periods are 4 weeks or 5 half-lives, whichever is longer.

f) Belimumab therapy within 6 months before randomization or during the study

g) Subjects who have taken rituximab within 12 months prior to randomization; for subjects who received rituximab prior to this 12-month period, the B cell count should be within normal range. Rituximab is prohibited during the study.

h) Abatacept therapy within 6 months prior to randomization or during the study.

i) Therapy with other biologics such as tocilizumab and anakinra within 8 weeks prior to randomization or during the study.

j) Cyclosporine or tacrolimus therapy within 8 weeks prior to randomization or during the study.

k) Therapy with sulfasalazine, or similar drugs within 8 weeks prior to randomization or during the study.

l) IV immunoglobulin (IVIG) within 8 weeks prior to randomization or during the study.

m) Diquafosol or rebamipide therapy within 4 weeks before randomization or during the study.

n) For oral CS restrictions, see Section SLE 5.1.

o) IM, IV, IA, intrabursal, or modified-release CS treatment within 4 weeks prior to randomization or during the study.

p) **Not Applicable per Revised Protocol 01 -** Treatment with disease-modifying antirheumatic drugs (DMARD) treatments or immunomodulators other than MTX < 8 weeks prior to randomization. The MTX dose must be stable for ≥ 12 weeks; new initiation or dose changes during treatment are not permitted.

q) **Not Applicable per Revised Protocol 03 -** Antimalarial treatments (chloroquine and quinacrine) are permitted but must be stable; new initiation or change in dose during treatment is not permitted. **HCQ whole blood concentration > 2 µg/mL (at screening only) is exclusionary**. HCQ dose > 400 mg/day, new initiation, or dose increases during treatment are not permitted.

r) Anti-TNF therapy such as adalimumab, certolizumab, etanercept, golimumab, infliximab, or TNF biosimilars within 3 months prior to randomization or during the study.

s) **Not applicable per Revised Protocol 03** - Administration of a live vaccine within 90 days or an inactivated vaccine within 30 days before randomization; furthermore, live or inactivated vaccines should not be used during treatment or within the 14 days following last dose.

t) Treatment with anticoagulant or antiplatelet therapies, including aspirin for cardioprotection, within 2 weeks prior to randomization or during the study.

u) Prior exposure to BTK inhibitors such as ibrutinib, acalabrutinib, or experimental drugs (eg, tirabrutinib, vecabrutinib, zanubrutinib, ARQ-531, fenebrutinib [GDC-0853], or others).

v) **Not applicable per Revised Protocol 03** - Treatment with DMARDs (excluding HCQ) or immunomodulators within 4 weeks before randomization; MTX treatment within 12 weeks before randomization or during the study. **HCQ whole blood concentration >2 µg/mL (at screening only) is exclusionary**. HCQ dose > 400 mg/day, new initiation or dose increases during treatment are not permitted.

w) Antimalarial treatments (chloroquine, HCQ, and quinacrine) are permitted but must be stable; new initiation or change in dose during treatment is not permitted. **HCQ whole blood concentration > 2 µg/mL (at screening only) is exclusionary**. HCQ dose > 400 mg/day, new initiation, or dose increases during treatment are not permitted.

x) Administration of all live vaccines is prohibited within 90 days before randomization. Administration of inactivated vaccines and nonlive vaccines, including those for influenza and SARS-CoV-2, is prohibited within 30 days before randomization. See SLE Table 6 for corresponding on-treatment and posttreatment restrictions.

y) Treatment with DMARDs (excluding HCQ) or immunomodulators beyond required washout period before randomization; MTX treatment within 12 weeks before randomization or during the study. **HCQ whole blood concentration > 2 µg/mL (at screening only) is exclusionary**. HCQ dose > 400 mg/day, new initiation, or dose increases during treatment are not permitted.

6) Physical and Laboratory Test Findings: SLE Sub-protocol

a) Clinically significant abnormalities on chest x-ray or ECG

b) Clinically significant abnormalities in laboratory tests including the following:
   i. Serum alanine aminotransferase (ALT) > 2× ULN
   ii. Serum aspartate aminotransferase (AST) > 2× ULN
   iii. Serum total bilirubin > 1.5× ULN (does not apply to subjects with Gilbert's syndrome)
   iv. Hemoglobin < 8 g/dL (< 80 g/L) or, if due to hemolytic anemia related to SLE, < 7 g/dL (< 70 g/L)
   v. Proteinuria > 3.0 g/day (> 3,000 mg/day) or equivalent level of proteinuria as assessed by UPCR (3 mg/mg or 339 mg/mmol)
   vi. Estimated glomerular filtration rate (eGFR) < 50 mL/min/1.73 m^2 as calculated by the central laboratory
   vii. Serum creatinine > 2.0 mg/dL (> 177 µmol/L)
   viii. Absolute WBC count < 2.5× 10^3/µL (< 2.5× 10^9/L)
   ix. Neutrophil count < 1000/µL (< 1.0× 10^9/L)
   x. Platelet count < 75× 10^3/µL (< 75× 10^9/L), if considered part of SLE disease activity without increased risk of bleeding

c) Any other significant laboratory or procedure abnormalities that, in the opinion of the investigator, might pose unacceptable risk to the subject during the study

d) Blood pressure (BP) > Grade 1 hypertension (> 159 mmHg systolic and > 99 mmHg diastolic) according to the 2018 ESC/ESH Guidelines for the management of arterial hypertension.

e) The following exclusionary ECG observations:
   i. QT interval with Fridericia's correction (QTcF): > 480 msec
   ii. QRS: > 120 msec
   iii. Complete heart block
   iv. Left bundle branch block
   v. Mobitz II second-degree atrioventricular block
   vi. Atrial fibrillation or flutter

7) Other Exclusion Criteria: SLE Sub-protocol

a) Prisoners or subjects who are involuntarily incarcerated. (Note: under certain specific circumstances and subject to local law a person who has been imprisoned may be included or permitted to continue as a subject. Strict conditions apply and BMS approval is required.)

b) Subjects who are employed by the Sponsor, clinical research organizations, or study site

c) Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness

d) Inability to comply with the study protocol

e) Inability to comply with restrictions as listed in Section SLE 5.3

SLE 5.3 Lifestyle Restrictions

Study restrictions for contraception use by WOCBP and male subjects who are partners of WOCBP (APPENDIX 4) are required for this study.

SLE 5.3.1 Meals and Dietary Restrictions

With the exception of the 8-hour fasting requirement prior to blood sample collection for lipid panel and fasting glucose blood testing, no meal or dietary restrictions are required for this study. However, subjects are advised to consume in moderation (avoiding more than a single serving a day) cruciferous vegetables, such as cabbage, brussels sprouts, watercress, etc, as well as grapefruit and Seville oranges. Quinine (tonic water), St. John's wort and herbal medications are not allowed.

SLE 5.3.2 Caffeine, Alcohol, Tobacco, and Cannabinoids

With the exception of cannabinoid products, which are not allowed, and prohibited alcohol abuse as defined by the Diagnostic Criteria for Drug and Alcohol Abuse in the DSM 5 within six months prior to randomization, and prohibited alcohol use in subjects receiving MTX therapy (see Section SLE 5.2), there are no restrictions on caffeine, alcohol, or tobacco use for this study. However, subjects who use tobacco or alcohol should be counseled for potential contraindications with nonstudy treatments as appropriate, and continued study participation should be based on investigator judgment. Subjects are advised to abstain from excessive consumption of caffeine-containing drinks.

SLE 5.3.3 Activity

With the exception of the restrictions surrounding the use of contraceptives during sexual activity mentioned above and included in the SoA (Section SLE 1.3), no activity restrictions are required for this study.

SLE 5.3.4 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but who are not subsequently randomized or entered in the study or included in the analysis population. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects, 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. Additional screening data from screen failure subjects, such as clinical data for disease assessment, laboratory tests, and other clinically relevant data, may be required.

SLE 5.3.5 Rescreening and Retesting During Screening Period

This SLE sub-protocol permits the rescreening of a subject who has been previously screen failed. If rescreened, the subject must be re-consented and will be assigned a new identification number, and a full screening visit must be performed again. A subject can only be rescreened 1 time (ie, if the subject fails 1 rescreening attempt, no additional rescreening is allowed).

Laboratory parameters and/or other assessments that are included in SLE Table 1 (Screening Procedural Outline for SLE sub-protocol) that initially do not meet eligibility requirements within the screening period may be repeated once in an effort to find all possible well-qualified subjects. Consultation with the Medical Monitor or [redacted] Lupus Central Review Services may be needed to identify whether repeat testing of any particular parameter is clinically relevant.

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

SLE 6 TREATMENT

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

Study treatment includes both Investigational (Medicinal) Product (IP/IMP) and Noninvestigational (Medicinal) Product (non-IP/Non-IMP) and is shown in SLE Table 4.

An IP, also known as IMP in some regions, is defined as a pharmaceutical form of an active substance or PBO 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 SOC for a given diagnosis, may be considered as non-IPs.

SLE Table 4 Study Treatments for IM014029

Product Description and Dosage Form[a]	Potency	IP/ Non-IP	Blinded or Open-Label	Packaging/ Appearance	Storage Conditions (Per Label)
Branebrutinib oral capsule	3 mg dose × 3 capsules (9 mg total dose)	IP	Blinded	HDPE bottles (33 capsules/bottle) with child-resistant cap and heat-induction seal (tamper-evidence and moisture barrier); size #0 hard gelatin capsules	Store refrigerated at 2°C to 8°C (36°F to 46°F) in original packaging; protected from moisture
PBO matching Branebrutinib oral capsule	NA	IP	Blinded	HDPE bottles (33 capsules/bottle) with child-resistant cap and heat-induction seal (tamper-evidence and moisture barrier); size #0 hard gelatin capsules	Store refrigerated at 2°C to 8°C (36°F to 46°F) in original packaging; protected from moisture

HDPE = high-density polyethylene; IP = investigational product; NA = not applicable; PBO = placebo

[a] Dosages of 0.5 mg are also available but are not planned for use in this protocol.

SLE 6.1 Treatments Administered

The investigator must ensure that the IP will be used only in accordance with the protocol. The selection and timing of dose for each subject is shown in SLE Table 5. Study treatment will be supplied in bottles (branebrutinib and PBO). If a subject forgets a dose, but remembers within 12 hours of the expected dose, the dose should be taken. Any dose > 12 hours should be missed, and the next expected dose should be taken at the usual time. No dose reductions or modifications are allowed.

SLE Table 5 Selection and Timing of Dose

Study Treatment	Unit Dose Strength	Dosage Formulation Frequency of Administration	Route of Administration
Branebrutinib 9 mg	3 mg	3 active capsules; QD	Oral
PBO	0 mg	3 PBO capsules; QD	Oral

PBO = placebo; QD = once daily

Note: At all study visits, the study treatment should not be taken at home but should be taken to the site by the subject; at the site, the study treatment should be taken only when instructed by the site study staff according to the schedule listed below. These requirements also apply to concomitant medications at Day 1 and Week 4 only; at these visits, concomitant medications will be administered together with the study treatment at the site.

When multiple assessments are conducted at a single visit, the following is the order in which they should be performed:

1. Patient-reported Outcomes (eg, Subject Global Assessment [SGA], EQ-5 D-5 L, etc)
2. Safety assessments (eg, vitals, AEs)
3. Investigator-administered Assessments (eg, Physician Global Assessment [PGA], joint count, etc)
4. Laboratory tests (eg, safety laboratory tests, PK assessments, biomarker assessments)
5. Treatment dosing

Doses of branebrutinib at 9 mg (3x3 mg capsules) or matching placebo are to be administered orally q24h (one time/day) with water and may be taken with or without food. The drug should be taken every morning at approximately the same time.

On Day 1 and at Weeks 4, 8, 16, and 24, study drug will be administered in the morning at the study site after blood samples have been collected and questionnaires have been completed. In addition, on Day 1 and at Week 4, branebrutinib will be administered together with concomitant medications to allow predose sampling for concomitant medication. Branebrutinib and concomitant medications are to be taken together with water.

SLE 6.2 Method of Treatment Assignment

Subjects will be centrally randomized according to a computer-generated block randomization scheme using IRT to the SLE sub-protocol depending on disease type determined at screening. Subjects in this sub-protocol will be randomized in a 3:1 ratio to receive double-blind branebrutinib 9 mg or PBO QD from Week 0 to Week 24.

At the time of the screening visit, after written informed consent is obtained and before any study-related procedures are performed, the investigative site will access the enrollment option of the IRT system for assignment of a subject number. This number is assigned sequentially by the system and will be unique across all sites. If a potential subject is rescreened, a new identification number will be used.

Randomized schedules will be generated by the IRT vendor.

Randomization will be stratified by immunosuppressant use (yes/no).

Before the study is initiated, each investigator will receive log-in information and directions on how to access the IRT. Study treatment will be dispensed at the study visits as listed in the SoA (Section SLE 1.3).

SLE 6.3 Blinding

Blinded treatment assignments will be managed using IRT. All capsules (branebrutinib 3 mg and PBO) are identical in appearance. Capsules will be supplied in tamper-evident high-density polyethylene (HDPE) bottles with each daily dose made up of either active or PBO capsules (as presented in SLE Table 4). Investigative site staff, Sponsor and designee personnel, and subjects and their families will remain blinded to treatment assignments.

[redacted]

Blinding of treatment assignment is critical to the integrity of this clinical study. However, in the event of a medical emergency or pregnancy in an individual subject in which knowledge of the IP is critical to the subject's management, the blind for that subject may be broken by the investigator. The subject's safety takes priority over any other considerations in determining if a treatment assignment should be unblinded

Before breaking the blind of an individual subject's treatment, the investigator should determine that the unblinded information is necessary, ie, that it will alter the subject's immediate management. In many cases, particularly when the emergency is clearly not related to the IP, the problem may be properly managed by assuming that the subject is receiving active product. It is highly desirable that the decision to unblind treatment assignment be discussed with the Medical Monitor, but the investigator always has ultimate authority for the decision to unblind. The Principal Investigator (PI) should only call in for emergency unblinding AFTER the decision to discontinue the subject has been made.

In case of an emergency, the investigator has unrestricted access to randomization information via IRT and is capable of breaking the blind through the IRT system without prior approval from the Sponsor. After the unblinding, the investigator shall notify the Medical Monitor and/or study director. For information on how to unblind in an emergency, consult the IRT manual. Subject and unblinded treatment information and the reason for the blind being broken must be recorded on the appropriate study status page of the electronic case report form (eCRF). After unblinding via IRT, the investigator shall notify the Medical Monitor.

Any request to unblind a subject for nonemergency purposes should be discussed with the Medical Monitor.

In cases of accidental unblinding, contact the Medical Monitor and ensure every attempt is made to preserve the blind.

Designated staff of BMS Company may be unblinded (obtain the randomization codes) prior to database lock to facilitate the bioanalytical analysis of PK samples and immunogenicity. A bioanalytical scientist in the Bioanalytical Sciences department of BMS Company (or a designee in the external central bioanalytical laboratory) will be unblinded to (may obtain) the randomized treatment assignments in order to minimize unnecessary bioanalytical analysis of samples.

SLE 6.4 Dosage Modification

There is no provision for dose modification of study treatment. If a subject interrupts or temporarily discontinues treatment due to an AE, study treatment can be restarted in consultation with the Medical Monitor.

SLE 6.5 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 subjects. 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 BMS or designee should be contacted immediately.

Branebrutinib and PBO should be stored per labeled conditions in tamper-evident HDPE bottles (see SLE Table 4).

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).

Further guidance and information for final disposition of unused study treatment are provided in APPENDIX 2.

SLE 6.5.1 Retained Samples for Bioavailability/Bioequivalence

At the time of receipt of the IP by the investigator or designee, BMS will specify the appropriate number of containers or units to select for retention, the conditions of sample storage, required duration of sample retention, and provisions for returning or disposing of the IP. When samples are selected, containers or units should be placed in packaging with a tamper-evident seal provided by BMS. Package labeling should clearly identify the contents as bioavailability/bioequivalence (BA/BE) samples and state that the IP should be stored in the restricted area with limited access.

SLE 6.6 Treatment Compliance

Study treatment compliance will be periodically monitored using standard drug accountability procedures (comparing the number of capsules returned to number dispensed, considering the expected regimen and any reported missed doses). Drug accountability will be reviewed by the site study staff at each visit to confirm treatment compliance. Site staff will discuss discrepancies with the subject at each on-treatment study visit and remind the subject of the importance of compliance with the assigned regimen. See Section SLE 8.3 for information related to treatment overdose.

SLE 6.7 Concomitant Therapy

SLE 6.7.1 Prohibited and/or Restricted Treatments

Table 1 in the IM014029 Master Protocol lists exclusions and restrictions for all concomitant medications, regardless of indication. SLE Table 6 presents prohibited and/or restricted medications taken by subjects with SLE prior to or during study treatment administration with branebrutinib. All prior concomitant medications taken for SLE since diagnosis must be recorded on the eCRF. All prior and/or concomitant medications taken for any indication within 4 weeks prior to study drug administration must be recorded on the eCRF. The prior use of medications after a sufficient washout period prior to study randomization is allowed for some medications, as indicated in the table, and must be recorded in the eCRF. Details of prohibited (excluded) and/or restricted medications are provided in Section SLE 5.2.

SLE Table 6 Prohibited and Restricted Medications

Type of Medication	Examples of Medications	Restrictions	Required Washout Period Prior to and Postrandomization
BTK inhibitors	Marketed drugs, eg, ibrutinib, acalabrutinib Experimental drugs, eg, tirabrutinib, vecabrutinib, zanubrutinib, ARQ-531, GDC-0853, and any others	Prohibited lifetime use	Not applicable
JAK inhibitors	Tofacitinib, baricitinib, filgotinib, and upadacitinib	Prohibited during the study	8 weeks
Oral CS	Prednisone or equivalent	For subjects taking oral CS as monotherapy, CS must have been taken for ≥ 6 weeks prior to	4 weeks if not continuing as background SOC

SLE Table 6 Prohibited and Restricted Medications

Type of Medication	Examples of Medications	Restrictions	Required Washout Period Prior to and Postrandomization
		the screening visit at a dose ≥ 7.5 mg/day and ≤ 40 mg/day prednisone (or prednisone equivalent), must be at a stable dose for ≥ 2 weeks prior to the screening visit and remain stable until randomization. For subjects taking oral CS not as monotherapy, the CS dose must be stable for ≥ 2 weeks before the screening visit, cannot exceed 40 mg/day at screening, and must remain stable until randomization.	
Other CS	IM, IA, intrabursal, IV, and oral modified-release CS	Prohibited during the study	4 weeks
	Topical and inhaled CS	Topical and inhaled CS use is permitted but must follow a stable regimen throughout the study and cannot be used on an as-needed basis. Discontinuation of topical steroids should be allowed if lesions/rash resolve completely. Inhaled CS for nonlupus conditions will not count against the maximum CS dose..	Not applicable
Antimalarial drugs	Chloroquine and quinacrine	Must have been taken for ≥ 12 weeks before the screening visit and must be at a stable dose for ≥ 8 weeks before the screening visit and remain stable until randomization and throughout study participation. New initiation or change in dose during treatment is not permitted	12 weeks if not continuing as background SOC
	Hydroxychloroquine (HCQ)	Doses of > 400 mg/day are not permitted New initiation or dose increase during treatment is not permitted. Whole blood levels at screening must be ≤ 2 µg/mL	12 weeks if not continuing as background SOC
Anticoagulant or Antiplatelet therapies	Anticoagulant or antiplatelet therapies, including aspirin for cardioprotection	Treatment with anticoagulant or antiplatelet therapies, including aspirin for cardioprotection, within 2 weeks prior to randomization or during the study	2 weeks

SLE Table 6 Prohibited and Restricted Medications

Type of Medication	Examples of Medications	Restrictions	Required Washout Period Prior to and Postrandomization
Anti-TNF therapy	Adalimumab, certolizumab, etanercept, golimumab, infliximab, and TNF biosimilars	Prohibited during the study	3 months
Biologics	Rituximab	Prohibited during the study	12 months
	Belimumab	Prohibited during the study	6 months
	Abatacept	Prohibited during the study	6 months
	Other Biologics, including tocilizumab, anakinra		8 weeks
	IVIG	Prohibited during the study	8 weeks
Immunosuppressants (allowed) Note: combinations of immunosuppressants are **not** allowed	Azathioprine, 6-MP, MTX, leflunomide, MMF	Must have been taken for ≥ 12 weeks before the screening visit and must be at a stable dose for ≥ 8 weeks before the screening visit and remain stable until randomization and throughout study participation. New initiation or dose changes during treatment are not permitted.	12 weeks if not continuing as background SOC, except leflunomide 36 weeks before screening
Immunosuppressants (prohibited)	Cyclosporine, tacrolimus, thalidomide and similar (oral); topical calcineurin inhibitors (tacrolimus, pimecrolimus)	Prohibited during the study	8 weeks
	Cyclophosphamide	Prohibited during the study	24 weeks
Other DMARDs (prohibited)	Sulfasalazine and similar	Prohibited during the study	8 weeks
Other DMARDs (allowed)	Dapsone	Must have been taken for ≥ 12 weeks before the screening visit and must be at a stable dose for ≥ 8 weeks before the screening visit and remain stable until randomization and throughout study participation. New initiation or dose changes during treatment are not permitted.	8 weeks, if not continued as background SOC
NSAIDs	Ibuprofen, etc	Only 1 oral NSAID is allowed concurrently. Can be combined with 1 or more topical NSAID but must be on a stable regimen	Not allowed on days of study visits until after study assessments are performed
Nonnarcotic analgesics	Acetaminophen	Brief course for up to 7 days allowed	Not applicable
Narcotic analgesics	Oxycodone and, hydrocodone	Prohibited during the study	Not applicable
Immunization against agents other than	All live vaccines	Prohibited during the study	90 days before and 28 days after EOT

SLE Table 6 Prohibited and Restricted Medications

Type of Medication	Examples of Medications	Restrictions	Required Washout Period Prior to and Postrandomization
influenza or SARS-CoV-2	Nonlive vaccines unassociated with influenza or SARS-CoV-2		30 days before and 14 days after EOT
Immunization for influenza or SARS-CoV-2	All live vaccines Nonlive vaccines for influenza or SARS-CoV-2	Prohibited during the study Not allowed during the screening period within 30 days prior to randomization During the Treatment and Follow-up Periods, vaccine doses must be given at least 5 days before a study visit. Doses may be given on a study visit day once all protocol-specified procedures are complete.	90 days before and 28 days after EOT
Other treatments	Diquafosol, rebamipide	Prohibited during the study	4 weeks

BTK = Bruton's tyrosine kinase; CS = corticosteroid; DMARD = disease-modifying antirheumatic drug; EOT = end of treatment; IA = intra-articular; IM = intramuscular; IV = intravenous; IVIG = intravenous immunoglobulin; JAK = Janus kinase; MTX = methotrexate; NSAID = nonsteroidal anti-inflammatory drug; SLE = systemic lupus erythematosus; SOC = standard of care; TNF = tumor necrosis factor

Chronic medications, such as statins and antidepressants, that could be sensitive to the modulation of CYP2C8/P-gp, (and other potentially relevant drug metabolizing enzymes that may lead to drug-drug interaction with branebrutinib) and with sufficient representation in the study population (eg, > 10% per sub-protocol) are allowed in the study for accompanying conditions. For optional measurement of the concentrations of these medications, PK samples will be collected predose and 2 hours postdose at Week 0 (Day 1) and Week 4 (Day 29) for potential post-hoc analysis. These analyses will be based on the totality of information about the frequency of use of the drugs, clinical manifestations of possible interactions, availability of validated bioanalytical assays and therapeutic index. When performed, the results of these analyses, will be reported separately, along with the reasons for the selection. Concentrations of HCQ will also be measured and reported.

The dosing of allowed chronic medications must be maintained at the same level throughout the study unless safety concerns arise. Any changes of dose will be recorded, and additional PK sampling may be performed as a result.

Tobacco use will be allowed in the study. Branebrutinib concentrations will be compared between smoking and nonsmoking subgroups to evaluate the effect of smoking on glutathione-s-transferase mediated metabolism of branebrutinib.

No new concomitant medications (prescription, over-the-counter, or herbal) are to be administered during the study unless they are prescribed for treatment of specific clinical events. Any concomitant therapies must be recorded on the eCRF.

For subjects on immunosuppressant background therapy, the investigator must refer to the label for any potential interaction with concomitant medications:

SLE 6.7.2 Oral Corticosteroid Taper or Rescue for SLE Flare

Oral CS taper is detailed in Section SLE 8.1.1.10.

A maximum of 1 burst of oral CS rescue therapy is permitted in response to increased SLE disease activity up to Week 12 during the treatment period at the investigator's discretion.

- Rescue therapy must not exceed 40 mg/day prednisone or equivalent and must return within 10 days to the previous CS dose used before initiation of rescue therapy.
- Rescue therapy other than prednisone or equivalent is not permitted.

If a subject requires CS rescue therapy after the first 12 weeks, the subject will be considered a nonresponder for analysis purposes but will continue to receive study treatment.

SLE 6.7.3 Other Restrictions and Precautions

No other restrictions and precautions have been identified.

SLE 6.8 Treatment After the End of the Study

At the end of the study, BMS will not continue to provide BMS-supplied study treatment to subjects/investigators unless BMS chooses to extend the study. The investigator should ensure that the subject receives appropriate SOC to treat the condition under study.

SLE 7 DISCONTINUATION CRITERIA

SLE 7.1 Discontinuation from Study Treatment

SLE 7.1.1 Permanent Discontinuation from Study Treatment

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

- A subject requests to stop study treatment – Subjects 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 subject specifically withdraws consent for any further contact with him/her or persons previously authorized by the subject 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 subject; if treatment is discontinued due to an AE, the AE eCRF must be completed to show that the AE caused discontinuation.
- Termination of the study program by BMS.
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness.

- Unblinding of a subject's treatment assignment for any reason (emergency or nonemergency).
- Inability or failure to comply with protocol requirements.
- Pregnancy.

Discontinuation of the study treatment should be considered by the investigator for abnormal liver tests indicative of drug-induced liver injury (DILI; see Section SLE 8.2.8 for definition) when the DILI meets one of the conditions necessary to be defined as an SAE outlined in APPENDIX 3, or if the investigator believes that discontinuation is in the best interest of the subject.

In the case of pregnancy, the investigator must immediately, within 24 hours of awareness of the pregnancy, notify the 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 subject safety). Refer to Section SLE 8.2.6.

All subjects who discontinue study treatment should comply with protocol-specified follow-up procedures as outlined in the SoA (Section SLE 1.3). The only exception to this requirement is when a subject withdraws consent for all study procedures including posttreatment 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). Following the decision to permanently discontinue a subject from treatment, an EOT visit should be performed as soon as possible, followed by a Safety follow-up (FU) visit approximately 4 weeks later – both according to Table 2 of Section SLE 1.3.

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

SLE 7.1.2 Temporary Discontinuation from Study Treatment

Branebrutinib may be discontinued temporarily at the discretion of the investigator/Medical Monitor due to AE, laboratory abnormality, or overdose (SLE 8.3).

Branebrutinib may be discontinued temporarily due to concomitant medication use (Master Protocol Table 1), as follows:

- Digoxin, "For acute use only; exclude at baseline; limit highest dose and monitor trough concentrations; stop treatment with branebrutinib during treatment with digoxin and for 3 days afterwards."
- Posaconazole: "Dose up to 300 mg QD can be used as maintenance dose, for acute infections stop using branebrutinib until dosing with posaconazole is discontinued."

SLE 7.1.3 Post-study Treatment Study Follow-up

Subjects who discontinue study treatment will not be followed beyond the planned Safety FU Visit.

SLE 7.2 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.

- Subjects 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 and entered on the appropriate eCRF page.
- In the event that vital status (whether the subject 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 subject withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

The following procedures must be performed upon subject withdrawal:

- Assessments for the end of treatment (EOT) visit must be performed, provided that the subject has not withdrawn consent for these activities.
- All required eCRF pages must be completed, including the date of and explanation for the withdrawal.

SLE 7.3 Lost to Follow-up

- All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject.
- Lost to follow-up is defined by the inability to reach the subject after a minimum of 3 documented phone calls, faxes, or emails as well as lack of response by subject to 1 registered mail letter. All attempts should be documented in the subject's medical records.
- If it is determined that the subject 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 subject's informed consent, then the investigator may use a Sponsor retained third-party representative to assist site staff with obtaining subject'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 subject remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the subject's medical records.

SLE 8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and timing are summarized in the SoA (Section SLE 1.3).

- Protocol waivers or exemptions are not allowed.
- All immediate safety concerns must be discussed with the Medical Monitor immediately upon occurrence or awareness to determine if the subject should continue or discontinue treatment.
- Adherence to the study design requirements, including those specified in the SoA (Section SLE 1.3), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria before randomization. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the subject's routine clinical management (eg, BP, physical examination, medical history) on the day of the screening visit and obtained before signing of the informed consent may be used for screening provided the procedure meets the protocol-defined criteria and has been performed within the timeframe defined in the SoA (Section SLE 1.3).

SLE 8.1 Efficacy Assessments

The PI, or sub-investigator, designated by the PI and confirmed by the Sponsor, should perform all clinical assessments at a site visit. The sub-investigator may be a Doctor of Medicine or Doctor of Osteopathy, Physician's Assistant, or Nurse Practitioner with experience in the diagnosis and management of subjects with SLE.

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

- Every effort must be made to ensure the same investigator performs all of the investigator-administered assessments for a given subject at each visit and throughout the study to minimize inter-observer variation.
- If the investigator is unable to complete the assessment at a given visit, the approved back-up investigator may complete the assessment.
- Assessments are to be conducted at approximately the same time of day throughout the duration of the study for each subject**.**
- Visits should be scheduled with the availability of the specific investigator managing a given subject taken into account.

Assessments conducted on Day 1, Week 0 must be performed per protocol (assessments performed as part of SOC may not be used in lieu of these assessments). Procedures not specified in the protocol that are part of standard care may be performed if they do not interfere with study procedures; any data arising from such procedures are not to be reported in the eCRF.

SLE 8.1.1 Investigator-administered Assessments

SLE 8.1.1.1 SLICC 2012 Classification Criteria for SLE

For diagnosis of SLE in this study, the following SLICC 2012 criteria for SLE classification[76] are required: Fulfillment of at least 4 criteria with at least 1 clinical criterion and 1 immunologic criterion (criteria are cumulative and need not be presented concurrently) (APPENDIX 5).

SLE 8.1.1.2 SLICC/ACR Damage Index

The SLICC/ACR Damage Index (SDI) assesses damage based on a weighted scoring system for assessments in the following areas: ocular, neuropsychiatric, renal, pulmonary, cardiovascular, gastrointestinal, musculoskeletal, skin, gonadal, endocrine, and malignancy. Damage is defined as nonreversible change, not related to active inflammation, occurring since the onset of lupus, ascertained by clinical assessment and present for at least 6 months unless otherwise stated. Repeat episodes must occur at least 6 months apart to score 2. The same lesions cannot be scored twice (APPENDIX 6).

SLE 8.1.1.3 BILAG–2004 Index

The BILAG-2004 Index is a translational index with 97 items in 9 organ systems (Constitutional, Mucocutaneous, Neuropsychiatric, Musculoskeletal, Cardiorespiratory, Gastrointestinal, Ophthalmic, Renal and Hematological) and is based on the principle of the physician's intention to treat. It captures changing severity of clinical manifestations comparing the current monthly activity to prior monthly activity. Only active SLE manifestations are scored. Damage, or manifestations due to non-SLE conditions are not scored. The investigator scores items based on Index definitions, from which an organ system grade is derived.

- Grade A represents severe disease activity
- Grade B represents moderate disease activity
- Grade C indicates mild stable disease
- Grade D indicates inactive disease but previously affected
- Grade E indicates system never involved

BILAG Grading will be performed by [redacted] Central Review Services based on investigator scoring after data has been reviewed, discrepancies resolved and data confirmed complete (APPENDIX 7).

SLE 8.1.1.4 BILAG-based Composite Lupus Assessment

BILAG-based composite lupus assessment (BICLA) response is defined as:

1. At least one gradation of improvement in baseline BILAG scores in all body systems with moderate or severe disease activity at entry (eg, all A (severe disease) scores falling to B (moderate), C (mild), or D (no activity) and all B scores falling to C or D);
2. No new BILAG A or more than one new BILAG B scores;
3. No worsening of total SLEDAI score from baseline;
4. No significant deterioration (< 10%) in PGA and
5. No treatment failure (initiation of nonprotocol treatment).

SLE 8.1.1.5 BILAG–2004 Index-defined SLE Flare

- The BILAG-2004 SLE flare is calculated programmatically (see also SLE 3); severity of flare is defined as:

- Severe flare: Any BILAG-2004 A grade in any body system due to 1 or more items that are scored new or worse
- Moderate flare: ≥ 2 B grades that are each due to 1 or more items scored new or worse
- Mild flare: 1 B grade due to items that are scored new or worse; or ≥ 3 new or recurrent C grades due to items that are scored new or worse
- No flare: Meeting none of the criteria for mild, moderate, or severe

SLE 8.1.1.6 SLE Disease Activity Index 2000 (SLEDAI-2K)

The SLEDAI-2K is used to describe changes in disease activity from one monthly visit to the next. It is meant to convey manifestations due to active SLE and not due to damage or due to non-SLE comorbidities, effects of therapies, etc. This index has been validated for use over a 10-day period as well as over a 30-day period.

The SLEDAI-2K is a global index providing a total score of overall disease activity ranging from 0 to 105, with higher scores representing more active disease. A total of 24 manifestations of SLE are included on the SLEDAI-2K, including both clinical and laboratory parameters. Each manifestation is documented as either present or absent. Findings are considered present if they have met the SLEDAI-2K definition not just on the day of the visit but at any time during the interval period from one monthly visit to the next. Each manifestation that is present on the SLEDAI-2K is given a weighted score and the sum of these is the total SLEDAI-2K score (APPENDIX 8).

SLE 8.1.1.7 Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI)

The CLASI assesses cutaneous disease activity and damage by regions of the body, demarcated for areas most commonly affected by SLE rash; points are given for presence of erythema, scale, hypertrophy, mucous membrane lesions, recent hair loss, and physician-observed alopecia. For the damage assessments, points are given for dyspigmentation, extent of scarring, and scarring alopecia.

The modified CLASI (mCLASI) used in this study is defined as the activity portions of CLASI that describe skin erythema and scale/hypertrophy and inflammation of the scalp. Damage, oral ulcers, diffuse alopecia without scalp inflammation, and recent hair loss (alone or with diffuse noninflammatory alopecia) are excluded from the mCLASI score. The percentage of patients who entered the study with a positive mCLASI activity score (≥ 10) and who achieved a ≥ 50% decrease from baseline at Week 24 is considered to likely represent a clinically meaningful improvement[77] (APPENDIX 9).

SLE 8.1.1.8 Physician Global Assessment (PGA) of SLE Disease Activity

The investigator will rate the overall status of the subject in response to the following statement:

"How do you assess your patient's (the subject's) current SLE activity as compared to the activity and Physician Global Assessment at the last visit?" (APPENDIX 10).

SLE 8.1.1.9 SLE 40-joint Count

The SLE 40-joint count includes bilateral wrists, elbows, ankles, knees, interphalangeal joints of the thumb, individual proximal interphalangeal joints of the hand, second through fifth metacarpophalangeal joints of the hand, and individual metatarsophalangeal joints of the feet (which make up the 36-joint count).[13, 14, 15] To allow the 28-joint count evaluation, bilateral first metacarpophalangeal joints and shoulders are also included, bringing the total joint count to 40. Each joint is evaluated based upon the presence or absence of tenderness, swelling, and both tenderness and swelling related to SLE disease activity. The eCRF includes questions regarding the effect on function due to active SLE arthritis.

Missing, replaced, ankylosed, or arthrodesed joints will be identified by the investigator at the screening visit and will be excluded from evaluation during the study. The locations (or a listing) of surgical procedures should be documented in the subject's source documents/eCRF pages.

SLE 8.1.1.10 Corticosteroid Taper

For subjects taking oral CS as monotherapy, CS must have been taken for ≥ 6 weeks prior to the screening visit at a dose ≥ 7.5 mg/day and ≤ 40 mg/day prednisone (or prednisone equivalent). The dose must be stable for ≥ 2 weeks prior to the screening visit and must remain stable until randomization.
For subjects taking oral CS not as monotherapy, the CS dose must be stable for ≥ 2 weeks before the screening visit, cannot exceed 40 mg/day at screening, and must remain stable until randomization.

For subjects receiving CS (prednisone or equivalent), Investigators must assess the subject's suitability for CS taper at each visit, and the rules for CS tapering during the treatment period are as follows:

- Tapering of CS may begin at any time after the first dose of IP on Day 1, must be started by Week 8, and completed by the Week 16 visit.
- For all subjects, the CS dose must be ≤ 10 mg/day prednisone or equivalent by Week 16. If this is not possible, the subject will remain on CS treatment, but will be defined as a nonresponder for analysis purposes.
- During CS taper from Week 8 through Week 16, the CS dose must be tapered unless the following is observed:
  - Scoring of new or worse in any of the parameters that support BILAG A or B.
  - Tapering is required if disease activity has not worsened. The investigator must document justification for any decision not to taper on the appropriate eCRF at each appropriate visit.
  - The CS dose must remain stable from Week 16 until Week 24.

During the CS tapering process, stepping back to the previous dose level (if needed to adequately manage disease activity) is not considered rescue. During CS taper, however, a requirement to return to a CS dose 2 or more prior dose levels is considered to be rescue, and the subject will be considered a nonresponder for analysis purposes.

SLE 8.1.2 Patient-reported Outcomes

Patient-reported questionnaires studied in SLE have included generic general health questionnaires, rheumatology questionnaires, and SLE disease-specific questionnaires. Patient-reported outcomes will be recorded electronically in eCOA devices provided by the Sponsor or designee to the sites.

SLE 8.1.2.1 Subject Global Assessment of Disease Activity (SGA)

The SGA is a visual analog scale (VAS) (10 cm/100 mm) used to assess the subject's overall assessment of Lupus disease (APPENDIX 11).

SLE 8.1.2.2 Patient-Reported Outcomes Measurement Information System-Fatigue Instrument Form 6a

The Patient-Reported Outcomes Measurement Information System (PROMIS™), Form 6a, provides item banks that offer the potential for patient-reported outcomes (PRO) measurement that is efficient (minimizes item number without compromising reliability), flexible (enables optional use of interchangeable items), and precise (has minimal error in estimate) measurement of commonly studied PROs.[78, 79, 80, 81] In the health outcomes measurement perspective, for example, fatigue is divided conceptually into the experience of fatigue (such as its intensity, frequency, and duration), and the impact of fatigue upon physical, mental, and social activities. The fatigue item bank consists of 95 items assessing the intensity, frequency, and impact of fatigue. Most PROMIS items employ response scales with 5 options (APPENDIX 12).

SLE 8.1.2.3 Euro Quality of Life Five Dimensions Questionnaire: 5-Level Version (EQ-5 D-5 L)

The EQ-5 D-5 L consists of 2 parts – the EQ-5 D-5 L descriptive system and the EQ VAS. The descriptive system comprises the same 5 dimensions as the EQ-5 D-3 L (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). Each dimension has 5 levels: no problems; slight problems; moderate problems; severe problems; and extreme problems. The respondent indicates his/her health state by ticking in the box against the most appropriate statement in each of the 5 dimensions. The resulting 1-digit number expresses the level selected for that dimension. The digits for all 5 dimensions can then be combined in a number describing the respondent's health state.

The numbers 1 through 5 have no arithmetic properties and should not be used as a cardinal score. During the development of the EQ-5 D-5 L, the opportunity was also taken to improve some of the wording in the dimensions to enhance consistency and facilitate understanding. For example, the old wording of "confined to bed" to indicate the upper extreme in the EQ-5 D-3 L has been replaced with "I am unable to walk about," which is more consistent with the wording within the Mobility dimension and with the extreme levels on other dimensions.

The EQ VAS records the respondent's self-rated health on a 20-cm vertical VAS with endpoints labeled "the best health you can imagine" and "the worst health you can imagine." This

information can be used as a quantitative measure of health as judged by the individual respondents. The instructions for the EQ VAS task have also been simplified (APPENDIX 13).

SLE 8.1.2.4 SLE Pain Numeric Rating Score

In this assessment, subjects use a numeric rating score (NRS) to assess the level of pain they attribute to their Lupus, overall, in the past week (APPENDIX 14).

SLE 8.2 Adverse Events

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

AEs will be reported by the subject (or, when appropriate, by a caregiver or surrogate).

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 subject to discontinue before completing the study.

Contacts for SAE reporting are specified in APPENDIX 3.

SLE 8.2.1 AEs of Interest

AEIs are AEs for a particular product or class of products that a Sponsor may wish to monitor carefully. AEIs may be serious or nonserious. Such events may require further investigation to better characterize and understand them. In the branebrutinib clinical development program, infection AEs have been identified as potential AEIs; however, there has been no definitive assessment on the causal relationship between these events and treatment with branebrutinib. Therefore, additional information about infection AEs may be collected on the eCRF in order to better characterize and understand them.

SLE 8.2.2 Time Period and Frequency for Collecting AE and SAE Information

The collection of nonserious AE information should begin at initiation of study treatment until discharge, at the timepoints specified in the SoA (Section SLE 1.3). Nonserious AE information should also be collected from the start of a PBO lead-in period or other observational period intended to establish a baseline status for the subjects. The Reference Safety Information in Sections 5.6.1 and 5.6.2 of the IB[12] should be used to determine the expectedness of SAEs for expedited reporting.

All SAEs must be collected from the time of signing the consent, including those thought to be associated with protocol-specified procedures and within 30 days of discontinuation of dosing or subject's participation in the study if the last scheduled visit occurs at a later time.

The investigator must report any SAE that occurs after these time periods and that is believed to be related to study drug or protocol-specified procedure.

- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the appropriate section of the designated eCRF.

- 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 subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject 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.

SLE 8.2.3 Method of Detecting AEs and SAEs

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.) Nonserious SLE-related AEs will be collected solely on the disease assessment instruments and will not be reported as AEs, unless they are characterized as SAEs.

SLE 8.2.4 Follow-up of AEs and SAEs

- Nonserious AEs should be followed to resolution, 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 eCRF. Completion of supplemental eCRFs 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 subject at subsequent visits/contacts. All SAEs, and nonserious AEIs (as defined in Section SLE 8.2.1) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section SLE 7.3).

Further information on follow-up procedures is provided in APPENDIX 3.

SLE 8.2.5 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 subjects 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.

The 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 (CFR) 21 CFR Parts 312 and 320. A SUSAR is a subset of SAEs and will be reported to the appropriate regulatory authorities and investigators following local and global guidelines and requirements.

SLE 8.2.6 Pregnancy

If, following initiation of the study treatment, it is subsequently discovered that a subject is pregnant or may have been pregnant at the time of study exposure, including during at least 5 half-lives after product administration, the investigator must immediately notify [redacted] Drug Safety of this event and complete and forward a Pregnancy Surveillance Form to [redacted] Drug Safety within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in APPENDIX 3.

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

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 subject should be reported to [redacted] Drug Safety. 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.

SLE 8.2.7 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the AE eCRF page.

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

If a laboratory test result meets the definition of an AE or SAE, the laboratory test result should be reported as an AE or SAE and submitted to [redacted] Drug Safety, as specified in APPENDIX 3.

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).

SLE 8.2.8 Potential DILI

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs meeting the defined criteria must be reported as SAEs (see Section SLE 8.2 and APPENDIX 3 for reporting details).

Potential DILI is defined as:

1) 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 ALT or AST elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, preexisting chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

SLE 8.2.9 Other Safety Considerations

Any significant worsening of a preexisting medical condition noted during interim or final physical examination, electrocardiogram (ECG), x-ray filming, or any other potential safety assessment required or not required by protocol should also be recorded as a nonserious AE or SAE, as appropriate, and reported accordingly.

SLE 8.3 Overdose

For this study, any dose of branebrutinib greater than 2 daily doses of study treatment within a 24-hour time period will be considered an overdose. See APPENDIX 3 for AE assessment and reporting procedures regarding suspected overdose and intentional overdose.

Based on the IB, there has been no clinical experience with overdose of branebrutinib.[12] There is no known specific antidote for overdose with branebrutinib.

In the event of an overdose, the investigator should:

1) Contact the Medical Monitor immediately.
2) Closely monitor the subject for AEs/SAEs and laboratory abnormalities.
3) Obtain a plasma sample for PK analysis within 4 hours of the overdose if requested by the Medical Monitor (determined on a case-by-case basis).
4) Document the quantity of the excess dose as well as the duration of the overdosing in the source documentation.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the subject.

SLE 8.4 Safety

Planned time points for all safety assessments are listed in the SoA (Section SLE 1.3).

SLE 8.4.1 Physical Examinations

A complete physical examination will include general appearance, vital signs, eyes, ears, nose, mouth, throat, neck, respiratory, cardiovascular, respiratory, gastrointestinal/abdomen, lymphatic, musculoskeletal, skin, psychiatric, and neurologic examinations. A targeted physical examination

will include any organ system associated with an AE, a laboratory abnormality, or an SLE activity that cannot be captured on the 40-joint Count or CLASI at a clinical site visit.

SLE 8.4.2 Vital Signs

Refer to SoA (Section SLE 1.3).

SLE 8.4.3 Electrocardiograms

A 12-lead ECG will be performed at the visits indicated in the SoA (Section SLE 1.3). The subject will remain supine for 5 to 10 minutes prior to the ECG and must have lab work done after the tracing so that the ECG results remain as accurate as possible. The ECG results will be read by the primary study investigator or a designee.

SLE 8.4.4 TB Screening and Chest Imaging

A subject must not have active signs or symptoms of TB, as judged by the investigator, to be eligible for the study.

In addition to a complete physical examination and medical history to evaluate exposure to TB, all subjects will have a screening test, an IGRA (eg, QuantiFERON®-TB Gold) performed centrally. A subject with an indeterminate IGRA test result from the central laboratory must be retested for confirmation. If the second result is again indeterminate, the subject will be excluded from the study, unless there is documentation of a local negative TB Spot test result. If the second result from the central laboratory is positive, the subject should be considered as having LTBI provided there are no signs or symptoms of active TB. If the second result is negative, the subject may be eligible provided no other exclusion criteria for TB are met. A chest x-ray is also required if one has not been performed within 6 months of screening; a copy of the radiology report must be on file and reviewed by the investigator. If unable to obtain central laboratory results, an IGRA test could be obtained locally, after consultation with the [redacted] Medical Monitor.

SLE 8.4.5 Clinical Safety Laboratory Assessments

A central laboratory will perform assessments of safety laboratory assessments (except urine pregnancy tests and ESR) and provide reference ranges and laboratory reports. Investigators must document their reviews of each laboratory safety report. Any laboratory test result that the investigator considers clinically relevant is to be recorded on the appropriate AE page of the eCRF (Section SLE 8.2.7). Additional safety assessments may be performed at local laboratories at the investigator's discretion. The laboratory parameters to be assessed are included in SLE Table 7.

In addition, serum or urine pregnancy testing will be performed for WOCBP.

SLE Table 7 Clinical Safety Laboratory Assessments

Hematology	
Hemoglobin Hematocrit Total leukocyte count, including manual differential Platelet count Red blood cell count Prothrombin time/INR PTT aPTT	
Serum Chemistry	
Aspartate aminotransferase Alanine aminotransferase Gamma glutamyltransferase High-sensitivity C-reactive protein Total bilirubin Direct bilirubin Alkaline phosphatase Lactate dehydrogenase Creatinine Blood urea nitrogen Uric acid Fasting glucose (nonfasting at screening only) Creatinine clearance – screening only Estimated glomerular filtration rate	Total Protein Albumin Sodium Potassium Chloride Calcium Phosphorus Magnesium Creatine kinase[a] Fasting lipid panel (total cholesterol, high-density lipoprotein, low-density lipoprotein, and triglycerides; nonfasting at screening only)
Urinalysis	
Protein Glucose Blood Leukocyte esterase Specific gravity pH	Microscopic examination of sediment
Urine chemistry – Spot urine for UPCR	
Infectious Serologies	
Anti-HCV antibodies with reflex testing of HCV RNA if positive HBsAg Anti-HbsAb Anti-HbcAb Anti-HIV-1 and anti-HIV-2 antibody	
Other Analyses	
[redacted] Tuberculosis test (QuantiFERON®-TB Gold) at screening Direct Coomb's test (only if clinically indicated) Whole blood HCQ level (in subjects taking HCQ) Pregnancy Test for WOCBP (serum or urine β-HCG test every 4 weeks) Follicle-stimulating hormone if needed to confirm menopausal status (see APPENDIX 4), at screening HbA1c Thyroid-stimulating hormone (if above normal reference range, test free T4; if below normal range, test free T4 and T3) [redacted] Erythrocyte sedimentation rate RF C3, C4	

SLE Table 7 Clinical Safety Laboratory Assessments

Autoantibodies (ANA, anti-dsDNA, [redacted])
T cells, B cells, natural killer cells
Beta-2-microglobulin

[redacted]; ANA = antinuclear antibody; aPTT = activated partial thromboplastin time; β-HCG = beta-human chorionic gonadotropin; C3, C4 = serum complement C3 and C4; DNA = deoxyribonucleic acid; dsDNA = double-stranded deoxyribonucleic acid; HbcAb = hepatitis B core antibody; HbsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; [redacted]; IR = international normalized ratio; PT = prothrombin time; PTT = partial thromboplastin time; RF = rheumatoid factor; RNA = ribonucleic acid; [redacted]; [redacted] T3 = tri-iodothyronine; T4 = thyroxine; TB = tuberculosis; ULN = upper limit of normal; UPCR = urine protein/creatinine ratio; WOCBP = women of childbearing potential

[a] If the creatine kinase is > 2.5× ULN, reflex testing of creatine kinase-MB and troponin I will be required.

SLE 8.4.6 Imaging Safety Assessment

Any incidental findings of potential clinical relevance on chest x-ray or any additional imaging performed that is not directly associated with the objectives of the protocol should be evaluated and handled by the study investigator as per standard medical/clinical judgment. Images may be requested for submission to the assigned imaging core lab for central analysis.

SLE 8.5 PK of Branebrutinib

The PK sampling schedule for branebrutinib, its metabolites, and concomitant medications will be harmonized among all treatments and sub-protocols where applicable.

For the predose and postdose PK assessments of branebrutinib and metabolites, samples will be collected from 2 groups of subjects—all study subjects who receive branebrutinib comprise one group; and subjects enrolled at preselected clinical sites only and who will also have extended PK sampling comprise the second group (SLE Table 8).

Samples collected from all study subjects who receive branebrutinib will be analyzed for branebrutinib PK only, including samples drawn on days scheduled solely for predose samples. Samples collected from subjects at the preselected clinical sites will be analyzed for both branebrutinib and metabolites as indicated in SLE Table 8, and will be divided into 2 collection tubes, one tube for branebrutinib and one tube for metabolites analysis.

In general, predose (trough) concentrations will be assessed to evaluate the attainment of steady-state and accumulation. It is expected that steady-state will be achieved for all analytes at Week 4, after 28 days of continuous dosing.

Pharmacokinetic samples may also be used in correlation analyses for evaluation of PK/PD and the effect of pharmacogenomics (PGx), and may be used for other correlation analyses as well. The sampling schedule is based on available information on branebrutinib and its metabolites.

(Samples for PK analysis collected from subjects receiving PBO will not be analyzed for branebrutinib or metabolites).

Branebrutinib and Metabolite Analysis:

Branebrutinib PK samples will be analyzed by a vendor using a validated assay. Plasma samples for metabolites will be analyzed by the BMS bioanalytical laboratory. These analyses will be reported separately. The BMS laboratory will be unblinded before the end of the study and will not communicate unblinded information to the BMS or [redacted] study teams. Where the data allow, individual subject PK parameter values for branebrutinib and its metabolites will be derived from plasma concentration data versus time by noncompartmental methods with a validated PK analysis program. Actual times will be used for the analyses.

For all study subjects, the branebrutinib PK parameters listed below will be calculated and summarized with data up to 4 hours postdose. Accumulation ratios for Cmax and AUC(0-4) will also be calculated.

Cmax	Maximum observed concentration
Tmax	Time to maximum concentration
Ctrough	Trough observed plasma concentration
AUC(0-4)	Area under the plasma concentration-time curve from time zero to the 4-hour dosing period

For subjects at preselected sites with extended sampling, separate plasma concentrations of branebrutinib and select metabolites at all timepoints will be summarized by time point. The branebrutinib and its metabolites PK parameters listed below will be calculated and summarized.

Cmax	Maximum observed concentration
Tmax	Time to maximum concentration
AUC(0-T)	Area under the plasma concentration-time curve from time zero to time of last quantified concentration
AUC(TAU)	Area under the concentration-time curve to the end of the dosing period
Ctrough	Trough observed plasma concentration

SLE Table 8 lists the complete sampling schedule for assessment of the PK of branebrutinib, metabolites, and concomitant medications in subjects with SLE.

To assess steady-state concentrations of branebrutinib, a total of 5 predose PK samples (approximately 4 mL each) will be drawn from all study subjects at Week 0 (Day 1), Week 4 (Day 29), Week 8 (Day 57), Week 16 (Day 113), and Week 24 (Day 169). (Note that these samples will be drawn within a 1-hour window before the next dose is administered.) For subjects at preselected sites with extended sampling, predose PK samples collected at Week 8 (Day 57) will also be aliquoted to assess metabolite concentrations.

For postdose sampling, all study subjects will have branebrutinib PK samples drawn at Week 0 (Day 1), Week 8 (Day 57), and Week 24 (Day 169) at the 0.5, 1, 2, and 4-hour time points, a total of 14 samples. (Note that these samples will be drawn within ±15 min from the given time points.) For subjects at preselected sites with extended sampling, postdose PK samples will be aliquoted to assess metabolite concentrations at these time points.

In addition, for subjects at preselected sites with extended sampling, a total of 7 postdose PK samples will be drawn and assessed for both branebrutinib and metabolite concentrations at Week 0 (Day 1) and Week 8 (Day 57) at approximately 06:00 hours, from 08:00 to 10:00 hours (flexible window), and from 10:00 to 12:00 hours (flexible window). Samples will also be collected at Week 0 (Day 2) approximately 24:00 hours postdose (predose of branebrutinib on Day 2). Efforts should be made to collect the samples within these windows; however, any sample drawn outside the prespecified windows will not be considered a protocol deviation. Both planned and actual time points at which the blood samples will be taken will be recorded and used in analysis and modeling.

Concomitant Medications

Concomitant medications that are sensitive substrates of CYP2C8 and other potentially relevant drug metabolizing enzymes that may have a drug-drug interaction with branebrutinib and P-gp transporter may be measured (post-hoc) in subjects receiving PBO and active treatment. Samples for the PK assessment of the concentrations of relevant concomitant medications will be collected at Week 0 and Week 4 from all study subjects. Samples for PK analysis collected from subjects receiving branebrutinib or PBO will be analyzed for HCQ and other relevant concomitant comedications provided that these subjects are receiving HCQ and other relevant concomitant comedications.

Detailed instructions for the collection, labeling, processing, storage, shipping, and disposition of all PK blood samples are provided in the Laboratory Manual.

SLE Table 8 PK Sampling Schedule for Branebrutinib, Metabolites, and Concomitant Medications

Study Day	Study Week	Event	Time (Relative to Branebrutinib Dose) Hours:Minutes	Branebrutinib	Metabolites (collected from subjects at preselected sites only)	Concom Meds [a,b,c]	Comments
1	0	Predose[d]	00:00	X		X [a,b,c]	• Predose PK samples will be collected from all study subjects to assess branebrutinib and relevant concomitant medications; • For subjects on HCQ, whole blood samples will be collected for HCQ level assessment.
1	0	Postdose[e]	00:30	X	X		• Postdose PK samples collected from all study subjects at these time points will be assessed for branebrutinib; • Postdose PK samples collected at these time points from subjects at preselected clinical sites will also be assessed for metabolites; • Postdose PK samples collected at 2 hours after dosing will be assessed for relevant concomitant medications; • For subjects on HCQ, whole blood samples will be collected for HCQ level assessment.
1	0	Postdose	01:00	X	X		
1	0	Postdose	02:00	X	X	X [a,b,c]	
1	0	Postdose	04:00	X	X		
1	0	Postdose	06:00	X	X		• Postdose PK samples collected from subjects at preselected clinical sites only will be assessed for branebrutinib and metabolites at these time points.
1	0	Postdose	08:00-10:00	X	X		
1	0	Postdose	10:00-12:00	X	X		
2	0	Postdose[f]	24:00	X	X		
29	4	Predose	00:00	X		X [a,b,c]	• Predose PK samples will be collected from all study subjects for assessment of branebrutinib and concomitant medications; • For subjects on HCQ, whole blood samples will be collected for HCQ level assessment.
29	4	Postdose	02:00			X [a,b,c]	• Plasma samples will be collected from all study subjects at 2 hours after dosing for assessment of relevant concomitant medications; • For subjects on HCQ, whole blood samples will be collected in addition for HCQ level assessment.

SLE Table 8 PK Sampling Schedule for Branebrutinib, Metabolites, and Concomitant Medications

Study Day	Study Week	Event	Time (Relative to Branebrutinib Dose) Hours:Minutes	Branebrutinib	Metabolites (collected from subjects at preselected sites only)	Concom Meds [a,b,c]	Comments
57	8	Predose	00:00	X	X		• Predose and postdose PK samples collected from all study subjects will be assessed at these time points for branebrutinib only; • Predose and postdose PK samples collected at these time points from subjects at preselected clinical sites will also be assessed for metabolites.
57	8	Postdose	00:30	X	X		
57	8	Postdose	01:00	X	X		
57	8	Postdose	02:00	X	X		
57	8	Postdose	04:00	X	X		
57	8	Postdose	06:00	X	X		• Postdose PK samples collected from subjects at preselected clinical sites only will be assessed for branebrutinib and metabolites at these time points.
57	8	Postdose	08:00-10:00	X	X		
57	8	Postdose	10:00-12:00	X	X		
113	16	Predose	00:00	X			• Predose PK samples taken from all study subjects will be assessed for branebrutinib only.
169	24	Predose	00:00	X			• Predose PK samples taken from all study subjects will be assessed for branebrutinib only.
169	24	Postdose	00:30	X			• Postdose PK Samples taken from all study subjects will be assessed at these time points for branebrutinib only.
169	24	Postdose	01:00	X			
169	24	Postdose	02:00	X			
169	24	Postdose	04:00	X			

PK = pharmacokinetic; Concom Meds = concomitant medications; HCQ = hydroxychloroquine.

[a] Concentrations of Concomitant medications that are sensitive substrates of CYP2C8 and other potentially relevant drug metabolizing enzymes that may have a drug-drug interaction with branebrutinib and P-gp transporter may be evaluated post-hoc for subjects receiving PBO and active treatment at predose of branebrutinib on Day 1 and Day 29 (see Section SLE 8.5.1).

[b] For subjects taking HCQ on-study, whole blood samples will be taken at predose and 2 hours after dosing with the IP on Day 1 (Week 0) and Day 29 (Week 4) (see Section SLE 8.5.1).

[c] Subjects who are on HCQ will be informed to bring HCQ to the clinic on Day 1 and Day 29 for simultaneous dosing with branebrutinib and not to take it at home on those 2 days. Similarly, subjects who are on other prescription concomitant medications will also be informed to bring them to the clinic on Day 1 and Day 29 for simultaneous dosing with branebrutinib, but only when it is safe for subjects and operationally feasible. This should be based on the investigator's discretion with consideration that the medications which should not be delayed until the time of dosing in the clinic should be taken at home. The self-reported time for all prescription medications taken at home should be recorded as accurately as possible.

[d] Predose sample to be drawn within 1 hour before dose administration.

[e] Postdose sample to be drawn within ±15 min of the given time points.

[f] PK sample must be drawn before the IP dose is administered on Day 2.

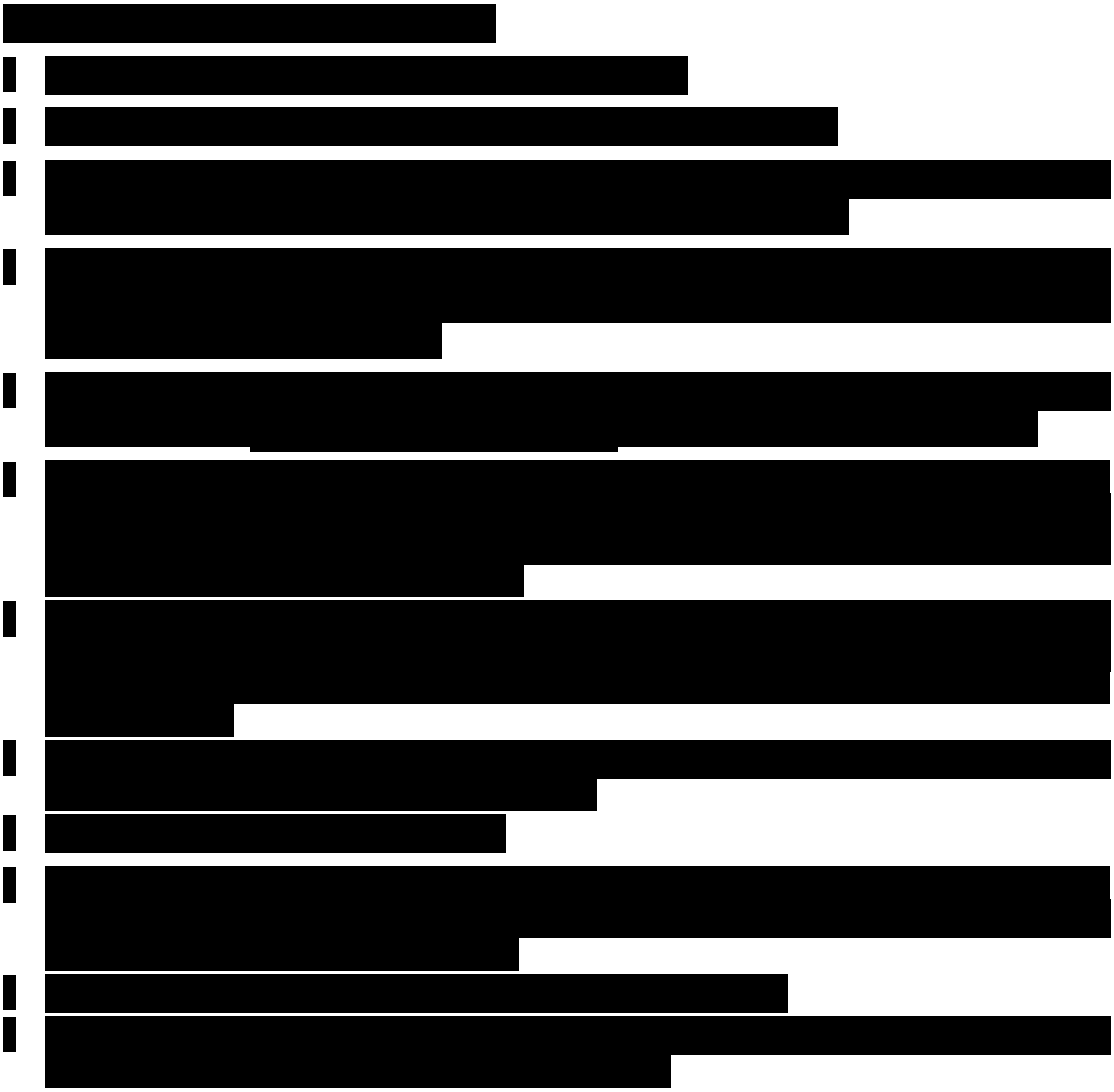
SLE 8.5.1 PK of Potential Concomitant Medications

Concentrations of concomitant medications that are sensitive substrates of CYP2C8 and other potentially relevant drug metabolizing enzymes and P-gp transporter may be evaluated for subjects receiving PBO and active treatment with the bioanalytical analysis as part of a retrospective analysis. HCQ will be among the concomitant medications. The retrospective analysis will be conducted after review of the enrollment records, reported concomitant medication use within the enrolled population and on the incidence threshold and relevance to drug interaction with branebrutinib based on preclinical and clinical data. Other confounding factors will be evaluated as part of the analysis to avoid inclusion of bias or artifact results. Subjects who are on HCQ will be informed to bring HCQ to the clinic on Day 1 and Day 29 for simultaneous dosing with branebrutinib and not to take it at home on those 2 days. Similarly, subjects who are on other prescription concomitant medications will also be informed to bring them to the clinic on Day 1 and Day 29 for simultaneous dosing with branebrutinib, but only when it is safe for subjects and operationally feasible. This should be based on the investigator's discretion with consideration that the medications which should not be delayed until the time of dosing in the clinic should be taken at home. The self-reported time for all prescription medications taken at home should be recorded as accurately as possible.

Concentrations of the relevant concomitant medications will be measured post-hoc using samples collected predose of branebrutinib or placebo on both Day 1 and Day 29 (Week 4; at which point accumulation of branebrutinib and its metabolites is expected to achieve steady-state). In addition to predose samples on Day 1 and Day 29, samples will also be collected at 2 hours after dosing with branebrutinib or placebo to evaluate the concentration of relevant concomitant medications, including HCQ. Bioanalytical analysis of all relevant concomitant medications will be conducted post-hoc. The doses of the concomitant drugs and the time they are taken, will be carefully recorded at all times (including Day 1 on Week 0 and on Day 29 on Week 4). Actual and dose-normalized concentrations will be listed, summarized, and compared between posttreatment and pretreatment of branebrutinib and PBO separately; other covariates such as MTX use, gender, etc. can be added to the comparison as needed.

Detailed instructions for PK sample collection for the relevant concomitant medications, labeling, processing, storage, shipping, and disposition are provided in the Laboratory Manual. While blood samples will be used for the analysis of HCQ, plasma samples will be analyzed for the other relevant concomitant medications by available validated assays. The results of these post hoc analyses will not be recorded in the clinical study report (CSR).

[redacted]



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[redacted]

SLE 8.7 Health Economics OR Medical Resource Utilization and Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters will not be evaluated in this study.

SLE 9 STATISTICAL CONSIDERATIONS

SLE 9.1 Sample Size Determination

Sample size is calculated based on the estimated effect size for the primary endpoint comparison between branebrutinib and PBO treatment groups. The primary endpoint for the SLE sub-protocol is ≥ 50% decrease from baseline mCLASI activity score in subjects with a baseline mCLASI activity score ≥ 10, at Week 24 and CS (prednisone or equivalent) ≤ 10 mg/day at Week 20 and Week 24.

Estimates for PBO response rates, treatment differences, and common standard deviations were obtained from the published literature. [75]

Assuming a total sample size of 60 subjects randomized in a blinded fashion in a 3:1 ratio to branebrutinib (45 subjects) or PBO (15 subjects) and a treatment difference of 25% with a PBO response of 30% for mCLASI at Week 24, the 95% CI is expected to exclude 0 (expected 95% CI based on a z-test = 2%, 56%).

SLE 9.2 Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled Set	All subjects who sign informed consent.
Full Analysis Set (FAS)	All subjects who were randomized. Following the intent-to-treat principle, subjects will be analyzed according to the treatment assigned at randomization. The FAS will be the primary efficacy analysis population. This is the same as the intent-to-treat population.
Per Protocol Set (PPS):	A subset of the FAS who are compliant with study treatment and who do not have any statistically relevant protocol deviations that may impact the primary efficacy endpoint assessments. The PPS will be analyzed according to the treatment assigned at randomization. The PPS may be a supportive efficacy analysis population.
Safety Analysis Set	All randomized subjects who receive at least 1 dose of double-blind study treatment. Subjects will be analyzed according to treatment received.
PK	All randomized subjects who receive at least 1 dose of branebrutinib and have any available branebrutinib concentration data. Subjects will be analyzed according to the treatment received during the PK collection.
Biomarker	All randomized subjects who receive at least 1 dose of double-blind study treatment and have at least 1 posttreatment biomarker measurement.

SLE 9.3 Endpoints

The following sections outline the efficacy endpoints for the SLE sub-protocol.

SLE 9.3.1 Primary Endpoint

Proportion of subjects with

- ≥ 50% decrease from baseline mCLASI activity score in subjects with a baseline mCLASI activity score ≥ 10, at Week 24

  AND

- CS (prednisone or equivalent) ≤ 10 mg/day at Week 20 and Week 24

SLE 9.3.2 Secondary Endpoints

The following are the secondary efficacy endpoints as defined at Week 24:

- Change from baseline in SLEDAI-2K score
- BICLA response

SLE 9.3.3 Additional Endpoints

The following are the additional efficacy endpoints as defined at Week 24:

- Change from baseline in:
    - Autoantibody titers (ANA, anti-dsDNA)
    - Complement (C3, C4)
    - High-sensitivity C-reactive protein (hsCRP)
    - Erythrocyte sedimentation rate (ESR)
    - SGA of Disease Activity
    - PGA of Disease Activity
    - Tender joint counts (TJC), swollen joint counts (SJC), and TJC + SJC in subjects with arthritis at baseline
    - SDI (also change from baseline at the EOT visit, if prior to Week 24)
    - EQ-5 D-5 L score
    - PROMIS Fatigue 6 a
    - Pain NRS

SLE 9.3.4 PK Endpoints

- Concentration values and PK parameters of branebrutinib and metabolites of clinical interest

SLE 9.4 Statistical Analyses

The SAP will be developed and finalized before database lock. Section SLE 9.4.1 provides a summary of planned statistical analyses of the primary and secondary endpoints. Additional and exploratory endpoints will be summarized in a descriptive manner.

SLE 9.4.1 Efficacy Analyses

Efficacy data will be summarized using the FAS. Data will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum), unless otherwise specified, for continuous variables, and frequency distributions (counts and percentages) for categorical variables. Efficacy data will be summarized separately for the SLE sub-protocol and with each sub-protocol combined for variables that are similar among the sub-protocols.

For the SLE sub-protocol, data will be presented for the following treatments:

- Branebrutinib
- PBO

Endpoint	Statistical Analysis Methods
Primary	General Analysis Methodology Response rates of branebrutinib compared to PBO for the primary endpoint will be analyzed using a Cochran-Mantel-Haenszel (CMH) test stratified by immunosuppressant use (yes/no). The 95% CI for each treatment group response rate and the difference in response rate for branebrutinib compared to PBO will be provided. If expected cell counts are not sufficient, then Fisher's exact test will be used. Since this sub-protocol is not powered to determine statistical significance, P-values will be added descriptively. Supportive Analyses Supportive analyses using logistic regression for the primary endpoint may be performed to incorporate additional covariates of interest and to confirm primary analysis results. The odds ratio and the corresponding 95% CI will be provided. Bayesian borrowing to utilize historical controls may also be performed as supportive analyses. Details will be provided in the SAP if needed. Imputation Method Nonresponder imputation will be used for binary endpoints for subjects who discontinue study treatment early, start a protocol-prohibited

Endpoint	Statistical Analysis Methods
	medication/therapy prior to the specified timepoint, or otherwise have missing endpoint data for the specified timepoint. Other imputation methods may be considered for sensitivity analyses and will be described in the SAP if used.
Secondary/ Additional	<u>General Analysis Methodology</u> Response rates of branebrutinib compared to PBO for binary endpoints will be analyzed using a CMH test stratified by immunosuppressant use (yes/no). The 95% CI for each treatment group response rate and the difference in response rate for branebrutinib compared to PBO will be provided. If expected cell counts are not sufficient, then Fisher's exact test will be used. Continuous endpoints (change from baseline values) will be analyzed using analysis of covariance. The baseline value of the endpoint being tested will be added into the model as a covariate. Treatment differences based on least-squares means and corresponding 2-sided 95% CIs will be provided for the difference between branebrutinib and PBO. <u>Supportive Analyses</u> Supportive analyses using logistic regression for the primary endpoint may be performed to incorporate additional covariates of interest and to confirm primary analysis results. The odds ratio and the corresponding 95% CI will be provided. Supportive analyses for continuous endpoints may be performed using MMRM to investigate response over time. <u>Imputation Method</u> Nonresponder imputation will be used for binary endpoints for subjects who discontinue study treatment early, start a protocol-prohibited medication/therapy prior to the specified timepoint, or otherwise have missing endpoint data for the specified timepoint. Other imputation methods may be considered for sensitivity analyses and will be described in the SAP if used. <u>Testing Strategy for Secondary Endpoints</u> There will be no alpha level adjustment for multiple endpoint testing.

SLE 9.4.1.1 Subgroup Analyses

Subgroup analyses will be conducted for the primary and secondary efficacy endpoints on the FAS population. Subgroups that may be evaluated include the following:

- Gender

- Race
- Tobacco use

Additional subgroups defined for descriptive summaries may be specified in the SAP.

SLE 9.4.2 Safety Analyses

Safety data will be descriptive in nature and will be summarized using the Safety Analysis Set. Data will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum), unless otherwise specified, for continuous variables and frequency distributions (counts and percentages) for categorical variables. Safety data will be summarized separately for each sub-protocol and with all sub-protocols combined.

Data will be presented for the following treatments:

- Branebrutinib
- PBO

SLE 9.4.2.1 Adverse Events

TEAEs are defined as AEs that occur after the subject received first dose of study treatment or if a preexisting condition worsens in severity or becomes serious after receiving the first dose of study treatment up to 30 days after the last dose of study treatment. All reported TEAEs, SAEs, deaths, AEs leading to study treatment discontinuation, and AEIs will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. AEIs in this study may include infections, influenza, tuberculosis, and herpes.

SLE 9.4.2.2 Clinical Laboratory Tests

Laboratory parameters will be summarized as absolute and change from baseline values by visit. Baseline values are defined as the last nonmissing value prior to the first dose of study treatment. Marked abnormalities summarized by visit and shift tables will also be provided. For clinical laboratory test results, marked abnormalities will be defined in the SAP.

SLE 9.4.2.3 Vital Signs and ECGs

Vital signs and ECGs will be summarized as absolute and change from baseline values by visit. Baseline values are defined as the last nonmissing value prior to the first dose of study treatment. Marked abnormalities will be summarized by visit as well. For vital signs and ECGs, marked abnormalities will be defined in the SAP.

SLE 9.4.3 Other Analyses

The PK, PD, and exploratory biomarker analyses will be described in the SAP finalized before database lock. Any population PK analysis and PD analyses will be presented separately from the main CSR.

SLE 9.4.4 Analysis and Reporting

After all subjects in the SLE sub-protocol have finished the study and the data have been locked for the sub-protocol, analyses of the efficacy and safety data for the sub-protocol will be performed in order to aid in planning for subsequent clinical development. Details of these analyses will be described in the SAP. The study team responsible for managing the study, including Medical Monitors, will remain blinded to treatment assignment and the results of safety analysis until full database lock and treatment unblinding has occurred. The data will be reported only after completion of all 3 sub-protocols.

Protocol Number: IM014029
IND Number: 142401
EX-US Non-IND
EUDRACT Number: 2019-002205-22
Date: 01-Jul-2019
Revised Date: 01-Dec-2021

Clinical Protocol IM014029:

PSS SUB-PROTOCOL

A Randomized, Placebo-Controlled, Double-Blind, Multicenter Study to Assess the Efficacy and Safety of Branebrutinib Treatment in Subjects with Active Systemic Lupus Erythematosus or, Primary Sjögren's Syndrome, or Branebrutinib Treatment Followed by Open-label Abatacept Treatment in Subjects with Active Rheumatoid Arthritis

Protocol Amendment 04 pSS

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PSS 1 SUB-PROTOCOL SUMMARY

pSS 1.1 Synopsis

Protocol Title: A Randomized, Placebo-Controlled, Double-Blind, Multicenter Study to Assess the Efficacy and Safety of Branebrutinib Treatment in Subjects with Active Systemic Lupus Erythematosus or Primary Sjögren's Syndrome, or Branebrutinib Treatment Followed by Open-label Abatacept Treatment in Subjects with Active Rheumatoid Arthritis

Short Title:

Placebo-Controlled, Double-Blind Study to Assess the Efficacy and Safety of Branebrutinib in Primary Sjögren's Syndrome: pSS Sub-protocol

Study Phase:

Phase 2a

pSS Sub-protocol Rationale:

The Study IM014029 primary Sjögren's syndrome (pSS) sub-protocol is designed to evaluate the efficacy and safety of branebrutinib in addition to background disease therapy in the treatment of subjects with moderate to severe pSS. Based on several key underlying molecular mechanisms of pSS targeted by inhibition of Bruton's tyrosine kinase (BTK), branebrutinib may be effective in the treatment of pSS.

There is no currently approved treatment that targets the underlying mechanism(s) of pSS, indicating a clear unmet medical need in this patient population.

The European League Against Rheumatism (EULAR) Sjögren's Syndrome Disease Activity Index (ESSDAI), which is designed to measure systemic disease activity across 12 organ-specific domains, and the EULAR Sjögren's Syndrome Patients Reported Index (ESSPRI), which measures subjective symptoms of dryness, pain, and fatigue, have recently been developed and validated for evaluation of therapeutic agents in pSS. Subsequent work has defined the patient-level relevant cut-offs for change for both the ESSDAI and ESSPRI scores for use in clinical studies. The disease activity levels for ESSDAI were defined (low activity < 5; moderate activity ≥ 5 to ≤ 13; and high activity ≥ 14). The minimum clinically important improvement (MCII) for ESSDAI was defined as an improvement of ≥ 3 points, and for ESSPRI, the MCII was defined as a decrease of at least one point or 15%.

ESSDAI-defined disease activity levels will enable the enrollment of patients with moderate to severe disease activity in this sub-protocol (ESSDAI ≥ 6). Limiting the population to those subjects with an ESSDAI of at least 6 will enable adequate detection of MCII of ≥ 3 points to discriminate between the effects of active treatment and placebo (PBO). Considering the small sample size and the relatively short treatment duration (24 weeks) of this study, ensuring sufficient patients are enrolled who have disease characteristics amenable to improvement will enable better signal detection for this asset to help guide future development.

In an early phase clinical study, it is critical to ensure that as many subjects as possible enter the study with multiple active, "responsive" ESSDAI domains, so that treatment effects might be observed in as many domains as possible. This will provide a more robust dataset to aid the design of subsequent clinical studies. To meet this end, all subjects will be required to have a positive score in at least 1 of the following "responsive" domains (articular, biological, glandular, hematological, or lymphadenopathy) contributing to their composite ESSDAI score of 6 or more to enter the study. In addition, positive score(s) from any of the other 7 ESSDAI domains will help ensure an interpretable study.

pSS Sub-protocol Study Population:

The study population will include male and female subjects aged 18 (or age of majority) to 75 years inclusive at screening with moderate to severe pSS.

pSS Sub-protocol Key Inclusion/Exclusion Criteria:

a) Diagnosed with pSS ≤ 7 years before screening
b) Subjects diagnosed or classified as having pSS (defined as Sjögren's syndrome in the absence of another immune-mediated disease or rheumatologic condition) based on the 2016 American College of Rheumatology (ACR)-EULAR Classification Criteria for pSS, with disease duration from time since diagnosis of at least 16 weeks prior to screening, with moderate to severe activity per ESSDAI
c) ESSDAI score of ≥ 6, including disease activity (any score > 0) in at least one of the following domains: glandular, articular, hematological, biological, lymphadenopathy
d) Positive anti-Ro/Sjögren's syndrome-associated antigen A (SSA), plus at least one of the following at screening, as determined by central laboratory:
    - [redacted]

- [redacted]
- positive rheumatoid factor (RF)
- positive cryoglobulin test (must be performed at local laboratory)
- IgG > 16 g/L

e) A stimulated salivary flow rate > 0.05 mL/minute or unstimulated salivary flow rate > 0.01 mL/minute at screening and randomization

f) Subjects with a diagnosis of a systemic immune-mediated disease other than pSS, such as RA, SLE, mixed connective tissue disease, or systemic sclerosis that can better explain the majority of the symptoms (ie, secondary SS) are excluded

g) Subjects who have another immune-mediated disease or inflammatory condition that could interfere with assessment of response of pSS to therapy (eg, immunoglobulin G4-related disease, systemic sclerosis, inflammatory bowel disease, gout) are excluded.

h) Subjects with any other medical condition associated with sicca syndrome (eg, history of head and neck radiation treatment, diabetes mellitus, sarcoidosis, chronic graft-versus-host disease), and subjects with sicca symptoms secondary to ongoing medication use based on the investigator's assessment, are excluded.

i) Subjects with active fibromyalgia with pain symptoms or signs that would interfere with joint assessment or requiring adjustment in medication within the 3 months before screening to control symptoms are excluded. Subjects with fibromyalgia that is well controlled on stable treatment may otherwise be considered.

j) Subjects with severe complications of pSS at the time of screening, including, but not restricted to, the following, are excluded:
   - Vasculitis with renal, digestive, cardiac, pulmonary or central nervous system (CNS) involvement characterized as severe (note: cutaneous vasculitis is allowed)
   - Active CNS or peripheral nervous system involvement requiring moderate to high-dose corticosteroids (CS > 10 mg/day)
   - Renal disease including but not limited to the following:
     – Interstitial nephritis
     – Glomerulonephritis
     – Nephrotic syndrome with proteinuria > 3 g/day or UPCR > 339 mg/mmol and/or serum creatinine ≥ 2.0 mg/dL; interstitial nephritis with proteinuria < 1.5 g/day or UPCR < 169.5 mg/mmol and serum creatinine < 1.5 mg/dL may be included
   - Severe pulmonary disease based on the investigator's assessment
   - Active myositis requiring more than the maximum dose of CS
   - Any type of lymphoma

k) Subjects hospitalized with PCR-proven or suspected COVID-19 infection (unless for quarantine/observation) within the 3 months prior to randomization, as well as any subjects with any sequelae of prior COVID-19 infection at screening, regardless of time since infection, are excluded.

pSS Sub-protocol Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To compare the efficacy of branebrutinib with PBO at Week 24 in the treatment of subjects with pSS	Proportion of subjects with at least 3 of the following at Week 24: • Decrease of ≥ 1 point or 15% from baseline in the ESSPRI Total Score • Decrease of ≥ 3 points from baseline in ESSDAI score • Decrease of ≥ 25% from baseline in ocular staining score, or if normal score at baseline no change to abnormal • Increase of ≥ 25% from baseline in stimulated salivary flow • Improvement in one or more serological markers (RF, IgG, complement C3 or C4, cryoglobulin)
Additional	
• To compare the efficacy of branebrutinib with PBO at Week 24 in the treatment of subjects with pSS	• Decrease of ≥ 1 point or 15% in the ESSPRI Total Score • Decrease of ≥ 3 points from baseline in ESSDAI score • Decrease of ≥ 25% from baseline in ocular staining score, or if normal score at baseline no change to abnormal • Increase of ≥ 25% from baseline in Schirmer's test score, or if normal score at baseline no change to abnormal • Increase of ≥ 25% from baseline in tear break-up time (TBUT), or if normal score at baseline no change to abnormal • Increase of ≥ 25% from baseline in stimulated salivary flow • Improvement in one or more serological markers (RF, IgG, complement C3 or C4, cryoglobulin) • Change from baseline in autoantibody titers, hsCRP, and ESR • Change from baseline in DAS28-CRP • Change from baseline in the EQ-5 D-5 L score • Change from baseline in PROMIS Fatigue 6 a • Changes from baseline in PGA and SGA • Changes from baseline in NRS for Mouth and Eye Dryness
Safety	
• To compare the safety and tolerability of branebrutinib with PBO in subjects with pSS	• Number and proportion of subjects experiencing SAEs, AEs, and abnormalities in laboratory parameters, vital signs, and ECGs
Exploratory	
[redacted]	

pSS Sub-protocol Objectives and Endpoints:

Objectives	Endpoints
[redacted]	

[redacted]
AE = adverse event; ANA = antinuclear antibody; [redacted]; BTK = Bruton's tyrosine kinase; [redacted]; dsDNA = double-stranded deoxyribonucleic acid; ECG = electrocardiogram; EQ-5 D-5 L = Euro Quality of Life Five Dimensions Questionnaire: 5 Level version; ESR = erythrocyte sedimentation rate; ESSDAI = European League Against Rheumatism Disease Activity Index; ESSPRI = European League Against Rheumatism Patient-reported Index; hsCRP = high-sensitivity C-reactive protein; [redacted]; Ig = immunoglobulin; IL = interleukin; [redacted] NRS = numeric rating score; PBO = placebo; PGA = Physician Global Assessment; PK = pharmacokinetic; PROMIS = Patient-Reported Outcomes Measurement Information System; pSS = primary Sjögren's syndrome; [redacted] SAE = serious adverse event; [redacted]; SGA = Subject Global Assessment; [redacted] TBUT = tear break-up time; [redacted]

pSS Sub-protocol Overall Design:

- This is a double-blind, PBO-controlled Phase 2a study sub-protocol to evaluate the effect of branebrutinib (BMS-986195) in subjects with pSS. All subjects will receive background therapy for their primary disease as appropriate.
- Subjects will receive double-blind oral branebrutinib 9 mg or PBO treatment once daily for 24 weeks (Week 0 to Week 24).
- Treatment assignment will be conducted by randomization. Subjects will undergo screening evaluations to determine eligibility within 28 days prior to administration of study medication. Following the screening process, if eligible for study participation, subjects will be randomized to receive branebrutinib or PBO treatment in a 2:1 ratio. Randomization will be stratified by hydroxychloroquine (HCQ) use (yes/no).

pSS Sub-protocol Number of Subjects:

It is expected that approximately 45 subjects will be randomized in the pSS sub-protocol.

pSS Sub-protocol Duration:

The total duration of participation in the pSS sub-protocol is approximately 32 weeks and will be divided into the following periods: screening (up to 4 weeks), double-blind PBO-controlled treatment for 24 weeks (Week 0 to Week 24), and follow-up (4 weeks).

pSS Sub-protocol Study Treatment:

Study Drug for IM014029		
Medication	**Potency**	**IP/Non-IP**
Branebrutinib	9 mg QD, oral	IP
Branebrutinib PBO	QD, oral	IP

IP = investigational product; PBO = placebo; QD = once daily

pSS Sub-protocol Statistical Methods

Sample size is calculated based on the estimated effect size for the primary endpoint comparison between branebrutinib and PBO treatment groups. The primary endpoint for the pSS sub-protocol is pSS composite response at Week 24.

Estimates for response rates were obtained from the published literature. Sample size justification is provided below:

Assuming a total sample size of 45 subjects randomized in a blinded fashion at a 2:1 ratio to branebrutinib (30 subjects) or PBO (15 subjects) and a treatment difference of 30% with a PBO response of 20% for the pSS composite response at Week 24, the 95% CI is expected to exclude 0 (expected 95% CI based on a z-test = 3%, 57%).

Categorical data will be summarized by treatment group as frequency counts and percentages. Continuous data will be summarized by treatment group using n, mean, standard deviation, median, minimum, and maximum unless otherwise specified. Efficacy data will be summarized separately for each sub-protocol and with each sub-protocol combined for variables that are similar among the sub-protocols. Primary analysis for each sub-protocol will be performed after all subjects finish the study within a sub-protocol. There will be no alpha level adjustment for multiple endpoint testing.

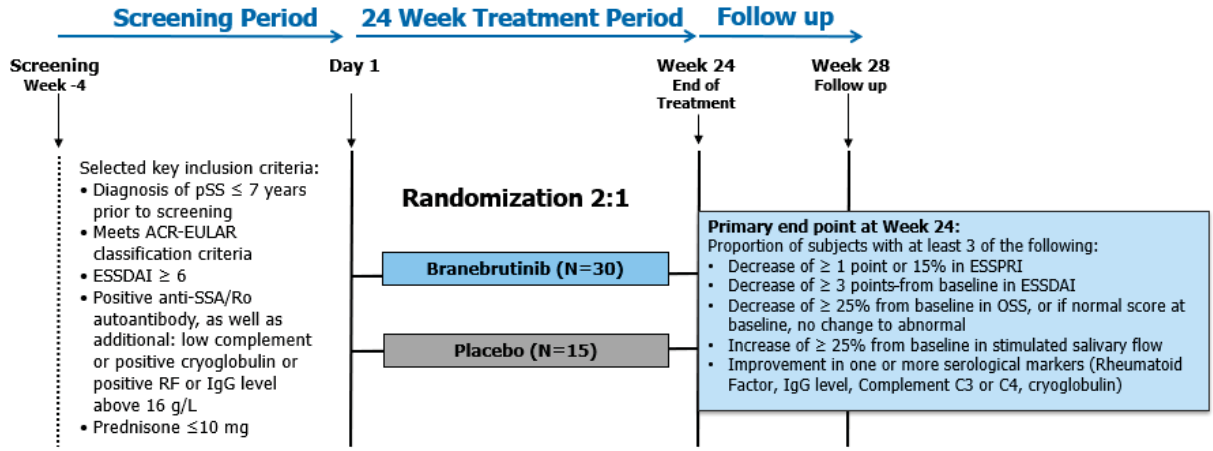
The primary endpoint will be analyzed using analysis of covariance. The baseline value of the endpoint being tested will be added into the model as a covariate and HCQ use (yes/no) and treatment as fixed effects. Treatment differences based on least-squares means and corresponding 2-sided 95% CIs will be provided for the difference between branebrutinib and PBO. The mixed model repeated measures analyses may be used in supportive analyses for continuous endpoints. Bayesian borrowing to utilize historical controls may also be performed as supportive analyses. Details will be provided in the SAP if needed.

Missing data are addressed in these models and assumed to be missing at random.

TEAEs and SAEs will be summarized using counts and percentages of subjects experiencing the event as well as the number of events by system organ class, preferred term, and treatment group.

Physical examinations findings, vital signs, clinical laboratory test results, and electrocardiogram results will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) for continuous variables and frequency distributions (counts and percentages) for categorical variables. Safety data will be summarized separately for each sub-protocol and with all sub-protocols combined.

pSS 1.2 Schema



ACR = American College of Rheumatology; Anti-SSA = anti-Sjögren's Syndrome-associated antigen A antibody; ESSDAI = European League Against Rheumatism Sjögren's Syndrome Disease Activity Index; ESSPRI = European League Against Rheumatism Patient-reported Index; EULAR = European League Against Rheumatism; IgG = immunoglobulin G; OSS = ocular staining score; pSS = primary Sjögren's syndrome

pSS 1.3 Schedule of Activities

pSS Table 1 Screening Procedural Outline Branebrutinib Study IM014029

Procedure	Screening (V1)	Notes
Eligibility Assessments		
Informed Consent	X	A subject is considered enrolled only when a protocol-specific ICF is signed; this includes subjects at preselected clinical sites consenting to participate in extended PK sampling in addition to the sampling scheduled for all study subjects.
Enroll subject in the IRT system	X	
Inclusion/Exclusion Criteria	X	Includes: pSS diagnosis (≤ 7 years before screening) based on 2016 ACR-EULAR criteria. Positive anti-Ro/SSA autoantibody (2016 ACR-EULAR Classification Criteria for pSS) plus at least 1 of the following: low C3, low C4, positive RF, positive cryoglobulin test or IgG > 16 g/L [a] ESSDAI score ≥ 6
pSS History, pSS-related Treatment	X	
General Medical History	X	
History of Tobacco Use	X	Nonsmoker, light or heavy smoker.
Patient-reported Outcomes		
Mouth Dryness (NRS)	X	Collected on eCOA device.
Eye Dryness (NRS)	X	Collected on eCOA device.
ESSPRI	X	Collected on eCOA device.
SGA	X	Collected on eCOA device.
EQ-5 D-5 L	X	Collected on eCOA device.
PROMIS-Fatigue 6 a	X	Collected on eCOA device.
Clinical Assessments		
ESSDAI	X	Entered into EDC by site.
Stimulated/unstimulated salivary flow	X	Entered into EDC by site (refer to Section pSS 8.1.1.2 for details). Can be performed by site staff trained on study-specific requirements and delegated by PI accordingly.

pSS Table 1 Screening Procedural Outline Branebrutinib Study IM014029

Procedure	Screening (V1)	Notes
Tender (68)/swollen (66) joint count	X	Entered into EDC by site.
PGA	X	Entered into EDC by site.
Salivary Gland Ultrasonography (SG-US)		
SG-US	X	Perform approximately 14 days prior to randomization to allow review and perform repeat, if required [b].
Safety Assessments		
Physical Examination (PE)	X	Complete PE.
Physical Assessments	X	
Vital Signs	X	Includes height (screening only) and weight, body temperature (ear or oral), respiratory rate, seated BP, and seated heart rate. BP and heart rate should be measured after the subject has been resting quietly for at least 5 minutes.
ECG	X	ECGs should be recorded after the subject has been supine for at least 5 minutes.
Chest imaging (eg, chest x-ray)	X	Chest imaging is required if not performed within 6 months of screening visit; copy of radiology report must be on file and reviewed by the investigator.
Prior and Concomitant Medication Use	X	Includes prescription, over-the-counter medications, and herbal supplements. All concomitant medications to be reviewed by the Medical Monitor and clinical pharmacology asset lead.
SAE Assessment	X	All SAEs must be collected from the time of signing the consent, including those thought to be associated with protocol-specified procedures and within 30 days of discontinuation of dosing or subject's participation in the study if the last scheduled visit occurs at a later time.
Laboratory Tests		Includes blood and urine samples.
Hematology	X	CBC with differential.
Serum Chemistry Panel	X	Includes liver function testing.
Lipid Panel	X	Nonfasting.
Urinalysis	X	
HbA1c	X	If HbA1c $\geq$ 9 consult Medical Monitor.
TSH	X	If out of normal range (high or low), consult the Medical Monitor.
UPCR	X	

pSS Table 1 Screening Procedural Outline Branebrutinib Study IM014029

Procedure	Screening (V1)	Notes
eGFR	X	
ESR	X	Local laboratory assessment by site.
[redacted]	[redacted]	
HCQ concentration [c]	X	To be reviewed by the Medical Monitor and clinical pharmacology asset lead.
[redacted]	[redacted]	
Anti-dsDNA	X	
Anti-Ro/SSA	X	
Anti-La/SSB	X	
Cryoglobulin test	X	Local laboratory assessment by site.
[redacted]	[redacted]	
[redacted]	[redacted]	
Infectious Serology	X	Includes HCV antibody, HBsAg, HBsAb, HBcAb, and HIV antibodies.
TB Test (IGRA; eg, QuantiFERON®-TB Gold)	X	
Pregnancy Test (Serum or Urine)	X	WOCBP only. Must have negative pregnancy test within 24 hours prior to the start of treatment.
FSH	X	For select women only; serum FSH level will be determined to confirm menopausal status. See APPENDIX 4 for definition and Section pSS 5.1 for reproductive status inclusion criteria.
Biomarker Sampling		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

pSS Table 1 Screening Procedural Outline Branebrutinib Study IM014029

Procedure	Screening (V1)	Notes
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted] anti-La/SSB = Sjögren's syndrome-associated antigen B; anti Ro/SSA = Sjögren's syndrome-associated antigen A;; [redacted]; [redacted]; BP = blood pressure; [redacted]; CBC = complete blood count; [redacted] DNA = deoxyribonucleic acid; dsDNA = double-stranded deoxyribonucleic acid; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; ESR = erythrocyte sedimentation rate; EQ-5 D-5 L = Euro Quality of Life 5 Dimensions Questionnaire: 5-Level version; ESSDAI = EULAR Sjögren's Syndrome Disease Activity Index; ESSPRI = EULAR Sjögren's Syndrome Patient-reported Index; EULAR = European League Against Rheumatism; FSH = follicle-stimulating hormone; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HCQ = hydroxychloroquine; HIV = human immunodeficiency virus; [redacted]; ICF = informed consent form; IGRA = interferon gamma-release assay; IL = interleukin; IRT = interactive response technology; [redacted]; NRS = numeric rating score; PGA = Physician Global Assessment; PI = principal investigator; PK = pharmacokinetic; [redacted]; [redacted] SAE = serious adverse event; SGA = subject's global assessment; TB = tuberculosis; [redacted]; TSH = thyroid-stimulating hormone; UPCR = urine protein:creatinine ratio; WOCBP = women of childbearing potential

[a] Testing for anti-Ro/SSA and anti-La/SSB autoantibodies may be repeated once during screening for subjects who otherwise qualify according to inclusion criteria but have initial negative anti-Ro/SSA and anti-La/SSB.

[b] Perform approximately 14 days prior to randomization to allow review and perform repeat, if required.

[c] For subjects taking HCQ concomitantly, a sample of whole blood will be drawn for HCQ PK analysis.

[redacted]

[redacted]

When multiple assessments are conducted at a single visit, the following is the order in which they should be performed:

1) Patient-reported Outcomes (eg, SGA, EQ-5 D-5 L, etc)
2) Safety assessments (eg, vitals, AEs)
3) Investigator-administered Assessments (eg, PGA, joint count, etc)
4) Laboratory tests (eg, safety laboratory tests, PK assessments, biomarker assessments)

pSS Table 2 Procedural Outline Branebrutinib Study IM014029 (Week 0 to Week 28)

Procedure	W0 D1 V2	W2 D15 (± 3 d) V3	W4 D29 (± 3 d) V4	W8 D57 (± 3 d) V5	W12 D85 (± 3 d) V6	W16 D113 (± 3 d) V7	W20 D141 (± 3 d) V8	W24 D169 (± 3 d) V9 (EOT) [a]	W28 D197 (± 3 d) V10 Safety FU	Notes
Patient-reported Outcomes										
SGA	X		X	X	X	X	X	X	X	Collected on eCOA device.
ESSPRI	X		X	X	X	X	X	X	X	Collected on eCOA device.
Mouth dryness (NRS)	X		X	X	X	X	X	X	X	Collected on eCOA device.
Eye dryness (NRS)	X		X	X	X	X	X	X	X	Collected on eCOA device.
EQ-5 D-5 L	X				X			X	X	Collected on eCOA device.
Fatigue (PROMIS-Fatigue 6 a)	X				X			X	X	Collected on eCOA device.
Safety Assessments										
Complete Physical Examination (PE)	X								X	
Targeted Physical Examination		X	X	X	X	X	X	X		
Body Weight	X		X	X	X	X	X	X	X	
Vital Signs	X	X	X	X	X	X	X	X	X	Temperature (ear or oral), respiratory rate, seated BP, and seated heart rate; BP and heart rate should be measured after the subject has been resting quietly for at least 5 minutes.
ECG	X	X	X	X	X	X	X	X	X	ECGs should be recorded after the subject has been supine for at least 5 minutes.

pSS Table 2 Procedural Outline Branebrutinib Study IM014029 (Week 0 to Week 28)

Procedure	W0 D1 V2	W2 D15 (± 3 d) V3	W4 D29 (± 3 d) V4	W8 D57 (± 3 d) V5	W12 D85 (± 3 d) V6	W16 D113 (± 3 d) V7	W20 D141 (± 3 d) V8	W24 D169 (± 3 d) V9 (EOT) [a]	W28 D197 (± 3 d) V10 Safety FU	Notes
Concomitant Medication Use	X	X	X	X	X	X	X	X	X	
AE and SAE Assessment	X	X	X	X	X	X	X	X	X	Nonserious AEs must be collected from the time of the first dose of the study drug through the date of the follow-up or last visit.
Clinical Assessments										
ESSDAI	X		X	X	X	X	X	X	X	Entered into EDC by site.
Stimulated/unstimulated salivary flow	X				X			X	X	Entered into EDC by site (refer to Section pSS 8.1.1.2 for details). Can be performed by site staff trained on study-specific requirements and delegated by PI accordingly.
Tender (68)/swollen (66) joint count	X		X	X	X	X	X	X	X	Entered into EDC by site.
PGA	X		X	X	X	X	X	X	X	Entered into EDC by site.
DAS28-CRP	X		X	X	X	X	X	X	X	Scores calculated programmatically.
LGF: Tear Break-up Time, Ocular Staining Score, Schirmer's Test	X				X			X		LGF/Ocular staining tests must be done within 5 days prior to Day 1 or, if done on Day 1, must be done before administration of IP; on-study LGF assessments

pSS Table 2 Procedural Outline Branebrutinib Study IM014029 (Week 0 to Week 28)

Procedure	W0 D1 V2	W2 D15 (± 3 d) V3	W4 D29 (± 3 d) V4	W8 D57 (± 3 d) V5	W12 D85 (± 3 d) V6	W16 D113 (± 3 d) V7	W20 D141 (± 3 d) V8	W24 D169 (± 3 d) V9 (EOT) [a]	W28 D197 (± 3 d) V10 Safety FU	Notes
										have a 5-day window around Week 12/24 visits.
Salivary/Parotid Gland Biopsy (Optional Substudy)										
Salivary/Parotid Gland Biopsy 28-day window	X							X		Subject consent required.
Salivary Gland Ultrasonography (SG-US)										
SG-US [b] 7-day window					X			X		Parotid and submandibular glands on both sides.
Laboratory Tests										
Hematology	X	X	X	X	X	X	X	X	X	
Serum Chemistry Panel	X	X	X	X	X	X	X	X	X	
Lipid Panel (Fasting)	X		X	X	X	X	X	X	X	
Urinalysis	X	X	X	X	X	X	X	X	X	
HbA1c								X	X	
UPCR	X	X	X	X	X	X	X	X	X	
eGFR	X	X	X	X	X	X	X	X	X	
ESR	X	X	X	X	X	X	X	X	X	Local laboratory assessment by site.
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
HCQ concentration	X		X							Predose and 2 hours postdose. Collected as part of concomitant medications PK (refer to

pSS Table 2 Procedural Outline Branebrutinib Study IM014029 (Week 0 to Week 28)

Procedure	W0 D1 V2	W2 D15 (± 3 d) V3	W4 D29 (± 3 d) V4	W8 D57 (± 3 d) V5	W12 D85 (± 3 d) V6	W16 D113 (± 3 d) V7	W20 D141 (± 3 d) V8	W24 D169 (± 3 d) V9 (EOT) [a]	W28 D197 (± 3 d) V10 Safety FU	Notes
										Section pSS 8.5, pSS Table 8).
[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Cryoglobulin test	X		X	X	X	X	X	X	X	Local laboratory assessment by site.
[redacted]	[redacted]				[redacted]			[redacted]		
[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
hsCRP	X	X	X	X	X	X	X	X	X	
Beta-2-microglobulin	X	X	X	X	X	X	X	X	X	
TBNK	X	X	X		X			X	X	
[redacted]	[redacted]		[redacted]		[redacted]	[redacted]		[redacted]	[redacted]	
Pregnancy Test (serum or urine)	X		X	X	X	X	X	X	X	WOCBP only. Must have negative pregnancy test within 24 hours prior to the start of treatment.
[redacted]	[redacted]							[redacted]		[redacted]
PK Assessments										
Standard blood samples for the PK of branebrutinib [c]	X		X	X		X		X		Refer to Section pSS 8.5, pSS Table 8 for details.

pSS Table 2 Procedural Outline Branebrutinib Study IM014029 (Week 0 to Week 28)

Procedure	W0 D1 V2	W2 D15 (± 3 d) V3	W4 D29 (± 3 d) V4	W8 D57 (± 3 d) V5	W12 D85 (± 3 d) V6	W16 D113 (± 3 d) V7	W20 D141 (± 3 d) V8	W24 D169 (± 3 d) V9 (EOT) [a]	W28 D197 (± 3 d) V10 Safety FU	Notes
Blood samples at preselected sites for the PK of branebrutinib and metabolites [d]	X			X						Refer to Section pSS 8.5, pSS Table 8 for details.
Blood samples for the PK assessment of concomitant medications [e]	X		X							Refer to Section pSS 8.5, pSS Table 8 for details.
Biomarker Sampling										
[redacted]										
[redacted]										
[redacted]										
[redacted]										
[redacted]										
[redacted]										
[redacted]										

pSS Table 2 Procedural Outline Branebrutinib Study IM014029 (Week 0 to Week 28)

Procedure	W0 D1 V2	W2 D15 (± 3 d) V3	W4 D29 (± 3 d) V4	W8 D57 (± 3 d) V5	W12 D85 (± 3 d) V6	W16 D113 (± 3 d) V7	W20 D141 (± 3 d) V8	W24 D169 (± 3 d) V9 (EOT) [a]	W28 D197 (± 3 d) V10 Safety FU	Notes
[redacted]	[redacted]		[redacted]		[redacted]			[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]		[redacted]			[redacted]	[redacted]	[redacted]
[redacted]	[redacted]							[redacted]		[redacted]
Study Treatment										
Randomize	X									
Dispense/Administer Study Treatment	X	X	X	X	X	X	X	X		Note: At Week 2 and Week 24 the subject is requested to bring IP to the site visit and IP is administered at the site; no new kit is dispensed at these visits.
Study Treatment Compliance		X	X	X	X	X	X	X	X [h]	

[redacted]; AE = adverse event; ANA = antinuclear antibody; [redacted]; BP = blood pressure; BTK = Bruton's tyrosine kinase; [redacted]; d = day; DAS28-CRP = Disease Activity Score-28 C-reactive protein; dsDNA = double-stranded DNA; ECG = electrocardiogram; eCRF = electronic case report form; EDC = RAVE electronic data capture; eGFR = estimated glomerular filtration rate; EOT = end of treatment; EQ-5 D 5 L = EuroQol-5 D-5 L; ESR = erythrocyte sedimentation rate; ESSDAI = EULAR Sjögren's Syndrome Disease Activity Index; ESSPRI = EULAR Sjögren's Syndrome Patient-reported Index; FU = follow-up; hsCRP = high-sensitivity C-reactive protein; Ig = immunoglobulin; [redacted]; IP = investigational product; LGF = lacrimal gland function; NRS = numeric rating score; PGA = Physician Global Assessment; PI = principal investigator; PK = pharmacokinetic; PROMIS = Patient-Reported Outcomes Measurement Information System; [redacted]; RNA = ribonucleic acid; [redacted]; SAE = serious adverse event; SGA = Subject Global Assessment; SG-US = salivary gland ultrasonography; SSA = Sjögren's syndrome-associated antigen A; SSB = Sjögren's syndrome-associated antigen B; SG-US = salivary gland ultrasonography; TBNK = T, B, and natural killer cells; UPCR = urine protein:creatinine ratio; V = visit; WOCBP = women of childbearing potential

[a] If the decision has been made for a subject to permanently discontinue treatment before the planned Week 24 visit (Section pSS 7.1.1), the subject should undergo a Week 24 EOT visit as specified in the Week 24 column of this table, followed by a Week 28 Safety FU visit, 4 weeks (±3 d) later, as specified in the Week 28 column of this table. The appropriate eCRF pages for the EOT and Safety FU visits should be completed accordingly.

[b] Subjects who terminate the study early require a SG-US examination at the EOT visit only if that visit is ≥ 4 weeks from the date of randomization or ≥ 4 weeks from Week 12 and should have the EOT SG-US examination NO MORE than 7 days from the EOT visit.

[c] Blood samples for the PK assessment of branebrutinib concentrations will be taken predose from all study subjects at Week 0 (Day 1), Week 4 (Day 29), Week 8 (Day 57), Week 16 (Day 113), and Week 24 (Day 169), and postdose at Week 0 (Day 1), Week 8 (Day 57), and Week 24 (Day 169) at approximately 0.5, 1, 2, and 4 hours after dosing.

[d] At preselected clinical sites only, blood samples for the PK assessment of branebrutinib and its metabolites concentrations will be taken predose at Week 8 (Day 57); and postdose at Week 0 (Day 1) and Week 8 (Day 57) at approximately 0.5, 1, 2, and 4 hours. In addition, samples will be taken postdose at 6 hours and from 8-10 hours (flexible window) and 10-12 hours (flexible window) on the same days. A PK sample will also be drawn at Week 0 (Day 2) at 24 hours after dosing (predose of branebrutinib on Day 2). (For these assessments, collected blood samples will be aliquoted into 2 tubes.)

[e] Blood samples for PK assessment of relevant concomitant medications that are sensitive substrates of CYP2C8 and other potentially relevant drug metabolizing enzymes and P-gp transporter may be measured post-hoc. For these concomitant medications, plasma samples will be collected predose and 2 hours postdose at Week 0 (Day 1) and Week 4 (Day 29). For subjects taking HCQ on-study, whole blood samples at predose and 2 hours postdose of branebrutinib on both Day 1 (Week 0) and Day 29 (Week 4) will be collected in addition for the assessment of HCQ level.

[redacted]

[h] Study treatment compliance is to be performed at Week 28 only if the subject's study participation has completed and the subject failed to return study drug at the prior visit.

When multiple assessments are conducted at a single visit, the following is the order in which they should be performed:

1. Patient-reported Outcomes (eg, SGA, EQ-5 D-5 L, etc)
2. Safety assessments (eg, vitals, AEs)
3. Investigator-administered Assessments (eg, PGA, joint count, etc)
4. Laboratory tests (eg, safety laboratory tests, PK assessments, biomarker assessments)
5. Treatment dosing

PSS 2 INTRODUCTION

An overall introduction to this protocol employing a master protocol design for 3 separate immune-mediated indications is provided in Section Master 1.2.

pSS 2.1 Background and Research Hypothesis

The pSS sub-protocol for Study IM014029 is designed to evaluate the efficacy and safety of branebrutinib in addition to background disease therapy in the treatment of subjects with moderate to severe pSS. Based on several key underlying molecular mechanisms of pSS targeted by BTK inhibition, we will test the hypothesis that branebrutinib is effective in the treatment of subjects with pSS.

pSS is a complex chronic, systemic, immune-mediated disease affecting the exocrine glands characterized by lymphocytic infiltration of salivary and lacrimal glands, systemic manifestations including renal, pulmonary and neurological complications, and increased incidence of lymphoma.[17] The disease is chronic and damage is slowly progressive, often initially presenting as persistent dryness of the mouth and eyes due to functional impairment of the salivary and lacrimal glands. While the disease was previously considered to be a localized or glandular disease, pSS is now increasingly recognized as a systemic disease. More than half of pSS patients experience extraglandular symptoms, including overwhelming fatigue, arthralgias and myalgias, and Raynaud's phenomenon. Extraglandular manifestations may also involve the joints, lungs, skin, kidneys, and nervous system, and are responsible for many of the primary salient features of disease reported by subjects. The disease is heterogeneous, and not all subjects exhibit all of the same symptoms. Similarly, as our understanding of the pathophysiology of the disease improves, it is clear that various immunologic mechanisms drive disease.

B and T cells play key roles in the pathobiology of pSS.[17] As evidenced by hypergammaglobulinemia, alterations in B cell subpopulations, ectopic germinal center-like structures in the affected glands, and increased risk of lymphoma, B cells are critical in driving the disease.[17] B cells produce autoantibodies such as anti-Ro/SSA and anti-La/SSB that can amplify the production of Type I IFNs and deposit at sites of inflammation in the glands, leading to the production of pro-inflammatory cytokines.[17] Within salivary glands, ectopic germinal center-like structures have been identified, which likely serve as primary sites for B cell-T cell interactions.[18] BlyS, which drives B cell proliferation and survival, has been shown to be elevated both in the serum and salivary glands of pSS subjects.[19, 20, 21] Recently, increased levels of BTK protein have been observed in circulating B cells of patients with pSS and appear to correlate with RF levels and parotid gland T cell infiltration.[4] Since BTK plays an essential role in the mediation of BCR response to autoantigen and pro-inflammatory signaling in B cells, BTK inhibition may target key underlying molecular mechanisms of pSS. On this basis, the BTK inhibitor branebrutinib will be tested for efficacy in the treatment of this patient population.

There is no currently approved treatment that targets the underlying mechanism(s) of pSS, indicating a clear unmet medical need in this patient population.

The European League Against Rheumatism (EULAR) Sjögren's Syndrome Disease Activity Index (ESSDAI), which is designed to measure systemic disease activity across 12 organ-specific domains, and the EULAR Sjögren's Syndrome Patient-reported Index (ESSPRI), which measures subjective symptoms of dryness, pain, and fatigue, have recently been developed and validated for evaluation of therapeutic agents in pSS. Subsequent work has defined the patient-level relevant cut-offs for change for both the ESSDAI and ESSPRI scores for use in clinical studies. The disease activity levels for ESSDAI were defined (low activity < 5, moderate activity ≥ 5 and ≤ 13, and high activity ≥ 14). The MCII for ESSDAI was defined as an improvement of ≥ 3 points, and for ESSPRI, the minimally clinically important improvement (MCII) was defined as a decrease of at least one point or 15%.

ESSDAI-defined disease activity levels will enable the enrollment of a moderate to severe disease activity sub-protocol in this study (ESSDAI ≥ 6). Limiting the population to subjects with an ESSDAI of at least 6 will enable adequate detection of the MCII of ≥ 3 points to discriminate between the effects of active treatment and PBO. Considering the small sample size and the relatively short treatment duration (24 weeks) of this study, ensuring sufficient patients are enrolled who have disease characteristics amenable to improvement will enable better signal detection for this asset to help guide future development.

In the context of an early phase clinical study, it is reasonable to ensure that as many subjects as possible enter the study with multiple active, responsive ESSDAI domains, so that treatment effects might be observed in as many domains as possible, as this will provide a more robust dataset to aid the design of subsequent clinical studies. To meet this end, all subjects will be required to have a positive score in at least 1 of the following responsive domains (articular, biological, glandular, hematological, or lymphadenopathy) contributing to their composite ESSDAI score of 6 or more to enter the study, in addition to positive score(s) from any of the other 7 ESSDAI domains that may be active in qualifying patients.

pSS 2.1.1 Study Hypotheses

Since BTK plays a central role in the pathology of pSS, the hypothesis of this study is that BTK inhibition will provide benefit in the treatment of subjects with moderate to severe pSS.

pSS 2.2 Benefit/Risk Assessment

At this early stage in the development of branebrutinib for the treatment of immune-mediated disorders, assessments of benefit and risk rely on nonclinical data and data from completed Phase 1 studies in healthy volunteer subjects. The proposed 9 mg QD dosing regimen reflects implementation of appropriate safety margins (> 500× based on the AUC in rats and dogs at the NOAEL [20 mg/kg/day and 15 mg/kg/day in rats and dogs, respectively]) and is within the range of doses tested in the FIH study (Study IM014001[37]).

The effects of BTK inhibition by branebrutinib have been documented in pharmacology studies, and the potential for benefit in RA and SLE have been demonstrated by nonclinical studies using mouse models of RA and SLE. branebrutinib demonstrated robust in vivo efficacy in CIA and CAIA murine models of RA, protecting against clinically evident disease, histological joint

damage, and bone mineral density loss. In both models, maximal efficacy was observed with ≥ 95% inactivation of BTK in vivo. Similarly, potent efficacy was observed in a mouse model (New Zealand Black and New Zealand White) of lupus-induced nephritis (see branebrutinib IB Section 4.1.1.2[12] for further details).

Findings in nonclinical toxicology studies were consistent with expectations based on the pharmacology of branebrutinib and included on-target PD effects such as decreases in B cells, suppression of keyhole limpet hemocyanin-specific IgM and IgG responses, and dose-related germinal center lymphoid depletion of minimal to moderate severity in the gut-associated lymphatic tissue.

branebrutinib-related pancreatic toxicity was identified in oral SD rat toxicity studies with up to 6 months of exposure.[39, 40, 41] Findings related to branebrutinib were noted at all doses, and were generally islet-centric (see the branebrutinib IB[12] for further details). These pancreatic lesions are similar to those observed with other BTK inhibitors and represent an exacerbation of an age-related pancreatic finding specific to rats.[42, 43, 44, 45] As such, these findings were considered nonadverse. The FDA has acknowledged that pancreatic lesions observed in rats treated with BTK inhibitors are unlikely to have relevance to the safety assessment for human subjects treated with this drug class.

With the exception of an unrelated SAE that was consistent with the subject's medical history, AEs in the FIH study (Study IM014001[37]) were mild to moderate, reversible, and consistent with expectations based on nonclinical experience.

Based upon the mechanism of action of the compound (immunosuppression), BMS has implemented additional assessments and risk mitigation approaches (including careful consideration of appropriate exclusion criteria and monitoring of subjects during and after dosing) in combination with conventional safety monitoring. In Parts A, B, C, and D of the FIH study,[37] there were no dose-related elevations of amylase, lipase, or fasting glucose; no decreases in WBCs or Ig levels; and no clinically significant infections; however, this protocol continues to stipulate exclusion criteria (eg, assessment for LTBI and chronic viral infections) and clinical and laboratory monitoring to reduce the risk of infection.

Because of the slow return of BTK activity following the discontinuation of branebrutinib dosing (based on post-hoc analyses following Study IM014001), BTK occupancy was found to be between 10% and 30% with a steep downward trend following treatment with 10 mg branebrutinib for 2 weeks), the duration of postdose follow-up of 4 weeks was chosen to account for the time needed to recover BTK activity.

To minimize risk to participating subjects, this protocol has inclusion and exclusion criteria appropriate to the populations and proposed treatments, as well as frequent study visits for safety assessments. Blinded safety data will be reviewed on an ongoing basis by the BMS Medical Monitor and pharmacovigilance group to look for emerging safety trends or issues, and an independent external DMC will be in place for the duration of the study.

In order to provide active study treatment while receiving PBO treatment for a maximum of 24 weeks, subjects in the pSS sub-protocol will also receive protocol-defined SOC therapy for

their primary disease. Although successful CS tapering for those taking ≥ 10 mg/day will be encouraged as appropriate, inability to taper or a requirement to increase the CS dose to protect a subject's safety or well-being will not be prohibited by the protocol.

The risk for drug-DDIs with branebrutinib has previously been assessed. The potential for clinically relevant DDIs of branebrutinib with substrates of a number of enzymes and transporters (cytochrome P450 [CYP]1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, and organic anion transporting polypeptide OATP1B1 and 1B3) is likely to be minimal based on the low projected therapeutic concentration (Cmax < 0.20 μM) and high serum protein binding.[46] Based on the results of Study IM014013 and in vitro studies, branebrutinib may affect the PK of drugs that are sensitive substrates of CYP2C8 and P-glycoprotein (P-gp) as a weak inhibitor. Therefore, until more knowledge is gained, drugs that are sensitive substrates of CYP2C8 and P-gp may be restricted or excluded based on their therapeutic window and metabolism.

In vivo studies to evaluate the developmental and reproductive effects of branebrutinib have shown developmental toxicity in rabbits (at an exposure multiple of 53× relative to the dose of 9 mg proposed for this study) that were associated with maternal mortality (IB Section 4.3.5[12]). At the NOAEL of 40 mg/kg/day, the safety margin was 16× compared to the human AUC at 10 mg MAD. branebrutinib was not associated with maternal or developmental toxicity in pregnant rats at exposure multiples up to 437× (versus human AUC at 10 mg MAD). Based on the exposure safety multiple, there is minimal risk to WOCBP. However, to ensure safety, the study will require WOCBP to use highly effective contraception, and pregnant women will not be enrolled in this study. It is not known whether branebrutinib passes into human milk. Therefore, breastfeeding women will also not be enrolled in this study. The DDI study with oral contraceptives (Study IM014023) demonstrated lack of PK interaction,[47] which ensures efficacy of hormonal contraception co-administered with branebrutinib.

PSS 3 OBJECTIVES AND ENDPOINTS

pSS Table 3 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To compare the efficacy of branebrutinib with PBO at Week 24 in the treatment of subjects with pSS	Proportion of subjects with at least 3 of the following at Week 24: • Decrease of ≥ 1 point or 15% from baseline in the ESSPRI Total Score • Decrease of ≥ 3 points from baseline in ESSDAI score • Decrease of ≥ 25% from baseline in ocular staining score, or if normal score at baseline no change to abnormal • Increase of ≥ 25% from baseline in stimulated salivary flow • Improvement in one or more serological markers (RF, IgG, complement C3 or C4, cryoglobulin)
Additional	
• To compare the efficacy of branebrutinib with PBO at Week 24 in the treatment of subjects with pSS	• Decrease of ≥ 1 point or 15% in the ESSPRI Total Score • Decrease of ≥ 3 points from baseline in ESSDAI score • Decrease of ≥ 25% from baseline in ocular staining score, or if normal score at baseline no change to abnormal • Increase of ≥ 25% from baseline in Schirmer's test score, or if normal score at baseline no change to abnormal • Increase of ≥ 25% from baseline in TBUT, or if normal score at baseline no change to abnormal • Increase of ≥ 25% from baseline in stimulated salivary flow • Improvement in one or more serological markers (RF, IgG, complement C3 or C4, cryoglobulin) • Change from baseline in autoantibody titers, hsCRP, and ESR • Change from baseline in DAS28-CRP • Change from baseline in the EQ-5 D-5 L score • Change from baseline in PROMIS Fatigue 6 a • Changes from baseline in PGA and SGA • Changes from baseline in NRS for Mouth and Eye Dryness
Safety	
• To compare the safety and tolerability of branebrutinib with PBO in subjects with pSS	• Number and proportion of subjects experiencing SAEs, AEs, and abnormalities in laboratory parameters, vital signs, and ECGs
Exploratory	
• [redacted]	

pSS Table 3 Objectives and Endpoints

Objectives	Endpoints
[redacted]	

[redacted] ADME = absorption, distribution, metabolism, and excretion; AE = adverse event; ANA = antinuclear antibody; [redacted]; BTK = Bruton's tyrosine kinase; [redacted]; dsDNA = double-stranded deoxyribonucleic acid; ECG = electrocardiogram; EQ-5 D-5 L = Euro Quality of Life Five Dimensions Questionnaire: 5 Level version; ESR = erythrocyte sedimentation rate; ESSDAI = European League Against Rheumatism Disease Activity Index; ESSPRI = European League Against Rheumatism Patient-reported Index; hsCRP = high-sensitivity C-reactive protein; [redacted]; Ig = immunoglobulin; IL = interleukin; [redacted]; NRS = numeric rating score; PBO = placebo; PGA = Physician Global Assessment; PK = pharmacokinetic; PROMIS = Patient-Reported Outcomes Measurement Information System; pSS = primary Sjögren's syndrome; [redacted]; SAE = serious adverse event; [redacted]; SGA = Subject Global Assessment; [redacted]; TBUT = tear break-up time; [redacted]

PSS 4 STUDY DESIGN

pSS 4.1 Overall Design

- This is a double-blind, PBO-controlled multicenter Phase 2a study to assess the effect of branebrutinib treatment concomitant with background disease therapy within protocol-defined limits in subjects with moderate to severe pSS.
- Approximately 45 subjects will be randomized in the pSS sub-protocol. Sample size considerations are presented in Section pSS 9.1 Sample Size Determination.
- For the pSS sub-protocol, there will be a 24-week double-blind PBO-controlled treatment period in which subjects will receive branebrutinib 9 mg or PBO QD.

- Blinded treatment assignment will be conducted by randomization on Day 1 and managed by IRT. Subjects will undergo screening evaluations to determine eligibility within 28 days prior to administration of study medication. After successfully meeting entry criteria and completing screening assessments, subjects in the pSS sub-protocol will be randomized in a blinded manner to receive branebrutinib 9 mg or PBO in a 2:1 ratio.
- The total duration of participation in the pSS sub-protocol will be approximately 32 weeks and will be divided into the following periods: screening (up to 4 weeks [28 days]), double-blind PBO-controlled treatment for 24 weeks (Week 0 to Week 24), and follow-up (4 weeks).
- Efficacy and safety will be assessed throughout the study (see Section pSS 8.1 Efficacy Assessments, Section pSS 8.2 Adverse Events, and Section pSS 8.4 Safety for details of assessments). Blood samples will be collected for PK and biomarker clinical laboratory assessments (see Section pSS 8.5, Section pSS 8.5.1, [redacted], respectively, for details of assessments).
- An independent DMC will assess study findings on a periodic basis (Section pSS 4.1.1).

The study design schematic for the pSS sub-protocol is presented in Section pSS 1.2.

pSS 4.1.1 DMC and Other External Committees

To ensure the safety of study subjects, across all sub-protocols, an external independent DMC consisting of 2 experienced rheumatologists, an infectious disease clinician, and a statistician will be established for ongoing evaluation of safety assessments, AEs, and laboratory measurements. An independent reporting statistician not involved in the conduct of the study will be designated to provide the DMC with essential safety data unblinded to treatment during the study, if required.

The DMC will conduct at regular, prespecified intervals and on an ad hoc basis if warranted, safety review meetings throughout the study to ensure that the benefit and risks of study participation remain acceptable. Ad hoc meetings may be initiated by the DMC or by the Sponsor based on emerging new safety information. Based on the DMC's assessment, recommendations of protocol modifications or other actions may occur, including but not limited to sample size adjustment, study modification, or discontinuation of the study or one or more of the sub-studies. In addition, hold of enrollment, pending more detailed assessment may be requested.

Blinded SUSARs will be sent to the DMC members on an ongoing basis. SAEs will be sent to the DMC on a monthly basis or on an ongoing basis as requested by the DMC.

The DMC will review safety data including but not limited to SAEs and AEIs. At the request of the DMC, designated personnel will provide further information on the medical assessment for a specific case.

The DMC may also consider external data from other branebrutinib studies that may be initiated in future or from novel scientific information that may be generated on branebrutinib or other BTK inhibitors.

Further details of DMC responsibilities, specific timing of safety reviews, content, and methods of data reports, authorities, processes, and procedures will be specified in the DMC charter.

pSS 4.2 Number of Subjects

It is expected that approximately 45 subjects will be randomized in the pSS sub-protocol.

Details regarding sample size determination are provided in Section pSS 9.1.

pSS 4.3 End of Study Definition

The start of the study is defined as the date that the first subject signs the informed consent. The end of the pSS sub-protocol is defined as the last visit of the last subject to complete the study or the final scheduled procedure shown in the SoA (Section pSS 1.3). Study completion for the pSS sub-protocol is defined as the final date on which data for the primary endpoint was or is expected to be collected, if this is not the same. The master protocol study will be reported only after the last endpoint has been analyzed for all 3 sub-protocols.

The total duration of study participation for subjects in the pSS sub-protocol is expected to be approximately 32 weeks.

pSS 4.4 Scientific Rationale for Study Design

(Please refer to Master Section 1.2 for rationale supporting the choice of a master protocol design to evaluate the safety and efficacy of branebrutinib in 3 immune-mediated/autoantibody-related diseases.)

The pathology of pSS involves several signaling events regulated by BTK, as described in Section pSS 2.1. It is therefore hypothesized that BTK inhibition will result in clinical benefits in subjects with pSS.

Because there is no currently approved treatment for pSS that targets the underlying mechanism(s) of the disease, there is not an appropriate active comparator to use in this study. All subjects will continue on their commonly used disease modifiers and symptomatic therapies (including hydroxychloroquine, pilocarpine, cevimeline, cyclosporine eye drops, artificial tears/saliva, and low-dose oral CS) for the duration of the screening and dosing periods, thus mitigating the impact of receiving a PBO.

A PBO control will be included in the pSS sub-protocol to allow the effects of treatment, both desired and adverse, to be appropriately compared against active treatment, with effort to minimize treatment period on PBO, as well as to allow continuation of certain background therapy within protocol-defined limits.

pSS 4.5 Justification for Dose

The selection of the branebrutinib dose and regimen to be assessed in this study was based on findings in the FIH and nonclinical studies.

In the MAD panels (Part B) of the FIH study (Study IM014001), healthy subjects received branebrutinib orally QD for 14 days at 4 dose levels (0.3, 1, 3, and 10 mg; n = 6 per dose).[37] Increases in Cmax and AUC(TAU) were approximately dose proportional within the dose levels tested. The mean T-HALF was shorter than 2 hours across the dose range tested, indicating that

branebrutinib was rapidly eliminated from the body. Consequently, as expected, accumulation at steady-state after multiple daily dosing was negligible.

The safety profile of branebrutinib 3 mg and 10 mg doses in Study IM014001 demonstrated lack of dose effects on safety. The drug was well-tolerated at both dose levels with most AEs also observed for the subjects treated with PBO. The AEs mainly included headache and upper respiratory tract infection. Based on the AUC in rats at the NOAEL (61,900 ng•h/mL), the safety multiple in humans after multiple doses of 10 mg is > 500×.[12] In this study, the dose level of branebrutinib will be 9 mg; therefore, the safety margin is sufficient for humans participating in the study.

The dose for branebrutinib was selected based on data from biomarkers obtained in post-hoc analysis of Study IM014001. The biomarkers evaluated were BTK occupancy by branebrutinib, inhibition of ex vivo stimulated CD69 expression, and plasma CXCL13 levels. The maximum occupancy reached ≥ 99% at branebrutinib doses of 1 mg and above (100%; maximum occupancy at doses ≥ 3 mg); however, the time to reach maximum occupancy was faster and maintained for a longer duration at 3 mg and 10 mg doses (solution formulation). The variability of the effect was lower for the higher dose of 10 mg. A similar result was obtained for CD69 inhibition, while the largest median inhibition in CD69 expression was observed at the branebrutinib 10 mg dose. The highest inhibition of plasma levels of CXCL13 was also obtained at the 10 mg dose level. Considering the higher variability and expression of BTK in patients with immune-mediated disorders,[4] the higher dose is expected to sustain more stable inhibition of BTK for chronic treatment of heterogenous patients.

The comparison of exposure between the branebrutinib 10 mg solution formulation from Study IM014001 and the branebrutinib 9 mg capsule formulation (3 × 3 mg) from Day 1 Cycle 2 in Study IM014023 demonstrated comparable exposure for Cmax and AUC(TAU) with only slight delay in Tmax for capsule formulation. Thus, the use of 3 × 3 mg capsules of branebrutinib is expected to be equivalent to the 10 mg solution formulation in terms of exposure, safety, and PD effects considering the specifics of the patient population.

The exposure for this dose level is also much lower than the safety limit for exposure identified in preclinical studies; as previously mentioned, based on the AUC in rats at the NOAEL, the safety multiple in humans after multiple doses of 10 mg is > 500×.

In summary, the dose to evaluate the PD response with optimal safety and efficacy was chosen to be 9 mg branebrutinib administered as 3 × 3 mg capsules (details of treatment administration are provided in Section pSS 6.1).

PSS 5 STUDY POPULATION

Eligibility criteria for this sub-protocol have been carefully considered for the safety of the study subjects and to ensure that the results of the study can be interpreted. It is imperative that randomized subjects meet all eligibility criteria.

Screening evaluations must be completed and reviewed by the investigator to confirm whether potential subjects are eligible. The investigator will maintain a screening log to record details of

all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable. Subject eligibility will be reviewed and confirmed by the Medical Monitor or [redacted] Central Review Services prior to randomization.

pSS 5.1 Inclusion Criteria

To be eligible to participate in this study, an individual must meet all of the following criteria:

1) **Signed Written Informed Consent: pSS Sub-protocol**
   a) Willing to participate in the study after completing all informed consent procedures and sign the ICF
   b) Willing and able to complete all study-specific procedures and visits
2) **Age and Reproductive Status: pSS Sub-protocol**
   a) **Not Applicable per Revised Protocol 02 -** Male and female patients, aged 18 years (or age of majority) to 65 years, inclusive
   b) **Not Applicable per Revised Protocol 02 -** WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of β-HCG) within 24 hours prior to the start of study treatment.
   c) **Not Applicable per Revised Protocol 02 -** Women must not be breastfeeding.
   d) **Not Applicable per Revised Protocol 02 -** WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study treatment(s) branebrutinib or PBO, 30 days before screening and 33 days posttreatment completion or longer based on country-specific label for other background therapy.
   e) **Not Applicable per Revised Protocol 02 -** Male subjects who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception and fetal protection (APPENDIX 4) for the duration of treatment with study treatment(s) (branebrutinib or PBO) plus 33 days after the final dose of study treatment, or longer based on country-specific label for other background therapy. In addition, male subjects must be willing to refrain from sperm donation during this time.
   f) **Not Applicable per Revised Protocol 02 -** WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements, and still must undergo pregnancy testing as described in this section.

Investigators shall counsel WOCBP, and male subjects 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 study drug, 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.

   g) **Not Applicable per Revised Protocol 03 -** Female Participants
   h) **Not Applicable per Revised Protocol 03 -** Male Participants

i) Female Subjects

i.) Females, ages 18 years or local age of majority to 75 years, inclusive

ii.) Women who are not of childbearing potential are exempt from contraceptive requirements. Women subjects must have documented proof that they are not of childbearing potential.

iii.) WOCBP must have a negative highly sensitive pregnancy test (minimum sensitivity 25 IU/L or equivalent units of 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.

iv.) Additional requirements for pregnancy testing during and after study intervention are located in Section pSS 1.3, SoA

v.) 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

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

vii.) WOCBP are permitted to use hormonal contraception methods (as described in APPENDIX 4)

viii.) A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one 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, for at least 30 days before screening and at least 33 days posttreatment completion or longer based on country-specific label for other background therapy and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction for the same time period

j) Male Subjects

i.) Males, ages 18 years or local age of majority to 75 years, inclusive.

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 subjects 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 subjects 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 33 days after the last dose of study intervention or longer based on country-specific label for other background therapy.

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 33 days after the last dose of study intervention in the male participant or longer based on country-specific label for other background therapy.

vi.) Male subjects 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 subjects have undergone a successful vasectomy, during the intervention period and for at least 33 days after the last dose of study intervention or longer based on country-specific label for other background therapy.

vii.) Male subjects must refrain from donating sperm during the intervention period and for at least 33 days after the last dose of study intervention or longer based on country-specific label for other background therapy.

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

3) Type of Subject and Target Disease Characteristics: pSS Sub-protocol

a) Diagnosed with pSS ≤ 7 years before screening

b) Subjects diagnosed or classified as having pSS (primary Sjögren's syndrome is defined as Sjögren's syndrome in the absence of another immune-mediated disease or rheumatologic condition) based on the 2016 ACR-EULAR Classification Criteria for pSS, with disease duration from time since diagnosis of at least 16 weeks prior to screening with moderate to severe activity per ESSDAI

c) ESSDAI score of ≥ 6, including disease activity (any score > 0) in at least one of the following domains: glandular, articular, hematological, biological, lymphadenopathy

d) Positive anti-Ro/SSA plus at least one of the following at screening, as determined by central laboratory:

- low C3
- low C4
- positive for RF
- positive cryoglobulin test (must be performed at local laboratory)
- IgG > 16 g/L

e) **Not Applicable per Revised Protocol 03 -** A stimulated salivary flow of > 0.05 mL/minute at screening and randomization, or unstimulated whole saliva secretion > 0.01 mL/minute

f) A stimulated salivary flow rate > 0.05 mL/minute or unstimulated saliva flow rate > 0.01 mL/minute at screening and randomization.

4) Medications for Target Disease: pSS Sub-protocol

a) **Not Applicable per Revised Protocol 03 -** Requirements for subjects who are receiving chronic therapy with oral NSAIDs (including marketed cyclooxygenase-2 inhibitors) are

as follows; exceptions or changes may be possible with approval by the [redacted] Medical Monitor:

- The oral NSAID dose must be stable for 14 days before the screening visit and must remain stable until randomization and throughout the study.
- No more than 1 oral NSAID may be used (at a stable dose) during the study and may be combined with topical NSAIDs.
- Use of 1 or more topical NSAID is permitted but must follow a stable regimen throughout the study.
- Oral NSAIDs may not be taken on days of study visits.

b) **Not Applicable per Revised Protocol 03 -** Standard of care is required for ≥ 12 weeks before the screening visit and must be at a stable dose for ≥ 8 weeks before the screening visit and remain stable until randomization and throughout study participation. Details for specific medications are as follows:

- Antimalarials: -HCQ monotherapy is permitted. Also see exclusion criteria below regarding HCQ dose limitation and exclusionary screening HCQ levels.
- Patients on HCQ must have an ophthalmology assessment within 6 months prior to randomization, confirming no findings of HCQ induced retinal toxicity.

c) **Not Applicable per Revised Protocol 03 -** CS:

- Oral CS use is permitted, but the dose must be ≤ 10 mg/day prednisone or equivalent and stable for ≥ 28 days before randomization and throughout study participation.
- Topical and inhaled CS use is permitted but must follow a stable regimen throughout the study and cannot be used on an as-needed basis. Inhaled CS for non-pSS conditions will not count against the maximum CS dose.
- IM, IA, intrabursal, IV, and modified-release CS are prohibited within 4 weeks before randomization or during the study.

d) Sialogogues, eg cevimeline, pilocarpine, **must be held** for 48 hours before the screening visit saliva flow testing

e) On study visit days, dried fruit slices, maltose lozenges, xylitol gum or candy, regular, sugarless or sugar-free gum or hard candies, or artificial saliva sprays or drops must be stopped **2 hours** before stimulated/unstimulated salivary flow measurements are taken

f) Requirements for subjects who are receiving chronic therapy with oral NSAIDs (including marketed cyclooxygenase-2 inhibitors) are as follows; exceptions or changes may be possible with approval by the [redacted] Medical Monitor:

- The oral NSAID dose must be stable for 14 days before the screening visit and must remain stable until randomization and throughout the study.
- No more than 1 oral NSAID may be used (at a stable dose) during the study and may be combined with topical NSAIDs.
- Use of 1 or more topical NSAID is permitted but must follow a stable regimen throughout the study.
- Oral NSAIDs may not be taken on days of study visits until after all study assessments have been completed.

g) SOC with HCQ is allowed provided treatment started ≥ 12 weeks before the screening visit and must be at a stable dose for ≥ 8 weeks before the screening visit and remain stable until randomization and throughout study participation. Details are as follows:
   - Antimalarials: HCQ monotherapy is permitted. Also see exclusion criteria below regarding HCQ dose limitation and exclusionary screening HCQ levels.
   - Subjects on HCQ must have an ophthalmology assessment within 6 months prior to randomization, confirming no findings of HCQ induced retinal toxicity.

h) CS:
   - Oral CS use is permitted, but the dose must be ≤ 10 mg/day prednisone or equivalent and stable for ≥ 28 days before randomization and throughout study participation.
   - Topical and inhaled CS use is permitted but must follow a stable regimen throughout the study and cannot be used on an as-needed basis. Inhaled CS for non-pSS conditions will not count against the maximum CS dose.
   - IM, IA, intrabursal, IV, and modified-release CS are prohibited within 4 weeks before randomization.

5) Other Inclusion Criteria: pSS Sub-protocol

a) Subject re-enrollment (rescreening): This study permits the re-enrollment of a subject that has discontinued the study as a pretreatment (screening) failure (ie, subject has not been randomized/has not been treated). If re-enrolled, the subject must be re-consented.

pSS 5.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in the sub-protocol to which the subject is randomized in the study:

1) General Medical Conditions and History: pSS Sub-protocol

a) Any major illness/condition or evidence of an unstable clinical condition (eg, renal, hepatic, hematologic, gastrointestinal, endocrine, pulmonary, immunologic, psychiatric) or local active infection/infectious illness that, in the investigator's judgment, will substantially increase the risk to the subject if he or she participates in the study

b) Any major surgery within the last 30 days before the first dose of study treatment, or any surgery planned during the course of the study

c) Cancer or history of cancer or lymphoproliferative disease (other than adequately treated cutaneous basal cell or squamous cell carcinoma with no evidence of recurrence within the previous 5 years), including pre-lymphoma (pseudolymphoma of the orbit and small intestine, lymphomatoid granulomatosis, angioimmunoblastic lymphadenopathy, and lymphoid interstitial pneumonitis)

d) Class III or IV congestive heart failure as defined by the NYHA or any recent onset of heart failure resulting in NYHA Class III/IV symptoms

e) Acute coronary syndrome (eg, myocardial infarction, unstable angina pectoris) and/or any history of significant cerebrovascular disease within 24 weeks before screening

f) Current or recent (within 3 months before randomization) gastrointestinal disease, including gastrointestinal surgery, that could impact the absorption of study treatment

g) Inability to tolerate oral medication

h) Inability to tolerate venipuncture and/or inadequate venous access

i) Recent (within 6 months before randomization) drug or alcohol abuse as defined by the Diagnostic Criteria for Drug and Alcohol Abuse in the Diagnostic and Statistical Manual 5 (DSM 5)

j) Any other sound medical, psychiatric, and/or social reason as determined by the investigator

k) Subjects with a diagnosis of antiphospholipid antibody syndrome

l) Significant blood loss (> 500 mL) or blood transfusion within 4 weeks before randomization

m) **Not Applicable per Revised Protocol 03 -** Subjects with non-pSS concomitant illness (eg, asthma) that, in the opinion of the investigator, is likely to require additional systemic glucocorticosteroid therapy during the study

n) Any prior history of atrial fibrillation or flutter.

o) Subjects with non-pSS concomitant illness (eg, asthma) that, in the opinion of the investigator, is likely to require additional systemic CS therapy during the study.

2) Findings Related to Possible Infection: pSS Sub-protocol

a) **Not Applicable per Revised Protocol 03 -** Any of the following TB criteria:

- History of active TB prior to screening visit, regardless of completion of adequate treatment
- Signs or symptoms of active TB (eg, fever, cough, night sweats, and weight loss) during screening as judged by the investigator
- Any imaging of the chest (eg, chest x-ray, chest CT scan) obtained during the screening period, or anytime within 6 months prior to screening with documentation, showing evidence of current active or old pulmonary TB
- LTBI defined as positive IGRA, by QuantiFERON-TB Gold testing at screening, in the absence of clinical manifestations Note: Subject may be eligible if (i) there are no current signs or symptoms of active TB and (ii) subject has received adequate documented treatment for LTBI within 5 years of screening.

  Note: An IGRA test that is indeterminate with no signs or symptoms of active TB must be retested for confirmation. If the second test is again indeterminate the subject will be excluded from the study. If the retest is positive, the subject should be treated as having LTBI. If the retest is negative, subject may be eligible provided no other exclusion criteria for TB are met.

b) Hepatitis C, hepatitis B, or HIV infection as demonstrated by a positive blood screen for anti-HCV confirmed by positive reflex HCV RNA test, HBsAg, HBcAb, or HIV-1 and -2 antibody. Subjects who have been vaccinated for hepatitis B (HBsAb-positive) are not excluded.

   Note: Subjects who are newly found to be HIV-positive should be directed to appropriate follow-up care.

c) History of congenital or acquired immunodeficiency.

d) Known active infection, or any major episode of infection requiring hospitalization or treatment with parenteral (IM or IV) antimicrobial agents (eg, antibiotics, antiviral, antifungal, or antiparasitic agents) within 30 days of randomization, or completion of oral antimicrobial agents within 2 weeks of randomization.

e) Previous history of recurrent herpes zoster (more than 1 episode), disseminated herpes simplex, or influenza infection within 12 weeks before randomization or a history of disseminated/complicated herpes zoster infection (multidermatomal involvement, ophthalmic zoster, CNS involvement, or postherpetic neuralgia).

f) Chronic infection within 4 weeks of randomization (eg, pneumocystis, CMV, invasive bacterial or fungal infections, or atypical mycobacteria).

g) Any of the following TB criteria:

- History of active TB prior to screening visit, regardless of completion of adequate treatment
- Signs or symptoms of active TB (eg, fever, cough, night sweats, and weight loss) during screening as judged by the investigator
- Any imaging of the chest (eg, chest x-ray, chest CT scan) obtained during the screening period, or anytime within 6 months prior to screening, with documentation showing evidence of current active or old pulmonary TB
- LTBI defined as positive IGRA, by QuantiFERON-TB Gold testing at screening, in the absence of clinical manifestations Note: Subject may be eligible if (i) there are no current signs or symptoms of active TB and (ii) subject has received adequate documented treatment for LTBI within 5 years of screening; this treatment must have been completed as defined by local guidance and documented in the subject study file. Incomplete or ongoing treatment is unacceptable.

  Note: An IGRA test that is indeterminate with no signs or symptoms of active TB must be retested for confirmation. If the second test is again indeterminate, the subject will be excluded from the study, unless there is documentation of a local negative TB Spot test result. If the retest is positive, the subject should be treated as having LTBI. If the retest is negative, the subject may be eligible provided no other exclusion criteria for TB are met.

h) Subjects hospitalized with PCR-proven or suspected COVID-19 infection (unless for quarantine/observation) within the 3 months prior to randomization, as well as any subjects with any sequelae of prior COVID-19 infection at screening, regardless of time since infection.

3) Allergies and Adverse Drug Reaction: pSS Sub-protocol

a) History of allergy to BTK inhibitors or related compounds

b) History of any serious condition induced by drug allergy (such as anaphylaxis or hepatotoxicity)

4) Target Disease Exclusions/Exceptions: pSS Sub-protocol

a) Subjects who have a systemic immune-mediated disease other than pSS, such as RA, SLE, mixed connective tissue disease, or systemic sclerosis, that can better explain the majority of the symptoms (ie, secondary SS)

b) Subjects who have another immune-mediated disease or inflammatory condition that could interfere with assessment of response of pSS to therapy (eg, IgG4-related disease, systemic sclerosis, inflammatory bowel disease, gout)

c) Subjects with any other medical condition associated with sicca syndrome (eg, history of head and neck radiation treatment, diabetes mellitus, sarcoidosis, chronic graft-versus-host disease), subjects with sicca symptoms secondary to ongoing medication use based on the investigator's assessment

d) Active fibromyalgia with pain symptoms or signs that would interfere with joint assessment or requiring adjustment in medication within the 3 months before screening to control symptoms; subjects with fibromyalgia that is well controlled on stable treatment may otherwise be considered

e) Severe complications of pSS at the time of screening, including, but not restricted to, the following:

- Vasculitis with renal, digestive, cardiac, pulmonary or CNS involvement characterized as severe (note: cutaneous vasculitis is allowed)
- Active CNS or peripheral nervous system (PNS) involvement requiring high-dose steroids (> 10 mg/day)
- Renal disease including but not limited to the following:
  - Interstitial nephritis
  - Glomerulonephritis
  - Nephrotic syndrome with proteinuria > 3 g/day or UPCR > 339 mg/mmol and/or serum creatinine ≥ 2.0 mg/dL; subjects with interstitial nephritis with proteinuria < 1.5 g/day or UPCR < 169.5 mg/mmol and serum creatinine < 1.5 mg/dL may be included
- Severe pulmonary disease based on the investigator's assessment
- Active myositis requiring more than the maximum dose of CS
- Any type of lymphoma

5) Prior/Concomitant Therapy: pSS Sub-protocol

a) Inability to comply with restrictions and prohibited treatments as listed in Section pSS 6.7 Concomitant Therapy; inability to comply with discontinuation requirements (Section pSS 7.1)

b) **Not Applicable per Revised Protocol 03 -** Previous exposure to BTK inhibitors such as ibrutinib, acalabrutinib, or experimental drugs such as tirabrutinib, vecabrutinib, zanibrutinib, ARQ-531, GDC-0853, or any others

c) Exposure to JAK inhibitors such as tofacitinib, baricitinib, filgotinib, or upadacitinib within 8 weeks before randomization or during the study

d) Abatacept therapy within 6 months before randomization or during the study

e) Therapy with other biologics such as tocilizumab and anakinra within 8 weeks before randomization or during the study

f) Other investigational agents must be discontinued at least 12 weeks or 5 half-lives before screening, whichever is longer

g) **Not Applicable per Revised Protocol 03 -** Required discontinuation periods for immunomodulatory drugs (other than HCQ, which is permitted as monotherapy; see

exclusion criterion 5u for details of HCQ use), eg, cyclosporine, tacrolimus, etc or biologic drugs (including those specifically listed below) are provided in Section pSS 5.2. If a drug is not specifically listed, consult the [redacted] Medical Monitor for guidance. Usual discontinuation periods are 4 weeks or 5 half-lives whichever is longer.

h) Belimumab therapy within 6 months before randomization or during the study

i) Leflunomide therapy within 36 weeks before screening or during the study

j) Cyclosporine or tacrolimus therapy within 8 weeks before randomization or during the study

k) Therapy with azathioprine, sulfasalazine, or similar drugs within 8 weeks before randomization or during the study

l) IVIG therapy within 8 weeks before randomization or during the study

m) Diquafosol or rebamipide therapy within 4 weeks before randomization or during the study

n) Sialogogues, eg cevimeline, pilocarpine, must be taken on a stable dose regimen for 8 weeks prior to randomization and remain stable throughout the study, except as specified before certain visits when lacrimal and/or salivary gland testing will be performed. Sialogogues **must be held** for 48 hours before screening, Day 1, Week 12, Week 24 and Week 28 visits until after tests for tear production (Schirmer's, ocular staining score, tear break-up time) and stimulated/unstimulated salivary flow measurements have been performed. If lacrimal gland function (LGF) testing is done on a day other than the rest of the study assessments sialogogues **must be held** for 12 hours before lacrimal testing is performed.

o) Subjects who have a history of refractive eye surgeries (including but not limited to laser-assisted in situ keratomileusis, photorefractive keratectomy, and laser epithelial keratomileusis)

p) Subjects who have a history of full-thickness corneal transplantation (penetrating keratoplasty); however, subjects who have had endothelial keratoplasty are not excluded.

q) Subjects who have had cataract surgery within 6 months prior to randomization

r) Subjects are not permitted to have new installation of lacrimal punctum plugs within 4 weeks of randomization. Subjects with existing lacrimal punctum plugs are permitted to enroll, and have these plugs replaced as necessary during the study.

s) For oral CS restrictions, see Section pSS 6.7.1.

t) Other CS: IM, IV, IA, or oral modified-release CS treatment within 4 weeks before randomization or during the study

u) **Not Applicable per Revised Protocol 03 -** Treatment with DMARDs (excluding HCQ) or immunomodulators within 4 weeks before randomization; MTX treatment within 12 weeks before randomization or during the study. **HCQ whole blood concentration >2 µg/mL (at screening only) is exclusionary**. HCQ dose > 400 mg/day, new initiation, or dose increases during treatment are not permitted.

v) Antimalarial treatment (HCQ is permitted, but must be stable; initiation or change in dose during treatment is not permitted. Quinacrine or chloroquine treatment is not permitted during the study or within 4 weeks before randomization. For HCQ, see above criterion for requirements.

w) Current or past approved or investigational biologic DMARD treatments (eg, IL-6 inhibitors, IL-1 inhibitors, T cell modulators, and anti-CD20 agents [eg, rituximab]), other than abatacept treatment, within 12 months before randomization or during the study

x) Anti-TNF therapy such as adalimumab, certolizumab, etanercept, golimumab, infliximab, or biosimilars within 3 months before randomization or during the study

y) **Not applicable per Revised Protocol 03 -** Administration of a live vaccine within 90 days or an inactivated vaccine within 30 days before randomization; furthermore, live or inactivated vaccines should not be used during treatment or within the 14 days following the final dose of study treatment

z) Treatment with tricyclic antidepressants (eg, amitriptyline, desipramine, doxepin, imipramine, nortriptyline, trimipramine) or quetiapine, within 4 weeks before randomization

aa) Treatment with anticoagulant or antiplatelet therapies, including aspirin for cardioprotection, within 2 weeks prior to randomization or during the study

bb) Previous exposure to BTK inhibitors such as ibrutinib, acalabrutinib, or experimental drugs such as tirabrutinib, vecabrutinib, zanubrutinib, ARQ-531, GDC-0853, or any others

cc) Required discontinuation periods for immunomodulatory drugs (other than HCQ), eg, cyclosporine, tacrolimus, etc, or biologic drugs (including those specifically listed below) are detailed in pSS Table 6. If a drug is not specifically listed, consult the [redacted] Medical Monitor for guidance. Usual discontinuation periods are 4 weeks or 5 half-lives whichever is longer.

dd) Treatment with DMARDs (excluding HCQ) or immunomodulators beyond required washout period before randomization; MTX treatment within 12 weeks before randomization or during the study. **HCQ whole blood concentration >2 µg/mL (at screening only) is exclusionary**. HCQ dose > 400 mg/day, new initiation, or dose increases during treatment are not permitted.

ee) Administration of all live vaccines is prohibited within 90 days before randomization. Administration of inactivated vaccines and nonlive vaccines, including those for influenza and SARS-CoV-2, is prohibited within 30 days before randomization. See Section pSS Table 6 for corresponding on-treatment and posttreatment restrictions.

6) Physical and Laboratory Test Findings: pSS Sub-protocol

a) Clinically significant abnormalities on chest x-ray or ECG

b) Clinically significant abnormalities in laboratory tests including the following:

i. Serum ALT > 2× ULN, unless explicitly related to the indication based on the investigator's judgment.

ii. Serum AST > 2× ULN, unless explicitly related to indication based on the investigator's judgment.

iii. Serum total bilirubin > 1.5× ULN (does not apply to subjects with Gilbert's syndrome)

iv. Hemoglobin < 8 g/dL (< 80 g/L)

v. Proteinuria > 3.0 g/day (> 3,000 mg/day) or equivalent level of proteinuria as assessed by UPCR (3 mg/mg or 339 mg/mmol)

vi. eGFR < 50 mL/min/1.73 m^2 as calculated by the central laboratory

vii. Serum creatinine > 2.0 mg/dL (> 177 µmol/L)
viii. Absolute WBC count < 2.5×10^3/µL (< 2.5×10^9/L)
ix. Absolute neutrophil count < 1000/µL (< 1.0×10^9/L)
x. Platelet count < 100×10^3/µL (< 100×10^9/L)

c) Any other significant laboratory or procedure abnormalities that, in the opinion of the investigator, might pose unacceptable risk to the subject during the study.

d) BP > Grade 1 hypertension (> 159 mmHg systolic and > 99 mmHg diastolic) according to the 2018 ESC/ESH Guidelines for the management of arterial hypertension.

e) The following exclusionary ECG observations:

i. QTcF: > 480 msec
ii. QRS: > 120 msec
iii. Complete heart block
iv. Left bundle branch block
v. Mobitz II second-degree atrioventricular block
vi. Atrial fibrillation or flutter

7) Other Exclusion Criteria: pSS Sub-protocol

a) Prisoners or subjects who are involuntarily incarcerated. (Note: under certain specific circumstances and subject to local law a person who has been imprisoned may be included or permitted to continue as a subject. Strict conditions apply and BMS approval is required.)

b) Subjects who are employed by the Sponsor, clinical research organizations, or study site.

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

d) Inability to comply with the study protocol.

e) Inability to comply with restrictions as listed in Section pSS 5.3.

pSS 5.3 Lifestyle Restrictions

Study restrictions for contraception use by WOCBP and male subjects who are partners of WOCBP (APPENDIX 4) are required for this study.

pSS 5.3.1 Meals and Dietary Restrictions

With the exception of the 8-hour fasting requirement prior to blood sample collection for lipid panel and fasting glucose blood testing, no meal or dietary restrictions are required for this study. However, subjects are advised to consume in moderation (avoiding more than a single serving a day) cruciferous vegetables, such as cabbage, brussels sprouts, watercress, etc, as well as grapefruit and Seville oranges. Quinine (tonic water), St. John's wort and herbal medications are not allowed.

pSS 5.3.2 Caffeine, Alcohol, Tobacco, and Cannabinoids

With the exception of cannabinoids, which are not allowed, and prohibited alcohol abuse as defined by the Diagnostic Criteria for Drug and Alcohol Abuse in the DSM 5 within six months prior to randomization, and the restrictions described in pSS 5.3.1, there are no restrictions on caffeine, alcohol, or tobacco use for this study. However, subjects who use tobacco or alcohol

should be counseled for potential contraindications with nonstudy treatments as appropriate, and continued study participation should be based on investigator judgment.

pSS 5.3.3 Activity

With the exception of the restrictions surrounding the use of contraceptives during sexual activity mentioned above and included in Section pSS 1.3 Schedule of Activities, no activity restrictions are required for this study.

pSS 5.4 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but who are not subsequently randomized or entered in the study or included in the analysis population. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects, to meet the 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. Additional screening data from screen failure subjects, such as clinical data for disease assessment, laboratory tests, and other clinically relevant data, may be required.

pSS 5.4.1 Retesting During Screening Period

This pSS sub-protocol permits the rescreening of a subject who has been previously failed screening. If rescreened, the subject must be re-consented and will be assigned a new identification number, and a full screening visit must be performed again. A subject can only be rescreened 1 time (ie, if the subject fails 1 rescreening attempt, no additional rescreening is allowed).

Laboratory parameters and/or other assessments that initially do not meet eligibility requirements within the screening period may be repeated once in an effort to find all possible well-qualified subjects. Consultation with the Medical Monitor may be needed to identify whether repeat testing of any particular parameter is clinically relevant.

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

PSS 6 TREATMENT

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

Study treatment includes both IP/IMP and non-IP/Non-IMP and is shown in pSS Table 4.

An IP, also known as investigational medicinal product in some regions, is defined as a pharmaceutical form of an active substance or PBO 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 SOC for a given diagnosis, may be considered as noninvestigational products.

pSS Table 4 Study Treatments for IM014029

Product Description/ Class and Dosage Form	Potency	IP/ Non-IP	Blinded or Open-Label	Packaging/ Appearance	Storage Conditions (per label)
Branebrutinib oral capsule	3 mg dose × 3 capsules (9 mg total dose)[a]	IP	Blinded	HDPE bottles (33 capsules/bottle) with child-resistant cap and heat-induction seal (tamper-evidence and moisture barrier); size #0 hard gelatin capsules	Store refrigerated at 2° to 8°C (36° to 46°F) in original packaging; protected from moisture
PBO matching branebrutinib oral capsule	NA	IP	Blinded	HDPE bottles (33 capsules/bottle) with child-resistant cap and heat-induction seal (tamper-evidence and moisture barrier); size #0 hard gelatin capsules	Store refrigerated at 2° to 8°C (36° to 46°F) in original packaging; protected from moisture

HDPE = high-density polyethylene; IP = investigational product; NA = not applicable; PBO = placebo.

[a] Dosages of 0.5 mg are also available but are not planned for use in this protocol.

pSS 6.1 Treatments Administered

The investigator must ensure that the IP will be used only in accordance with the protocol. The selection and timing of dose for each subject is shown in pSS Table 5. Study treatment will be supplied in bottles (branebrutinib and PBO). If a subject forgets a dose, but remembers within 12 hours of the expected dose, the dose should be taken. Any dose > 12 hours should be missed, and the next expected dose should be taken at the usual time. No dose reductions or modifications are allowed.

pSS Table 5 Selection and Timing of Dose

Study Treatment	Unit Dose Strength	Dosage Formulation Frequency of Administration	Route of Administration
Branebrutinib 9 mg	3 mg	3 active capsules; QD	Oral
PBO	0 mg	3 PBO capsules; QD	Oral

N/A = not applicable; PBO = placebo; QD = once daily

Note: At all study visits, the study treatment should not be taken at home but should be taken to the site by the subject; at the site, the study treatment should be taken only when instructed by the site study staff according to the schedule listed below. These requirements also apply to concomitant medications at Day 1 and Week 4 only; at these visits, concomitant medications will be administered together with the study treatment.

When multiple assessments are conducted at a single visit, the following is the order in which they should be performed:

- Patient-reported Outcomes (eg, SGA, EQ-5 D-5 L, etc)
- Safety assessments (eg, vitals, AEs)
- Investigator-administered Assessments (eg, PGA, joint count, etc)
- Laboratory tests (eg, safety laboratory tests, PK assessments, biomarker assessments)
- Treatment dosing

Doses of branebrutinib at 9 mg (3x3 mg capsules) or matching placebo are to be administered orally q24h (one time/day) with water and may be taken with or without food. The drug should be taken every morning at approximately the same time.

On Day 1 and at Weeks 4, 8, 16, and 24, study drug will be administered in the morning at the study site after blood samples have been collected and questionnaires have been completed. In addition, on Day 1 and at Week 4, branebrutinib will be administered together with concomitant medications to allow predose sampling for concomitant medication. Branebrutinib and concomitant medications are to be taken together with water.

pSS 6.2 Method of Treatment Assignment

Subjects will be centrally randomized according to a computer-generated block randomization scheme using IRT to the pSS sub-protocol depending on disease type determined at screening. Subjects in this sub-protocol will be randomized in a 2:1 ratio to receive double-blind branebrutinib 9 mg or PBO QD from Week 0 to Week 24.

At the time of the screening visit, after written informed consent is obtained and before any study-related procedures are performed, the investigative site will access the enrollment option of the IRT system for assignment of a subject number. This number is assigned sequentially by the system and will be unique across all sites. If a potential subject is rescreened, a new identification number will be used.

Randomized schedules will be generated by the IRT vendor.

Randomization will be stratified by HCQ use (yes/no).

Before the study is initiated, each investigator will receive log-in information and directions on how to access the IRT. Study treatment will be dispensed at the study visits as listed in the SoA (Section pSS 1.3).

pSS 6.3 Blinding

Blinded treatment assignments will be managed using IRT. All capsules (branebrutinib 3 mg and PBO) are identical in appearance. Capsules will be supplied in tamper-evident HDPE bottles with each daily dose made up of either active or PBO capsules (as presented in pSS Table 4). Investigative site staff, Sponsor and designee personnel, and subjects and their families will remain blinded to treatment assignments.

[redacted]

Blinding of treatment assignment is critical to the integrity of this clinical study. However, in the event of a medical emergency or pregnancy in an individual subject in which knowledge of the IP is critical to the subject's management, the blind for that subject may be broken by the investigator. The subject's safety takes priority over any other considerations in determining if a treatment assignment should be unblinded.

Before breaking the blind of an individual subject's treatment, the investigator should determine that the unblinded information is necessary, ie, that it will alter the subject's immediate management. In many cases, particularly when the emergency is clearly not related to the IP, the problem may be properly managed by assuming that the subject is receiving active product. It is highly desirable that the decision to unblind treatment assignment be discussed with the Medical Monitor, but the investigator always has ultimate authority for the decision to unblind. The PI should only call in for emergency unblinding AFTER the decision to discontinue the subject has been made.

In case of an emergency, the investigator has unrestricted access to randomization information via IRT and is capable of breaking the blind through the IRT system without prior approval from the Sponsor. After the unblinding, the investigator shall notify the Medical Monitor and/or study director. For information on how to unblind in an emergency, consult the IRT manual. Subject and unblinded treatment information and the reason for the blind being broken must be recorded on the appropriate study status page of the eCRF. After unblinding via IRT, the investigator shall notify the Medical Monitor.

Any request to unblind a subject for nonemergency purposes should be discussed with the Medical Monitor.

In cases of accidental unblinding, contact the Medical Monitor and ensure every attempt is made to preserve the blind.

Designated staff of BMS Company may be unblinded (obtain the randomization codes) prior to database lock to facilitate the bioanalytical analysis of PK samples and immunogenicity. A bioanalytical scientist in the Bioanalytical Sciences department of BMS Company (or a designee in the external central bioanalytical laboratory) will be unblinded to (may obtain) the randomized treatment assignments in order to minimize unnecessary bioanalytical analysis of samples.

pSS 6.4 Dosage Modification

There is no provision for dose modification of study treatment. If a subject interrupts or discontinues temporarily treatment due to an AE, study treatment can be restarted in consultation with the Medical Monitor.

pSS 6.5 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 investigational product is only dispensed to study subjects. 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 BMS or designee should be contacted immediately.

Branebrutinib and PBO should be stored per labeled conditions in tamper-evident HDPE bottles.

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).

Further guidance and information for final disposition of unused study treatment are provided in APPENDIX 2.

pSS 6.5.1 Retained Samples for Bioavailability/Bioequivalence

At the time of receipt of the IP by the investigator or designees, BMS will specify the appropriate number of containers or units to select for retention, the conditions of sample storage, required duration of sample retention, and provisions for returning or disposing of the investigational product. When samples are selected, containers or units should be placed in packaging with a tamper-evident seal provided by BMS. Package labeling should clearly identify the contents as bioavailability/bioequivalence samples and state that the investigational product should be stored in the restricted area with limited access.

pSS 6.6 Treatment Compliance

Study treatment compliance will be periodically monitored using standard drug accountability procedures (comparing the number of capsules returned to number dispensed, considering the expected regimen and any reported missed doses). Drug accountability will be reviewed by the site study staff at each visit to confirm treatment compliance. Site staff will discuss discrepancies with the subject at each on-treatment study visit and remind the subject of the importance of compliance with the assigned regimen. See Section pSS 8.3 for information related to treatment overdose.

pSS 6.7 Concomitant Therapy

pSS 6.7.1 Prohibited and/or Restricted Treatments

Table 1 in the IM014029 Master Protocol lists exclusions and restrictions for all concomitant medications, regardless of indication. pSS Table 6 presents prohibited and/or restricted medications taken by subjects with pSS prior to or during study treatment administration with

branebrutinib. All prior concomitant medications taken for pSS since diagnosis must be recorded on the eCRF. All prior and/or concomitant medications taken for any indication within 4 weeks prior to study drug administration must be recorded on the eCRF. The prior use of medications after a sufficient washout period prior to study randomization is allowed for some medications, as indicated in the table and must be recorded in the eCRF. Details of prohibited (excluded) and/or restricted medications are provided in Section pSS 5.2.

pSS Table 6 Prohibited and Restricted Medications

Type of Medication	Examples of Medications	Restrictions	Required Washout Period Prior to and Postrandomization
BTK inhibitors	Marketed drugs, eg, ibrutinib, acalabrutinib; Experimental drugs, eg, tirabrutinib, vecabrutinib, zanubrutinib, ARQ-531, GDC-0853, and any others	Prohibited lifetime use	Not applicable
JAK inhibitors	Tofacitinib, baricitinib, filgotinib, and upadacitinib	Prohibited during the study	8 weeks
Oral CS	prednisone	Stable dose of ≤ 10 mg/day for ≥ 28 days before randomization; dose must remain stable throughout study	If not continuing as background SOC must discontinue 4 weeks before randomization.
Other CS	IM, IA, intrabursal, IV, and oral modified-release CS	Prohibited during the study	4 weeks
	Topical CS	Stable regimen throughout study; may not be used on an as-needed basis	Not applicable
	Inhaled CS	Must follow stable regimen throughout the study; cannot be used on as-needed basis; allowed only for nonrheumatologic indications	Not applicable
Antimalarial drugs	Chloroquine and quinacrine	Prohibited during the study	8 weeks
	Hydroxychloroquine	> 400 mg/day; no initiation or dose change during the study; whole blood concentration at screening must be ≤ 2 µg/mL	If not continuing as SOC, must discontinue 8 weeks before randomization
Anticoagulant or Antiplatelet therapies	Anticoagulant or antiplatelet therapies, including aspirin for cardioprotection	Treatment with anticoagulant or antiplatelet therapies, including aspirin for cardioprotection, within 2 weeks prior to randomization or during the study	2 weeks
Tricyclic Antidepressants	Amitriptyline, desipramine, doxepin, imipramine, nortriptyline, trimipramine) or quetiapine	Treatment with tricyclic antidepressants (within 4 weeks before randomization)	4 weeks

pSS Table 6 Prohibited and Restricted Medications

Type of Medication	Examples of Medications	Restrictions	Required Washout Period Prior to and Postrandomization
Anti-TNF therapy	Adalimumab, certolizumab, etanercept, golimumab, infliximab, and TNF biosimilars	Prohibited during the study	3 months
Biologics	Rituximab	Prohibited during the study	12 months
	Belimumab	Prohibited during the study	6 months
	Abatacept	Prohibited during the study	6 months
Other Biologics	tocilizumab, anakinra	Prohibited during the study	8 weeks
	IVIG	Prohibited during the study	8 weeks
DMARD	MTX	Prohibited during the study	12 weeks
Other DMARDs	Leflunomide	Prohibited during the study	36 weeks before **screening**
	Cyclosporine and tacrolimus	Prohibited during the study; cyclosporin eye drops are permitted	8 weeks
	Cyclophosphamide	Prohibited during the study	24 weeks
	Azathioprine, sulfasalazine, and similar	Prohibited during the study	8 weeks
Sialogogues	Cevimeline, pilocarpine	Must be taken on a stable dose regimen for 8 weeks prior to randomization and remain stable throughout the study, except as specified here and in Section pSS 5.2	**Must be held** for 48 hours before screening, Day 1, Week 12, Week 24 and Week 28 visits until after tests for tear production and stimulated/unstimulated salivary flow rate measurements have been performed. If LGF testing is done on a day separate from other study assessments sialogogues **must be held** for 12 hours before lacrimal testing is performed
Saliva stimulants	Dried fruit slices, maltose lozenges, xylitol gum or candy, regular, sugarless or sugar-free gum or hard candies, artificial saliva sprays or drops		On study visit days must be stopped **2 hours** before stimulated/unstimulated salivary flow rate measurements are taken

pSS Table 6 Prohibited and Restricted Medications

Type of Medication	Examples of Medications	Restrictions	Required Washout Period Prior to and Postrandomization
Antihistamines	Diphenhydramine, hydroxyzine, loratadine and similar	Must be taken on a stable dose regimen for 4 weeks prior to randomization (if a required concomitant medication for co-morbid condition) and remain stable throughout the study except as specified in pSS 8.1.1.2	Must be held for 12 hours before screening, Day 1, Week 12, Week 24 and Week 28 visits until after tests for unstimulated/stimulated saliva flow measurements have been performed.
Autologous serum eye drops	Formulated autologous serum eye drops	Prohibited throughout the study	Discontinue at screening visit
NSAIDs (see inclusion criterion 4a in Section pSS 5.1)	Ibuprofen, etc	Only one oral NSAID is allowed; may be combined with ≥ 1 topical NSAID but regimen must be stable	Not allowed on days of study visits until study assessments performed.
Non-narcotic analgesics	Acetaminophen	Brief course for up to 7 days allowed	Not applicable
Narcotic analgesics	Oxycodone and hydrocodone	Prohibited during the study	Not applicable
Immunization against agents other than influenza or SARS-CoV-2	All live vaccines Nonlive vaccines unassociated with influenza or SARS-CoV-2	Prohibited during the study	90 days before and 28 days after EOT 30 days before and 14 days after EOT
Immunization for influenza or SARS-CoV-2	All live vaccines Nonlive vaccines for influenza or SARS-CoV-2	Prohibited during the study Not allowed during the screening period within 30 days prior to randomization During the Treatment and Follow-up Periods, vaccine doses must be given at least 5 days before a study visit; doses may be given on a study day visit once all protocol-specific procedures are complete.	90 days before and 28 days after EOT
	Inactivated and protein-based vaccines	Prohibited during the study	30 days before randomization and 14 days after EOT
Other treatments	Diquafosol, rebamipide	Prohibited during the study	4 weeks

BLQ = below limit of quantitation; BTK = Bruton's tyrosine kinase; CS = corticosteroid; DMARDs = disease-modifying antirheumatic drugs; EOT = end of treatment; IA = intra-articular; IM = intramuscular; IV = intravenous; IVIG = intravenous immunoglobulin; JAK = Janus kinase; LGF = lacrimal gland function; MTX = methotrexate; NSAIDs = nonsteroidal anti-inflammatory drugs; TNF = tumor necrosis factor

Chronic medications, such as statins and antidepressants, that could be sensitive to modulation of CYP2C8/P-gp (and other potentially relevant drug metabolizing enzymes that may lead to drug-drug interaction with branebrutinib) and with sufficient representation in the study population (eg, > 10% per sub-protocol), are allowed in the study for accompanying conditions. For optional measurement of the concentrations of these medications, PK samples will be collected predose and 2 hours postdose at Week 0 (Day 1) and Week 4 (Day 29) for potential post-hoc analysis. These analyses will be based on the totality of information about the frequency of use of the drugs, clinical manifestations of possible interactions, availability of validated bioanalytical assays, and therapeutic index. When performed, the results of these analyses will be reported separately, along with the reasons for the selection. Concentrations of HCQ will also be measured and reported. The dosing of allowed chronic medications must be maintained at the same level throughout the study unless safety concerns arise. Any changes of dose will be recorded, and additional PK sampling may be performed as a result.

Tobacco use will be allowed in the study. Branebrutinib concentrations will be compared between smoking and nonsmoking subgroups to evaluate the effect of smoking on glutathione-s-transferase mediated metabolism of branebrutinib.

No new concomitant medications (prescription, over-the-counter or herbal) are to be administered during the study unless they are prescribed for treatment of specific clinical events. Any concomitant therapies must be recorded on the eCRF.

For subjects on any background therapy, the investigator must refer to the label for any potential interaction with concomitant medications.

pSS 6.7.2 Oral Corticosteroid Rescue

A maximum of 1 burst of oral CS rescue therapy is permitted in response to increased pSS disease activity up to Week 12 during the treatment period at the investigator's discretion.

- Rescue therapy must not exceed 20 mg/day prednisone or equivalent and must return within 7 days to the previous CS dose used before initiation of rescue therapy.
- Rescue therapy other than prednisone or equivalent is not permitted.

If a subject requires CS rescue therapy after the first 12 weeks, the subject will be considered a nonresponder for analysis purposes but will continue to receive study treatment.

pSS 6.7.3 Other Restrictions and Precautions

No other restrictions and precautions have been identified.

pSS 6.8 Treatment After the End of the Study

At the end of the study, BMS will not continue to provide BMS-supplied study treatment to subjects/investigators unless BMS chooses to extend the study. The investigator should ensure that the subject receives appropriate SOC to treat the condition under study.

PSS 7 DISCONTINUATION CRITERIA

pSS 7.1 Discontinuation from Study Treatment

pSS 7.1.1 Permanent Discontinuation from Study Treatment

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

- A subject requests to stop study treatment; subjects 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 subject specifically withdraws consent for any further contact with him/her or persons previously authorized by the subject to provide this information.
- Any clinical AE, laboratory abnormality, or intercurrent illness that, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject. If treatment is discontinued due to an AE, the AE eCRF must be completed to show that the AE caused discontinuation.
- Termination of the study program 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.
- Unblinding of a subject's treatment assignment for any reason (emergency or nonemergency).
- Inability or failure to comply with protocol requirements.
- Pregnancy.

Discontinuation of the study treatment for abnormal liver tests indicative of DILI (see Section pSS 8.2.8 for definition) should be considered by the investigator when the DILI meets one of the conditions necessary to be defined as an SAE outlined in APPENDIX 3 or if the investigator believes that it is in the best interest of the subject.

In the case of pregnancy, the investigator must immediately, within 24 hours of awareness of the pregnancy, notify the 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 subject safety). Refer to Section pSS 8.2.6.

All subjects who discontinue study treatment should comply with protocol-specified follow-up procedures as outlined in the SoA (Section pSS 1.3). The only exception to this requirement is when a subject withdraws consent for all study procedures including posttreatment 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). Following the decision to permanently discontinue a subject from treatment, an EOT visit should be performed as soon as possible, followed by a Safety FU visit approximately 4 weeks later – both according to Table 2 of Section pSS 1.3.

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

pSS 7.1.2 Temporary Discontinuation from Study Treatment

Branebrutinib may be discontinued temporarily at the discretion of the investigator/Medical Monitor due to AE, laboratory abnormality or overdose (pSS 8.3).

Branebrutinib may be discontinued temporarily due to concomitant medication use (Master Protocol Table 1), as follows:

- Digoxin, "For acute use only; exclude at baseline; limit highest dose and monitor trough concentrations; stop treatment with branebrutinib during treatment with digoxin and for 3 days afterwards."
- Posaconazole: "Dose up to 300 mg QD can be used as maintenance dose, for acute infections stop using branebrutinib until dosing with posaconazole is discontinued."

pSS 7.1.3 Post-study Treatment Study Follow-up

Subjects who discontinue study treatment will not be followed beyond the planned Safety FU Visit.

pSS 7.2 Discontinuation from the Study

Subjects 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 subject specifically withdraws consent for any further contact with him/her or persons previously authorized by the subject to provide this information.

- Subjects 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 and entered on the appropriate eCRF page.
- In the event that vital status (whether the subject 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 subject withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

The following procedures must be performed upon subject withdrawal:

- Assessments for the EOT visit must be performed, provided that the subject has not withdrawn consent for these activities.

All required eCRF pages must be completed, including the date of and explanation for the withdrawal.

pSS 7.3 Lost to Follow-up

- All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject.
- Lost to follow-up is defined by the inability to reach the subject after a minimum of 3 documented phone calls, faxes, or emails as well as lack of response by subject to 1 registered mail letter. All attempts should be documented in the subject's medical records.

- If it is determined that the subject 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 subject's informed consent, then the investigator may use a Sponsor retained third-party representative to assist site staff with obtaining subject'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 subject remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the subject's medical records.

PSS 8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and timing are summarized in the SoA (Section pSS 1.3).
- Protocol waivers or exemptions are not allowed.
- All immediate safety concerns must be discussed with the Medical Monitor immediately upon occurrence or awareness to determine if the subject should continue or discontinue treatment.
- Adherence to the study design requirements, including those specified in the SoA (Section pSS 1.3), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria before randomization. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the subject's routine clinical management (eg, BP, physical examination, medical history) and obtained on the day of the screening visit and obtained before signing of the informed consent may be used for screening provided the procedure meets the protocol-defined criteria and has been performed within the timeframe defined in the SoA (Section pSS 1.3).

pSS 8.1 Efficacy Assessments

The PI or sub-investigator, designated by the PI and confirmed by the Sponsor, should perform all clinical assessments at a given visit, with the exception of the ocular assessments and salivary flow assessments. The sub-investigator may be a Doctor of Medicine or Doctor of Osteopathy, Physician's Assistant, or Nurse Practitioner with experience in the diagnosis and management of subjects with pSS. The ocular assessments are to be performed by the Sponsor-approved ophthalmologist/optometrist and the salivary flow tests are to be performed by a trained site staff member, as designated by the PI.

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

- Every effort must be made to ensure the same investigator performs the assessments for a given subject at each visit and throughout the study to minimize inter-observer variation.

- If the investigator is unable to complete the assessment at a given visit, the approved back-up investigator may complete the assessment.
- Assessments are to be conducted at approximately the same time of day throughout the duration of the study for each subject**.**
- Visits should be scheduled with the availability of the specific investigator managing a given subject taken into account.

The requirements above also apply to the ocular assessments.

pSS 8.1.1 Investigator-administered Assessments

pSS 8.1.1.1 ESSDAI

The ESSDAI is a systemic activity index designed to measure disease activity in subjects with pSS. The ESSDAI includes 12 domains (ie, organ systems: cutaneous, respiratory, renal, articular, muscular, CNS, PNS, hematological, glandular, constitutional, lymphadenopathic, biological). Each domain is divided into 3 to 4 levels of activity. The definition of each activity level is provided by a detailed description of what should be considered in that item. Sites should only use the versions of the assessment scale provided by the Sponsor for this study and should ensure that all enrolled subjects have a positive score in at least one of these responsive domains: articular, biological, glandular, hematological, or lymphadenopathy. Investigators should assess the ESSDAI parameters as described by Seror et al.[84] The ESSDAI will be completed at the visits noted in the SoA (Section pSS 1.3). Results from each assessment will be recorded in site source records as well as in the corresponding eCRF. See also Section pSS 1.1 for further details on the use of ESSDAI to facilitate enrollment of subjects with moderate to severe disease activity and to define the MCII for ESSDAI assessments. (APPENDIX 15)

pSS 8.1.1.2 Stimulated/Unstimulated Salivary Flow in pSS

Evidence of residual salivary function is required for inclusion in the study. A stimulated salivary flow rate of > 0.05 mL/minute[85] or unstimulated salivary flow rate of > 0.01 mL/minute is required for entry and will be assessed at screening and randomization (both tests should be performed at screening and randomization, but the minimum flow requirement from only one is needed for inclusion). Subjects should refrain from eating, drinking, smoking or chewing gum for at least 90 minutes prior to the test procedures. Subjects should be instructed to not use parasympathomimetic agents, such as pilocarpine and cevimeline for the 48 hours prior to salivary assessments (see also Master Protocol 1.5), to withhold antihistamines for 12 hours before the assessments and to not use artificial saliva on the day of the assessment. On-study salivary assessments will be performed at Week 12, Week 24, and Week 28. The assessments should be performed by the same assessor at approximately the same time of day as the baseline salivary assessment, if at all possible. Collection procedure requirements are detailed in the pSS Quick Reference Guide. Saliva collected for unstimulated salivary flow assessments may also be stored for exploratory biomarker analysis.

pSS 8.1.1.3 Lacrimal Gland Function (Tear Break-up Time, Ocular Staining Score, Schirmer's Test)

The following procedures should be performed at pre-identified visit days by an ophthalmologist or optometrist trained in the diagnosis and treatment of patients with Sjögren's syndrome and according to the methods described in Whitcher, et al.[86] A visit window of ± 5 days to perform the ophthalmologic assessments is acceptable (baseline Day 1 assessment can be performed up to 5 days prior to dosing only), but all assessments must be performed during the same visit in the order outlined below. Subjects should not use cyclosporine eye drops or artificial tears on the day of the visit for 12 hours prior to the assessment. Autologous serum eye drops should be discontinued at the screening visit and are prohibited throughout the study. The use of alternative ocular dyes may be permitted per local standards and/or regulations, after consultation with the Medical Monitor.

- Tear Break-up Time (TBUT): Determined by instilling fluorescein dye and evaluating the stability of the pre-corneal tear film. After several blinks, the tear film is examined using a broad beam of the slit lamp (biomicroscope) with a cobalt blue filter. The TBUT, defined as the time in seconds between the subject's last blink and the first appearance of a random dry spot on the corneal surface, is measured 3 times and recorded. The mean value will be calculated programmatically.
- Ocular Staining Score: The test is performed by instillation of fluorescein dye and either Lissamine Green or Rose Bengal dye to stain the cornea and conjunctiva, respectively. After instilling the dye, the ocular surface is examined through a slit lamp (biomicroscope) the staining pattern is recorded per the method described in Whitcher, et al.
- Schirmer's test: To be completed last and at least 15 minutes after completing the Ocular Staining Score. The test (without anesthesia) is performed by placing a narrow-calibrated filter-paper strip in the inferior cul-de-sac of each eye. Aqueous tear production is measured by the length in millimeters that the strip wets during the 5-minute test period.

Detailed procedure requirements are available in the pSS Quick Reference Guide (QRG). The results from each procedure will be recorded in site source records as well as entered into the corresponding eCRF.

pSS 8.1.1.4 Tender Joint Count 68/Swollen Joint Count 66 (TJC68/SJC66) – pSS Sub-protocol

At specified visits the 66/68 joint count will be used to determine the number of inflamed joints (tender and/or swollen) due to pSS activity. The same PI or sub-investigator following the subject shall perform this assessment at all visits: 68 joints (34 joints on each side of the subject's body) will be examined for tenderness and/or swelling. They include: 2 temporomandibular joints (TMJs), 2 sternoclavicular joints, 2 acromioclavicular joints, 2 shoulder joints, 2 elbow joints, 2 wrist joints, 10 metacarpophalangeal joints, 2 interphalangeal joints of the thumb, 8 proximal interphalangeal joints of the hands, 8 distal interphalangeal joints of the hands, 2 hip joints, 2 knee joints, 2 ankle joints, 2 tarsi, 10 metatarsophalangeal joints of the feet, 2 great toes (first proximal interphalangeal joint of the feet), and 8 proximal interphalangeal joints of the feet. Joints will be

assessed for tenderness by pressure and joint manipulation on physical examination. The subject will be asked for pain sensations on these manipulations and watched for spontaneous pain reactions. Any positive response on pressure, movement, or both will then be translated into a single tender-versus-nontender dichotomy. Swelling is defined as palpable fluctuating synovitis of the joint. Only joint tenderness or swelling of an inflammatory origin due to pSS should be scored. Arthralgias or synovitis due to other causes such as osteoarthritis, infectious, metabolic, RA, or other immune-mediated diseases should be excluded. Sixty-six (66) joints (the above 68 excluding both hips) will be assessed and classified as swollen or not swollen due to active pSS synovitis. Swelling secondary to osteoarthrosis will be assessed as not swollen, unless there is unmistakable fluctuation due to active pSS synovitis.

Missing, replaced, ankylosed, or arthrodesed joints will be identified by the investigator at the screening visit and will be excluded from evaluation during the study. The locations (or a listing) of surgical procedures should be documented in the subject's source documents/eCRF pages.

pSS 8.1.1.5 Disease Activity Score 28-C-Reactive Protein for pSS

The DAS28-C-reactive protein (DAS28-CRP) is used to assess whether a subject has a significant improvement of disease activity compared to baseline. It is a composite index using the number of tender joints and swollen joints (specified in the 28 Joint Count), the CRP laboratory result, and the subject's global assessment of health related to pSS on a visual analog scale. The score will be calculated programmatically (APPENDIX 16).

pSS 8.1.1.6 Physician Global Assessment (PGA) of pSS Disease Activity

The investigator will rate the overall status of the subject in response to the following statement:

"How do you assess your patient's (the subject's) current Primary Sjogren's disease activity as compared to the activity and Physician Global Assessment at the last visit?" (APPENDIX 17).

pSS 8.1.2 Patient-reported Assessments

Patient-reported assessments used in pSS studies have included questionnaires about the subject's general health, rheumatology, and pSS disease, and the subjects responses to these health outcomes instruments are to be recorded electronically on eCOA devices provided by the Sponsor or designee to the sites.

pSS 8.1.2.1 ESSPRI

The ESSPRI was developed as 3-question symptom index for dryness, fatigue, and pain in subjects with pSS. Dryness, pain, somatic and mental fatigue were identified as the main symptoms in patients with pSS in studies conducted during the development of the Profile of Fatigue and Discomfort (PROFAD) and Sicca Symptoms Inventory. The ESSPRI performed satisfactorily for evaluation of patients' symptoms and has the advantage that it is easy to use. It was hypothesized that a single 0 to 10 numerical scale for each domain was sufficient to assess these symptoms (APPENDIX 18).

pSS 8.1.2.2 Numeric Rating Scale (NRS) for Mouth and Eye Dryness

NRS scales for mouth and eye dryness will be used to assess a subject's perception of change in these specific symptoms using the same wording found in the EULAR ESSPRI instrument for dryness referencing the specific organs.

pSS 8.1.2.3 Subject Global Assessment (SGA) of Disease Activity

SGA is an NRS used by the subject to make an overall assessment of the subject's Sjogren's disease in the past week (APPENDIX 19).

pSS 8.1.2.4 PROMIS-Fatigue Instrument, Form 6 a

The PROMIS™ Form 6 a, provides item banks that offer the potential for PRO measurement that is efficient (minimizes item number without compromising reliability), flexible (enables optional use of interchangeable items), and precise (has minimal error in estimate) measurement of commonly studied PROs.[78, 79, 80, 81] In the health outcomes measurement perspective, for example, fatigue is divided conceptually into the experience of fatigue (such as its intensity, frequency, and duration), and the impact of fatigue upon physical, mental, and social activities. The fatigue item bank consists of 95 items assessing the intensity, frequency, and impact of fatigue. Most PROMIS items employ response scales with 5 options (see APPENDIX 12).

pSS 8.1.2.5 Euro Quality of Life Five Dimensions Questionnaire: 5-Level Version (EQ-5 D-5 L)

The EQ-5 D-5 L consists of 2 parts – the EQ-5 D-5 L descriptive system and the EQ VAS. The descriptive system comprises the same 5 dimensions as the EQ-5 D-3 L (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). Each dimension has 5 levels: no problems; slight problems; moderate problems; severe problems; and extreme problems. The respondent indicates his/her health state by ticking in the box against the most appropriate statement in each of the 5 dimensions. The resulting 1-digit number expresses the level selected for that dimension. The digits for all 5 dimensions can then be combined in a number describing the respondent's health state.

The numbers 1 through 5 have no arithmetic properties and should not be used as a cardinal score. During the development of the EQ-5 D-5 L, the opportunity was also taken to improve some of the wording in the dimensions to enhance consistency and facilitate understanding. For example, the old wording of "confined to bed" to indicate the upper extreme in the EQ-5 D-3 L has been replaced with "I am unable to walk about" which is more consistent with the wording within the Mobility dimension and with the extreme levels on other dimensions.

The EQ VAS records the respondent's self-rated health on a 20-cm vertical VAS with endpoints labeled "the best health you can imagine" and "the worst health you can imagine." This information can be used as a quantitative measure of health as judged by the individual respondents. The instructions for the EQ VAS task have also been simplified (APPENDIX 13).

pSS 8.1.3 Salivary Gland Ultrasonography

Salivary gland ultrasonography (SG-US) is a noninvasive tool that has been proven effective for identifying structural abnormalities of the salivary glands and diagnosing pSS.[87]

Each subject in the pSS sub-protocol will have 3 SG-US examinations at screening, Week 12 and Week 24 (pSS 1.3). The parotid and submandibular glands will be scanned on both sides (4 main salivary glands). Screening visit scans may be repeated to ensure quality baseline data.

At screening, the SG-US should be performed approximately 14 days prior to randomization to allow review and to repeat, if required.

Week 12 and Week 24 SG-US examinations are to be performed within 7 days of both scheduled Week 12 visit and Week 24 visits. Subjects who terminate the study early require a SG-US examination at the EOT visit only if that visit is ≥ 4 weeks from the date of randomization or ≥ 4 weeks from Week 12 and should have the EOT SG-US examination NO MORE than 7 days from the EOT visit.

Each site will be trained for the acquisition of SG-US examinations by an imaging core laboratory to maximize the quality and the consistency of the imaging data. Each investigator will assess the SG-US data according to local procedures. The results will not be reported in the study's eCRFs, although any incidental findings detected with the SG-US evaluation must be recorded in the study's eCRF and followed-up by an investigator as appropriate.

The SG-US data will be centrally evaluated at an imaging core laboratory by independent readers blinded to the study arms, clinical information, and the chronology of SG-US acquisitions. Two readers will independently evaluate the data and a consensus evaluation will be performed in case of discrepancy.

The following scale will be used to evaluate the SG-US data. The echostructure of each gland will be graded on a scale of 0 to 3 as an exploratory assessment:

- Grade 0: normal parenchyma;
- Grade 1: minimal change - mild inhomogeneity without anechoic/hypoechoic areas;
- Grade 2: moderate change - moderate inhomogeneity with focal anechoic/hypoechoic areas;
- Grade 3: severe change - diffuse inhomogeneity with anechoic/hypoechoic areas occupying the entire gland surface.

Details about the procedures involved in the conduct of SG-US assessments will be provided in the Imaging Charter.

Because the salivary gland ultrasonography in pSS is a fast-evolving research field and given the exploratory nature of these assessments, additional scoring and analysis methodologies may be implemented.

[redacted]

[redacted]

pSS 8.2 Adverse Events

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

AEs will be reported by the subject (or, when appropriate, by a caregiver or surrogate).

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 subject to discontinue before completing the study.

Contacts for SAE reporting are specified in APPENDIX 3.

pSS 8.2.1 AEs of Interest

AEIs are AEs for a particular product or class of products that a Sponsor may wish to monitor carefully. AEIs may be serious or nonserious. Such events may require further investigation to better characterize and understand them. In the branebrutinib clinical development program, infection AEs have been identified as potential AEIs; however, there has been no definitive assessment on the causal relationship between these events and treatment with branebrutinib. Therefore, additional information about infection AEs may be collected on the eCRF in order to better characterize and understand them.

pSS 8.2.2 Time Period and Frequency for Collecting AE and SAE Information

The collection of nonserious AE information should begin at initiation of study treatment until discharge, at the timepoints specified in the SoA (Section pSS 1.3). Nonserious AE information should also be collected from the start of a PBO lead-in period or other observational period intended to establish a baseline status for the subjects. The Reference Safety Information in Sections 5.6.1 and 5.6.2 of the IB[12] should be used to determine the expectedness of SAEs for expedited reporting.

All SAEs must be collected from the time of signing the consent, including those thought to be associated with protocol-specified procedures and within 30 days of discontinuation of dosing or subject's participation in the study if the last scheduled visit occurs at a later time.

The investigator must report any SAE that occurs after these time periods and that is believed to be related to study drug or protocol-specified procedure.

- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the appropriate section of the designated eCRF.
- 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 subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject 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.

pSS 8.2.3 Method of Detecting AEs and SAEs

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.) Nonserious pSS-related AEs will be collected solely on the disease assessment instruments and will not be reported as AEs unless characterized as an SAE

pSS 8.2.4 Follow-up of AEs and SAEs

- Nonserious AEs should be followed to resolution, 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 eCRF. Completion of supplemental eCRFs 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 subject at subsequent visits/contacts. All SAEs, and nonserious AEIs (as defined in Section pSS 8.2.1) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section pSS 7.3).

Further information on follow-up procedures is provided in APPENDIX 3.

pSS 8.2.5 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 subjects 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 IRB/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 (CFR) 21 CFR, Parts 312 and 320. A SUSAR is a subset of SAEs and will be reported to the appropriate regulatory authorities and investigators following local and global guidelines and requirements.

pSS 8.2.6 Pregnancy

If, following initiation of the study treatment, it is subsequently discovered that a subject is pregnant or may have been pregnant at the time of study exposure, including during at least 5 half-lives after product administration, the investigator must immediately notify [redacted] Drug Safety of this event and complete and forward a Pregnancy Surveillance Form to [redacted] Drug Safety within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in APPENDIX 3.

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

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 subject should be reported to [redacted] Drug Safety. 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.

pSS 8.2.7 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the AE eCRF page.

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

If a laboratory test result meets the definition of an AE or SAE, the laboratory test result should be reported as an AE or SAE and submitted to [redacted] Drug Safety, as specified in APPENDIX 3.

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).

pSS 8.2.8 Potential DILI

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs meeting the defined criteria must be reported as SAEs (see Section pSS 8.2 and APPENDIX 3 for reporting details).

Potential DILI is defined as:

1) 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 ALT or AST elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, preexisting chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

pSS 8.2.9 Other Safety Considerations

Any significant worsening of a preexisting medical condition noted during interim or final physical examination, electrocardiogram (ECG), x-ray filming, or any other potential safety assessment required or not required by protocol should also be recorded as a nonserious AE or SAE, as appropriate, and reported accordingly.

pSS 8.3 Overdose

For this study, any dose of branebrutinib greater than 2 daily doses of study treatment within a 24-hour time period will be considered an overdose. See APPENDIX 3 for AE assessment and reporting procedures regarding suspected overdose and intentional overdose.

Based on the IB, there has been no clinical experience with overdose of branebrutinib.[12] There is no known specific antidote for overdose with branebrutinib.

In the event of an overdose, the investigator should:

1) Contact the Medical Monitor immediately.
2) Closely monitor the subject for AEs/SAEs and laboratory abnormalities.
3) Obtain a plasma sample for PK analysis within 4 hours of the overdose if requested by the Medical Monitor (determined on a case-by-case basis).
4) Document the quantity of the excess dose as well as the duration of the overdosing in the source documentation.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the subject.

pSS 8.4 Safety

Planned time points for all safety assessments are listed in the SoA (Section pSS 1.3).

pSS 8.4.1 Physical Examinations

A complete physical examination will include general appearance, vital signs, eyes, ears, nose, mouth, throat, neck, respiratory, cardiovascular, respiratory, gastrointestinal/abdomen, lymphatic, musculoskeletal, skin, psychiatric, and neurologic exams. A targeted physical examination will include any organ system associated with an AE, a laboratory abnormality, or a pSS activity not captured elsewhere.

pSS 8.4.2 Vital Signs

Refer to SoA (Section pSS 1.3).

pSS 8.4.3 Electrocardiograms

A 12-lead ECG will be performed at the visits indicated in the SoA (Section pSS 1.3). The subject will remain supine for 5 to 10 minutes prior to the ECG and must have lab work done after the tracing so that the ECG results remain as accurate as possible. The ECG results will be read by the primary study investigator or a designee.

pSS 8.4.4 TB Screening and Chest Imaging

A subject must not have active signs or symptoms of TB, as judged by the investigator, to be eligible for the study.

In addition to a complete physical examination and medical history to evaluate exposure to TB, all subjects will have a screening test, an IGRA (eg, QuantiFERON®-TB Gold) performed centrally. A subject with an indeterminate IGRA test result from the central laboratory must be retested for confirmation. If the second result is again indeterminate, the subject will be excluded from the study, unless there is documentation of a local negative TB Spot test result. If the second result from the central laboratory is positive, the subject should be considered as having LTBI provided there are no signs or symptoms of active TB. If the second result is negative, the subject may be eligible provided no other exclusion criteria for TB are met. A chest x-ray is also required if one has not been performed within 6 months of screening; a copy of the radiology report must be on file and reviewed by the investigator. If unable to obtain central laboratory results, an IGRA test could be obtained locally, after consultation with the [redacted] Medical Monitor.

pSS 8.4.5 Clinical Safety Laboratory Assessments

A central laboratory will perform assessments of safety laboratory assessments (except urine pregnancy tests, cryoglobulin, and ESR) and provide reference ranges and laboratory reports. Investigators must document their reviews of each laboratory safety report. Any laboratory test result that the investigator considers clinically relevant is to be recorded on the appropriate AE page of the eCRF (Section pSS 8.2.7). Additional safety assessments may be performed at local laboratories at the investigator's discretion. The laboratory parameters to be assessed are included in pSS Table 7.

In addition, serum or urine pregnancy testing will be performed for WOCBP.

pSS Table 7 Clinical Safety Laboratory Assessments

Hematology	
Hemoglobin Hematocrit Total leukocyte count, including manual differential Platelet count Red blood cell count Prothrombin time/INR PTT aPTT	
Serum Chemistry	
Aspartate aminotransferase Alanine aminotransferase Gamma glutamyltransferase hsCRP Total bilirubin Direct bilirubin Alkaline phosphatase Lactate dehydrogenase Creatinine Blood urea nitrogen Uric acid Fasting glucose (nonfasting at screening only) Creatinine clearance – screening only Estimated glomerular filtration rate	Total Protein Albumin Sodium Potassium Chloride Calcium Phosphorus Magnesium Creatine kinase[a] Fasting lipid panel (total cholesterol, high-density lipoprotein, low-density lipoprotein, and triglycerides; nonfasting at screening only)
Urinalysis	
Protein Glucose Blood Leukocyte esterase Specific gravity pH	Microscopic examination of sediment
Urine chemistry – Spot urine for urine protein:creatinine ratio (UPCR)	
Infectious Serologies	
Anti-HCV antibodies with reflex testing of HCV RNA if positive HBsAg Anti-HBsAb Anti-HBcAb Anti-HIV-1 and anti-HIV-2 antibody	
Other Analyses	
Serum will be collected at baseline (Week 0) and at the EOT (Week 24) for optional measurements of anti-SARS-CoV-2 immunoglobulins. Tuberculosis test (QuantiFERON®-TB Gold) at screening only Direct Coomb's test (only if clinically indicated) Whole blood HCQ level (in subjects taking HCQ) Pregnancy Test for WOCBP (serum or urine β-HCG test every 4 weeks) Follicle-stimulating hormone if needed to confirm menopausal status (see APPENDIX 4), at screening HbA1c Thyroid-stimulating hormone (if above normal reference range, test free T4; if below normal range, test free T4 and T3) [redacted] Erythrocyte sedimentation rate [redacted]	

pSS Table 7 Clinical Safety Laboratory Assessments

[redacted]
T cells, B cells, natural killer cells
Beta-2-microglobulin
Cryoglobulin

[redacted] aPTT = activated partial thromboplastin time; β-HCG = beta-human chorionic gonadotropin; [redacted]; DNA = deoxyribonucleic acid; dsDNA = double-stranded DNA; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; hsCRP = hjgh-sensitivity C-reactive protein; Ig = immunoglobulin; INR = international normalization ratio; PTT = partial thromboplastin time; RNA = ribonucleic acid; [redacted]; Sm = Smith; SSA = Sjögren's syndrome antigen A; SSB = Sjögren's syndrome antigen B; T3 = tri-iodothyronine; T4 = thyroxine; TB = tuberculosis; ULN = upper limit of normal; WOCBP = women of childbearing potential

[a] If the creatine kinase is > 2.5× ULN, reflex testing of creatine kinase-MB and troponin I will be required.

pSS 8.4.6 Imaging Safety Assessment

Any incidental findings of potential clinical relevance on chest x-ray or any additional imaging performed that is not directly associated with the objectives of the protocol should be evaluated and handled by the study investigator as per standard medical/clinical judgment. Images may be requested for submission to the assigned imaging core lab for central analysis.

pSS 8.5 PK of Branebrutinib

The PK sampling schedule for branebrutinib, its metabolites, and concomitant medications will be harmonized among all treatments and sub-protocols where applicable.

For the predose and postdose PK assessments of branebrutinib and metabolites, samples will be collected from 2 groups of subjects—all study subjects will comprise one group; and subjects at preselected clinical sites only and who will also have extended PK sampling comprise the second group (pSS Table 8).

Samples collected from all study subjects who receive branebrutinib will be analyzed for branebrutinib PK only, including samples drawn on days scheduled solely for predose samples. Samples collected from subjects at the preselected clinical sites will be analyzed for both branebrutinib and metabolites as indicated in pSS Table 8 and will be divided into 2 collection tubes, one tube for branebrutinib and one tube for metabolites analyses.

In general, predose (trough) concentrations will be assessed to evaluate the attainment of steady-state and accumulation. It is expected that steady-state will be achieved for all analytes at Week 4 after 28 days of continuous dosing.

Pharmacokinetic samples may also be used in correlation analyses for evaluation of PK/PD and the effect of pharmacogenomics (PGx), and may be used for other correlation analyses as well. The sampling schedule is based on available information on branebrutinib and its metabolites.

(Samples for PK analysis collected from subjects receiving PBO will not be analyzed for branebrutinib or metabolites.)

Branebrutinib and Metabolites Analysis:

Branebrutinib PK samples will be analyzed by a vendor using a validated assay. Plasma samples for metabolites will be analyzed by the BMS bioanalytical laboratory. These analyses will be reported separately. The BMS laboratory will be unblinded before the end of the study and will not communicate unblinded information to the BMS [redacted] study teams. Where the data allow, individual subject PK parameter values for branebrutinib and its metabolites will be derived from plasma concentration data versus time by noncompartmental methods with a validated PK analysis program. Actual times will be used for the analyses.

For all study subjects, the branebrutinib PK parameters listed below will be calculated and summarized with data up to 4 hours postdose. Accumulation ratios for Cmax and AUC0-4 will also be calculated.

Cmax	Maximum observed concentration
Tmax	Time to maximum concentration
Ctrough	Trough observed plasma concentration
AUC(0-4)	Area under the plasma concentration-time curve from time zero to the 4-hour dosing period

For subjects at preselected sites with extended sampling, separate plasma concentrations of branebrutinib and select metabolites at all timepoints will be summarized by time point. The branebrutinib and metabolites PK parameters listed below will be calculated and summarized.

Cmax	Maximum observed concentration
Tmax	Time to maximum concentration
AUC(0-T)	Area under the plasma concentration-time curve from time zero to time of last quantified concentration
AUC(TAU)	Area under the concentration-time curve to the end of the dosing period
Ctrough	Trough observed plasma concentration

pSS Table 8 lists the complete sampling schedule for assessment of the PK of branebrutinib, metabolites, and concomitant medications in subjects with pSS.

To assess steady-state concentrations of branebrutinib, a total of 5 predose PK samples (approximately 4 mL each) will be drawn from all study subjects at Week 0 (Day 1), Week 4 (Day 29), Week 8 (Day 57), Week 16 (Day 113), and Week 24 (Day 169). (Note that these samples will be drawn within a 1-hour window before the next dose is administered.) For subjects at preselected sites with extended sampling, predose PK samples collected at Week 8 (Day 57) will also be aliquoted to assess metabolite concentrations.

For postdose sampling, all study subjects will have branebrutinib PK samples drawn at Week 0 (Day 1), Week 8 (Day 57), and Week 24 (Day 169) at the 0.5, 1, 2, and 4-hour time points, a total of 14 samples. (Note that these samples will be drawn within ±15 min from the given time points.) For subjects at preselected sites with extended sampling, postdose PK samples will be aliquoted to assess metabolite concentrations at these time points.

In addition, for subjects at preselected sites with extended sampling, a total of 7 postdose PK samples will be drawn and assessed for both branebrutinib and metabolite concentrations at Week 0 (Day 1) and Week 8 (Day 57) at approximately 06:00 hours, and from 08:00 to 10:00 hours (flexible window), and from 10:00 to 12:00 hours (flexible window). Samples will also be collected at Week 0 (Day 2) at approximately 24:00 hours postdose (predose of branebrutinib on Day 2). Efforts should be made to collect the samples within these windows; however, any sample drawn outside the prespecified window will not be considered a protocol deviation. Both planned and actual time points at which the blood samples will be taken will be recorded and used in analysis and modeling.

Concomitant Medications

Concentrations of concomitant medications that are sensitive substrates of CYP2C8 and other potentially relevant drug metabolizing enzymes that may have a drug-drug interaction with branebrutinib and P-gp transporter may be measured (post-hoc) in subjects receiving PBO and active treatment. Samples for the PK assessment of the relevant concomitant medications will be collected at Week 0 and Week 4 from all study subjects. Samples for PK analysis collected from subjects receiving branebrutinib or PBO will be analyzed for HCQ and other relevant concomitant comedications provided that these subjects are receiving HCQ and other relevant concomitant comedications.

Detailed instructions for the collection, labeling, processing, storage, shipping, and disposition of all PK blood samples are provided in the Laboratory Manual.

pSS Table 8 PK Sampling for Branebrutinib, Metabolites, and Concomitant Medications

Study Day	Study Week	Event	Time (Relative to Branebrutinib Dose) Hours:Minutes	Branebrutinib	Metabolites (collected from subjects at preselected sites)	Concom Meds[a,b,c]	Comments
1	0	Predose	00:00	X		X[a,b,c]	• Predose PK samples will be collected from all study subjects to assess branebrutinib and relevant concomitant medications; • For subjects on HCQ, whole blood samples will be collected for HCQ level assessment.
1	0	Postdose	00:30	X	X		• Postdose PK samples collected from all study subjects at these time points will be assessed for branebrutinib; • Postdose PK samples collected at these time points from subjects at preselected clinical sites will also be assessed for metabolites; • Postdose PK samples collected at 2 hours after dosing, will be assessed for relevant
1	0	Postdose	01:00	X	X		
1	0	Postdose	02:00	X	X	X[a,b,c]	
1	0	Postdose	04:00	X	X		

pSS Table 8 PK Sampling for Branebrutinib, Metabolites, and Concomitant Medications

Study Day	Study Week	Event	Time (Relative to Branebrutinib Dose) Hours:Minutes	Branebrutinib	Metabolites (collected from subjects at preselected sites)	Concom Meds[a,b,c]	Comments
							concomitant medications; • For subjects on HCQ, whole blood samples will be collected for HCQ level assessment.
1	0	Postdose	06:00	X	X		• Postdose PK samples collected from subjects at preselected clinical sites only will be assessed for branebrutinib and metabolites at these time points.
1	0	Postdose	08:00-10:00	X	X		
1	0	Postdose	10:00-12:00	X	X		
2	0	Postdose[d]	24:00	X	X		
29	4	Predose	00:00	X		X[a,b,c]	• Predose PK samples will be collected from all study subjects for assessment of branebrutinib and concomitant medications; • For subjects on HCQ, whole blood samples will be collected for HCQ level assessment.
29	4	Postdose	02:00			X[a,b,c]	• Plasma samples will be collected from all study subjects at 2 hours after dosing for assessment of relevant concomitant medications; • For subjects on HCQ, whole blood samples will be collected in addition for HCQ level assessment.
57	8	Predose	00:00	X	X		• Predose and postdose PK samples collected at these time points from all study subjects will be assessed for branebrutinib only. • Predose and postdose PK samples collected at these time points from subjects at preselected clinical sites will also be assessed for metabolites.
57	8	Postdose	00:30	X	X		
57	8	Postdose	01:00	X	X		
57	8	Postdose	02:00	X	X		
57	8	Postdose	04:00	X	X		
57	8	Postdose	06:00	X	X		• Postdose PK samples collected at preselected clinical sites only will be assessed at these time points for branebrutinib and metabolites.
57	8	Postdose	08:00-10:00	X	X		
57	8	Postdose	10:00-12:00	X	X		
113	16	Predose	00:00	X			• Predose PK samples taken from all study subjects will be assessed for branebrutinib only.

pSS Table 8 PK Sampling for Branebrutinib, Metabolites, and Concomitant Medications

Study Day	Study Week	Event	Time (Relative to Branebrutinib Dose) Hours:Minutes	Branebrutinib	Metabolites (collected from subjects at preselected sites)	Concom Meds[a,b,c]	Comments
169	24	Predose	00:00	X			• Predose PK samples taken from all study subjects will be assessed for branebrutinib only.
169	24	Postdose	00:30	X			• Postdose PK Samples taken at these time points from all study subjects will be assessed for branebrutinib only.
169	24	Postdose	01:00	X			
169	24	Postdose	02:00	X			
169	24	Postdose	04:00	X			

NA = not applicable; PK = pharmacokinetic; Concom Meds = concomitant medications; HCQ = hydroxychloroquine.

[a] Concentrations of concomitant medications that are sensitive substrates of CYP2C8 and other potentially relevant drug metabolizing enzymes that may have a drug-drug interaction with branebrutinib and P-gp transporter may be evaluated post-hoc for subjects receiving PBO and active treatment at predose of branebrutinib on Day 1 and Day 29 (see Section pSS 8.5.1).

[b] For subjects taking HCQ on-study, whole blood samples will be taken at predose and 2 hours after dosing with the IP on Day 1 (Week 0) and Day 29 (Week 4) (see Section pSS 8.5.1).

[c] Subjects who are on HCQ will be informed to bring HCQ to the clinic on Day 1 and Day 29 for simultaneous dosing with branebrutinib and not to take it at home on those 2 days. Similarly, subjects who are on other prescription concomitant medications will also be informed to bring them to the clinic on Day 1 and Day 29 for simultaneous dosing with branebrutinib, but only when it is safe for subjects and operationally feasible. This should be based on the investigator's discretion with consideration that the medications which should not be delayed until the time of dosing in the clinic should be taken at home. The self-reported time for all prescription medications taken at home should be recorded as accurately as possible.

[d] PK sample must be drawn before the IP dose is administered on Day 2.

pSS 8.5.1 PK of Potential Concomitant Medications

Concentrations of Concomitant medications that are sensitive substrates of CYP2C8 and other potentially relevant drug metabolizing enzymes and P-gp transporter may be evaluated for subjects receiving PBO and active treatment with the bioanalytical analysis as part of a retrospective analysis. HCQ will be among the concomitant medications. The retrospective analysis will be conducted after review of the enrollment records, reported concomitant medication use within the enrolled population and on the incidence threshold and relevance to drug interaction with branebrutinib based on preclinical and clinical data. Other confounding factors will be evaluated as part of the analysis to avoid inclusion of bias or artifact results.

Subjects who are on HCQ will be informed to bring HCQ to the clinic on Day 1 and Day 29 for simultaneous dosing with branebrutinib and not to take it at home on those 2 days. Similarly, subjects who are on other prescription concomitant medications will also be informed to bring them to the clinic on Day 1 and Day 29 for simultaneous dosing with branebrutinib, but only when it is safe for subjects and operationally feasible. This should be based on the investigator's

discretion with consideration that the medications which should not be delayed until the time of dosing in the clinic should be taken at home. The self-reported time for all prescription medications taken at home should be recorded as accurately as possible.

The concentrations of relevant concomitant medications will be measured, post-hoc, using samples collected predose of branebrutinib or placebo on both Day 1 and Day 29 (Week 4; at which point accumulation of branebrutinib and its metabolites is expected to achieve steady-state). In addition to predose samples on Day 1 and Day 29, samples will also be collected at 2 hours after dosing with branebrutinib or placebo to evaluate the concentration of relevant concomitant medications, including HCQ. Bioanalytical analysis of all relevant concomitant medications will be conducted post-hoc. The doses of the concomitant drugs and the time they are taken, will be carefully recorded at all times (including Day 1 on Week 0 and on Day 29 on Week 4). Actual and dose-normalized concentrations will be listed, summarized, and compared between posttreatment and pretreatment of branebrutinib and PBO separately; other covariates such as MTX use, gender, etc. can be added to the comparison as needed.

Detailed instructions for PK sample collection for the relevant concomitant medications, labeling, processing, storage, shipping, and disposition are provided in the Laboratory Manual. While blood samples will be used for the analysis of HCQ, plasma samples will be analyzed for the other relevant concomitant medications by available validated assays. The results of these post hoc analyses will not be recorded in the CSR.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]	[redacted]
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[redacted]	[redacted]
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[redacted]	[redacted]
[redacted]	[redacted]
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[redacted]

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[redacted]

pSS 8.7 Health Economics OR Medical Resource Utilization and Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters will not be evaluated in this study.

PSS 9 STATISTICAL CONSIDERATIONS

pSS 9.1 Sample Size Determination

Sample size is calculated based on the estimated effect size for the primary endpoint comparison between branebrutinib and PBO treatment groups. The primary endpoint for the pSS sub-protocol is pSS composite response at Week 24.

Estimates for response rates were obtained from the published literature.[82, 83] Sample size justification is provided below:

Assuming a total sample size of 45 subjects randomized in a blinded fashion at a 2:1 ratio to branebrutinib (30 subjects) or PBO (15 subjects) and a treatment difference of 30% with a PBO response of 20% for the pSS composite response at Week 24, the 95% CI is expected to exclude 0 (expected 95% CI based on a z-test = 3%, 57%).

pSS 9.2 Populations for Analyses

The following analysis sets will be used in the summary and analysis of study data:

Population	Description
Enrolled Set	All subjects who sign informed consent.
FAS	All subjects who are randomized. Following the intent-to-treat principle, subjects will be analyzed according to the treatment assigned at randomization. The FAS will be the primary efficacy analysis population. This is the same as the intent-to-treat population.
PPS	A subset of the FAS who are compliant with study treatment and who do not have any statistically relevant protocol deviations that may impact the primary efficacy endpoint assessments. The PPS will be analyzed according to the treatment assigned at randomization. The PPS will be a supportive efficacy analysis population.
Safety Analysis Set	All randomized subjects who receive at least 1 dose of double-blind study treatment. Subjects will be analyzed according to treatment received. In case subjects take the incorrect treatment, the following scenario will be considered: • For subjects who should be receiving branebrutinib treatment, if the subject took any placebo dose, the subject will still be counted in branebrutinib treatment group for safety analysis set unless the subject took placebo throughout the entire course. For subjects who should be receiving placebo treatment, if the subject took any branebrutinib dose, the subject will be counted in the branebrutinib treatment group for safety analysis set.

Population	Description
PK	All randomized subjects who receive at least 1 dose of branebrutinib and have any available branebrutinib concentration data. Subjects will be analyzed according to treatment received during the PK collection.
Biomarker	All randomized subjects who receive at least 1 dose of double-blinded study treatment and have at least 1 posttreatment biomarker measurement.

pSS 9.3 Endpoints

The following sections outline the efficacy endpoints for this study.

pSS 9.3.1 Primary Endpoint

Proportion of subjects with at least 3 of the following at Week 24:

- Decrease of ≥ 1 point or 15% from baseline in the ESSPRI Total Score
- Decrease of ≥ 3 points from baseline in ESSDAI score
- Decrease of ≥ 25% from baseline in ocular staining score or, if normal score at baseline no change to abnormal
- Increase of ≥ 25% from baseline in stimulated salivary flow
- Improvement in one or more serological markers (RF, IgG, complement C3 or C4, cryoglobulin)

pSS 9.3.2 Additional Endpoints

The following are the additional efficacy endpoints as defined at Week 24:

Proportion of subjects with the following at Week 24:

- Decrease of ≥ 1 point or 15% in the ESSPRI Total Score
- Decrease of ≥ 3 points from baseline in ESSDAI score
- Decrease of ≥ 25% from baseline in ocular staining score or, if normal score at baseline no change to abnormal
- Increase of ≥ 25% from baseline in Schirmer's test score or, if normal score at baseline no change to abnormal
- Increase of ≥ 25% from baseline in TBUT or, if normal score at baseline no change to abnormal
- Increase of ≥ 25% from baseline in stimulated salivary flow
- Improvement in one or more serological markers (RF, IgG, complement C3 or C4, cryoglobulin)

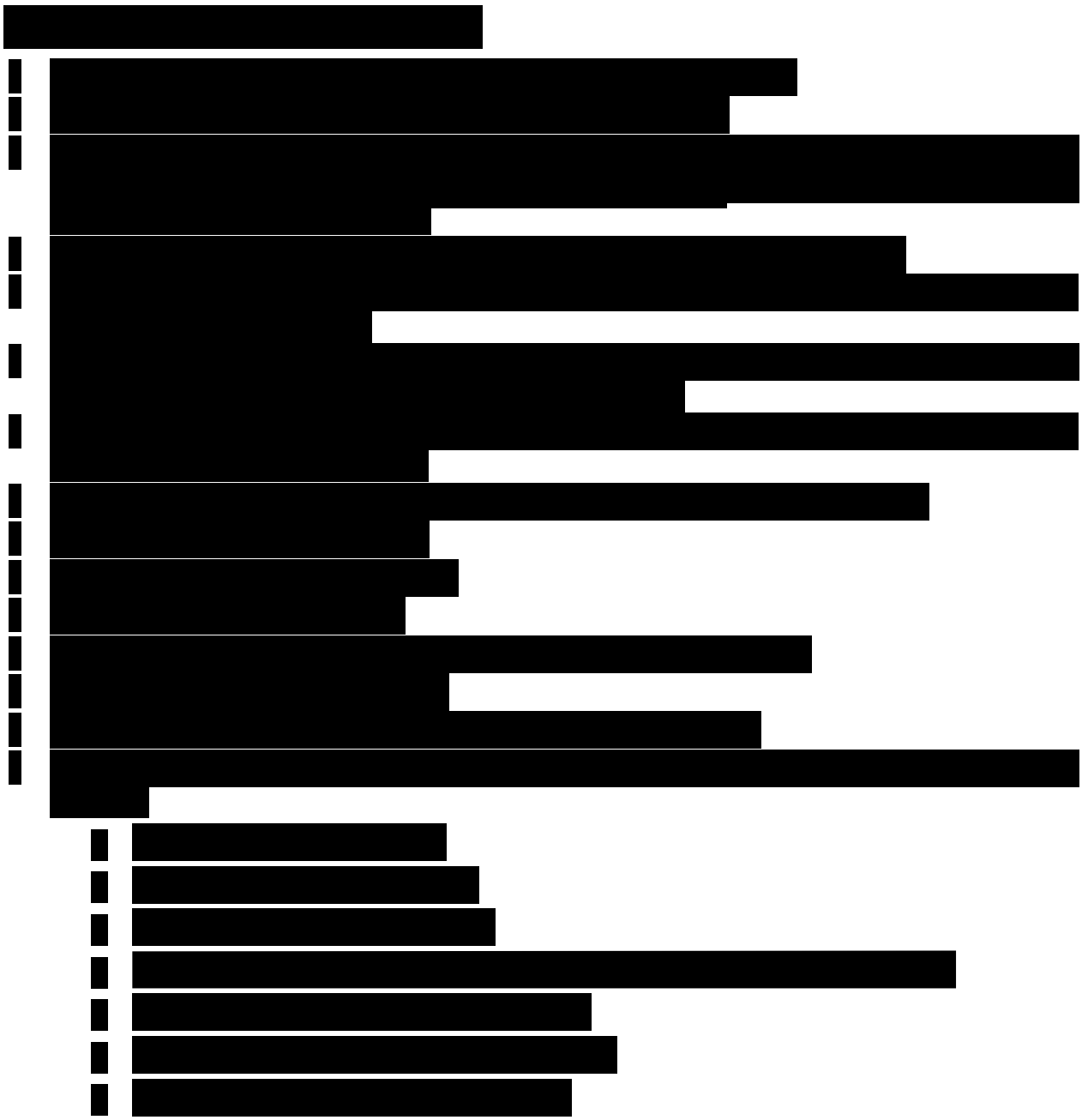
Change from baseline in:

- Autoantibody titers, hsCRP, and ESR at Week 24

- DAS28-CRP
- EQ-5 D-5 L scores at Week 24
- PROMIS Fatigue 6 a
- PGA and SGA
- NRS for Mouth and Eye Dryness

pSS 9.3.3 PK Endpoints

- Concentration values and PK parameters of branebrutinib and metabolites of clinical interest



pSS 9.4 Statistical Analyses

The SAP will be developed and finalized before database lock. Section pSS 9.4.1 provides a summary of planned statistical analyses of the primary and secondary efficacy endpoints. Additional and exploratory endpoints will be summarized in a descriptive manner.

pSS 9.4.1 Efficacy Analyses

Efficacy data will be summarized using the FAS. Data will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum), unless otherwise specified, for continuous variables and frequency distributions (counts and percentages) for categorical variables. Efficacy data will be summarized separately for each sub-protocol and with each sub-protocol combined for variables that are similar among the sub-protocols.

For the pSS sub-protocol, data will be presented for the following treatments:

- Branebrutinib
- PBO

Endpoint	Statistical Analysis Methods
Primary	General Analysis Methodology Response rates of branebrutinib compared to PBO for binary endpoints (responder/nonresponder) will be analyzed using a CMH test stratified by HCQ use. The 95% CI for each treatment group response rate and the difference in response rate for branebrutinib compared to PBO will be provided. If expected cell counts are not sufficient, then Fisher's exact test will be used. Since this sub-protocol is not powered to determine statistical significance, P-values will be added descriptively. Imputation Method Nonresponder imputation will be used for binary endpoints for subjects who discontinue study treatment early, start a protocol-prohibited medication/therapy prior to the specified timepoint, or otherwise have missing endpoint data for the specified timepoint. Other imputation methods may be considered for sensitivity analyses and will be described in the SAP if used.
Additional	General Analysis Methodology Response rates of branebrutinib compared to PBO for binary endpoints (responder/nonresponder) will be analyzed using a CMH test stratified by HCQ use. The 95% CI for each treatment group response rate and the difference in

Endpoint	Statistical Analysis Methods
	response rate for branebrutinib compared to PBO will be provided. If expected cell counts are not sufficient, then Fisher's exact test will be used. Continuous endpoints (change from baseline values) will be analyzed using analysis of covariance. The baseline value of the endpoint being tested will be added into the model as a covariate and HCQ use and treatment as fixed effects. Treatment differences based on least-squares means and corresponding 2-sided 95% CIs will be provided for the difference between branebrutinib and PBO. Supportive Analyses Supportive analyses for continuous endpoints may be performed using MMRM to investigate response over time. Bayesian borrowing to utilize historical controls may also be performed as supportive analyses. Details will be provided in the SAP if needed. Imputation Method Nonresponder imputation will be used for binary endpoints for subjects who discontinue study treatment early, start a protocol-prohibited medication/therapy prior to the specified timepoint, or otherwise have missing endpoint data for the specified timepoint. Other imputation methods may be considered for sensitivity analyses and will be described in the SAP if used. Testing Strategy for Additional Endpoints There will be no alpha level adjustment for multiple endpoint testing.

pSS 9.4.1.1 Subgroup Analyses

Subgroup analyses will be conducted for the primary and secondary efficacy endpoints on the FAS population. Subgroups that may be evaluated include the following:

- Gender
- Race
- Tobacco use

Additional subgroups defined for descriptive summaries may be specified in the SAP.

pSS 9.4.2 Safety Analyses

Safety data will be descriptive in nature and will be summarized using the Safety Analysis Set. Data will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum), unless otherwise specified, for continuous variables and frequency distributions (counts and percentages) for categorical variables. Safety data will be summarized separately for each sub-protocol and with all sub-protocols combined.

Data will be presented for the following treatments:

- Branebrutinib
- PBO

pSS 9.4.2.1 Adverse Events

TEAEs are defined as AEs that occur after the subject received first dose of study treatment or if a preexisting condition worsens in severity or becomes serious after receiving the first dose of study treatment up to 30 days after the last dose of study treatment. All reported TEAEs, SAEs, deaths, AEs leading to study treatment discontinuation, and target AEIs will be summarized by MedDRA system organ class and preferred term.

pSS 9.4.2.2 Clinical Laboratory Tests

Laboratory parameters will be summarized as absolute and change from baseline values by visit. Baseline values are defined as the last nonmissing value prior to the first dose of study treatment. Marked abnormalities summarized by visit and shift tables will also be provided. For clinical laboratory test results, marked abnormalities will be defined in the SAP.

pSS 9.4.2.3 Vital Signs and ECGs

Vital signs and ECGs will be summarized as absolute and change from baseline values by visit. Baseline values are defined as the last nonmissing value prior to the first dose of study treatment. Marked abnormalities will be summarized by visit as well. For vital signs and ECGs, marked abnormalities will be defined in the SAP.

pSS 9.4.3 Other Analyses

The PK, PD, and exploratory biomarker analyses will be described in the SAP finalized before database lock. Any population pharmacokinetics analysis and PD analyses will be presented separately from the main CSR.

pSS 9.4.4 Analysis and Reporting

After all subjects in the pSS sub-protocol have finished the study and the data have been locked for the sub-protocol, analyses of the efficacy and safety data for the sub-protocol will be performed in order to aid in planning for subsequent clinical development. Details of these analyses will be described in the SAP. The study team responsible for managing the study, including Medical Monitors, will remain blinded to treatment assignment and the results of safety analysis until full database lock and treatment unblinding has occurred. The data will be reported only after completion of all 3 sub-protocols.

Protocol Number: IM014029
IND Number: 142401
EX-US Non-IND
EUDRACT Number: 2019-002205-22
Date: 01-Jul-2019
Revised Date: 01-Dec-2021

Clinical Protocol IM014029:

RA SUB-PROTOCOL

A Randomized, Placebo-Controlled, Double-Blind, Multicenter Study to Assess the Efficacy and Safety of Branebrutinib Treatment in Subjects with Active Systemic Lupus Erythematosus or Primary Sjögren's Syndrome, or Branebrutinib Treatment Followed by Open-label Abatacept Treatment in Subjects with Active Rheumatoid Arthritis

Protocol Amendment 04 RA

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RA 1 SUB-PROTOCOL SUMMARY

RA 1.1 Synopsis

Protocol Title: A Randomized, Placebo-Controlled, Double-Blind, Multicenter Study to Assess the Efficacy and Safety of Branebrutinib Treatment in Subjects with Active Systemic Lupus Erythematosus or Primary Sjögren's Syndrome, or Branebrutinib Treatment Followed by Open-label Abatacept Treatment in Subjects with Active Rheumatoid Arthritis

Short Title:

Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of Branebrutinib Treatment Followed by Abatacept Treatment in Subjects with Rheumatoid Arthritis: RA Sub-protocol

Study Phase:

Phase 2a

RA Sub-protocol Rationale:

The Study IM014029 RA sub-protocol is designed to evaluate the efficacy and safety of branebrutinib, an oral, highly selective, irreversible inhibitor of Bruton's tyrosine kinase (BTK) in the treatment of moderate to severe adult-onset RA. The RA sub-protocol will also evaluate the safety and efficacy of switching to 12 weeks of treatment with abatacept after 12 weeks of treatment with branebrutinib or placebo.

BTK inhibition is expected to (1) inhibit antigen-dependent B cell signaling and function without depleting B cells,[2] (2) lead to decreases IC-mediated production of pro-inflammatory cytokines, (3) reduce IgG-containing IC signaling in monocytic cells, and (4) reduce IgE-containing signaling in mast cells and basophils.[8, 9, 10, 11] These processes are key pathogenic molecular mechanisms of immune-mediated diseases. Therefore, branebrutinib will be tested for efficacy in RA.

A PBO control is included in the RA sub-protocol of this study to allow the effects of treatment, both desired and adverse, to be appropriately attributed to the treatment received.

Despite recent progress in RA with a number of medications approved in the US and Europe,[12] unmet medical needs remain.[24] First, many agents approved for RA treatment have significant safety concerns, including the risk of serious or chronic infections, malignancies, and gastrointestinal perforation. Second, many patients respond only partially to currently available therapies, and only a minority of patients (< 10%) achieve true remission. Treatments that reduce osteoclasts and bone resorption may help to address some of these unmet medical needs.[25]

The IM014029 RA sub-protocol is designed to help determine if branebrutinib is biologically active and effective in the treatment of RA (see Section RA 4.4). The RA sub-protocol will also evaluate the safety and efficacy of switching to 12 weeks of treatment with abatacept after 12 weeks of treatment with branebrutinib or placebo.

RA Sub-protocol Study Population:

The study population will consist of male and female subjects aged 18 years (or age of majority) to 75 years inclusive at screening with moderate to severe adult-onset RA.

RA Sub-protocol Key Inclusion/Exclusion Criteria:

a) Documented diagnosis of adult-onset RA as defined by American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) 2010 standard criteria < 4 years before screening
b) ACR global functional status Class I to III
c) MTX inadequate response (MTX-IR) based on investigator's judgment
d) Minimum of 6 swollen and 6 tender joints on a 66/68 joint count at the screening and baseline visit
e) Evidence of swelling in at least 1 joint of the hand or wrist by clinical examination at the screening and baseline visit
f) Central laboratory results for hsCRP ≥ 0.6 mg/dL (6 mg/L) or site laboratory results for ESR ≥ 28 mm/h at the screening visit. These may be retested 1 time during screening period, if initial screening results are not within inclusion level.
g) Anti-citrullinated protein/peptide antibodies (ACPA) positive ≥ 30 U/mL (with a positive cut-off value of 10 U/mL for the central laboratory)
h) Subjects with juvenile idiopathic arthritis diagnosis or idiopathic arthritis onset before age 16 are excluded.
i) Subjects with documented Felty's syndrome are excluded.
j) Subjects with psoriatic arthritis are excluded.
k) Subjects with active fibromyalgia with pain symptoms or signs that would interfere with joint assessment or requiring adjustment in medication within the 3 months before screening to control symptoms are excluded. Subjects with fibromyalgia that is well controlled on stable treatment may otherwise be considered.
l) Subjects hospitalized with PCR-proven or suspected COVID-19 infection (unless for quarantine/observation) within the 3 months prior to randomization, as well as any subjects with any sequelae of prior COVID-19 infection at screening, regardless of time since infection, are excluded.

RA Sub-protocol Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To compare the efficacy of branebrutinib with PBO at Week 12 in the treatment of subjects with moderate to severe RA on a stable background of MTX who have had an inadequate response to MTX	• ACR50 response compared to baseline

RA Sub-protocol Objectives and Endpoints:

Objectives	Endpoints
Secondary/Additional Branebrutinib therapy: Day 1 to Week 12	
• To compare the efficacy of branebrutinib with PBO at Week 12 in the treatment of subjects with moderate to severe RA on a stable background of MTX who have had an inadequate response to MTX	**Secondary:** • Changes in efficacy measures, including DAS with 28 joint count and CRP or ESR [DAS28-CRP and DAS28-ESR], SDAI, and CDAI • ACR20 and ACR70 response compared to baseline
	Additional: • Change from baseline in autoantibody titers, change from baseline in BTK occupancy • Change from baseline in ACR component assessments: - Tender/Painful Joint Count (68) - Swollen Joint Count (66) - PGA of Arthritis - Subject Global Assessment of Disease Activity - hsCRP - HAQ-DI • Change from baseline in RAMRIS scores of synovitis, osteitis (bone marrow edema), bone erosion, and cartilage loss (joint-space narrowing) • Change from baseline in the EQ-5 D-5 L score • Change from baseline in PROMIS Fatigue 6 a
Additional Open-label abatacept therapy: Week 12 to Week 24	
• To evaluate the efficacy at Week 24 of switching from branebrutinib or PBO to abatacept at Week 12 in the treatment of subjects with moderate to severe RA on a stable background of MTX who have had an inadequate response to MTX	**Additional:** • Changes from Week 12 at Week 24 in efficacy measures, including DAS28-CRP and DAS28-ESR, SDAI, and CDAI • ACR20, ACR50, and ACR70 response at Week 24 based on activity at Week 12 after pretreatment with branebrutinib or PBO (treatment effect of abatacept following treatment with branebrutinib versus PBO) • Change from Week 12 to Week 24 in autoantibody titers, change from Week 12 to Week 24 in BTK occupancy • Change from Week 12 to Week 24 in ACR component assessments: – Tender/Painful Joint Count (68) – Swollen Joint Count (66) – PGA of Arthritis – Subject Global Assessment of Disease Activity – hsCRP – HAQ-DI

RA Sub-protocol Objectives and Endpoints:

Objectives	Endpoints
	• Change from Week 12 to Week 24 in RAMRIS scores of synovitis, osteitis (bone marrow edema), bone erosion, and cartilage loss (joint-space narrowing) • Change from Week 12 to Week 24 in the EQ-5 D-5 L score • Change from Week 12 to Week 24 in PROMIS Fatigue 6 a
Additional Branebrutinib followed by open-label abatacept therapy: Day 1 to Week 24	
• To evaluate the efficacy at Week 24 of branebrutinib or PBO treatment followed by abatacept treatment in subjects with moderate to severe RA on a stable background of MTX who have had an inadequate response to MTX	• Changes from baseline at Week 24 in efficacy measures, including DAS28-CRP, DAS28-ESR, SDAI, and CDAI • ACR20, ACR50, and ACR70 response at Week 24 compared to baseline • Change from baseline at Week 24 in PROMIS Fatigue 6 a
Safety	
• To evaluate the safety and tolerability at Week 24 of switching at Week 12 from branebrutinib or PBO to abatacept in subjects with RA	• Number and proportion of subjects experiencing SAEs, AEs, and abnormalities in laboratory parameters, vital signs, and ECGs
Exploratory	
• Evaluate the PK of branebrutinib and metabolites of clinical interest [redacted]	

[redacted] ACR = American College of Rheumatology; ADME = absorption, distribution, metabolism, and excretion; AE = adverse event; ANA = antinuclear antibodies; [redacted]; BTK = Bruton's tyrosine kinase; C = complement; CDAI = Clinical Disease Activity Index; CRP = C-reactive protein; CS = corticosteroid; [redacted] DAS28 = Disease Activity Score 28; [redacted]; ECG = electrocardiogram; EQ-5 D-5 L = Euro Quality of Life Five Dimensions Questionnaire: 5 Level version; ESR = erythrocyte sedimentation rate; HAQ-DI = Health Assessment

Questionnaire-Disease Index; hsCRP = high-sensitivity C-reactive protein; [redacted]; Ig = immunoglobulin; IL; = interleukin; MTX = methotrexate; PBO = placebo; PGA = physician global assessment; PK = pharmacokinetic; PROMIS = Patient-Reported Outcomes Measurement Information System; RA = rheumatoid arthritis; [redacted]; RNA = ribonucleic acid; [redacted] SAE = serious adverse event; [redacted] SDAI = Simplified Disease Activity Index; [redacted]

RA Sub-protocol Design:

- This is a double-blind, PBO-controlled Phase 2a study sub-protocol to evaluate the effect of branebrutinib (BMS-986195) in subjects with RA. All subjects will receive background therapy for their primary disease as appropriate.
- Subjects will receive double-blind branebrutinib 9 mg administered orally once daily (QD) or branebrutinib PBO for 12 weeks (Week 0 to Week 12). Note: the last day of dosing of branebrutinib or PBO in the RA sub-protocol should be the day prior to the Week 12/Day 85 visit.
- All subjects will receive an additional 12 weeks of treatment (Week 12 to Week 24) with open-label abatacept.
- Treatment assignment will be randomized. Subjects will undergo screening evaluations to determine eligibility within 28 days prior to administration of study medication. Following the screening process, if eligible for study participation, subjects will be randomized in the study to the RA sub-protocol in a 3:1 ratio for study treatment and PBO. No stratification will be imposed at randomization in this sub-protocol.

RA Sub-protocol Number of Subjects:

It is expected that 80 subjects will be randomized in the RA sub-protocol.

RA Sub-protocol Duration:

The total duration of participation in the RA sub-protocol is approximately 32 weeks and will be divided into the following periods: screening (up to 4 weeks), double-blind, PBO-controlled branebrutinib treatment for 12 weeks (Week 0 to Week 12), open-label treatment with abatacept for an additional 12 weeks (Week 12 to Week 24), and follow-up (4 weeks).

RA Sub-protocol Study Treatment:

Study Drug for IM014029		
Medication	**Potency**	**IP/Non-IP**
Branebrutinib	9 mg QD, oral	IP
Branebrutinib PBO	QD, oral	IP
Abatacept	125 mg QW, SC	IP

IP = investigational product; PBO = placebo; QD = once daily; QW = once weekly; SC = subcutaneous

RA Sub-protocol Statistical Methods:

Sample size is calculated based on the estimated effect size for the primary endpoint comparison between branebrutinib and PBO treatment groups. The primary endpoint for the RA sub-protocol is:

- ACR50 response at Week 12

Estimates for PBO response rates, treatment differences, and common standard deviations were obtained from the published literature. Sample size justification is provided below for the RA sub-protocol:

Assuming a total sample size of 80 subjects randomized in a blinded fashion at a 3:1 ratio to branebrutinib (60 subjects) or PBO (20 subjects), there will be 82% power to detect a treatment difference of 30% assuming the PBO response rate is 15% in ACR50 at Week 12 given a 1 sided, two-group test of a difference in binomial proportions with a 5% level of significance.

Categorical data will be summarized by treatment group as frequency counts and percentages. Continuous data will be summarized by treatment group using n, mean, standard deviation, median, minimum, and maximum unless otherwise specified. Efficacy data will be summarized separately for each sub-protocol and with each sub-protocol combined for variables that are similar among the sub-protocols. Primary analysis for each sub-protocol will be performed after all subjects finish the study within a sub-protocol. There will be no alpha level adjustment for multiple endpoint testing.

Response rates of branebrutinib compared to PBO for binary endpoints (responder/nonresponder) will be analyzed using a Chi-square test. The 95% CIs for each treatment group response rate and the difference in response rate for branebrutinib compared to PBO will be provided. If expected cell counts are not sufficient, then Fisher's exact test will be used.

Logistic regression models may be used in supportive analyses to incorporate additional covariates of interest.

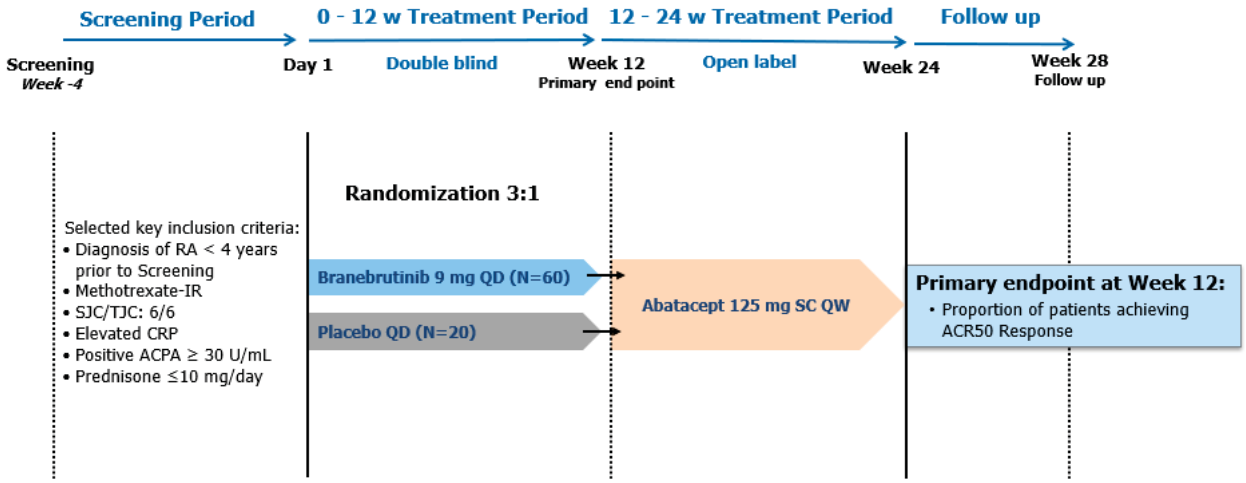
Continuous endpoints (change from baseline values) will be analyzed using analysis of covariance. The baseline value of the endpoint being tested will be added into the model as a covariate. Treatment differences based on least-squares means and corresponding 2-sided 95% CIs will be provided for the difference between branebrutinib and PBO. Bayesian borrowing to utilize historical controls may also be performed as supportive analyses. Details will be provided in the SAP if needed.

Nonresponder imputation will be used for binary endpoints for subjects who discontinue study treatment early, start a protocol-prohibited medication/therapy prior to the specified timepoint, or otherwise have missing endpoint data for the specified timepoint.

Supportive analyses for continuous endpoints may be performed using MMRM to investigate response over time with treatment, visit, treatment-by-visit interaction as the fixed effects and the baseline value of the endpoint as a covariate.

TEAEs and SAEs will be summarized using counts and percentages of subjects experiencing the event as well as the number of events by system organ class, preferred term, and treatment group. Physical examinations findings, vital signs, clinical laboratory test results, and ECG test results will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) for continuous variables and frequency distributions (counts and percentages) for categorical variables. Safety data will be summarized separately for each sub-protocol and with all sub-protocols combined.

RA 1.2 Schema



ACPA = anti-citrullinated protein/peptide antibody; ACR = American College of Rheumatology; CRP = C-reactive protein; IR = inadequate response; QD = once daily; QW = once weekly; RA = rheumatoid arthritis; SC = subcutaneous; SJC = swollen joint count; TJC = tender joint count; w = week

For the RA sub-protocol, abatacept 125 mg will be administered SC QW from Week 12 to Week 24.

RA 1.3 Schedule of Activities

RA Table 1 Screening Procedural Outline Branebrutinib Study IM014029

Procedure	Screening (V1)	Notes
Eligibility Assessments		
Informed Consent	X	A subject is considered enrolled only when a protocol-specific ICF is signed; this includes subjects at preselected clinical sites consenting to participate in extended PK sampling in addition to the sampling scheduled for all study subjects.
Enroll subject in the IRT system	X	
Inclusion/Exclusion Criteria	X	Includes: Documented RA diagnosis (< 4 years before screening) as defined by ACR/EULAR 2010 standard criteria. ACR global functional status Class I to III. MTX-IR based on investigator's judgment.
RA History; RA-related Treatment	X	
General Medical History	X	
History of Tobacco Use	X	Nonsmoker, light or heavy smoker.
Patient-reported Outcomes		
SGA of Disease Activity	X	Collected on eCOA device (refer to Section RA 8.1.1.4).
HAQ-DI	X	Collected on eCOA device (includes pain VAS for ACR calculation; refer to RA 8.1.1.1).
EQ-5 D-5 L	X	Collected on eCOA device (refer to Section RA 8.1.1.3).
PROMIS-Fatigue 6 a	X	Collected on eCOA device (refer to Section RA 8.1.1.2).
Safety Assessments		
Physical Examination	X	Complete physical examination.
Physical Assessments	X	
Vital Signs	X	Includes height (screening only) and weight, body temperature (ear or oral), respiratory rate, seated BP, and seated heart rate. BP and heart rate should be measured after the subject has been resting quietly for at least 5 minutes.
ECG	X	ECGs should be recorded after the subject has been supine for at least 5 minutes.

RA Table 1 Screening Procedural Outline Branebrutinib Study IM014029

Procedure	Screening (V1)	Notes
Chest Imaging (eg, Chest X-ray)	X	Chest imaging is required if not performed within 6 months of screening visit; copy of radiology report must be on file and reviewed by the investigator.
Prior and Concomitant Medication Use	X	Includes prescription, over-the-counter medications, and herbal supplements. All concomitant medications to be reviewed by the Medical Monitor and clinical pharmacology asset lead.
SAE Assessment	X	All SAEs must be collected from the time of signing the consent, including those thought to be associated with protocol-specified procedures and within 30 days of discontinuation of dosing or subject's participation in the study if the last scheduled visit occurs at a later time.
Clinical Assessments		
Tender/Swollen Joint Count (68/66)	X	Performed by independent joint count assessor. Collected on eCOA device (refer to Section RA 8.1.2.1).
PGA	X	Performed by investigator. Collected on eCOA device (refer to Section RA 8.1.2.2).
MRI of the hand/wrist that is clinically most swollen at screening will be imaged using a whole-body MRI system (RAMRIS) [a]	X	Perform approximately 14 days prior to randomization to allow review by imaging core lab and perform repeat, if required. MRI results obtained as part of the first screening instance may be used for rescreening, if the MRI performance date is within 30 days of randomization. (Refer to Section RA 8.1.2.3).
Composite Assessments of Disease Activity		
CDAI	X	Composite score calculated programmatically (Refer to Section RA 8.1.3).
SDAI	X	Composite score calculated programmatically (Refer to Section RA 8.1.3).
DAS28-CRP, DAS28-ESR	X	Composite score calculated programmatically (Refer to Section RA 8.1.3).
Laboratory Tests		**Includes blood and urine samples.**
Hematology	X	CBC with differential.
Serum Chemistry Panel	X	Includes liver function testing.
Lipid Panel	X	Nonfasting.
Urinalysis	X	
HbA1c	X	If HbA1c ≥ 9 consult Medical Monitor.
TSH	X	If out of normal range (high or low), consult the Medical Monitor.

RA Table 1 Screening Procedural Outline Branebrutinib Study IM014029

Procedure	Screening (V1)	Notes
UPCR	X	
eGFR	X	
ESR [b]	X	Performed at site.
ACPA	X	ACPA ≥ 30 U/mL (with a cut-off value of 10 U/mL for the central laboratory) as inclusion criterion.
RF	X	
hsCRP	X	Collected as central laboratory assessment.
Serology	X	Includes HCV antibody, HBsAg, HbsAb, HbcAb, and HIV antibodies.
TB Test (IGRA; eg, QuantiFERON®-TB Gold)	X	
Pregnancy Test (serum or urine)	X	WOCBP only. Must have negative pregnancy test within 24 hours prior to the start of treatment.
FSH	X	For select women only, serum FSH level will be determined to confirm menopausal status. See APPENDIX 4 for definition and Section RA 5.1 for reproductive status inclusion criteria.
Biomarker Assessments		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
[redacted]	[redacted]	

[redacted] ACR = American College of Rheumatology; [redacted] BP = blood pressure; CBC = complete blood count; CDAI = Clinical Disease Activity Index; CRP = C-reactive protein; [redacted]; DAS = Disease Activity Score; ECG = electrocardiogram; eCOA = Electronic Clinical Outcome Assessment; eGFR = estimated glomerular filtration rate; EQ-5 D-5 L = Euro Quality of Life 5 Dimensions Questionnaire: 5-Level version; ESR = erythrocyte sedimentation rate; EULAR = European League Against Rheumatism; FSH = follicle-stimulating hormone; HAQ-DI = Health Assessment Questionnaire – Disability Index; HbcAb = hepatitis B core antibody; HbsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; hsCRP = high-sensitivity C-reactive protein; ICF = informed consent form; IGRA = interferon gamma-release assay; [redacted]; IRT = interactive response technology; MRI = magnetic resonance imaging; MTX-IR = methotrexate-inadequate response; PA = posterior-anterior; PGA = Physician Global Assessment; PK = pharmacokinetic; PROMIS = Patient-reported Outcomes Measurement Information System; RA = rheumatoid arthritis; RAMRIS = Rheumatoid Arthritis Magnetic Resonance Imaging Scoring System; [redacted]; RF = rheumatoid factor; RNA = ribonucleic acid;

[redacted]; SAE = serious adverse event; SDAI = Simplified Disease Activity Index; SGA = Subject Global Assessment; TB = tuberculosis; [redacted] VAS = visual analog scale; WOCBP = women of childbearing potential

[a] The MRI conducted at screening is considered the baseline MRI for the study. If a subject requires rescreening, the MRI results obtained as part of the first screening instance may be used for the rescreening as long as the MRI performance date is within 30 days of randomization (scoring is done by a central imaging vendor).

[b] ESR laboratory samples should be collected and recorded by an unblinded staff member who does not perform/have access to other subject procedures, including joint counts. All ESR laboratory samples after screening should be collected and recorded in a blinded fashion. (Refer to RA 8.4.5).

[redacted]

[redacted]

When multiple assessments are conducted at a single visit, the following is the order in which they should be performed:

1. Patient-reported Outcomes (eg, SGA, EQ-5 D-5 L, etc)
2. Safety assessments (eg, vitals, AEs)
3. Investigator-administered Assessments (eg, PGA, joint count, etc)
4. Laboratory tests (eg, safety laboratory tests, PK assessments, biomarker assessments)

RA Table 2 Procedural Outline Branebrutinib Study IM014029 (Week 0 to Week 12)

Procedure	W0 D1 V2	W2 D15 (± 3 d) V3	W4 D29 (± 3 d) V4	W8 D57 (± 3 d) V5	W12 D85 (± 3 d) V6 (EOT) [a]	Notes
Patient-reported Outcomes						
SGA of Disease Activity	X	X	X	X	X	Collected on eCOA device (refer to Section RA 8.1.1.4).
HAQ-DI	X	X	X	X	X	Collected on eCOA device (includes pain VAS for ACR calculation; refer to Section RA 8.1.1.1).
EQ-5 D-5 L	X				X	Collected on eCOA device (refer to Section RA 8.1.1.3).
PROMIS-Fatigue 6 a	X				X	Collected on eCOA device (refer to Section RA 8.1.1.2).
Safety Assessments						
Complete Physical Examination	X				X	
Targeted Physical Examination		X	X	X		
Body Weight	X				X	
Vital Signs	X	X	X	X	X	Temperature (ear or oral), respiratory rate, seated BP, and seated heart rate; BP and heart rate should be measured after the subject has been resting quietly for at least 5 minutes.
ECG	X	X	X	X	X	ECGs should be recorded after the subject has been supine for at least 5 minutes.
Concomitant Medication Use	X	X	X	X	X	
AE and SAE Assessment	X	X	X	X	X	Nonserious AEs must be collected from the time of the first dose of the study drug through the date of the follow-up or last visit.
Clinical Assessments						
Tender/Swollen/Painful Joint Count (68/66)	X	X	X	X	X	Performed by independent joint count assessor. Collected on eCOA device (Refer to Section RA 8.1.2.1).

RA Table 2 Procedural Outline Branebrutinib Study IM014029 (Week 0 to Week 12)

Procedure	W0 D1 V2	W2 D15 (± 3 d) V3	W4 D29 (± 3 d) V4	W8 D57 (± 3 d) V5	W12 D85 (± 3 d) V6 (EOT) [a]	Notes
PGA	X	X	X	X	X	Performed by investigator. Collected on eCOA device (Refer to Section RA 8.1.2.2).
MRI of the hand/wrist that is clinically most swollen at screening will be imaged using a whole-body MRI system (RAMRIS) [b]					X	Perform within 7 days of scheduled visit (Refer to Section RA 8.1.2.3).
Composite Assessments of Disease Activity						
CDAI	X	X	X	X	X	Composite score calculated programmatically (Refer to Section RA 8.1.3).
SDAI	X	X	X	X	X	Composite score calculated programmatically (Refer to Section RA 8.1.3).
DAS28-CRP, DAS28-ESR	X	X	X	X	X	Composite score calculated programmatically (Refer to Section RA 8.1.3).
ACR 20/50/70	X	X	X	X	X	Composite score calculated programmatically (Refer to Section RA 8.1.3).
Laboratory Tests						
Hematology	X	X	X	X	X	
Serum Chemistry Panel	X	X	X	X	X	
Lipid Panel (Fasting)	X		X	X	X	
Urinalysis	X	X	X	X	X	
eGFR	X	X	X	X	X	
Beta-2-microglobulin	X	X	X	X	X	
ESR [c]	X	X	X	X	X	Performed at site.
[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	

RA Table 2 Procedural Outline Branebrutinib Study IM014029 (Week 0 to Week 12)

Procedure	W0 D1 V2	W2 D15 (± 3 d) V3	W4 D29 (± 3 d) V4	W8 D57 (± 3 d) V5	W12 D85 (± 3 d) V6 (EOT) [a]	Notes
[redacted]	[redacted]				[redacted]	
RF	X		X	X	X	
hsCRP	X	X	X	X	X	Collected as central laboratory assessment.
Pregnancy Test (serum or urine)	X		X	X	X	WOCBP only. Must have negative pregnancy test within 24 hours prior to the start of treatment.
TBNK	X	X	X		X	
Serum IgM, IgG, IgA, IgE, free Kappa/Lambda light chains	X		X		X	
[redacted]	[redacted]				[redacted]	[redacted]
PK Assessments						
Standard blood samples for the PK assessment of branebrutinib [d]	X		X	X		Refer to Section RA 8.5, RA Table 9 for details.
Blood samples at preselected sites for the PK assessment of branebrutinib and metabolites [e]	X			X		Refer to Section RA 8.5, RA Table 9 for details.
Blood samples for the PK assessment of concomitant medications [f]	X		X			Refer to Section RA 8.5, RA Table 9 for details.
Blood sample for the PK assessment of abatacept [g]					X	Predose only (sample is not required, if Week 12 is a subject's EOT visit).

RA Table 2 Procedural Outline Branebrutinib Study IM014029 (Week 0 to Week 12)

Procedure	W0 D1 V2	W2 D15 (± 3 d) V3	W4 D29 (± 3 d) V4	W8 D57 (± 3 d) V5	W12 D85 (± 3 d) V6 (EOT) [a]	Notes
Biomarkers						
[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
[redacted]	[redacted]		[redacted]		[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
[redacted]	[redacted]				[redacted]	[redacted]
Study Treatment						
Randomize	X					

RA Table 2 Procedural Outline Branebrutinib Study IM014029 (Week 0 to Week 12)

Procedure	W0 D1 V2	W2 D15 (± 3 d) V3	W4 D29 (± 3 d) V4	W8 D57 (± 3 d) V5	W12 D85 (± 3 d) V6 (EOT) [a]	Notes
Dispense/Administer Study Treatment	X	X	X	X	X [j, k]	Note: At Week 2 the subject is requested to bring IP to the site visit and IP is administered at the site; no new kit is dispensed at this visit.
Study Treatment Compliance		X	X	X	X	

[redacted] ACR = American College of Rheumatology; AE = adverse event; [redacted]; BP = blood pressure; BTK = Bruton's tyrosine kinase; CDAI = Clinical Disease Activity Index; [redacted] DAS28-CRP = Disease Activity Score 28-C-reactive protein; DAS28-ESR = DAS28-erythrocyte sedimentation rate; DNA = deoxyribonucleic acid; dsDNA = double-stranded deoxyribonucleic acid; ECG = electrocardiogram; eCRF = electronic case report form; eGFR = estimated glomerular filtration rate; EOT = end of treatment; EQ-5D-5L = Euro Quality of Life 5 Dimensions Questionnaire: 5-Level version; ESR = erythrocyte sedimentation rate; FU = follow-up; HAQ-DI = Health Assessment Questionnaire Disability Index; hsCRP = high-sensitivity C-reactive protein; Ig = immunoglobulin; [redacted]; IP = investigational product; MRI = magnetic resonance imaging; PBO = placebo; PGA = Physician Global Assessment; PK = pharmacokinetic; PROMIS = Patient-Reported Outcomes Measurement Information System; RAMRIS = Rheumatoid Arthritis Magnetic Resonance Imaging Scoring System; [redacted]; RF = rheumatoid factor; RNA = ribonucleic acid; SAE = serious adverse event; SDAI = Simplified Disease Activity Index; SGA = Subject Global Assessment; [redacted]; TBNK = T cells, B cells, natural killer cells; [redacted] V = visit; WOCBP = women of childbearing potential

[a] If the decision has been made for a subject to permanently discontinue treatment before the planned Week 12 visit (Section RA 7.1.1), the subject should undergo a Week 12 EOT visit, as specified in the Week 12 column of this table (RA Table 2) followed by a Week 28 Safety FU visit, 4 weeks (±3 days) later, as specified in the Week 28 column (RA Table 3). The appropriate eCRF pages for the EOT and Safety FU visits should be completed accordingly.

[b] Same hand/wrist imaged at screening; subjects who terminate the study early require an MRI at the EOT visit only if that visit is ≥ 4 weeks from the date of randomization or ≥ 4 weeks from Week 12 and should have the EOT MRI no more than 7 days from the EOT visit.

[c] ESR laboratory samples should be collected and recorded by an unblinded staff member who does not perform/have access to other subject procedures, including joint counts. All samples after screening should be collected and recorded in a blinded fashion. (Refer to Section RA 8.4.5).

[d] Blood samples for the PK assessment of branebrutinib concentrations will be taken predose in all study subjects on Week 0 (Day 1), and Week 8 (Day 57) and postdose at Week 8 (Day 57) at approximately 0.5, 1, 2, and 4 hours after dosing. At Week 4 (Day 29), samples will be taken predose only for the assessment of steady-state trough concentration of branebrutinib.

[e] At preselected clinical sites with extended sampling: blood samples will be taken from subjects at Week 0 (Day 1) and Week 8 (Day 57) at 0 hours (predose), and postdose at approximately 0.5, 1, 2, 4, and at 6 hours and from 8-10 hours (flexible window), 10-12 hours (flexible window), and at Week 0 (Day 2) at 24 hours after dosing (predose of branebrutinib on Day 2); collected blood samples will be divided into 2 tubes at each time point for the PK assessment of branebrutinib and its metabolites concentrations.

f Blood samples for PK assessment of relevant concomitant medications that are sensitive substrates of CYP2C8 and other potentially relevant drug metabolizing enzymes and P-gp transporter may be measured (post-hoc); as such, the levels of exposure for subjects receiving PBO and active treatment will be collected at Week 0 (Day 1) and Week 4 (Day 29) predose and 2 hours postdose.

g Blood sample for PK of abatacept not required if this is subject's EOT visit.

[redacted]

[redacted]

j The last day of dosing of branebrutinib or PBO in the RA sub-protocol should be the day prior to the Week 12/Day 85 visit.

k First dose of abatacept is to be administered at the Week 12 visit.

When multiple assessments are conducted at a single visit, the following is the order in which they should be performed:

1. Patient-reported Outcomes (eg, SGA, EQ-5 D-5 L, etc)
2. Safety assessments (eg, vitals, AEs)
3. Investigator-administered Assessments (eg, PGA, joint count, etc)
4. Laboratory tests (eg, safety laboratory tests, PK assessments, biomarker assessments)
5. Treatment dosing

RA Table 3 Procedural Outline Branebrutinib Study IM014029: Open-label Abatacept Therapy (Week 14 to Week 28)

Procedure	Week 14 D99 (± 3 d) V7	Week 16 D113 (± 3 d) V8	Week 20 D141 (± 3 d) V9	Week 24 D169 (± 3 d) V10 (EOT) [a]	Week 28 D197 (±3 d) V11 Safety FU	Notes
Patient-reported Outcomes						
SGA of Disease Activity	X	X	X	X	X	Collected on eCOA device (refer to Section RA 8.1.1.4).
HAQ-DI	X	X	X	X	X	Collected on eCOA device (includes pain VAS for ACR calculation; refer to Section RA 8.1.1.1).
EQ-5 D-5 L				X	X	Collected on eCOA device (refer to Section RA 8.1.1.3).
PROMIS-Fatigue 6 a				X	X	Collected on eCOA device (refer to Section RA 8.1.1.2).
Safety Assessments						
Complete Physical Examination					X	
Targeted Physical Examination	X	X	X	X		
Body Weight		X		X	X	
Vital Signs	X	X	X	X	X	Temperature (ear or oral), respiratory rate, seated BP, and seated heart rate; BP and heart rate should be measured after the subject has been resting quietly for at least 5 minutes.
ECG	X	X	X	X	X	ECGs should be recorded after the subject has been supine for at least 5 minutes.
Concomitant Medication Use	X	X	X	X	X	
AE and SAE Assessment	X	X	X	X	X	Nonserious AEs must be collected from the time of the first dose of the study drug through the date of the follow-up or last visit.

RA Table 3 Procedural Outline Branebrutinib Study IM014029: Open-label Abatacept Therapy (Week 14 to Week 28)

Procedure	Week 14 D99 (± 3 d) V7	Week 16 D113 (± 3 d) V8	Week 20 D141 (± 3 d) V9	Week 24 D169 (± 3 d) V10 (EOT) [a]	Week 28 D197 (±3 d) V11 Safety FU	Notes
Clinical Assessments						
Tender/Swollen Joint Count (68/66)	X	X	X	X	X	Performed by independent joint count assessor. Collected on eCOA device (Refer to Section RA 8.1.2.1).
PGA	X	X	X	X	X	Performed by investigator. Collected on eCOA device (Refer to Section RA 8.1.2.2).
MRI of the hand/wrist that is clinically most swollen at screening will be imaged using a whole-body MRI system. (RAMRIS) [b]				X		Perform within 7 days of scheduled visit (Refer to Section RA 8.1.2.3).
Composite-Assessments of Disease Activity						
CDAI		X		X	X	Composite score calculated programmatically (Refer to Section RA 8.1.2.1).
SDAI	X	X	X	X	X	Composite score calculated programmatically (Refer to Section RA 8.1.2.1).
DAS28-CRP, DAS28-ESR	X	X	X	X	X	Composite score calculated programmatically (Refer to Section RA 8.1.2.1).
ACR 20/50/70	X	X	X	X	X	Composite score calculated programmatically (Refer to Section RA 8.1.2.1).
Laboratory Tests						
Hematology	X	X	X	X	X	
Serum Chemistry Panel	X	X	X	X	X	
Lipid Panel (Fasting)		X		X	X	

RA Table 3 Procedural Outline Branebrutinib Study IM014029: Open-label Abatacept Therapy (Week 14 to Week 28)

Procedure	Week 14 D99 (± 3 d) V7	Week 16 D113 (± 3 d) V8	Week 20 D141 (± 3 d) V9	Week 24 D169 (± 3 d) V10 (EOT) [a]	Week 28 D197 (±3 d) V11 Safety FU	Notes
Urinalysis	X	X	X	X	X	
HbA1c				X	X	
eGFR	X	X	X	X	X	
ESR [c]	X	X	X	X	X	Performed at site.
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]				[redacted]		
RF		X	X	X	X	
hsCRP	X	X	X	X	X	Collected as central laboratory assessment.
TBNK	X	X		X	X	
Serum IgM, IgG, IgA, IgE, free Kappa/Lambda light chains		X		X	X	
Pregnancy Test (serum or urine)		X	X	X	X	WOCBP.
Immunogenicity (abatacept)	X	X	X	X	X	
[redacted]				[redacted]		[redacted]
PK Assessments						
Blood samples for the PK assessment of abatacept	X	X	X	X	X	Refer to Section RA 8.5, RA Table 10
Biomarker Sampling						
[redacted]		[redacted]		[redacted]	[redacted]	[redacted]

RA Table 3 Procedural Outline Branebrutinib Study IM014029: Open-label Abatacept Therapy (Week 14 to Week 28)

Procedure	Week 14 D99 (± 3 d) V7	Week 16 D113 (± 3 d) V8	Week 20 D141 (± 3 d) V9	Week 24 D169 (± 3 d) V10 (EOT) [a]	Week 28 D197 (±3 d) V11 Safety FU	Notes
[redacted]	[redacted]	[redacted]				[redacted]
[redacted]	[redacted]	[redacted]				[redacted]
[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]		[redacted]		[redacted]
[redacted]		[redacted]		[redacted]		[redacted]
[redacted]	[redacted]	[redacted]		[redacted]		[redacted]
[redacted]				[redacted]		[redacted]
Study Treatment						
Dispense/Administer Study Treatment	X	X	X			At Week 14 the subject is requested to bring IP to the site visit and IP is administered at the site; no new kit is dispensed at this visit. No IP administered or dispensed at Week 24.
Study Treatment Compliance	X	X	X	X	X [f]	

[redacted]; ACR = American College of Rheumatology; AE = adverse event; [redacted] CDAI = Clinical Disease Activity Index; [redacted]; DAS28 = Disease Activity Score 28; DNA = deoxyribonucleic acid; [redacted] ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; EQ-5D-5L = Euro Quality of Life 5 Dimensions Questionnaire: 5-Level version; ESR = erythrocyte sedimentation rate; ET = early termination; FU = follow-up; HAQ-DI = Health Assessment Questionnaire Disability Index; hsCRP = high-sensitivity C-reactive protein; Ig = immunoglobulin; [redacted]; IP = investigational product; MRI = magnetic resonance imaging; PGA = Physician Global Assessment; PK = pharmacokinetic; PROMIS = Patient-Reported Outcomes Measurement Information System; RAMRIS = Rheumatoid Arthritis Magnetic Resonance Imaging Scoring System; [redacted] RF = rheumatoid factor; RNA = ribonucleic acid; SAE = serious adverse event; SDAI = Simplified Disease Activity Index; SGA = Subject Global Assessment; [redacted] TBNK = T cells, B cells, natural killer cells; V = visit; WOCBP = women of childbearing potential.

[a] If the decision has been made for a subject to permanently discontinue (Section RA 7.1.1) treatment with abatacept before the planned Week 24 visit, the subject should undergo a Week 24 EOT visit as specified in the Week 24 column of this table followed by a Week 28 Safety FU visit, 4 weeks (±3 d) later, as specified in the Week 28 column of this table. The appropriate eCRF pages for the EOT and Safety FU visits should be completed accordingly.

[b] Same hand/wrist imaged at screening. Subjects who terminate the study early should have the ET MRI no more than 7 days from the EOT visit.

[c] ESR laboratory samples should be collected and recorded by an unblinded staff member who does not perform/have access to other subject procedures, including joint counts. All ESR laboratory samples after screening should be collected and recorded in a blinded fashion. (Refer to RA 8.4.5).

[redacted]

[f] Study treatment compliance is to be performed at Week 28 only if the subject's study participation has completed and the subject failed to return study drug at the prior visit.

When multiple assessments are conducted at a single visit, the following is the order in which they should be performed:

1. Patient-reported Outcomes (eg, SGA, EQ-5 D-5 L, etc)
2. Safety assessments (eg, vitals, AEs)
3. Investigator-administered Assessments (eg, PGA, joint count, etc)
4. Laboratory tests (eg, safety laboratory tests, PK assessments, biomarker assessments)
5. Treatment dosing

RA 2 INTRODUCTION

An overall introduction to this protocol employing a master protocol design for 3 separate immune-mediated indications is provided in Section Master 1.2.

RA 2.1 Background and Research Hypothesis

The Study IM014029 RA sub-protocol is designed to evaluate the efficacy and safety of branebrutinib in addition to background disease therapy in the treatment of subjects with moderate to severe adult-onset RA (see Section RA 4.4). The RA sub-protocol will also evaluate the safety and efficacy of switching to 12 weeks of treatment with abatacept after 12 weeks of treatment with branebrutinib or placebo.

RA is a systemic immune-mediated disease affecting 0.5 to 1.0% of the population that targets the joints (large and small), which develop synovial inflammation, leading to swelling, pain, stiffness, and dysfunction.[22] Constitutional symptoms such as fatigue, fever, and malaise are not uncommon and contribute to reduced quality of life. Additionally, patients with RA have a high risk for cardiovascular morbidity and reduced life span that correlates with disease severity, including an increased risk of cardiovascular disease.[23]

Despite recent progress in RA with a number of medications approved in the US and Europe,[12] unmet medical needs remain.[24] First, many agents approved for RA treatment have significant safety concerns, including the risk of serious or chronic infections, malignancies, and gastrointestinal perforation. Second, many patients respond only partially to currently available therapies, not many patients ever experience the end of RA destructive processes, and only a minority of patients (< 10%) achieve true remission. Treatments that reduce osteoclasts and bone resorption may help to address some of these unmet medical needs.[25]

BTK inhibition is expected to inhibit antigen-dependent B cell signaling and function without depleting B cells,[2] leading to reduction of IgG-containing ICs signaling in monocytic cells, and decreases in IC-mediated production of pro-inflammatory cytokines. Some evidence suggests that this may also reduce IgE-containing signaling in mast cells and basophils.[8, 9, 10, 11] These processes include key pathogenic mechanisms of immune-mediated diseases.

In RA, ICs are present in the joints and act on synovial macrophages to drive the production of cytokines, chemokines, and MMPs mediating disease pathology. Expression of Ig receptors FcγRIIa and FcγRIIIa is increased in monocytes/macrophages from RA patients,[26, 27, 28] and these cells produce higher levels of TNFα and MMPs than in healthy controls.[26] Signaling through Fcγ receptors is important in the activation of monocyte-derived dendritic cells.[29] Genome-wide association studies have identified FcγRIIIa to be associated with RA susceptibility.[30] Additionally, murine models of RA such as the CIA model have suggested a critical role of activating Fcγ receptors in disease pathogenesis.[31, 32] BTK is expressed in high levels in myeloid lineages and regulates the signaling pathways leading to expression of pro-inflammatory cytokines, chemokines, and cell adhesion molecules that are induced through IC binding to FcγRIIIa and FcγRIIa. BTK has also been implicated in FcγRI signaling in mast cells and basophils.[5, 6, 7, 33, 34]

Mast cells may contribute to the pathobiology of RA. The IgE ACPAs are present in patients with RA,[10] and the number of activated mast cells are increased in synovial tissue and correlate with disease activity.[8, 9, 11] Thus, inhibition of BTK will be tested to determine whether it has therapeutic benefit in RA.

BTK inhibition may also have a direct effect on bone damage in RA through its role on osteoclastogenesis. The differentiation of osteoclasts, which mediate bone destruction in RA, is regulated by RANKL acting through the RANK receptor on osteoclast precursors, and BTK has been shown to regulate RANK-dependent osteoclastogenesis.[35, 36]

In summary, this study will test whether effects of BTK inhibition on antigen-specific BCR-mediated B cell functions, IgG-containing IC signaling through Fcγ receptors in monocytic cells, IgE-containing signaling through the BTK-dependent receptor FcεRI in mast cells and basophils, as well as RANK-dependent osteoclastogenesis, could provide benefit in the treatment of RA.

A detailed description of the chemistry, pharmacology, efficacy, and safety of branebrutinib is provided in the IB.[12]

The RA sub-protocol will also evaluate the safety and efficacy of switching to 12 weeks of treatment with abatacept after 12 weeks of treatment with branebrutinib or placebo. A PBO control for branebrutinib is included in the RA sub-protocol to allow the effects of treatment, both desired and adverse, to be appropriately attributed to the treatment received. Safety monitoring, including laboratory monitoring, will be ongoing throughout the study, for subjects in all treatment arms, along with an independent DMC.

RA 2.1.1 Study Hypotheses

BTK plays a role in the pathology of RA. The first hypothesis to be tested is that BTK inhibition provides benefit in the treatment of moderate to severe adult-onset RA. The second hypothesis to be tested is to assess the safety and efficacy after switching from branebrutinib to abatacept.

RA 2.2 Benefit/Risk Assessment

RA 2.2.1 Branebrutinib

At this early stage in the development of branebrutinib for the treatment of immune-mediated disorders, assessments of benefit and risk rely on nonclinical data and data from completed Phase 1 studies in healthy volunteer subjects. The proposed 9 mg QD dosing regimen reflects implementation of appropriate safety margins (> 500× based on the AUC in rats and dogs at the NOAEL [20 mg/kg/day and 15 mg/kg/day in rats and dogs, respectively]) and is within the range of doses tested in the FIH study (Study IM014001[37]).

The effects of BTK inhibition by branebrutinib have been documented in pharmacology studies, and the potential for benefit has been demonstrated by nonclinical studies using mouse models of RA (see details of nonclinical toxicology findings and potential clinical benefits of branebrutinib in Section 1.5.1 Master Protocol: Benefit/Risk Assessment).

With the exception of an unrelated SAE that was consistent with the subject's medical history, AEs in the FIH study (Study IM014001[37]) were mild to moderate, reversible, and consistent with expectations based on nonclinical experience.

Based upon nonclinical toxicology findings and the mechanism of action of the compound (immunosuppression), BMS has also proactively implemented additional assessments, frequent study visits for safety assessments, risk mitigation approaches, and blinded safety reviews by BMS and an independent external DMC (see details in Section 1.5.1 Master Protocol: Benefit/Risk Assessment).

All subjects in the RA sub-protocol will receive either branebrutinib or PBO treatment for a maximum of 12 weeks while receiving protocol-defined SOC therapy for their RA. All subjects in the RA sub-protocol will also receive open-label abatacept from Week 12 to Week 24.

The risk for DDIs of branebrutinib with substrates of a number of enzymes and transporters are expected to be minimal, with the exception of drugs that are sensitive substrates of CYP2C8 and P-gp as a weak inhibitor (which may be restricted or excluded based on their therapeutic window and metabolism), as are developmental and reproductive effects of the study treatment in WOCBP (see details in Section 1.5 Master Protocol: Benefit/Risk Assessment).

RA 2.2.2 Open-label Therapy with Abatacept

Abatacept, a soluble fusion protein that consists of the extracellular domain of human CTLA-4 linked to the modified Fc (hinge, CH2, and CH3 domains) portion of human IgG1, is a selective co-stimulation modulator that inhibits T cell activation by binding to CD80 and CD86 molecules on antigen-presenting cells, thereby inhibiting interaction with CD28.

Abatacept is a biologic compound approved for the treatment of patients with active RA (see the abatacept IB[48] for properties and mechanisms of action of abatacept).

In clinical studies, abatacept demonstrated clear, consistent, and medically important benefit in the treatment of signs and symptoms of RA, improving physical function, reducing the progression of structural damage, and improving the quality of life in subjects with moderate to severe RA who were MTX-naïve, or were inadequate responders to MTX or anti-TNF therapies.[49]

With over 27,754 patient-years of abatacept exposure, clinical studies of abatacept provide extensive experience characterizing the safety and efficacy/effectiveness of abatacept.[49] Review of safety data from the ongoing long-term extensions of the clinical studies reveals a consistent safety profile for abatacept over time. However, there are inherent limitations to the assessment of infrequent AEs in clinical programs. Abatacept was first approved in 2005. Since that time, there have been an estimated 648,974 patient-years of exposure to abatacept in the marketplace. Postmarketing reports have not altered the favorable benefit-risk profile for abatacept and its safety profile remains generally similar to that established during the clinical studies. There remains limited information in patients with hepatic and renal impairment, and use in elderly subjects.

Based on the clinical study experience in adults, the identified risks associated with the use of abatacept include infections (some of which may be serious or fatal), infusion-related reactions

(IV only), and systemic injection reactions (SC only).[49] The main potential risks include the development of malignancies and immune-mediated disorders, but an increased risk of these types of events has not been observed. The rate of immunogenicity has generally been low, and there has not been an apparent effect on safety, efficacy, or PK.

With regard to the developmental and reproductive effects of abatacept, the study treatment has been shown to have no effects on male or female fertility in rats, no teratogenic effects in rats and rabbits at doses up to 200 mg/kg daily (29-fold higher than the human 10 mg/kg dose based on AUC in rats and rabbits), and no adverse effects in offspring of rats treated with abatacept during early gestation and throughout the lactation period at doses up to 45 mg/kg (threefold higher than the human 10 mg/kg dose based on AUC). Abatacept has also been shown to cross the placenta in rats and rabbits. Because animal reproduction studies are not always predictive of human response, and because there are no adequate and well-controlled studies of abatacept use in pregnant women, pregnant and breastfeeding women will not be enrolled in this study and WOCBP will use protocol-specified highly effective contraceptive methods (APPENDIX 4). Further details of developmental/reproductive/toxicity effects of abatacept are provided in Section 1.5.2 Master Protocol: Benefit/Risk Assessment and in the Abatacept Development Safety Update Report[50].

Detailed information about the known and expected benefits and risks and reasonably anticipated AEs of branebrutinib and abatacept are provided in the branebrutinib IB[12] and the abatacept IB[48], respectively.

In summary, nonclinical data and clinical experience with branebrutinib in healthy subjects, and clinical experience with abatacept in subjects with RA, taken together with the design and study treatment dose selected for the current Phase 2a study indicate an overall favorable benefit/risk assessment for investigating branebrutinib treatment, and treatment of branebrutinib followed by abatacept, in subjects with RA.

RA 3 OBJECTIVES AND ENDPOINTS

RA Table 4 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To compare the efficacy of branebrutinib with PBO at Week 12 in the treatment of subjects with moderate to severe RA on a stable background of MTX who have had an inadequate response to MTX	• ACR50 response compared to baseline
Secondary/Additional Branebrutinib therapy: Day 1 to Week 12	
• To compare the efficacy of branebrutinib with PBO at Week 12 in the treatment of subjects with moderate to severe RA on a stable background of MTX who have had an inadequate response to MTX	**Secondary:** • Changes in efficacy measures, including DAS28-CRP and DAS28-ESR, SDAI, and CDAI • ACR20 and ACR70 response compared to baseline
	Additional: • Change from baseline in autoantibody titers, change from baseline in BTK occupancy • Change from baseline in ACR component assessments: – Tender/Painful Joint Count (68) – Swollen Joint Count (66) – PGA of Arthritis – Subject Global Assessment of Disease activity – hsCRP – HAQ-DI • Change from baseline in RAMRIS scores of synovitis, osteitis (bone marrow edema), bone erosion, and cartilage loss (joint-space narrowing) • Change from baseline in the EQ-5 D-5 L score • Change from baseline in PROMIS Fatigue 6 a
Additional Open-label abatacept therapy: Week 12 to Week 24	
• To evaluate the efficacy at Week 24 of switching from branebrutinib or PBO to abatacept at Week 12 in the treatment of subjects with moderate to severe RA on a stable background of MTX who have had an inadequate response to MTX	**Additional:** • Changes from Week 12 at Week 24 in efficacy measures, including DAS28-CRP, DAS28-ESR, SDAI, and CDAI • ACR20, ACR50, and ACR70 response at Week 24 based on activity at Week 12 after pretreatment with branebrutinib or PBO

RA Table 4 Objectives and Endpoints

Objectives	Endpoints
	(treatment effect of abatacept following treatment with branebrutinib versus PBO) • Change from Week 12 to Week 24 in autoantibody titers, change from Week 12 to Week 24 in BTK occupancy • Change from Week 12 to Week 24 in ACR component assessments: – Tender/Painful Joint Count (68) – Swollen Joint Count (66) – PGA of Arthritis – Subject Global Assessment of Disease Activity – hsCRP – HAQ-DI • Change from Week 12 to Week 24 in RAMRIS scores of synovitis, osteitis (bone marrow edema), bone erosion, and cartilage loss (joint-space narrowing) • Change from Week 12 to Week 24 in the EQ-5 D-5 L score • Change from Week 12 to Week 24 in PROMIS Fatigue 6 a
Additional Branebrutinib followed by open-label abatacept therapy: Day 1 to Week 24	
• To evaluate the efficacy at Week 24 of branebrutinib or PBO treatment followed by abatacept treatment in subjects with moderate to severe RA on a stable background of MTX who have had an inadequate response to MTX	**Additional:** • Changes from baseline at Week 24 in efficacy measures, including DAS28 CRP, DAS28-ESR, SDAI, and CDAI • ACR20, ACR50, and ACR70 response at Week 24 compared to baseline • Change from baseline at Week 24 in PROMIS Fatigue 6 a
Safety	
• To evaluate the safety and tolerability of switching from branebrutinib or PBO to abatacept in subjects with RA	• Number and proportion of subjects experiencing SAEs, AEs, and abnormalities in laboratory parameters, vital signs, and ECGs
Exploratory	
• Evaluate the PK of branebrutinib and metabolites of clinical interest [redacted]	

RA Table 4 Objectives and Endpoints

Objectives	Endpoints
[redacted]	

[redacted] ACR = American College of Rheumatology; ADME = absorption, distribution, metabolism, and excretion; AE = adverse event; [redacted]; BTK = Bruton's tyrosine kinase; C = complement; CDAI = Clinical Disease Activity Index; CRP = C-reactive protein; CS = corticosteroid; CXCL13 [redacted] DAS28 = Disease Activity Score 28; [redacted]; ECG = electrocardiogram; EQ-5 D-5 L = Euro Quality of Life Five Dimensions Questionnaire: 5 Level version; ESR = erythrocyte sedimentation rate; HAQ-DI = Health Assessment Questionnaire-Disease Index; hsCRP = high-sensitivity C-reactive protein; [redacted] Ig = immunoglobulin; IL; = interleukin; MTX = methotrexate; PBO = placebo; PGA = physician global assessment; PK = pharmacokinetic; PROMIS = Patient-Reported Outcomes Measurement Information System; RA = rheumatoid arthritis; [redacted]; RNA = ribonucleic acid; [redacted] SAE = serious adverse event; [redacted]; [redacted] SDAI = Simplified Disease Activity Index; [redacted];

RA 4 STUDY DESIGN

RA 4.1 Overall Design

This is a double-blind, PBO-controlled multicenter study to assess the effect of branebrutinib treatment and branebrutinib followed by abatacept (also named BMS-188667 and Orencia™) 125 mg SC QW in subjects with moderate to severe adult-onset RA.

- The RA study population will consist of male and female subjects aged 18 years (or age of majority) to 75 years inclusive at screening with moderate to severe adult-onset RA.
- Approximately 80 subjects will be randomized to the RA sub-protocol. Sample size considerations are presented in Section RA 9.1 Sample Size Determination.
- For all subjects there will be a 12-week double-blind PBO-controlled treatment period in which subjects will receive branebrutinib 9 mg or branebrutinib PBO. Note: the last day of dosing of branebrutinib or PBO in the RA sub-protocol should be the day prior to the Week 12/Day 85 visit.
- Blinded treatment assignment will be conducted by randomization on Day 1 and managed by IRT. Subjects will undergo screening evaluations to determine eligibility within 28 days prior to administration of study medication. After successfully meeting entry criteria and completing

screening assessments, subjects will be randomized (3:1 ratio) in a blinded manner to branebrutinib 9 mg or PBO QD.

- No stratification will be imposed at randomization in this sub-protocol.
- The total duration of participation in the RA sub-protocol will be approximately 32 weeks and will be divided into the following periods: screening (up to 4 weeks), double-blind PBO-controlled treatment with branebrutinib for 12 weeks (Week 0 to Week 12), open-label abatacept treatment for an additional 12 weeks (Week 12 to Week 24), and follow-up (4 weeks).
- Efficacy and safety will be assessed throughout the study (see Section RA 8.1 Efficacy Assessments, Section RA 8.2 Adverse Events, and Section RA 8.4 Safety for details of assessments). Blood samples will be collected for PK and biomarker clinical laboratory assessments (see Section RA 8.5 and Section RA 8.6, respectively, for details of assessments).
- An independent DMC will assess study findings on a periodic basis (Section RA 4.1.1).

The RA study design schematic is found in Section RA 1.2.

RA 4.1.1 DMC and Other External Committees

To ensure the safety of study subjects, across all sub-protocols, an external independent DMC consisting of 2 experienced rheumatologists, an infectious disease clinician, and a statistician will be established for ongoing evaluation of safety assessments, AEs, and laboratory measurements. An independent reporting statistician not involved in the conduct of the study will be designated to provide the DMC with essential safety data unblinded to treatment during the study, if required.

The DMC will conduct at regular, prespecified intervals and on an ad hoc basis if warranted, safety review meetings throughout the study to ensure that the benefit and risks of study participation remain acceptable. Ad hoc meetings may be initiated by the DMC or by the Sponsor based on emerging new safety information. Based on the DMC's assessment, recommendations of protocol modifications or other actions may occur, including but not limited to sample size adjustment, study modification, or discontinuation of the study or one or more of the sub-studies. In addition, hold of enrollment, pending more detailed assessment may be requested.

Blinded SUSARs will be sent to the DMC members on an ongoing basis. SAEs will be sent to the DMC on a monthly basis or on an ongoing basis as requested by the DMC.

The DMC will review safety data including but not limited to SAEs and AEIs. At the request of the DMC, designated personnel will provide further information on the medical assessment for a specific case.

The DMC may also consider external data from other branebrutinib studies that may be initiated in future or from novel scientific information that may be generated on branebrutinib or other BTK inhibitors.

Further details of DMC responsibilities, specific timing of safety reviews, content, and methods of data reports, authorities, processes, and procedures will be specified in the DMC charter.

RA 4.2 Number of Subjects

It is expected that approximately 80 subjects will be randomized in the RA sub-protocol.

Further details regarding sample size determination are provided in Section RA 9.1.

RA 4.3 End of Study Definition

The start of the study is defined as the date that the first subject signs the informed consent. The end of the RA sub-protocol is defined as the last visit of the last subject to complete the study or the final scheduled procedure shown in the SoA (Section RA 1.3). Study completion for the RA sub-protocol is defined as the final date on which data for the primary endpoint was or is expected to be collected, if this is not the same. The master protocol study will be reported only after the last endpoint has been analyzed for all 3 sub-protocols.

The total duration of study participation for subjects in the RA sub-protocol is expected to be approximately 32 weeks.

RA 4.4 Scientific Rationale for Study Design

(Please refer to Master Section 1.2 for rationale supporting the choice of a master protocol design to evaluate the safety and efficacy of branebrutinib in 3 immune-mediated/autoantibody-related diseases.)

In the RA sub-protocol, for ethical reasons, the branebrutinib PBO treatment arm will be limited to 12 weeks to limit duration of treatment without active treatment, beyond background therapy, in subjects with active disease. This design is aligned with regulatory guidance on PBO arms in studies with subjects with active RA.[88] All subjects in the RA sub-protocol, including the branebrutinib PBO arm, will also continue receiving background MTX during the study.

The standard approved dose of abatacept (125 mg SC QW) was selected for open-label treatment for all subjects from Week 12 to Week 24., given the acceptable safety profile of abatacept at this approved dose for RA, Safety monitoring, including laboratory monitoring, will be ongoing throughout the study for subjects in this sub-protocol, along with an independent DMC.

Complete details of the study design are provided in Section RA 4.1.

RA 4.5 Justification for Dose

The selection of the branebrutinib dose and regimen to be assessed in this study was based on findings in the FIH and nonclinical studies.

In the MAD panels (Part B) of the FIH study (Study IM014001), healthy subjects received branebrutinib solution QD for 14 days at 4 dose levels (0.3, 1, 3, and 10 mg; n = 6 per dose).[37] Increases in Cmax and AUC(TAU) were approximately dose proportional within the dose levels tested. The mean T-HALF was shorter than 2 hours across the dose range tested, indicating that branebrutinib was rapidly eliminated from the body. Consequently, as expected, accumulation at steady-state after multiple daily dosing was negligible.

The safety between branebrutinib 3 mg and 10 mg doses in Study IM014001 demonstrated lack of dose effects on safety profile. The drug was well-tolerated at both dose levels with most AEs also observed for the subjects treated with PBO. The AEs mainly included headache and upper respiratory tract infection. Based on the AUC in rats at the NOAEL (61,900 ng•h/mL), the safety multiple in humans after multiple doses of 10 mg is > 500×.[12] In this study, the dose level of branebrutinib will be 9 mg; therefore, the safety margin is sufficient for humans participating in the study.

The dose for branebrutinib was selected based on the totality of data from multiple biomarkers obtained through post-hoc analysis from Study IM014001. The biomarkers evaluated were BTK occupancy by branebrutinib, inhibition of ex vivo stimulated CD69 expression, and plasma CXCL13 levels. The maximum occupancy reached ≥ 99% at branebrutinib doses of 1 mg and above (100%; maximum occupancy at doses ≥ 3 mg); however, the time to reach maximum occupancy was faster and maintained for a longer duration at 3 mg and 10 mg doses (solution formulation). The variability of the effect was lower for the higher dose of 10 mg. A similar result was obtained for CD69 inhibition, while the largest median inhibition in CD69 expression was observed at the branebrutinib 10 mg dose. The highest inhibition of plasma levels of CXCL13 was also obtained at the 10 mg dose level. Considering the higher variability and expression of BTK in patients with RA and other immune-mediated disorders,[4] the higher dose is expected to sustain more stable inhibition of BTK for chronic treatment of patients.

The comparison of exposure between the branebrutinib 10 mg solution formulation from Study IM014001 and the branebrutinib 9 mg capsule formulation (3 × 3 mg) from Day 1 Cycle 2 in Study IM014023 demonstrated comparable exposure for Cmax and AUC(TAU) with only slight delay in Tmax for capsule formulation. Thus, the use of 3 × 3 mg capsules of branebrutinib is expected to be equivalent to the 10 mg solution formulation in terms of exposure, safety, and PD effects considering the specifics of the patient population.

The exposure for this dose level is also much lower than the safety limit for exposure identified in preclinical studies; as previously mentioned, based on the AUC in rats at the NOAEL, the safety multiple in humans after multiple doses of 10 mg is > 500×.

In summary, the dose to evaluate the PD response with high-level, safe exposure and achieve optimal efficacy was chosen to be 9 mg branebrutinib administered as 3 × 3 mg capsules (details of treatment administration are provided in Section RA 6.1).

With regard to use of abatacept, it is proposed that this study be conducted using the abatacept SC 125 mg prefilled syringe with weekly administration in subjects with RA; the same dose and dosing regimen used in patients with RA in Study IM101174,[38] as well as the approved dose of this biologic used in the treatment of active RA. Study IM101174 clearly established that the weekly 125 mg SC and monthly ~10 mg/kg IV dosing were therapeutically equivalent in RA, with both dosing regimens consistently delivering abatacept Cminss of 10 µg/mL and above, the exposure associated with near-maximal efficacy response in RA, in patients across all body weights.

RA 5 STUDY POPULATION

Eligibility criteria for this sub-protocol have been carefully considered for the safety of the study subjects and to ensure that the results of the study can be interpreted. It is imperative that randomized subjects meet all eligibility criteria.

Screening evaluations must be completed and reviewed to confirm whether potential subjects are eligible. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

RA 5.1 Inclusion Criteria

To be eligible to participate in the RA sub-protocol for this study, an individual must meet all of the following criteria:

1) **Signed Written Informed Consent: RA Sub-protocol**
   a) Willing to participate in the study after completing all informed consent procedures and sign the ICF
   b) Willing and able to complete all study-specific procedures and visits
2) **Age and Reproductive Status: RA Sub-protocol**
   a) **Not Applicable per Revised Protocol 02 -** Male and female patients, aged 18 years (or age of majority) to 65 years, inclusive
   b) **Not Applicable per Revised Protocol 02 -** WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of β-HCG) within 24 hours prior to the start of study treatment.
   c) **Not Applicable per Revised Protocol 02 -** Women must not be breastfeeding.
   d) **Not Applicable per Revised Protocol 02 -** WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study treatment(s) branebrutinib or PBO, 30 days before screening and 33 days posttreatment completion or longer based on country-specific label for other background therapy. After Week 12, due to the use of abatacept study treatment, the subject must agree to follow instructions for contraception for 70 days after the final dose of study treatment, or longer based on country-specific label for other background therapy.
   e) **Not Applicable per Revised Protocol 02 -** Male subjects who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception and fetal protection (APPENDIX 4) for the duration of treatment with study treatment(s) plus 33 days after the final dose of study treatment, or longer based on country-specific label for other background therapy. In addition, male subjects must be willing to refrain from sperm donation during this time.
   f) **Not Applicable per Revised Protocol 02 -** WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements, and still must undergo pregnancy testing as described in this section.
   g) This criterion does not exist. Letter g) was omitted in error in Revised Protocol 02.
   h) This criterion does not exist. Letter h) was omitted in error in Revised Protocol 02.

i) This criterion does not exist. Letter i) was omitted in error in Revised Protocol 02.

j) This criterion does not exist. Letter j) was omitted in error in Revised Protocol 02.

Investigators shall counsel WOCBP, and male subjects 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 study drug, 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.

k) **Not Applicable per Revised Protocol 03 -** Female Participants

l) **Not Applicable per Revised Protocol 03 -** Male Participants

m) Female Subjects

i. Females, ages 18 years or local age of majority to 75 years, inclusive

ii. Women subjects must have documented proof that they are not of childbearing potential. Women who are not of childbearing potential are exempt from contraceptive requirements

iii. WOCBP must have a negative highly sensitive pregnancy test (minimum sensitivity 25 IU/L or equivalent units of 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

iv. Additional requirements for pregnancy testing during and after study intervention are located in Section RA 1.3, SoA

v. 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

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

vii. WOCBP are permitted to use hormonal contraception methods (as described in APPENDIX 4)

viii. A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one 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, for at least 30 days before screening and at least 33 days posttreatment completion or longer based on country-specific label for other background therapy and agrees not to donate eggs (ova, oocytes) for

the purpose of reproduction for the same time period. After Week 12, due to the use of abatacept study treatment, the participant must agree to use a contraceptive method that is highly effective for 14 weeks posttreatment completion or longer based on country-specific label for other background therapy and must agree not to donate eggs (ova, oocytes) for the purpose of reproduction for the same time period.

n) Male Subjects
   i. Males, ages 18 years or local age of majority to 75 years, inclusive
   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 subjects 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 subjects 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 33 days after the last dose of study intervention or longer based on country-specific label for other background therapy.
   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 33 days after the last dose of study intervention in the male participant or longer based on country-specific label for other background therapy.
   vi. Male subjects 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 subjects have undergone a successful vasectomy, during the intervention period and for at least 33 days after the last dose of study intervention or longer based on country-specific label for other background therapy.
   vii. Male subjects must refrain from donating sperm during the intervention period and at least 33 days after the last dose of study intervention or longer based on country-specific label for other background therapy.
   viii. Breastfeeding partners should be advised to consult their healthcare providers about using appropriate highly effective contraception during the time the participant is required to use condoms.

3) Type of Subject and Target Disease Characteristics: RA Sub-protocol

a) **Not Applicable per Revised Protocol 03 -** Documented diagnosis of adult-onset RA as defined by American College of Rheumatology (ACR)/EULAR 2010 standard criteria < 2 years before screening

b) ACR global functional status Class I to III

c) **Not Applicable per Revised Protocol 03 -** MTX-IR based on investigator's judgment; MTX requirements are as follows:
   i. Subjects must have been taking MTX for at least 3 months at a minimal weekly dose of 15 mg (maximum 25 mg/week) and at a stable dose and administration route for

4 weeks before randomization. A lower dose of MTX is permitted if documented that a dose of 15 mg weekly was not possible due to toxicity or intolerance and the dose is at least 10 mg MTX at the screening visit.

ii. In Canada, and any other applicable country, a minimum dose of 7.5 mg per week is permitted.

iii. Subjects using IM or SC MTX for administration of their weekly dose are eligible.

d) Minimum of 6 swollen and 6 tender joints on a 66/68 joint count at the screening and baseline visit.

e) Evidence of swelling in at least 1 joint of the hand or wrist by clinical examination at the screening and baseline visit.

f) Central laboratory results for hsCRP ≥ 0.6 mg/dL (6 mg/L) or site laboratory results for ESR ≥ 28 mm/hour at the screening visit. These may be retested 1 time during screening period, if initial screening results are not within inclusion level.

g) ACPA positive ≥ 30 U/mL (with a positive cut-off value of 10 U/mL for the central laboratory).

h) Documented diagnosis of adult-onset RA as defined by American College of Rheumatology (ACR)/EULAR 2010 standard criteria < 4 years before screening.

i) MTX-IR based on investigator's judgment; MTX requirements are as follows:

i. Subjects must have been taking MTX for ≥ 12 weeks at a minimal weekly dose of 15 mg (maximum 25 mg/week) and at a stable dose and administration route for 12 weeks before randomization. A lower dose of MTX is permitted if documented that a dose of 15 mg weekly was not possible due to toxicity or intolerance and the dose is at least 10 mg MTX at the screening visit.

ii. In Canada, and any other applicable country, a minimum dose of 7.5 mg per week is permitted.

iii. Subjects using IM or SC MTX for administration of their weekly dose are eligible.

4) Medications for Target Disease: RA Sub-protocol

a) Requirements for subjects who are receiving chronic therapy with NSAIDs (including marketed cyclooxygenase-2 inhibitors) are as follows; exceptions or changes may be possible with approval by the [redacted] Medical Monitor:

i. The NSAID dose must be stable for 14 days before the screening visit and must remain stable until randomization and throughout the study.

ii. No more than 1 oral NSAID may be used (at a stable dose) during the study and may be combined with topical NSAIDs.

iii. Use of 1 or more topical NSAID is permitted, but must follow a stable regimen throughout the study.

b) **Not Applicable per Revised Protocol 03 -** Standard of care is required for ≥ 12 weeks before the screening visit and must be at a stable dose for ≥ 8 weeks before the screening visit and remain stable until randomization and throughout study participation. Details for specific medications are as follows:

i. MTX: Subjects must have been taking MTX for at least 12 weeks at a minimal weekly dose of 15 mg (maximum 25 mg/week) and at a stable dose and administration route for 4 weeks before randomization. A lower dose of MTX is

permitted if documented that a dose of 15 mg weekly was not possible due to toxicity or intolerance and the dose is at least 10 mg MTX at the screening visit.

ii. Oral CS use is permitted, but the dose must be ≤ 10 mg/day prednisone or equivalent and stable for ≥ 28 days before randomization and throughout study participation. Further specifications are as follows:

1) Topical and inhaled CS use is permitted but must follow a stable regimen throughout the study and cannot be used on an as-needed basis. Inhaled CS for non-RA conditions will not count against the maximum CS dose.

2) IM, IA, intrabursal, IV, and modified-release CS use is prohibited within 4 weeks before screening

c) SOC is required for ≥ 12 weeks before the screening visit and must be at a stable dose for ≥ 8 weeks before the screening visit and remain stable until randomization and throughout study participation. Details for specific medications are as follows:

i. MTX: Subjects must have been taking MTX for ≥ 12 weeks at a minimal weekly dose of 15 mg (maximum 25 mg/week) and at a stable dose and administration route for 12 weeks before randomization. A lower dose of MTX is permitted if documented that a dose of 15 mg weekly was not possible due to toxicity or intolerance and the dose is at least 10 mg MTX at the screening visit.

ii. Oral CS use is permitted, but the dose must be ≤ 10 mg/day prednisone or equivalent and stable for ≥ 28 days before randomization and throughout study participation. Further specifications are as follows:

1) Topical and inhaled CS use is permitted but must follow a stable regimen throughout the study and cannot be used on an as-needed basis. Inhaled CS for non-RA conditions will not count against the maximum CS dose.

2) IM, IA, intrabursal, IV, and modified-release CS use is prohibited within 4 weeks before screening.

5) Other Inclusion Criteria: RA Sub-protocol

a) Subject re-enrollment (rescreening): This study permits the re-enrollment of a subject that has discontinued the study as a pretreatment (screening) failure (ie, subject has not been randomized/has not been treated). If re-enrolled, the subject must be re-consented.

RA 5.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in the RA sub-protocol:

1) General Medical Conditions and History: RA Sub-protocol

a) Any major illness/condition or evidence of an unstable clinical condition (eg, renal, hepatic, hematologic, gastrointestinal, endocrine, pulmonary, immunologic, psychiatric) or local active infection/infectious illness that, in the investigator's judgment, will substantially increase the risk to the subject if he or she participates in the study

b) Any major surgery within the last 30 days before the first dose of study treatment, or any surgery planned during the course of the study

c) Cancer or history of cancer or lymphoproliferative disease (other than adequately treated cutaneous basal cell or squamous cell carcinoma with no evidence of recurrence within the

previous 5 years), including pre-lymphoma (pseudolymphoma of the orbit and small intestine, lymphomatoid granulomatosis, angioimmunoblastic lymphadenopathy, and lymphoid interstitial pneumonitis)

d) Class III or IV congestive heart failure as defined by the NYHA or any recent onset of heart failure resulting in NYHA Class III/IV symptoms

e) Acute coronary syndrome (eg, myocardial infarction, unstable angina pectoris) and/or any history of significant cerebrovascular disease within 24 weeks before screening

f) Current or recent (within 3 months before randomization) gastrointestinal disease, including gastrointestinal surgery, that could impact the absorption of study treatment

g) **Not Applicable per Revised Protocol 03 -** Subjects with non-RA concomitant illness that, in the opinion of the investigator, is likely to require additional systemic glucocorticosteroid therapy during the study (eg, asthma)

h) Significant blood loss (> 500 mL) or blood transfusion within 4 weeks before randomization

i) Inability to tolerate oral medication

j) Inability to tolerate venipuncture and/or inadequate venous access

k) Recent (within 6 months before randomization) drug or alcohol abuse as defined by the Diagnostic Criteria for Drug and Alcohol Abuse in the DSM 5

l) Subjects with a diagnosis of antiphospholipid antibody syndrome

m) Contraindication to magnetic resonance imaging (MRI); eg, magnetizable metallic parts/devices including cardiac pacemakers on and in the body, severe claustrophobia, body size incompatible with the scanner, sensitivity to gadolinium, severe renal insufficiency (ie, glomerular filtration rate (GFR) < 30 mL/min/1.73 m^2), and metallic tattoos. Complete contraindications are provided in the site MRI manual; however, the ultimate decision about subject appropriateness for MRI will be made by the radiologist and investigator in accordance with local standards and ethics committees.

n) Any other sound medical, psychiatric, and/or social reason as determined by the investigator

o) Any prior history of atrial fibrillation or flutter

p) Subjects with non-RA concomitant illness that, in the opinion of the investigator, is likely to require additional systemic CS therapy during the study (eg, asthma)

2) Findings Related to Possible Infection: RA Sub-protocol

a) **Not applicable per Revised Protocol 03 -** Any of the following TB criteria:

- History of active TB prior to screening visit, regardless of completion of adequate treatment
- Signs or symptoms of active TB (eg, fever, cough, night sweats, and weight loss) during screening as judged by the investigator
- Any imaging of the chest (eg, chest x-ray, chest CT scan) obtained during the screening period, or anytime within 6 months prior to screening with documentation, showing evidence of current active or old pulmonary TB
- LTBI defined as positive IGRA, by QuantiFERON-TB Gold testing at screening, in the absence of clinical manifestations Note: Subject may be eligible if (i) there are no

current signs or symptoms of active TB and (ii) subject has received adequate documented treatment for LTBI within 5 years of screening.

Note: An IGRA test that is indeterminate with no signs or symptoms of active TB must be retested for confirmation. If the second test is again indeterminate the subject will be excluded from the study. If the retest is positive, the subject should be treated as having LTBI. If the retest is negative, subject may be eligible provided no other exclusion criteria for TB are met.

b) **Not Applicable per Revised Protocol 03 -** Hepatitis C, hepatitis B, or HIV infection as demonstrated by a positive blood screen for anti-HCV confirmed by positive reflex HCV RNA test, HBsAg, HbcAb, or HIV-1 and -2 antibody. Subjects who have been vaccinated for hepatitis B (hepatitis B surface antibody [HbsAb]-positive) are not excluded.

c) **Not Applicable per Revised Protocol 03 -** Note: Subjects who are newly found to be HIV-positive should be directed to appropriate follow-up care.

d) History of congenital or acquired immunodeficiency

e) Known active infection, or any major episode of infection requiring hospitalization or treatment with parenteral (IM or IV) antimicrobial agents (eg, antibiotics, antiviral, antifungal, or antiparasitic agents) within 30 days of randomization, or completion of oral antimicrobial agents within 2 weeks of randomization

f) Previous history of recurrent herpes zoster (more than 1 episode), disseminated herpes simplex, or influenza infection within 12 weeks before randomization or a history of disseminated/complicated herpes zoster infection (multidermatomal involvement, ophthalmic zoster, CNS involvement, or postherpetic neuralgia)

g) Chronic infection within 4 weeks of randomization (eg, pneumocystis, CMV, invasive bacterial or fungal infections, or atypical mycobacteria)

h) Hospitalized with PCR-proven or suspected COVID-19 infection (unless for quarantine/observation) within the 3 months prior to randomization, as well any sequelae of prior COVID-19 infection at screening, regardless of time since infection.

i) Any of the following criteria:
   - History of active TB prior to screening visit, regardless of completion of adequate treatment
   - Signs or symptoms of active TB (eg, fever, cough, night sweats, and weight loss) during screening as judged by the investigator
     - Any imaging of the chest (eg, chest x-ray, chest CT scan) obtained during the screening period, or anytime within 6 months prior to screening, with documentation showing evidence of current active or old pulmonary TB.
   - LTBI defined as positive IGRA, by QuantiFERON-TB Gold testing at screening, in the absence of clinical manifestations Note: Subject may be eligible if (i) there are no current signs or symptoms of active TB and (ii) subject has received adequate documented treatment for LTBI within 5 years of screening; this treatment must have been completed as defined by local guidance and documented in the subject study file. Incomplete or ongoing treatment is unacceptable.

     Note: An IGRA test that is indeterminate with no signs or symptoms of active TB must be retested for confirmation. If the second test is again indeterminate, the subject will

be excluded from the study, unless there is documentation of a local negative TB Spot test result. If the retest is positive, the subject should be treated as having LTBI. If the retest is negative, the subject may be eligible provided no other exclusion criteria for TB are met.

j) Hepatitis C, hepatitis B, or HIV infection as demonstrated by a positive blood screen for anti-HCV confirmed by positive reflex HCV RNA test, HBsAg, HbcAb, or HIV-1 and 2 antibody. Subjects who have been vaccinated for hepatitis B (hepatitis B surface antibody [HbsAb]-positive) are not excluded.

Note: Subjects who are newly found to be HIV-positive should be directed to appropriate follow-up care.

3) Allergies and Adverse Drug Reaction: RA Sub-protocol

a) History of allergy to BTK inhibitors or related compounds

b) History of any serious condition induced by drug allergy (such as anaphylaxis or hepatotoxicity)

4) Target Disease Exclusions/Exceptions: RA Sub-protocol

a) Subjects with juvenile arthritis diagnosis or idiopathic arthritis onset before age 16 are excluded.

b) Subjects with documented Felty's syndrome are excluded.

c) Subjects with psoriatic arthritis are excluded.

d) Subjects with active fibromyalgia with pain symptoms or signs that would interfere with joint assessment or requiring adjustment in medication within the 3 months before screening to control symptoms are excluded. Subjects with fibromyalgia that is well controlled on stable treatment may otherwise be considered.

5) Prior/Concomitant Therapy: RA Sub-protocol

a) Inability to comply with restrictions and prohibited treatments as listed in Section RA 6.7 Concomitant Therapy; inability to comply with discontinuation requirements (Section RA 7.1).

b) Prior exposure to BTK inhibitors

c) Other investigational agents must be discontinued at least 12 weeks or 5 half-lives before screening, whichever is longer.

d) Previous exposure to JAK inhibitors such as tofacitinib, baricitinib, filgotinib, or upadacitinib.

e) Required discontinuation periods for immunomodulatory drugs (eg, cyclosporine, tacrolimus, etc.) or biologic drugs (including those specifically listed below) are provided in RA Table 7. If a drug is not specifically listed, consult the [redacted] Medical Monitor for guidance. Usual discontinuation periods are 4 weeks or 5 half-lives whichever is longer.

f) Current or past use of rituximab.

g) Current or past use of belimumab.

h) Subjects who have taken leflunomide within 36 weeks prior to screening and during the study.

i) Subjects who have taken IVIG within 8 weeks of randomization and during the study.

j) For oral CS restrictions, see Section RA 5.1.

k) IM, IV, IA, intrabursal, or modified-release CS treatment 4 weeks before randomization and during the study.

l) Treatment with DMARDs (including hydroxychloroquine) or immunomodulators other than MTX 4 weeks before randomization; the MTX dose must be stable for ≥ 12 weeks; new initiation or dose changes during treatment are not permitted. Hydroxychloroquine use is also prohibited during the study.

m) **Not Applicable per Revised Protocol 03 -** Use of antimalarial drugs (chloroquine and quinacrine) is prohibited within 4 weeks before randomization and during the study.

n) **Not applicable per Revised Protocol 03 -** Current or past approved or investigational biologic DMARD treatments (eg, TNF-inhibitors, IL-6 inhibitors, IL-1 inhibitors, T cell modulators, and anti-CD20 agents) are prohibited at any time prior to the study or during the study, with the exception of MTX (dose must be stable for ≥ 12 weeks before randomization and new initiation or dose changes during treatment are not permitted). Abatacept therapy is prohibited at any time prior to the study.

o) Subjects who have taken denosumab within 6 months before randomization and during the study; bisphosphonates are permitted

p) **Not Applicable per Revised Protocol 03 -** Administration of a live vaccine within 90 days or an inactivated vaccine within 30 days before randomization; furthermore, live and inactivated vaccines should not be used during treatment and should not be used within the 90 days or 14 days following last dose, respectively.

q) Treatment with anticoagulant or antiplatelet therapies, including aspirin for cardioprotection, within 2 weeks prior to randomization or during the study.

r) Diquafosol or rebamipide therapy within 4 weeks before randomization or during the study.

s) Use of antimalarial drugs (HCQ, chloroquine and quinacrine) is prohibited within 12 weeks before randomization and during the study.

t) Current or past approved or investigational biologic DMARD treatments (eg, TNF-inhibitors, IL-6 inhibitors, IL-1 inhibitors, T cell modulators, and anti-CD20 agents) are prohibited at any time prior to the study or during the study. Abatacept therapy is prohibited at any time prior to the study.

u) Administration of all live vaccines is prohibited within 90 days before randomization. Administration of inactivated vaccines and nonlive vaccines, including those for influenza and SARS-CoV-2, is prohibited within 30 days before randomization. See RA Table 7 for corresponding on-treatment and posttreatment restrictions.

6) Physical and Laboratory Test Findings: RA Sub-protocol

a) Clinically significant abnormalities on chest x-ray or ECG

b) Clinically significant abnormalities in laboratory tests including the following:

i. Serum ALT > 1.5× ULN.

ii. Serum AST > 1.5× ULN.

iii. Serum total bilirubin > 1.5× ULN (does not apply to subjects with Gilbert's syndrome).

iv. Hemoglobin < 8 g/dL (< 80 g/L).

v. eGFR < 50 mL/min/1.73 m^2 as calculated by the central laboratory; follow MTX usage guidelines with eGFR < 60 mL/min/1.73 m^2.
vi. Serum creatinine > 2.0 mg/dL (> 177 µmol/L).
vii. Absolute WBC count < 3.0× 10^3/µL (< 3.0× 10^9/L).
viii. Neutrophil count < 1000/µL (< 1.0× 10^9/L).
ix. Platelet count < 100× 10^3/µL (< 100× 10^9/L).

c) Any other significant laboratory or procedure abnormalities that, in the opinion of the investigator, might pose unacceptable risk to the subject during the study.
d) BP > Grade 1 hypertension (> 159 mmHg systolic and > 99 mmHg diastolic) according to the 2018 ESC/ESH Guidelines for the management of arterial hypertension
e) The following exclusionary ECG observations:

i. QTcF: > 480 msec
ii. QRS: > 120 msec
iii. Complete heart block
iv. Left bundle branch block
v. Mobitz II second-degree atrioventricular block
vi. Atrial fibrillation or flutter

7) Other Exclusion Criteria: RA Sub-protocol

a) Prisoners or subjects who are involuntarily incarcerated. (Note: under certain specific circumstances and subject to local law a person who has been imprisoned may be included or permitted to continue as a subject. Strict conditions apply and BMS approval is required.)
b) Subjects who are employed by the Sponsor, clinical research organizations, or study site
c) Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness
d) Inability to comply with the study protocol
e) Inability to comply with restrictions as listed in Section RA 5.3

RA 5.3 Lifestyle Restrictions

Study restrictions for contraception use by WOCBP and male subjects who are partners of WOCBP (APPENDIX 4) are required for this study.

RA 5.3.1 Meals and Dietary Restrictions

With the exception of the 8-hour fasting requirement prior to blood sample collection for lipid panel and fasting glucose blood testing, no meal or dietary restrictions are required for this study. However, subjects are advised to consume in moderation (avoiding more than a single serving a day) cruciferous vegetables, such as cabbage, brussels sprouts, watercress, etc, as well as grapefruit and Seville oranges. Quinine (tonic water), St. John's wort and herbal medications are not allowed.

RA 5.3.2 Caffeine, Alcohol, Tobacco, and Cannabinoids

With the exception of cannabinoids, which are not allowed, prohibited alcohol abuse as defined by the Diagnostic Criteria for Drug and Alcohol Abuse in the DSM 5 within six months prior to

randomization, and prohibited alcohol use in subjects receiving MTX therapy (see Section RA 5.2), there are no restrictions on caffeine, alcohol, or tobacco use for this study. However, subjects who use tobacco or alcohol should be counseled for potential contraindications with nonstudy treatments as appropriate, and continued study participation should be based on investigator judgment.

RA 5.3.3 Activity

With the exception of the restrictions surrounding the use of contraceptives during sexual activity mentioned above and included in Section RA 1.3 Schedule of Activities, no activity restrictions are required for this study.

RA 5.4 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but who are not subsequently randomized or entered in the study or included in the analysis population. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects, to meet the 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. Additional screening data from screen failure subjects, such as clinical data for disease assessment, laboratory tests, and other clinically relevant data, may be required.

RA 5.4.1 Rescreening and Retesting During Screening Period

This RA sub-protocol permits the rescreening of a subject who has been previously screen failed. If rescreened, the subject must be re-consented and will be assigned a new identification number, and a full screening visit must be performed again. A subject can only be rescreened 1 time (ie, if the subject fails 1 rescreening attempt, no additional rescreening is allowed).

Laboratory parameters and/or other assessments that are included in Section RA 1.3 (Screening Procedural Outline for RA sub-protocol) that initially do not meet eligibility requirements within the screening period may be repeated once in an effort to find all possible well-qualified subjects. Consultation with the Medical Monitor may be needed to identify whether repeat testing of a parameter is clinically relevant.

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

The MRI conducted at screening is considered the baseline MRI for the study. If a subject requires rescreening, the MRI results obtained as part of the first screening instance may be used for the rescreening, if the MRI performance date is within 30 days of randomization.

RA 6 TREATMENT

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

Study treatment includes both IP/IMP and non-IP/non-IMP and is shown in RA Table 5.

An investigational product, also known as investigational medicinal product in some regions, is defined as a pharmaceutical form of an active substance or PBO 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.

For the RA sub-protocol, it is required that all subjects have background MTX therapy but have had inadequate response to the treatment based on investigator's judgment.

Other medications used as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the SOC for a given diagnosis, may be considered as noninvestigational products.

RA Table 5 Study Treatments for IM014029

Product Description/ Class and Dosage Form	Potency	IP/ Non-IMP	Blinded or Open-Label	Packaging/ Appearance	Storage Conditions (per label)
Branebrutinib oral capsule[a]	3 mg dose × 3 capsules (9 mg total dose)	IP	Blinded	HDPE bottles (33 capsules/bottle) with child-resistant cap and heat-induction seal (tamper-evidence and moisture barrier); size #0 hard gelatin capsules	Store refrigerated at 2° to 8°C (36° to 46°F) in original packaging; protected from moisture
PBO matching branebrutinib oral capsule	NA	IP	Blinded	HDPE bottles (33 capsules/bottle) with child-resistant cap and heat-induction seal (tamper-evidence and moisture barrier); size #0 hard gelatin capsules	Store refrigerated at 2° to 8°C (36° to 46°F) in original packaging; protected from moisture
Abatacept SC injection	125 mg in 1 mL solution	IP	Open-label	Pack of 4 single-dose disposable prefilled glass syringes with passive needle safety guard. Solution is clear to slightly opalescent, and colorless to pale-yellow. Do not use if solution contains particulate matter or discoloration.	Store refrigerated at 2° to 8°C (36° to 46°F) in original package to protect from light until use. Do not allow to freeze.

HDPE = high-density polyethylene; IP = investigational product; NA = not applicable; PBO = placebo; SC = subcutaneous.

[a] Dosages of 0.5 mg are also available but are not planned for use in the current study.

RA 6.1 Treatments Administered

The investigator must ensure that the IP will be used only in accordance with the protocol. The selection and timing of dose for each subject is shown in RA Table 6. Study treatment will be supplied in bottles (branebrutinib and PBO) or prefilled syringes (abatacept). If a subject forgets a dose, but remembers within 12 hours of the expected dose, the dose should be taken. Any dose > 12 hours should be missed, and the next expected dose should be taken at the usual time. No dose reductions or modifications are allowed. For the open-label part of the study, all efforts should be made to have abatacept administered weekly on the same day of the week. If a dose is missed, contact the [redacted] Medical Monitor.

RA Table 6 Selection and Timing of Dose

Study Treatment	Unit Dose Strength	Dosage Formulation Frequency of Administration	Route of Administration
Branebrutinib 9 mg	3 mg	3 active capsules; QD[a]	Oral
Branebrutinib PBO	0 mg	3 PBO capsules; QD[a]	Oral
Abatacept	125 mg	Prefilled syringe; QW	SC

PBO = placebo; QD = once daily; QW = once weekly; SC = subcutaneous

[a] The last day of dosing of branebrutinib or PBO in the RA sub-protocol should be the day prior to the Week 12/Day 85 visit.

Note: At all study visits, the study treatment should not be taken at home but should be taken to the site by the subject; at the site, the study treatment should be taken only when instructed by the site study staff according to the schedule listed below. These requirements also apply to concomitant medications at Day 1 and Week 4 only; at these visits, concomitant medications will be administered together with the study treatment at the site.

When multiple assessments are conducted at a single visit, the following is the order in which they should be performed:

1. Patient-reported Outcomes (eg, SGA, EQ-5 D-5 L, etc)
2. Safety assessments (eg, vitals, AEs)
3. Investigator-administered Assessments (eg, PGA, joint count, etc)
4. Laboratory tests (eg, safety laboratory tests, PK assessments, biomarker assessments)
5. Treatment dosing

Doses of branebrutinib at 9 mg (3x3 mg capsules) or matching placebo are to be administered orally QD (one time/day) with water and may be taken with or without food. The drug should be taken every morning at approximately the same time.

On Day 1 and at Weeks 2, 4 and 8 (Day 57), study treatment will be administered in the morning at the study site after blood samples have been collected and questionnaires have been completed. In addition, on Day 1 and at Week 4, branebrutinib will be administered together with concomitant

medications to allow predose sampling for concomitant medication. Branebrutinib and concomitant medications are to be taken together with water.

RA 6.2 Method of Treatment Assignment

All subjects will be centrally randomized according to a computer-generated block randomization scheme using IRT to 1 of the 3 sub-protocols depending on disease type determined at screening. Subjects in this sub-protocol will be randomized in a 3:1 ratio to receive the same double-blind treatment from Week 0 to Week 12.

Subjects in the RA sub-protocol will receive open-label abatacept from Week 12 to Week 24.

At the time of the screening visit, the investigative site will access the enrollment option of the IRT system for assignment of a subject number after written informed consent is obtained and before any study-related procedures are performed. This number is assigned sequentially by the system and will be unique across all sites. If a potential subject is rescreened, a new identification number will be used.

Randomized schedules will be generated by the IRT vendor.

Stratification will not be employed.

Before the study is initiated, each investigator will receive log-in information and directions on how to access the IRT. Study treatment will be dispensed at the study visits as listed in the SoA (Section RA 1.3).

RA 6.3 Blinding

Blinded treatment assignments will be managed using IRT. All capsules (branebrutinib 3 mg and branebrutinib PBO) are identical in appearance. Capsules will be supplied in tamper-evident HDPE bottles with each daily dose made up of either active or PBO capsules (as presented in RA Table 5). Prefilled syringes for abatacept will be supplied in 4-packs (all 4 syringes in each pack will be active abatacept). Investigative site staff, Sponsor and designee personnel, and subjects and their families will remain blinded to treatment assignments.

In addition to the treatment blind, results from potentially unblinding biomarkers, whole blood BTK occupancy and pBTK from the baseline measurements on Day 1 onward will be blinded to the investigator and study personnel involved in the study at both the clinical site and the Sponsor, as required.

Blinding of treatment assignment is critical to the integrity of this clinical study. However, in the event of a medical emergency or pregnancy in an individual subject in which knowledge of the IP is critical to the subject's management, the blind for that subject may be broken by the investigator. The subject's safety takes priority over any other considerations in determining if a treatment assignment should be unblinded.

Before breaking the blind of an individual subject's treatment, the investigator should determine that the unblinded information is necessary, ie, that it will alter the subject's immediate management. In many cases, particularly when the emergency is clearly not related to the IP, the

problem may be properly managed by assuming that the subject is receiving active product. It is highly desirable that the decision to unblind treatment assignment be discussed with the Medical Monitor, but the investigator always has ultimate authority for the decision to unblind. The PI should only call in for emergency unblinding AFTER the decision to discontinue the subject has been made.

In case of an emergency, the investigator has unrestricted access to randomization information via IRT and is capable of breaking the blind through the IRT system without prior approval from the Sponsor. After the unblinding, the investigator shall notify the Medical Monitor and/or study director. For information on how to unblind in an emergency, consult the IRT manual. Subject and unblinded treatment information and the reason for the blind being broken must be recorded on the appropriate study status page of the eCRF. After unblinding via IRT, the investigator shall notify the Medical Monitor.

Any request to unblind a subject for nonemergency purposes should be discussed with the Medical Monitor.

In cases of accidental unblinding, contact the Medical Monitor and ensure every attempt is made to preserve the blind.

Designated staff of BMS Company may be unblinded (obtain the randomization codes) prior to database lock to facilitate the bioanalytical analysis of PK samples and immunogenicity. A bioanalytical scientist in the Bioanalytical Sciences department of BMS Company (or a designee in the external central bioanalytical laboratory) will be unblinded to (may obtain) the randomized treatment assignments in order to minimize unnecessary bioanalytical analysis of samples.

RA 6.4 Dosage Modification

There is no provision for dose modification of study treatment. If a subject interrupts or temporarily discontinues treatment due to an AE, study treatment can be restarted in consultation with the Medical Monitor.

RA 6.5 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 subjects. 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 BMS or designee should be contacted immediately.

Branebrutinib and branebrutinib PBO should be stored per labeled conditions in tamper-evident HDPE bottles. Abatacept should be stored per labeled conditions in prefilled syringes.

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).

Further guidance and information for final disposition of unused study treatment are provided in APPENDIX 2.

RA 6.5.1 Retained Samples for Bioavailability/Bioequivalence

At the time of receipt of the IP by the investigator or designees, BMS will specify the appropriate number of containers or units to select for retention, the conditions of sample storage, required duration of sample retention, and provisions for returning or disposing of the IP. When samples are selected, containers or units should be placed in packaging with a tamper-evident seal provided by BMS. Package labeling should clearly identify the contents as BA/BE samples and state that the IP should be stored in the restricted area with limited access.

RA 6.6 Treatment Compliance

Study treatment compliance will be periodically monitored using standard drug accountability procedures (comparing the number of capsules/prefilled syringes returned to number dispensed, considering the expected regimen and any reported missed doses). Drug accountability will be reviewed by the site study staff at each visit to confirm treatment compliance. Site staff will discuss discrepancies with the subject at each on-treatment study visit and remind the subject of the importance of compliance with the assigned regimen. See Section RA 8.3 for information related to treatment overdose.

RA 6.7 Concomitant Therapy

RA 6.7.1 Prohibited and Restricted Treatments

Table 1 in the IM014029 Master Protocol lists exclusions and restrictions for all concomitant medications, regardless of indication. RA Table 7 presents prohibited and/or restricted medications taken by subjects with RA prior to or during study treatment administration with branebrutinib. All prior concomitant medications taken for RA since diagnosis must be recorded on the eCRF. All prior and/or concomitant medications taken for any indication within 4 weeks prior to study drug administration must be recorded on the eCRF. The prior use of medications after a sufficient washout period prior to study randomization is allowed for some medications, as indicated in the table and must be recorded in the eCRF. Details of prohibited (excluded) and/or restricted medications are provided in Section RA 5.2.

RA Table 7 Prohibited and Restricted Medications

Type of Medication	Examples of Medications	Restrictions	Required Washout Period Prior to and Postrandomization
BTK inhibitors	Marketed drugs, eg, ibrutinib, acalabrutinib Experimental drugs, eg, tirabrutinib, vecabrutinib,	Prohibited lifetime use	Not applicable

RA Table 7 Prohibited and Restricted Medications

Type of Medication	Examples of Medications	Restrictions	Required Washout Period Prior to and Postrandomization
	zanubrutinib, ARQ-531, GDC-0853, and any others		
JAK inhibitors	Tofacitinib, baricitinib, filgotinib, and upadacitinib	Prohibited lifetime use	Not applicable
Oral CS	Prednisone or equivalent	Oral CS use is permitted, but the dose must be ≤ 10 mg/day prednisone or equivalent and stable for ≥ 28 days before randomization and throughout study participation	If not continuing as SOC must discontinue 4 weeks before randomization
Other CS	IM, IA, intrabursal, IV, and oral modified-release CS	Prohibited during the study	4 weeks
	Topical and Inhaled CS	Must follow stable regimen throughout the study; cannot be used on as-needed basis. Only allowed for nonrheumatologic indications. Inhaled CS for non-RA conditions will not count against the maximum CS dose	Not applicable
Antimalarial drugs	Chloroquine and quinacrine	Prohibited during the study	12 weeks
	Hydroxychloroquine	Prohibited during the study	12 weeks
Anticoagulant or Antiplatelet therapies	Anticoagulant or antiplatelet therapies, including aspirin for cardioprotection	Treatment with anticoagulant or antiplatelet therapies, including aspirin for cardioprotection, within 2 weeks prior to randomization or during the study	2 weeks
Anti-TNF therapy	Adalimumab, certolizumab, etanercept, golimumab, infliximab, and TNF biosimilars	Prohibited during the study	History of use prohibited
Biologics	Rituximab, belimumab Denosumab	Prohibited during the study	History of use prohibited 6 months
	Abatacept		Lifetime (naïve)
	Other Biologics, including tocilizumab, anakinra		History of use prohibited
	IVIG	Prohibited during the study	8 weeks
DMARD	MTX	Dose must be stable for ≥ 12 weeks before randomization. New initiation or dose	Not applicable

RA Table 7 Prohibited and Restricted Medications

Type of Medication	Examples of Medications	Restrictions	Required Washout Period Prior to and Postrandomization
		changes during treatment are not permitted.	
Other DMARDs	Leflunomide	Prohibited during the study	36 weeks prior to **screening**
	Cyclosporine and tacrolimus	Prohibited during the study	8 weeks
	Azathioprine, sulfasalazine, and similar	Prohibited during the study	8 weeks
	Gold salts (sodium aurothiomalate, auranofin) (seldom used today)	Prohibited during the study	12 weeks
NSAIDs	Ibuprofen, etc	Only 1 oral NSAID is allowed concurrently. Can be combined with 1 or more topical NSAID but must be on a stable regimen	Not allowed on day of study visit until after study assessments.
Non-narcotic analgesics	Acetaminophen	Brief course for up to 7 days allowed	Not applicable
Narcotic analgesics	Oxycodone and hydrocodone	Prohibited during the study	Not applicable
Immunization against agents other than influenza or SARS-CoV-2	All live vaccines Nonlive vaccines unassociated with influenza or SARS-CoV-2	Prohibited during the study	90 days before and 28 days after EOT 30 days before and 14 days after EOT
Immunization for influenza or SARS-CoV-2	All live vaccines Nonlive vaccines for influenza or SARS-CoV-2	Prohibited during the study Not allowed during the screening period within 30 days prior to randomization During the Treatment and Follow-up Periods, vaccine doses must be given at least 5 days before a study visit. Doses may be given on a study day visit once all protocol-specific procedures are complete.	90 days before and 28 days after EOT
Other treatments	Diquafosol, rebamipide	Prohibited during the study	4 weeks

BLQ = below limit of quantitation; BTK = Bruton's tyrosine kinase; CS = corticosteroid; EOT = end of treatment; DMARDs = disease-modifying anti-rheumatic drugs; IA = intra-articular; IM = intramuscular; IV = intravenous; IVIG = intravenous immunoglobulin; JAK = Janus kinase; MTX = methotrexate; NSAID = nonsteroidal

anti-inflammatory drug; pSS = primary Sjögren's syndrome; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus.

Chronic medications that could be sensitive to modulation of CYP2C8/P-gp (and other potentially relevant drug metabolizing enzymes that may lead to drug-drug interaction with branebrutinib) and with sufficient representation in the study population (eg, > 10% per sub-protocol), are allowed in the study for accompanying conditions, such as but not limited to statins and antidepressants. For optional measurement of the concentrations of these medications, PK samples will be collected at predose and 2 hours postdose at Week 0 (Day 1) and Week 4 (Day 29) for potential post-hoc analysis. The measurements of concentrations of the select concomitant medications can be performed after the end of the study and will be based on the totality of information about the frequency of use of the drugs, clinical manifestations of possible interactions, availability of validated bioanalytical assays and therapeutic index. The results of the post-hoc analysis of the concomitants medications, if performed, will be reported separately, together with the reasons for the selection. Additionally, concentrations of HCQ will be measured and reported.

The dosing of allowed chronic medications must be maintained at the same level throughout the study unless safety concerns arise. Any changes of dose will be recorded, and additional PK sampling may be performed as a result.

Tobacco use will be allowed in the study. Branebrutinib concentrations will be compared between smoking and nonsmoking subgroups to evaluate the effect of smoking on glutathione-s-transferase mediated metabolism of branebrutinib.

No new concomitant medications (prescription, over-the-counter or herbal) are to be administered during study unless they are prescribed for treatment of specific clinical events. Any concomitant therapies must be recorded on the eCRF.

For subjects on MTX background therapy, the investigator must refer to the label for any potential interaction with concomitant medications.

RA 6.7.2 Rescue Medications

No rescue treatment will be provided from Week 1 to Week 12. From Week 12 to Week 24, open-label abatacept treatment will be provided for all subjects. Any subject needing additional treatment for worsening of RA symptoms from Week 12 to Week 24 will receive SOC treatment for RA, but will be withdrawn from study treatment, and will be encouraged to complete the study safety assessments through Week 24 and the Week 28 FU visit.

RA 6.7.3 Other Restrictions and Precautions

No other restrictions and precautions have been identified.

RA 6.8 Treatment After the End of the Study

At the end of the study, BMS will not continue to provide BMS-supplied study treatment to subjects/investigators unless BMS chooses to extend the study. The investigator should ensure that the subject receives appropriate SOC to treat the condition under study.

RA 7 DISCONTINUATION CRITERIA

RA 7.1 Discontinuation from Study Treatment

RA 7.1.1 Permanent Discontinuation from Study Treatment

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

- A subject request to stop study treatment; subjects 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 subject specifically withdraws consent for any further contact with him/her or persons previously authorized by the subject to provide this information.
- Any clinical AE, laboratory abnormality, or intercurrent illness that, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject. If treatment is discontinued due to an AE, the AE eCRF must be completed to show that the AE caused discontinuation.
- Termination of the study program 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.
- Unblinding of a subject's treatment assignment for any reason (emergency or nonemergency).
- Inability or failure to comply with protocol requirements.
- Pregnancy.

Discontinuation of the study treatment for abnormal liver tests indicative of DILI (see Section RA 8.2.8 for definition) should be considered by the investigator when the DILI meets one of the conditions necessary to be defined as an SAE outlined in APPENDIX 3 or if the investigator believes that it is in the best interest of the subject.

In the case of pregnancy, the investigator must immediately, within 24 hours of awareness of the pregnancy, notify the 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 subject safety). Refer to Section RA 8.2.6.

All subjects who discontinue study treatment should comply with protocol-specified follow-up procedures as outlined in the SoA (Section RA 1.3). The only exception to this requirement is when a subject 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). Following the decision to permanently discontinue a subject from treatment, an EOT visit should be performed as soon as possible,

followed by a Safety FU visit approximately 4 weeks later – each respectively according to Table 2 and Table 3 of Section RA 1.3.

- If early permanent treatment discontinuation occurs during blinded treatment, then the EOT visit includes each activity specified for the Week 12 visit in RA Table 2.
- If early permanent treatment discontinuation occurs during open-label abatacept treatment, then the EOT visit includes each activity specified for the Week 24 visit in RA Table 3.

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

RA 7.1.2 Temporary Discontinuation from Study Treatment

Branebrutinib may be discontinued temporarily at the discretion of the investigator/Medical Monitor due to AE, laboratory abnormality or overdose (Section RA 8.3).

Branebrutinib may be discontinued temporarily due to concomitant medication use (Master Protocol Table 1), as follows:

- Digoxin, "For acute use only; exclude at baseline; limit highest dose and monitor trough concentrations; stop treatment with branebrutinib during treatment with digoxin and for 3 days afterwards."
- Posaconazole: "Dose up to 300 mg QD can be used as maintenance dose, for acute infections stop using branebrutinib until dosing with posaconazole is discontinued."

RA 7.1.3 Post-study Treatment Study Follow-up

Subjects who discontinue study treatment will not be followed beyond the planned Safety FU Visit.

RA 7.2 Discontinuation from the Study

Subjects 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 subject specifically withdraws consent for any further contact with him/her or persons previously authorized by the subject to provide this information.

- Subjects 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 and entered on the appropriate eCRF page.
- In the event that vital status (whether the subject 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 subject withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

The following procedures must be performed upon subject withdrawal:

- Assessments for the EOT visit must be performed, provided that the subject has not withdrawn consent for these activities.
- All required eCRF pages must be completed, including the date of and explanation for the withdrawal.

RA 7.3 Lost to Follow-up

- All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject.
- Lost to follow-up is defined by the inability to reach the subject after a minimum of 3 documented phone calls, faxes, or emails as well as lack of response by subject to 1 registered mail letter. All attempts should be documented in the subject's medical records.
- If it is determined that the subject 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 subject's informed consent, then the investigator may use a Sponsor retained third-party representative to assist site staff with obtaining subject'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 subject remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the subject's medical records.

RA 8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and timing are summarized in the SoA (Section RA 1.3).
- Protocol waivers or exemptions are not allowed.
- All immediate safety concerns must be discussed with the Medical Monitor immediately upon occurrence or awareness to determine if the subject should continue or discontinue treatment.
- Adherence to the study design requirements, including those specified in the SoA (Section RA 1.3), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria before randomization. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the subject's routine clinical management (eg, BP, physical examination, medical history) on the day of the screening visit and obtained before signing of the informed consent may be used for screening provided the procedure meets the protocol-defined criteria and has been performed within the timeframe defined in the SoA (Section RA 1.3).

RA 8.1 Efficacy Assessments

The following tests and procedures have been selected to evaluate the efficacy of branebrutinib and describe clinical improvements in subjects with RA and will be performed according to the SoA (Section RA 1.3).

The investigator will perform all efficacy- and safety-related assessments, except for the 66/68 joint count, which will be performed by an independent joint count assessor who is blinded to all other assessments (eg, safety evaluation, laboratory test assessments, etc). For both the investigator and independent joint count assessor, every effort must be made to ensure that the same individual performs the specified required assessments al all visits across the study for each subject. Visit scheduling must take into account the availability of necessary assessors. Training and instruction will be provided to ensure that joint count assessments are conducted in a standard manner across sites. If the evaluator(s) is unable to complete the evaluation, then a qualified individual with overlapping experience may perform the evaluation. Documentation of the individual performing the evaluation is to be recorded in source documents.

The PI, or sub-investigator designated by the PI and confirmed by the Sponsor, may be a Doctor of Medicine or Doctor of Osteopathy, Physician's Assistant, or Nurse Practitioner with experience in the diagnosis and management of subjects with RA.

All assessments should be performed or administered prior to study drug administration unless otherwise indicated. Assessments are to be conducted at approximately the same time of day throughout the duration of the study for a given subject**.** Assessments conducted on Day 1, Week 0 must be performed per protocol (assessments performed as part of SOC may not be used in lieu of these assessments). Procedures not specified in the protocol that are part of standard care may be performed if they do not interfere with study procedures; any data arising from such procedures are not to be reported in the eCRF.

RA 8.1.1 Patient-reported Outcomes

Patient-reported health outcomes, as studied in RA, include questionnaires and scales that focus on general health, rheumatology, and RA disease-specific issues. The results of these health outcomes will be recorded electronically on eCOA devices provided by the Sponsor or designee to the sites.

RA 8.1.1.1 Health Assessment Questionnaire Disability Index (HAQ-DI)

The HAQ-DI is a patient-completed questionnaire specific for RA, which assesses the degree of difficulty a patient has experienced in 8 domains: dressing/grooming; arising; eating; walking; hygiene; reach; grip; and other activities. A decrease from baseline in HAQ-DI score indicates improvement; a change of < 0.22 is considered to be clinically meaningful (APPENDIX 23). The results and scoring of the HAQ-DI will be captured on an eCOA device.

RA 8.1.1.2 PROMIS-Fatigue Instrument Form 6 a

The PROMIS™ Form 6 a, provides item banks that offer the potential for PRO measurement that is efficient (minimizes number of items without compromising reliability), flexible (enables

optional use of interchangeable items), and precise (has minimal error in estimate) measurement of commonly studied PROs.[78, 79, 80, 81] In the health outcomes measurement perspective, eg, the fatigue item bank consists of 95 items assessing the intensity, frequency, and duration of fatigue and the impact of fatigue upon physical, mental, and social activities. Most PROMIS items employ response scales with 5 options (APPENDIX 12).

RA 8.1.1.3 Euro Quality of Life Five Dimensions Questionnaire: 5-Level Version (EQ-5 D-5 L)

The EQ-5 D-5 L consists of 2 parts – the EQ-5 D-5 L descriptive system and the EQ VAS. The descriptive system comprises the same 5 dimensions as the EQ-5 D-3 L (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). Each dimension has 5 levels: no problems; slight problems; moderate problems; severe problems; and extreme problems. The respondent indicates his/her health state by ticking in the box against the most appropriate statement in each of the 5 dimensions. The resulting 1-digit number expresses the level selected for that dimension. The digits for all 5 dimensions can then be combined in a number describing the respondent's health state.

The numbers 1 through 5 have no arithmetic properties and should not be used as a cardinal score. During the development of the EQ-5 D-5 L, the opportunity was also taken to improve some of the wording in the dimensions to enhance consistency and facilitate understanding. For example, the old wording of "confined to bed" to indicate the upper extreme in the EQ-5 D-3 L has been replaced with "I am unable to walk about," which is more consistent with the wording within the Mobility dimension and with the extreme levels on other dimensions.

The EQ VAS records the respondent's self-rated health on a 20-cm vertical VAS with endpoints labeled "the best health you can imagine" and "the worst health you can imagine." This information can be used as a quantitative measure of health as judged by the individual respondents. The instructions for the EQ VAS task have also been simplified (APPENDIX 13).

RA 8.1.1.4 Subject Global Assessment of Disease Activity (SGA)

The SGA is a visual analog scale (VAS) a subject uses to rate the ways in which RA has effected them (APPENDIX 24).

RA 8.1.2 Clinical Assessments

RA 8.1.2.1 Tender Joint Count 68/Swollen Joint Count 66 (TJC68/SJC66) – RA Sub-protocol

The number of tender, painful, and swollen joints will be determined by examination of 68 joints (34 joints on each side of the subject's body) by an independent joint count assessor, and entered into the eCOA device. The 68 joints to be assessed and classified as tender or not tender include: 2 temporomandibular joints (TMJs), 2 sternoclavicular joints, 2 acromioclavicular joints, 2 shoulder joints, 2 elbow joints, 2 wrist joints, 10 metacarpophalangeal joints, 2 interphalangeal joints of the thumb, 8 proximal interphalangeal joints of the hands, 8 distal interphalangeal joints of the hands, 2 hip joints, 2 knee joints, 2 ankle joints, 2 tarsi, 10 metatarsophalangeal joints of the

feet, 2 great toes (first proximal interphalangeal joint of the feet), and 8 proximal interphalangeal joints of the feet.

Joints will be assessed for tenderness by pressure and joint manipulation on physical examination. The subject will be asked for pain sensations on these manipulations and watched for spontaneous pain reactions. Any positive response on pressure, movement, or both will then be translated into a single tender-versus-nontender dichotomy.

Sixty-six joints (68-joint count minus both hips) will be classified as either swollen or not swollen. Swelling is defined as palpable fluctuating synovitis of the joint. Swelling secondary to osteoarthrosis will be assessed as not swollen, unless there is unmistakable fluctuation.

Joint assessments of 1 particular subject should be performed (if at all possible) by the same assessor throughout the study to minimize inter-observer variation.

Missing, replaced, ankylosed, or arthrodesed joints will be identified by the assessor at the screening visit and will be excluded from evaluation during the study. The locations (or a listing) of surgical procedures should be documented in the subject's source documents/eCRF pages.

RA 8.1.2.2 Physician Global Assessment of Disease Activity (PGA)

The PGA is a VAS that the physician uses to assess the manner in which RA has affected the RA subject (APPENDIX 26).

RA 8.1.2.3 RA Magnetic Resonance Imaging (MRI) Scoring System

The MRI scanners used in the RA sub-protocol study must be deemed qualified by the Sponsor-assigned core imaging lab prior to subject scans. The hand/wrist that is clinically most swollen at screening will be imaged using a whole-body MRI system. The screening visit MRI is considered the baseline MRI assessment for this study. If a subject requires rescreening, the MRI results obtained at the initial screening visit may be used for the rescreening, if the MRI was obtained within 30 days of randomization. It is recommended that sites should schedule 2 MRI appointments with the radiology department 7 days apart in the event that an MRI exam needs to be repeated due to technical difficulties. MRI exams with quality issues identified at the investigator site or core imaging lab should be repeated within 7 days of notification.

The same hand/wrist that was imaged at screening will be imaged at Week 12 and Week 24 on the same MRI scanner as the one used at screening. The screening visit MRI is to be performed approximately 14 days prior to randomization. Week 12 and Week 24 MRI exams are to be performed within 7 days of both scheduled Week 12 visit and Week 24 visits. Subjects who terminate the study early require an MRI at the EOT visit only if that visit is ≥ 4 weeks from the date of randomization or ≥ 4 weeks from Week 12 and should have the EOT MRI no more than 7 days from the EOT visit.

Subjects with moderate renal insufficiency (ie, eGFR or GFR < 50 mL/min/1.73 m^2), will be excluded from the study, as they are at increased risk of nephrogenic systemic fibrosis, a rare, but serious, condition associated with the use of gadolinium-based MRI contrast agents. Subjects in the RA sub-protocol who enter the study with eGFR or GFR > 50 mL/min/1.73 m^2, but whose

levels decline to < 50 mL/min/1.73 m^2 during the study will be excluded from further imaging during the study.

Synovitis, osteitis (bone marrow edema), bone erosion, and cartilage loss (joint-space narrowing) will be scored according to the Outcomes Measurement in Rheumatology (OMERACT) Rheumatoid Arthritis Magnetic Resonance Imaging Scoring System (RAMRIS).[89] Change at follow-up from baseline in each RAMRIS score will be calculated. Scoring will be performed centrally by 2 independent, experienced readers who will be blinded to clinical details, radiographic findings, treatment arm, and the chronology of MRI exams (screening, Week 12, Week 24, and/or the EOT visit, if applicable).

Images will be submitted to a core imaging lab. Sites should be trained prior to scanning the first study subject. Image acquisition guidelines and submission process will be outlined in the Study IM014029 Imaging Manual to be provided by the core imaging lab (APPENDIX 25).

RA 8.1.3 Composite-Assessments of Disease Activity in Rheumatoid Arthritis (RA)

Composite indices or pooled indices are useful tools for the evaluation of disease activity in patients with RA. They allow the integration of various aspects of the disease into a single numerical value that may help to facilitate consistent patient care and improve patient compliance, both of which can lead to improved outcomes.

The Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI) are composite tools for the evaluation of disease activity in RA. They have been developed to provide physicians and patients with simple and more comprehensible instruments. Moreover, the CDAI is the only composite index that does not incorporate an acute-phase response and can therefore be used to conduct a disease activity evaluation essentially anytime and anywhere. These tools are not replacements for instruments such as the DAS28 but are options for different environments. The ACR Responder Index is a composite of clinical, laboratory, and functional measures in RA that assess the signs and symptoms of relief. ACR responses are presented as the minimal numerical improvement from baseline in the 68 tender joint count and the 66 swollen joint count and at least 3 of the 5 following disease assessment criteria: PGA, SGA, HAQ-DI, and ESR or hsCRP. These tools can be used in clinical studies.

- **The SDAI** is composed of the sum of the tender joint score (range 0 to 28), the swollen joint score (range 0 to 28), the SGA of disease activity (range 0 to 10, in increments of 0.5), the PGA of disease activity (range 0 to 10, in increments of 0.5), and C-reactive protein (range 0 to 10 mg/dL) (APPENDIX 20).
- **The CDAI** is composed of joint responses from the 66/68 Tender and Swollen Joint Count as well as the SGA and PGA of Disease Activity. At Week 12, for the RA cohort only, the CDAI score will be calculated as the sum of the tender joint score (range 0 to 28), the swollen joint score (range 0 to 28), the SGA of disease activity (range 0 to 10, in increments of 0.5), and the PGA of disease activity (range 0 to 10, in increments of 0.5). Unlike other measures, CDAI does not include the use of an acute-phase reactant (CRP or ESR). A CDAI score of > 22 represents high disease activity (APPENDIX 21).

- **The Disease Activity Score (DAS)** can be used to assess subjects' RA disease activity, determine whether it is under control and if any treatment adjustments are required. It can also assist in establishing a target score to aim for, help inform treatment decisions, and optimize disease management. DAS28-CRP (APPENDIX 16) and DSR28-ESR (APPENDIX 22) are composite outcome assessments that measure:
  - How many joints in the hands (including metacarpophalangeal and proximal interphalangeal joints but excluding distal interphalangeal joints), wrists, elbows, shoulders, and knees are swollen and/or tender over a total of 28.
  - CRP, or ESR, in the blood to measure the degree of inflammation.
  - SGA of disease activity.
  - The results are combined to produce the DAS28-CRP (or DAS28-ESR) score, which correlates with the extent of disease activity:
    - < 2.6: Disease remission
    - 2.6 – 3.2: Low disease activity
    - 3.2 – 5.1: Moderate disease activity
    - > 5.1: High disease activity
- **ACR Response Measures**
  - The ACR20 is a composite measure defined as both improvement of 20% in the number of tender and number of swollen joints, and a 20% improvement in 3 of the following 5 criteria: SGA, PGA, functional ability measure (eg, the Health Assessment Questionnaire [HAQ]), pain VAS, and ESR or CRP. [90]
  - The ACR50 and ACR70 are the same instruments with improvement levels defined as 50% and 70%, respectively, versus 20% for ACR20.

RA 8.2 Adverse Events

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

AEs will be reported by the subject (or, when appropriate, by a caregiver or surrogate,).

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 subject to discontinue before completing the study.

Contacts for SAE reporting are specified in APPENDIX 3.

RA 8.2.1 AEs of Interest

AEIs are AEs for a particular product or class of products that a Sponsor may wish to monitor carefully. AEIs may be serious or nonserious. Such events may require further investigation to better characterize and understand them. In the branebrutinib clinical development program, infection AEs have been identified as potential AEIs; however, there has been no definitive assessment on the causal relationship between these events and treatment with branebrutinib. Therefore, additional information about infection AEs may be collected on the eCRF in order to better characterize and understand them.

The core AEIs for abatacept encompass specific identified and potential risks based on the mechanism of action of abatacept and extensive data from clinical studies and postmarketing experience. For abatacept, infections and systemic injection reactions are considered by the Sponsor to be events for which there is adequate evidence of association with the product (identified risks). Malignancies, immune-mediated disorders, and infections associated with immunization with live vaccines are considered by the Sponsor to be events for which there is some basis for suspicion of an association with the product, but where this association has not been confirmed (potential risks). These AEIs will be closely monitored in the study.

RA 8.2.2 Time Period and Frequency for Collecting AE and SAE Information

The collection of nonserious AE information should begin at initiation of study treatment until discharge, at the timepoints specified in the SoA (Section RA 1.3). Nonserious AE information should also be collected from the start of a PBO lead-in period or other observational period intended to establish a baseline status for the subjects. The Reference Safety Information in Sections 5.6.1 and 5.6.2 of the IB[12] should be used to determine the expectedness of SAEs for expedited reporting.

All SAEs must be collected from the time of signing the consent, including those thought to be associated with protocol-specified procedures and within 30 days of discontinuation of dosing or subject's participation in the study if the last scheduled visit occurs at a later time.

The investigator must report any SAE that occurs after these time periods and that is believed to be related to study drug or protocol-specified procedure.

- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the appropriate section of the designated eCRF.
- 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 subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject 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.

RA 8.2.3 Method of Detecting AEs and SAEs

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.) Nonserious RA-related AE will be collected solely on the disease assessment instruments and will not be reported as AEs, unless characterized as an SAE.

RA 8.2.4 Follow-up of AEs and SAEs

- Nonserious AEs should be followed to resolution, stabilization, or reported as SAEs if they become serious (see APPENDIX 3).
- Follow-up is also required for nonserious AEs that cause 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 eCRF. Completion of supplemental eCRFs 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 subject at subsequent visits/contacts. All SAEs, and nonserious AEIs (as defined in Section RA 8.2.1) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section RA 7.3).

Further information on follow-up procedures is provided in APPENDIX 3.

RA 8.2.5 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 subjects 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 IRB/IEC, if appropriate according to local requirements.

The 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 (CFR) 21 CFR Parts 312 and 320. A SUSAR is a subset of SAEs and will be reported to the appropriate regulatory authorities and investigators following local and global guidelines and requirements.

RA 8.2.6 Pregnancy

If, following initiation of the study treatment, it is subsequently discovered that a subject is pregnant or may have been pregnant at the time of study exposure, including during at least 5 half-lives after product administration, the investigator must immediately notify [redacted] Drug Safety of this event and complete and forward a Pregnancy Surveillance Form to [redacted] Drug Safety within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in APPENDIX 3.

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

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 subject should be reported to [redacted] Drug Safety. 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.

RA 8.2.7 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the AE eCRF page.

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

If a laboratory test result meets the definition of an AE or SAE, the laboratory test result should be reported as an AE or SAE and submitted to [redacted] Drug Safety, as specified in APPENDIX 3.

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).

RA 8.2.8 Potential DILI

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs meeting the defined criteria must be reported as SAEs (See Section RA 8.2 and APPENDIX 3 for reporting details).

Potential DILI is defined as:

1) 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 ALT or AST elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, preexisting chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

RA 8.2.9 Management of Possible Hypersensitivity Reactions to Abatacept

Any Hypersensitivity resulting in severe, acute allergic reactions may occur as a result of the protein nature of abatacept. 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

exploratory flow, hypoxemia).

- Reduced BP or associated symptoms (eg, hypotonia/collapse, syncope, and incontinence).
- Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting).

Sites must be appropriately prepared to handle medical emergencies such as severe hypersensitivity including anaphylaxis. Subjects must be rapidly assessed and stabilized at the site and transferred to an emergency facility as required. If subjects experience symptoms of severe allergic reactions at home, they 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 subject. 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 healthcare personnel should be available to handle medical emergencies when they occur at the site.

RA 8.2.10 Other Safety Considerations

Any significant worsening of a preexisting medical condition noted during interim or final physical examination, electrocardiogram (ECG), x-ray filming, or any other potential safety assessment required or not required by protocol should also be recorded as a nonserious AE or SAE, as appropriate, and reported accordingly.

RA 8.3 Overdose

For this study, any dose of branebrutinib greater than 2 daily doses of study treatment within a 24-hour time period will be considered an overdose. See APPENDIX 3 for AE assessment and reporting procedures regarding suspected overdose and intentional overdose.

Based on the IB, there has been no clinical experience with overdose of branebrutinib.[12] There is no known specific antidote for overdose with branebrutinib.

Based on the abatacept package insert,[91] doses of abatacept up to 50 mg/kg have been administered IV without apparent toxic effect. In case of overdose, it is recommended that the subject be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment instituted.

In the event of an overdose for either study treatment, the investigator should:

1) Contact the Medical Monitor immediately.
2) Closely monitor the subject for AEs/SAEs and laboratory abnormalities.
3) Obtain a plasma sample for PK analysis within 4 hours of the overdose if requested by the Medical Monitor (determined on a case-by-case basis).
4) Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the subject.

RA 8.4 Safety

Planned time points for all safety assessments are listed in the SoA (Section RA 1.3).

RA 8.4.1 Physical Examinations

A complete physical examination will include general appearance, vital signs, eyes, ears, nose, mouth, throat, neck, respiratory, cardiovascular, respiratory, gastrointestinal/abdomen, lymphatic, musculoskeletal, skin, psychiatric, and neurologic examinations. A targeted physical examination will include any organ system associated with an AE, a laboratory abnormality, or an RA-related SAE not captured elsewhere.

RA 8.4.2 Vital Signs

Refer to RA SoA (Section RA 1.3).

RA 8.4.3 Electrocardiograms

A 12-lead ECG will be performed at the visits indicated in the SoA (Section RA 1.3). The subject will remain supine for 5 to 10 minutes prior to the ECG and must have lab work done after the tracing so that the ECG results remain as accurate as possible. The ECG results will be read by the primary study investigator or a designee.

RA 8.4.4 TB Screening and Chest Imaging

A subject must not have active signs or symptoms of TB, as judged by the investigator, to be eligible for the study.

In addition to a complete physical examination and medical history to evaluate exposure to TB, all subjects will have a screening test, an IGRA (eg, QuantiFERON®-TB Gold) performed centrally. A subject with an indeterminate IGRA test result from the central laboratory must be retested for confirmation. If the second result is again indeterminate, the subject will be excluded from the study, unless there is documentation of a local negative TB Spot test result. If the second result from the central laboratory is positive, the subject should be considered as having LTBI provided there are no signs or symptoms of active TB. If the second result is negative, the subject may be eligible provided no other exclusion criteria for TB are met. A chest x-ray is also required if one has not been performed within 6 months of screening; a copy of the radiology report must be on file and reviewed by the investigator. If unable to obtain central laboratory results, an IGRA test could be obtained locally, after consultation with the [redacted] Medical Monitor.

RA 8.4.5 Clinical Safety Laboratory Assessments

A central laboratory will perform assessments of safety laboratory assessments (except urine pregnancy tests and ESR) and provide reference ranges and laboratory reports. Investigators must document their reviews of each laboratory safety report. Any laboratory test result that the

investigator considers clinically relevant is to be recorded on the appropriate AE page of the eCRF (Section RA 8.2.7).

ESR laboratory samples should be collected and recorded by an unblinded staff member who does not perform/have access to other subject procedures, including joint counts. All samples after screening should be collected and recorded in a blinded fashion.

Additional safety assessments may be performed at local laboratories at the investigator's discretion. The laboratory parameters to be assessed are included in RA Table 8.

In addition, serum or urine pregnancy testing will be performed for WOCBP.

RA Table 8 Clinical Safety Laboratory Assessments

Hematology	
Hemoglobin Hematocrit Total leukocyte count, including manual differential Platelet count Red blood cell count Prothrombin time/INR PTT aPTT	
Serum Chemistry	
Aspartate aminotransferase Alanine aminotransferase Gamma glutamyltransferase hsCRP Total bilirubin Direct bilirubin Alkaline phosphatase Lactate dehydrogenase Creatinine Blood urea nitrogen Uric acid Fasting glucose (nonfasting at screening only) Creatinine clearance – screening only Estimated glomerular filtration rate	Total Protein Albumin Sodium Potassium Chloride Calcium Phosphorus Magnesium Creatine kinase[a] Fasting lipid panel (total cholesterol, high-density lipoprotein, low-density lipoprotein, and triglycerides; nonfasting at screening only)
Urinalysis	
Protein Glucose Blood Leukocyte esterase Specific gravity pH	Microscopic examination of sediment (if blood, protein, or leukocyte esterase are positive on dipstick)
Urine chemistry – Spot urine for urine protein:creatinine ratio	
Infectious Serologies	
Anti-HCV antibodies with reflex testing of HCV RNA if positive HBsAg Anti-HbsAb Anti-HbcAb Anti-HIV-1 and anti-HIV-2 antibody	
Other Analyses	

RA Table 8 Clinical Safety Laboratory Assessments

Serum will be collected at baseline (Week 0) and at the EOT visit (Week 24) for optional measurements of anti-SARS-CoV-2 immunoglobulins.
Tuberculosis test (QuantiFERON®-TB Gold) at screening
Direct Coomb's test (only if clinically indicated)
Pregnancy Test for WOCBP (serum or urine β-HCG test every 4 weeks)
Follicle-stimulating hormone if needed to confirm menopausal status (see APPENDIX 4), at screening
HbA1c
Thyroid-stimulating hormone (if above normal reference range, test free T4; if below normal range, test free T4 and T3)
IgM, IgG, IgA, IgE, free Kappa/Lambda light chains
Erythrocyte sedimentation rate
Rheumatoid factor
C3, C4
[redacted]
T cells, B cells, natural killer cells
Beta-2-microglobulin

[redacted] ANA = antinuclear antibody; aPTT = activated partial thromboplastin time; β-HCG = beta-human chorionic gonadotropin; C3, C4 = serum complement C3 and C4; DNA = deoxyribonucleic acid; [redacted]; EOT = end of treatment; HbcAb = hepatitis B core antibody; HbsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; hsCRP = high-sensitivity C-reactive protein; Ig = immunoglobulin; INR = international normalized ratio; PTT = partial thromboplastin time; RNA = ribonucleic acid; [redacted] Sm = Smith; [redacted]; T3 = tri-iodothyronine; T4 = thyroxine; TB = tuberculosis; ULN = upper limit of normal; WOCBP = women of childbearing potential

[a] If the creatine kinase is > 2.5× ULN, reflex testing of creatine kinase-MB and troponin I will be required.

RA 8.4.6 Imaging Safety Assessment

Any incidental findings of potential clinical relevance on chest x-ray or any additional imaging performed that is not directly associated with the objectives of the protocol should be evaluated and handled by the study investigator as per standard medical/clinical judgment. Images may be requested for submission to the assigned imaging core lab for central analysis. Assessment of hand and wrist MRI by the investigator is not expected.

RA 8.5 PK of Branebrutinib

The PK sampling schedule for branebrutinib, its metabolites, and concomitant medications will be harmonized among all treatments and sub-protocols where applicable.

For the predose and postdose PK assessments of branebrutinib and metabolites, samples will be collected from 2 groups of subjects—all study subjects who receive branebrutinib comprise one group; and subjects at preselected clinical sites only and who will have extended PK sampling comprise the second group (RA Table 9).

Samples collected from all study subjects who receive branebrutinib will be analyzed for branebrutinib PK only, including samples drawn on days scheduled solely for predose samples. Samples collected from subjects at the preselected clinical sites will be analyzed for both branebrutinib and metabolites at all scheduled time points as indicated in RA Table 9 and will be divided into 2 collection tubes, one tube for branebrutinib and one tube for metabolites analysis.

In general, predose (trough) concentrations will be assessed to evaluate the attainment of steady-state and accumulation. it is expected that steady-state will be achieved for all analytes at Week 4, after 28 days of continuous dosing.

Pharmacokinetic samples may also be used in correlation analyses for evaluation of PK/PD and the effect of pharmacogenomics (PGx) and used for other correlation analyses as well. The sampling schedule is based on available information on branebrutinib and its metabolites.

(Samples for PK analysis collected from subjects receiving PBO will not be analyzed for branebrutinib or metabolites.)

Branebrutinib and Metabolite Analysis:

Branebrutinib PK samples will be analyzed by a vendor using a validated assay. Plasma samples for metabolites will be analyzed by the BMS bioanalytical laboratory. These analyses will be reported separately. The BMS laboratory will be unblinded before the end of the study and will not communicate unblinded information to the BMS [redacted] study teams where the data allow. Individual subject PK parameter values for branebrutinib will be derived from plasma concentration data versus time by noncompartmental methods with a validated PK analysis program. Actual times will be used for the analyses.

For all study subjects, the branebrutinib PK parameters listed below will be calculated and summarized with data up to 4 hours postdose. Accumulation ratios for Cmax and AUC(0-4) will also be calculated.

Cmax	Maximum observed concentration
Tmax	Time to maximum concentration
Ctrough	Trough observed plasma concentration
AUC(0-4)	Area under the plasma concentration-time curve from time zero to the 4-hour dosing period

For subjects at preselected sites with extended sampling, separate PK concentrations of branebrutinib and select metabolites at all timepoints will be summarized by timepoint. The branebrutinib parameters listed below will be calculated and summarized.

Cmax	Maximum observed concentration
Tmax	Time to maximum concentration
AUC(0-T)	Area under the plasma concentration-time curve from time zero to time of last quantified concentration
AUC(TAU)	Area under the concentration-time curve to the end of the dosing period
Ctrough	Trough observed plasma concentration

RA Table 9 lists the complete sampling schedule for assessment of the PK of branebrutinib, metabolites, and concomitant medications in subjects with RA.

To assess steady-state concentrations of branebrutinib, a total of 2 predose PK samples (approximately 4 mL each) will be drawn from all study subjects at Week 0 (Day 1) and Week 4 (Day 29) (Note that these samples will be drawn within a 1-hour window before the next dose is administered.) For subjects at preselected sites with extended sampling, predose PK samples collected at Week 8 (Day 57) will be aliquoted to assess metabolite concentrations.

For postdose sampling, all study subjects will have branebrutinib PK samples drawn at Week 0 (Day 1) and Week 8 (Day 57) at the 0.5, 1, 2, and 4-hour time points. (Note that these samples will be drawn within ±15 min from the given time points.) For subjects at preselected sites with extended sampling, postdose PK samples will be aliquoted to assess metabolite concentrations at these time points.

In addition, for subjects at preselected sites with extended sampling, postdose PK samples will be drawn and assessed for both branebrutinib and metabolite concentrations at Week 0 (Day 1) and Week 8 (Day 57) at approximately 06:00 hours, and from 08:00 to 10:00 hours (flexible window) and from 10:00 to 12:00 hours (flexible window). Samples will also be collected at Week 0 (Day 2) approximately 24:00 hours postdose (predose of branebrutinib on Day 2). Efforts should be made to collect the samples within these windows; however, any sample drawn outside the prespecified windows will not be considered a protocol deviation. Both planned and actual time points at which the blood samples will be taken will be recorded and used in analysis and modeling.

Concomitant Medications

Concomitant medications that are sensitive substrates of CYP2C8 and other potentially relevant drug metabolizing enzymes that may lead to drug-drug interaction with branebrutinib and P-gp transporter may be measured (post-hoc) for the levels of exposure for subjects receiving PBO and active treatment. Samples for the PK assessment of the relevant concomitant medications will be collected at Week 0 and Week 4 from all study subjects. Samples for PK analysis collected from subjects receiving branebrutinib or PBO will be analyzed for HCQ and other relevant concomitant comedications provided that these subjects are receiving HCQ and other relevant concomitant comedications.

Detailed instructions for the collection, labeling, processing, storage, shipping, and disposition of all PK blood samples are provided in the Laboratory Manual.

RA Table 9 PK Sampling Schedule for Branebrutinib, Metabolites, and Concomitant Medications

Study Day	Study Week	Event	Time (Relative to Branebrutinib Dose) Hours:Minutes	Branebrutinib	Metabolites (collected from subjects at preselected sites)	Concom Meds a,b	Comments
1	0	Predose	00:00	X		X[a,b]	• Predose PK samples will be collected from all study subjects to assess concentrations of

RA Table 9 PK Sampling Schedule for Branebrutinib, Metabolites, and Concomitant Medications

Study Day	Study Week	Event	Time (Relative to Branebrutinib Dose) Hours:Minutes	Branebrutinib	Metabolites (collected from subjects at preselected sites)	Concom Meds a,b	Comments
							branebrutinib and relevant concomitant medications
1	0	Postdose	00:30	X	X		• Postdose PK samples collected from all study subjects at these time points will be assessed for branebrutinib; • Postdose PK samples collected at these time points from subjects at preselected clinical sites will also be assessed for metabolites; • Postdose PK samples collected at 2 hours after dosing, will be assessed for relevant concomitant medications.
1	0	Postdose	01:00	X	X		
1	0	Postdose	02:00	X	X	X[a,b]	
1	0	Postdose	04:00	X	X		
1	0	Postdose	06:00	X	X		• Postdose PK samples collected at these time points from subjects at preselected clinical sites only will be assessed for concentrations of branebrutinib and metabolites at these time points.
1	0	Postdose	08:00-10:00	X	X		
1	0	Postdose	10:00-12:00	X	X		
2	0	Postdose[c]	24:00	X	X		
29	4	Predose	00:00	X		X[a,b]	• Predose and postdose PK samples collected at these time points from all study subjects for branebrutinib (postdose branebrutinib PK samples are not to be collected at Week 4) and for relevant concomitant medications. • Plasma samples will be collected from all study subjects for assessment of relevant concomitant medications.
29	4	Postdose	02:00			X[a,b]	
57	8	Predose	00:00	X	X		• Predose and postdose PK samples collected at these time points from all study subjects will be assessed for branebrutinib only; • Predose and postdose PK samples collected at these time points from subjects at preselected clinical sites will also be assessed for concentrations of metabolites;
57	8	Postdose	00:30	X	X		
57	8	Postdose	01:00	X	X		
57	8	Postdose	02:00	X	X		
57	8	Postdose	04:00	X	X		
57	8	Postdose	06:00	X	X		

RA Table 9 PK Sampling Schedule for Branebrutinib, Metabolites, and Concomitant Medications

Study Day	Study Week	Event	Time (Relative to Branebrutinib Dose) Hours:Minutes	Branebrutinib	Metabolites (collected from subjects at preselected sites)	Concom Meds [a,b]	Comments
57	8	Postdose	08:00-10:00	X	X		• For subjects at preselected clinical sites with extended sampling, samples collected at these time points will be assessed for both branebrutinib and metabolites PK.
57	8	Postdose	10:00-12:00	X	X		

PK = pharmacokinetic; Concom Meds = concomitant medications.

[a] Concentrations of concomitant medications that are sensitive substrates of CYP2C8 and other potentially relevant drug metabolizing enzymes that may have a drug-drug interaction with branebrutinib and P-gp transporter may be evaluated post-hoc for subjects receiving PBO and active treatment at predose of branebrutinib on Day 1 and Day 29.

[b] Subjects being treated with prescription concomitant medications will be informed to bring them to the clinic on Day 1 and Day 29 for simultaneous dosing with branebrutinib, but only when it is safe for subjects and operationally feasible. This should be based on the investigator's discretion with consideration that the medications which should not be delayed until the time of dosing in the clinic should be taken at home. The self-reported time for all prescription medications taken at home should be recorded as accurately as possible.

[c] PK sample must be drawn before the branebrutinib dose is administered on Day 2.

RA 8.5.1 PK and Immunogenicity of Abatacept (Weeks 12 and Later)

The PK samples for abatacept and for immunogenicity analysis will be taken at predose at clinic visits for all subjects. The sampling schedule for abatacept is provided in RA Table 10.

Samples from all subjects receiving abatacept treatment will be analyzed for abatacept concentration as well as for antidrug antibodies (ADAs) and abatacept-neutralizing potential. Trough samples within a 30-minute window before each dose will be collected, as well as samples at the FU visit at early discontinuation or the EOT.

RA Table 10 PK and Immunogenicity Sampling Schedule for Abatacept

Study Day of Sample Collection	Study Week of Sample Collection	Event	Time (Relative to Branebrutinib Dose and Abatacept Dose) Hour:Minute	Blood Sample for PK and Immunogenicity/ Abatacept	Comment – All Samples Mandatory for All Subjects
85	12	Predose	00:00	X	Before the first dose of abatacept
99	14	Predose	00:00	X	Before the third dose of abatacept
113	16	Predose	00:00	X	
141	20	Predose	00:00	X	
169	24	--	00:00	X	Since abatacept is not administered at this visit, this blood sample is not collected predose; this sample is intended to be equivalent to trough concentration sampling
197	28-week FU	--	--	X	To evaluate elimination of abatacept and immunogenicity signal after stopping the dosing

FU = Safety follow-up; PK = pharmacokinetic

Detailed instructions for PK and ADA blood collection for abatacept, labeling, processing, storage, shipping, and disposition are provided in the Laboratory Manual. Plasma samples will be analyzed for abatacept and ADA/nanoantibodies (Nabs) to abatacept by validated assays.

The trough concentrations of abatacept will be listed and summarized by time point and can be compared between subjects who received treatment of branebrutinib versus PBO before the start of abatacept treatment.

The results of immunogenicity will be listed and summarized by time point as well as overall occurrence of ADA, Nabs, and time to onset of immune response and resolution, if available. The frequency of immunogenicity can be compared between subjects who received treatment of branebrutinib versus PBO before the start of abatacept treatment and correlated to trough concentrations.

RA 8.5.2 PK of Potential Concomitant Medications

Concentrations of Concomitant medications that are sensitive substrates of CYP2C8 and other potentially relevant drug metabolizing enzymes and P-gp transporter may be evaluated for subjects receiving PBO and active treatment with the bioanalytical analysis as part of a retrospective analysis. The retrospective analysis will be conducted after review of the enrollment records, reported concomitant medication use within the enrolled population and on the incidence threshold and relevance to drug interaction with branebrutinib based on preclinical and clinical data. Other confounding factors will be evaluated as part of the analysis to avoid inclusion of bias or artifact results.

Subjects who are on prescription concomitant medications will be informed to bring them to the clinic on Day 1 and Day 29 for simultaneous dosing with branebrutinib, but only when it is safe for subjects and operationally feasible. This should be based on the investigator's discretion with consideration that the medications which should not be delayed until the time of dosing in the clinic should be taken at home. The self-reported time for all prescription medications taken at home should be recorded as accurately as possible.

The concentration of the relevant concomitant medications will be measured using samples collected predose and 2 hours postdose of branebrutinib or placebo on both Day 1 and Day 29 (Week 4; at which point accumulation of branebrutinib and its metabolites is expected to achieve steady-state). Bioanalytical analysis of all relevant concomitant medications will be conducted post-hoc. The doses of the concomitant drugs and the time they are taken, will be carefully recorded at all times (including Day 1 in Week 0 and on Day 29 in Week 4). The doses of concomitant medications will be carefully recorded at all times. Actual and dose-normalized trough concentrations will be listed, summarized, and compared between posttreatment and pretreatment of branebrutinib and PBO separately; other covariates such as MTX use, gender, etc. can be added to the comparison as needed.

Detailed instructions for PK sample collection for the relevant concomitant medications, labeling, processing, storage, shipping, and disposition are provided in the Laboratory Manual. Plasma samples will be analyzed for all relevant concomitant medications by available validated assays. The results of post hoc analyses will not be recorded in the CSR.

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RA 8.7 Health Economics OR Medical Resource Utilization and Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters will not be evaluated in this study.

RA 9 STATISTICAL CONSIDERATIONS

RA 9.1 Sample Size Determination

Sample size is calculated based on the estimated effect size for the primary endpoint comparison between branebrutinib and PBO treatment groups. The primary endpoint for the RA sub-protocol is the ACR50 response at Week 12.

Estimates for PBO response rates, treatment differences, and common standard deviations were obtained from the published literature. [92,93] Sample size justification is provided below for the RA sub-protocol:

Assuming a total sample size of 80 subjects randomized in a blinded fashion at a 3:1 ratio to branebrutinib (60 subjects) or PBO (20 subjects), there will be 82% power to detect a treatment difference of 30% assuming the PBO response rate is 15% in ACR50 at Week 12, given a 1 sided, two-group test of a difference in binomial proportions with a 5% level of significance.

RA 9.2 Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled Set	All subjects who sign informed consent.
FAS	All subjects who are randomized. Following the intent-to-treat principle, subjects will be analyzed according to the treatment assigned at randomization. The FAS will be the primary efficacy analysis population. This is the same as the intent-to-treat population.
Full Abatacept Analysis Set (FAAS)	All FAS subjects who are dispensed Abatacept treatment.
PPS	A subset of the FAS wo are compliant with study treatment and who do not have any statistically relevant protocol deviations that may impact the primary efficacy endpoint assessments. The PPS will be analyzed according to the treatment assigned at randomization. The PPS will be a supportive efficacy analysis population.
Safety Analysis Set	All randomized subjects who receive at least 1 dose of double-blind study treatment. Subjects will be analyzed according to treatment received. In cases where the subjects take the incorrect treatment, the following scenario will be considered. • For subjects who should be receiving branebrutinib treatment during the blinded treatment period, if the subject took any placebo dose, the subject will still be counted in the branebrutinib treatment group for safety analysis set unless the subject took placebo throughout the entire course. • For subjects who should be receiving placebo treatment during double the blinded treatment period, if the subject took any

Population	Description
	branebrutinib dose, the subject will be counted in the branebrutinib treatment group for safety analysis set.
PK population for branebrutinib	All randomized subjects who receive at least 1 dose of branebrutinib and have any available branebrutinib concentration data.
Biomarker	All randomized subjects who receive at least 1 dose of double-blind study treatment and have at least 1 posttreatment biomarker measurement. Subjects will be analyzed according to treatment received.

RA 9.3 Endpoints

The following sections outline the efficacy endpoints for the RA sub-protocol:

RA 9.3.1 Primary Endpoint

- ACR50 response at Week 12 compared to baseline

RA 9.3.2 Secondary Endpoints

The following are the secondary efficacy endpoints as defined at Week 12:

- Change from baseline in:
  - DAS28-CRP
  - DAS28-ESR
  - SDAI
  - CDAI
- ACR20 response compared to baseline
- ACR70 response compared to baseline

RA 9.3.3 Additional Endpoints

The following are the additional efficacy endpoints as defined at Week 12:

- Change from baseline in:
  - Autoantibody titers
  - BTK occupancy
  - ACR component assessments:
    - Tender/painful joint count (68) and SJC (66)
    - PGA of Arthritis
    - SGA of disease activity
    - hsCRP
    - HAQ-DI

- RAMRIS scores of synovitis, osteitis (bone marrow edema), bone erosion, and cartilage loss (joint-space narrowing)
- EQ-5 D-5 L score
- PROMIS Fatigue 6 a

The following are the additional efficacy endpoints as defined at Week 24:

- Change from baseline in:
  - DAS28-CRP
  - DAS28-ESR
  - SDAI
  - CDAI
- ACR20 response compared to baseline
- ACR50 response compared to baseline
- ACR70 response compared to baseline
- Change from baseline in EQ-5 D-5 L score
- Change from baseline in PROMIS Fatigue 6 a
- Change from Week 12 to Week 24 in efficacy measures:
  - DAS28-CRP
  - DAS28-ESR
  - SDAI
  - CDAI
- ACR20 response at Week 24 based on activity at Week 12 after pretreatment with branebrutinib or PBO (treatment effect of abatacept following treatment with branebrutinib versus PBO)
- ACR50 response at Week 24 based on activity at Week 12 after pretreatment with branebrutinib or PBO (treatment effect of abatacept following treatment with branebrutinib versus PBO)
- ACR70 response at Week 24 based on activity at Week 12 after pretreatment with branebrutinib or PBO (treatment effect of abatacept following treatment with branebrutinib versus PBO)
- Change from Week 12 to Week 24 in:
  - Autoantibody titers
  - BTK occupancy
  - ACR component assessments:
    - Tender/painful joint count (68) and SJC (66)
    - PGA of Arthritis
    - SGA of disease activity
    - hsCRP

  - HAQ-DI
- RAMRIS scores of synovitis, osteitis (bone marrow edema), bone erosion, and cartilage loss (joint-space narrowing)
- EQ-5 D-5 L
- PROMIS Fatigue 6 a

RA 9.3.4 PK Endpoints

- Concentration values and PK parameters of branebrutinib and metabolites of clinical interest

RA 9.3.5 Exploratory Endpoints

- Evaluate the PK of branebrutinib and metabolites of clinical interest

RA 9.4 Statistical Analyses

The SAP will be developed and finalized before database lock. Section RA 9.4.1 provides a summary of planned statistical analyses of the primary and secondary efficacy endpoints. Additional and exploratory endpoints will be summarized in a descriptive manner.

RA 9.4.1 Efficacy Analyses

Efficacy data will be summarized using the FAS. Data will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum), unless otherwise specified, for continuous variables and frequency distributions (counts and percentages) for categorical variables. Efficacy data will be summarized separately for each sub-protocol and with each sub-protocol combined for variables that are similar among the sub-protocols.

For the RA sub-protocol, data through Week 12 will be presented for:

- Branebrutinib
- Branebrutinib PBO

After Week 12, data may be presented for the following treatments for the RA sub-protocol:

- Branebrutinib followed by Abatacept
- PBO followed by Abatacept
- Branebrutinib and PBO followed by Abatacept

Endpoint	Statistical Analysis Methods
Primary	General Analysis Methodology Response rates of branebrutinib compared to PBO for the primary endpoint will be analyzed using a Chi-square test. The 95% CI for each treatment group response rate and the difference in response rate for branebrutinib compared to PBO will be provided. If expected cell counts are not sufficient, then Fisher's exact test will be used. P-values will be provided. Supportive Analyses A Bayesian approach combines current study PBO data and PBO data from historical RA studies will be employed. The probability of response rate difference between branebrutinib and PBO greater than 30% will be calculated with derived posterior distribution. Fixed borrowing or dynamic borrowing method will be implemented. Imputation Method Nonresponder imputation will be used for binary endpoints for subjects who discontinue study treatment early, start a protocol-prohibited medication/therapy prior to the specified timepoint, or otherwise have missing endpoint data for the specified timepoint. Other imputation methods may be considered for sensitivity analyses and will be described in the SAP if used.
Secondary/ Additional	General Analysis Methodology Response rates of branebrutinib compared to PBO for binary endpoints (responder/nonresponder) will be analyzed using a Chi-square test. The 95% CI for each treatment group response rate and the difference in response rate for branebrutinib compared to PBO will be provided. If expected cell counts are not sufficient, then Fisher's exact test will be used. The same criteria used for primary endpoints for the nonresponder imputation will be applied for all secondary/additional binary endpoints. Continuous endpoints (change from baseline values) will be analyzed using analysis of covariance. The baseline value of the endpoint being tested will be added into the model as a covariate. Treatment differences based on

Endpoint	Statistical Analysis Methods
	least-squares means and corresponding 2-sided 95% CIs will be provided for the difference between branebrutinib and PBO. Supportive analyses for continuous endpoints may be performed using MMRM to investigate response over time. Missing data are addressed in these models and assumed to be MAR. Testing Strategy for Secondary Endpoints There will be no alpha level adjustment for multiple endpoint testing.

RA 9.4.1.1 Subgroup Analyses

Subgroup analyses will be conducted for the primary and secondary efficacy endpoints on the FAS population. Subgroups that may be evaluated include the following:

- Gender
- Race
- Tobacco use

Additional subgroups defined for descriptive summaries may be specified in the SAP.

RA 9.4.2 Safety Analyses

Safety data will be descriptive in nature and will be summarized using the Safety Analysis Set. Data will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum), unless otherwise specified, for continuous variables and frequency distributions (counts and percentages) for categorical variables. Safety data will be summarized separately for each sub-protocol and with all sub-protocols combined.

For the RA sub-protocol, data through Week 12 will be presented for:

- Branebrutinib
- Branebrutinib PBO

After Week 12, data may be presented for the following treatments for the RA sub-protocol:

- Branebrutinib followed by Abatacept
- PBO followed by Abatacept
- Branebrutinib and PBO followed by Abatacept

RA 9.4.2.1 Adverse Events

TEAEs are defined as AEs that occur after the subject received first dose of study treatment or if a preexisting condition worsens in severity or becomes serious after receiving the first dose of study treatment up to 30 days after the last dose of study treatment. All reported TEAEs, SAEs, deaths, AEs leading to study treatment discontinuation, and target AEIs will be summarized by MedDRA system organ class and preferred term.

RA 9.4.2.2 Clinical Laboratory Tests

Laboratory parameters will be summarized as absolute and change from baseline values by visit. Baseline values are defined as the last nonmissing value prior to the first dose of study treatment. Marked abnormalities summarized by visit and shift tables will also be provided. For clinical laboratory test results, marked abnormalities will be defined in the SAP.

RA 9.4.2.3 Vital Signs and ECGs

Vital signs and ECGs will be summarized as absolute and change from baseline values by visit. Baseline values are defined as the last nonmissing value prior to the first dose of study treatment. Marked abnormalities will be summarized by visit as well. For vital signs and ECGs, marked abnormalities will be defined in the SAP.

RA 9.4.3 Other Analyses

The PK, PD, and exploratory biomarker analyses will be described in the SAP finalized before database lock. Any population PK analysis and PD analyses will be presented separately from the main CSR.

RA 9.4.4 Analysis and Reporting

After all subjects in the RA sub-protocol have completed Week 12 efficacy assessments or discontinued treatment/study prior to Week 12, a database lock, inclusive of efficacy, safety, PK and PD, will occur for the RA sub-protocol. Analysis using data up to 12 weeks will be performed. Results of this 12-week analysis (100% of participants in RA sub-protocol) will be reviewed by an unblinded team that is independent of the study team responsible for study conduct. This activity will support early planning decisions on clinical development of the compound and will not change the conduct of this study (unless there is a safety concern). After all subjects in a sub-protocol have finished the respective sub-protocol and the data have been locked for that sub-protocol, final analyses for that sub-protocol will be performed. Details of these analyses will be described in the SAP.

The study team responsible for managing the study, including Medical Monitors, will remain blinded to treatment assignment and the results of safety analysis until full database lock and treatment unblinding has occurred. The data will be reported only after completion of all 3 sub-protocols.

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3 APPENDICES

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

ACPA	anti-citrullinated protein/peptide antibodies (also referred to as anti-CCP antibodies)
ACR	America College of Rheumatology
ADA	antidrug antibody
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
AEI	adverse events of interest
ALT	alanine aminotransferase
ANA	antinuclear antibodies
ANMAT	National Administration of Foods, Drugs and Medical Devices (Argentina)
[redacted]	[redacted]
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC (0-T)	area under the plasma concentration-time curve from time zero to time of last quantifiable concentration
AUC(TAU)	area under the concentration-time curve to the end of the dosing period
[redacted]	[redacted]
BA/BE	bioavailability/bioequivalence
[redacted]	[redacted]
BCR	B cell receptor
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte (Germany)
β-HCG	Beta-human chorionic gonadotropin
BID	twice daily
BILAG	British Isles Lupus Assessment Group
BlyS	B-lymphocyte stimulator (AKA BAFF)
BTK	Bruton's tyrosine kinase
C	complement
CD	cluster of differentiation
CDAI	Clinical Disease Activity Index
CEC	Central Ethics Committee
CH	constant region heavy chain
CI	confidence interval
CIA	collagen-induced arthritis
CLASI	Cutaneous Lupus Erythematosus Disease Area and Severity Index

Cmax	maximum observed concentration
Cminss	steady-state trough concentration
CMV	cytomegalovirus
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CRF	Case Report Form
CS	corticosteroid
CSR	clinical study report
CT	computed tomography
CTA	Clinical trial agreement
CTLA	cytotoxic T-lymphocyte-associated antigen
Ctrough	trough observed plasma concentration
CXCL13	C-X-C motif chemokine ligand 13
CYP	cytochrome P450
DAS28	Disease Activity Score 28
DDI	drug-drug interaction
DILI	drug-induced liver injury
DMARD	disease-modifying antirheumatic drug
DMC	Data Monitoring Committee
dsDNA	double-stranded deoxyribonucleic acid
DSM	Diagnostic and Statistical Manual of Mental Disorders
ECG	Electrocardiogram
eCOA	Electronic Clinical Outcome Assessment
eCRF	electronic case report form
EDC	RAVE electronic data capture
eGFR	estimated glomerular filtration rate
EOT	end of treatment
EQ	Euro Quality
EQ-5 D-5 L	Euro Quality of Life Five Dimensions Questionnaire: 5 Level version
ESR	erythrocyte sedimentation rate
ESSDAI	EULAR Sjögren's Syndrome Disease Activity Index
ESSPRI	EULAR Sjögren's Syndrome Patients Reported Index
EULAR	European League Against Rheumatism
FAS	full analysis set
FcεR	Fc epsilon receptor

FcγR	Fc gamma receptor
FDA	Food and Drug Administration
FIH	first-in-human
FU	follow-up
GCP	Good Clinical Practice
HAQ-DI	Health Assessment Questionnaire – Disease Activity
HbA1c	Hemoglobin A1c
HBV	hepatitis B virus
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HCQ	hydroxychloroquine
HDPE	high-density polyethylene
HIV	human immunodeficiency virus
hsCRP	high-sensitivity C-reactive protein
IA	intra-articular
IB	Investigator's Brochure
IC	immune complex
[redacted]	[redacted]
ICF	informed consent form
IEC	Independent Ethics Committee
IFN	interferon
Ig	immunoglobulin
IGRA	interferon gamma-release assay
IL	interleukin
IM	intramuscular
IRB	Institutional Review Board
IRT	interactive response technology
IV	intravenous(ly)
IVIG	intravenous immunoglobulin
JAK	Janus kinase
LOCF	last observation carried forward
LTBI	latent tuberculosis infection
MAD	multiple ascending dose
MCII	minimum clinically important improvement

mCLASI	Modified Cutaneous Lupus Erythematosus Disease Area and Severity Index
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MMF	Mycophenolate mofetil/mycophenolic acid
MMP	matrix metalloproteinase
MMRM	mixed model repeated measures
6-MP	6-mercaptopurine
MRI	magnetic resonance imaging
MTX	Methotrexate
MTX-IR	methotrexate-inadequate response
Nab	Nanoantibodies
NOAEL	no-observed-adverse-effect-level
NRS	Numeric rating score
NSAID	nonsteroidal anti-inflammatory drug
NYHA	New York Heart Association
OATP	organic anion transporting polypeptide
PASS	patient acceptable symptom rate
PBO	Placebo
pBTK	phosphorylated Bruton's tyrosine kinase
PCR	polymerase chain reaction
PD	pharmacodynamic(s)
PGA	Physician Global Assessment
P-gp	P-glycoprotein
PI	principal investigator
PK	pharmacokinetic(s)
PNS	peripheral nervous system
PRO	patient-reported outcome
PROFAD	Profile of Fatigue and Discomfort
PROMIS	Patient-Reported Outcomes Measurement Information System
pSS	primary Sjögren's syndrome
QD	once daily
QRG	Quick Reference Guide
QTcF	QT interval with Fridericia's correction
QW	once weekly
RA	rheumatoid arthritis
RAMRIS	Rheumatoid Arthritis Magnetic Resonance Imaging Scoring System

RANK	receptor activator of nuclear factor kappa beta
RANKL	receptor activator of nuclear factor kappa beta-ligand
RF	rheumatoid factor
RNA	ribonucleic acid
[redacted]	[redacted]
[redacted]	[redacted]
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SC	subcutaneous(ly)
[redacted]	[redacted]
SD	Sprague-Dawley
SDAI	Simplified Disease Activity Index
SDI	(SLICC/ACR) Disease Index
SGA	Subject Global Assessment
SG-US	salivary gland ultrasonography
SJC	swollen joint count
SJC68	Swollen joint count (68 joints)
SLE	systemic lupus erythematosus
SLEDAI-2K	Systemic Lupus Erythematosus Disease Activity Index 2000
SLICC	Systemic Lupus International Collaborating Clinics
Sm	Smith
SoA	schedule of activities
SOC	standard of care
ss	steady-state
[redacted]	[redacted]
[redacted]	[redacted]
SUSAR	suspected, unexpected serious adverse reaction
TB	tuberculosis
TBUT	tear break-up time
TBNK	T cells, B cells, and natural killer cells
TEAE	treatment-emergent adverse event
T-HALF	apparent elimination half-life
TJC	tender joint count
TJC66	Tender joint count (66 joints)

Tmax	time to maximum concentration
TMJ	temporomandibular joint
TNF	tumor necrosis factor
ULN	upper limit of normal
UPCR	urine protein:creatinine ratio
VAS	visual analog scale
WBC	white blood cell
WOCBP	woman of childbearing potential
XLA	X-linked agammaglobulinemia

APPENDIX 2 STUDY GOVERNANCE CONSIDERATIONS

The term ‘subject’ 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 eCRF is intended to refer to a person (subject) 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:

- Good Clinical Practice (GCP), as defined by the International Council for Harmonisation (ICH) in accordance with the ethical principles underlying European Union Directive 2001/20/EC United States (US) CFR Title 21, Part 50 (21CFR50) applicable local requirements.

The study will be conducted in compliance with the protocol. The protocol and any amendments and the subject 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 Sponsor or designee immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

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, written consent form, subject recruitment materials (eg, advertisements), and any other written information to be provided to subjects. The investigator or BMS should also provide the IRB/IEC with a copy of the IB or product labeling information to be provided to subjects 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.

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 for 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 subject: (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 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 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 are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

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

Investigators must:

- Provide a copy of the ICF and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be nontechnical and easily understood.
- Allow time necessary for subject to inquire about the details of the study.

- Obtain an ICF signed and personally dated by the subject and by the person who conducted the informed consent discussion.
- Obtain the IRB/IEC's written approval/favorable opinion of the written ICF and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.

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

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the subjects' signed ICF and, in the US, the subjects' signed Health Insurance Portability and Accountability Act Authorization.

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

The rights, safety, and well-being of the study subjects 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 study 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), AE 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 subject, including unique subject 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, if applicable • dates and initials of person responsible for investigational product dispensing/accountability, as per the Delegation of Authority Form.
Sourced by site, and not supplied by BMS or its vendors (examples include investigational product sourced from the sites stock or commercial supply, or a specialty pharmacy)	The investigator or designee accepts responsibility for documenting traceability and study drug integrity in accordance with requirements applicable under law and the standard operating procedures of the sourcing pharmacy. These records should include: • label identification number or batch number • amount dispensed to and returned by each subject, including unique subject identifiers • dates and initials of person responsible for investigational product dispensing/accountability, as per the Delegation of Authority Form.

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 case report form (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 an electronic SAE form is not available, a paper SAE form can be used. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by Sponsor or designee.

The confidentiality of records that could identify subjects 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 and 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. For electronic CRFs, review and approval/signature is completed electronically through the BMS electronic data capture tool. 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.
Study treatments sourced by site, not supplied by BMS (or its vendors) (eg, study treatments sourced from the site's 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 Standard Operating Procedures and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed, quantity disposed, and identification of the person disposing the containers. The method of disposal (eg, 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 study 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 nonstudy

treatments sourced by the site, not supplied by BMS, is solely the responsibility of the investigator or designee.

For sites that will not destroy study treatment on site, it is the investigator's or designee's responsibility to arrange for disposal of all empty study treatment containers, 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 return of full or partially used study treatments supplied by BMS or its vendors will be arranged by the responsible Study Monitor.

CLINICAL STUDY REPORT AND PUBLICATIONS

A Signatory investigator must be selected to sign the CSR.

For this protocol, the Signatory investigator will be selected as appropriate based on the following criteria:

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

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 (CTA) 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 CTA

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 preexisting medical condition in a clinical investigation subject administered study drug 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 drug, whether or not considered related to the study drug.

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 preexisting 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 DDI.
- 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 <u>NOT</u> 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 Definition: Any untoward medical occurrence that, at any dose:
Results in death
Is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe)
Requires inpatient hospitalization or 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 or permanent damage
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 subject 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 SLE 8.2.8 for the definition of potential DILI; same definition for all sub-protocols).

Pregnancy and potential DILI must follow the same transmission timing and processes to BMS as used for SAEs (see Section SLE 8.2.6 for reporting pregnancies; same for all sub-protocols).

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, evidences, 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 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 drug 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 drug, and pregnancies must be reported to [redacted] Drug Safety within 24 hours of awareness of the event.

SAEs must be recorded on the SAE Report Form. For studies capturing SAEs through electronic data capture (EDC), electronic submission is the required method for reporting. In the event the electronic system is unavailable for transmission, paper forms must be used and submitted immediately. 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 to:

SAE Email Address: [redacted]

SAE Fax Number:

Americas: [redacted]

Europe/East Asia Pacific: [redacted]

SAE Telephone Contact - For questions on SAE/pregnancy reporting, please call:

Americas: [redacted]

Europe/East Asia Pacific: [redacted]

APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

Note: Appendix 4 provides general information and definitions related to WOCBP and methods of contraception that can be applied to most clinical studies. For information specific to Study IM014029 regarding acceptable contraception requirements for female and male subjects, refer to Section 5.1 of each sub-protocol. Only the contraception methods as described in Section 5.1 are acceptable for this study.

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 judgment 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 subjects 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 subjects 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 subjects 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 subjects in studies where hormonal contraception is permitted by the study protocol)[b,c]
- Bilateral tubal occlusion

- Vasectomized partner

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.

Male subjects 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 subjects 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 subjects 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 subjects 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 subjects 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 subjects in studies where hormonal contraception is prohibited)
Unacceptable Methods of Contraception
• Periodic abstinence (calendar, symptothermal, post-ovulation methods) • Withdrawal (coitus interruptus) • Spermicide only • LAM

COLLECTION OF PREGNANCY INFORMATION

Guidance for collection of Pregnancy Information and outcome of pregnancy on the Pregnancy Surveillance Form is provided in Section 8.2.6 of each sub-protocol and the Appendix for Adverse Events and Serious Adverse Events Definitions and procedures for Evaluating, Follow-up, and Reporting.

APPENDIX 5 SYSTEMIC LUPUS INTERNATIONAL COLLABORATING CLINICS CLASSIFICATION (SLICC) CRITERIA FOR SYSTEMIC LUPUS ERYTHEMATOSUS

Requirements: ≥ 4 criteria (at least 1 clinical and 1 laboratory criteria)
OR biopsy-proven lupus nephritis with positive ANA or Anti-DNA

Clinical Criteria	Immunologic Criteria
1. Acute Cutaneous Lupus*	1. ANA
2. Chronic Cutaneous Lupus*	2. Anti-DNA
3. Oral or nasal ulcers *	3. Anti-Sm
4. Non-scarring alopecia	4. Antiphospholipid Ab *
5. Arthritis *	5. Low complement (C3, C4, CH50)
6. Serositis *	6. Direct Coombs' test (do not count in the presence of hemolytic anemia)
7. Renal *	
8. Neurologic *	
9. Hemolytic anemia	
10. Leukopenia *	
11. Thrombocytopenia (<100,000/mm^3)	

Notes:

CLINICAL CRITERIA

(1) Acute Cutaneous Lupus OR Subacute Cutaneous Lupus

- Acute cutaneous lupus: lupus malar rash (do not count if malar discoid), bullous lupus, toxic epidermal necrolysis variant of SLE, maculopapular lupus rash, photosensitive lupus rash (in the absence of dermatomyositis)
- Subacute cutaneous lupus: nonindurated psoriaform and/or annular polycyclic lesions that resolve without scarring, although occasionally with postinflammatory dyspigmentation or telangiectasias)

(2) Chronic Cutaneous Lupus

Classic discoid rash localized (above the neck) or generalized (above and below the neck), hypertrophic (verrucous) lupus, lupus panniculitis (profundus), mucosal lupus, lupus erythematosus tumidus, chilblains lupus, discoid lupus/lichen planus overlap

(3) Oral Ulcers OR Nasal Ulcers

- Oral: palate, buccal, tongue
- Nasal ulcers
- In the absence of other causes, such as vasculitis, Behcet's disease, infection (herpes virus), inflammatory bowel disease, reactive arthritis, and acidic foods

(4) Nonscarring alopecia

Diffuse thinning or hair fragility with visible broken hairs, in the absence of other causes such as alopecia areata, drugs, iron deficiency, and androgenic alopecia

(5) Synovitis involving 2 or more joints

- Characterized by swelling or effusion
- OR tenderness in 2 or more joints and at least 30 minutes of morning stiffness

(6) Serositis

- Typical pleurisy for more than 1 day OR pleural effusions OR pleural rub
- Typical pericardial pain (pain with recumbency improved by sitting forward) for more than 1 day OR pericardial effusion OR pericardial rub OR pericarditis by electrocardiography
- In the absence of other causes, such as infection, uremia, and Dressler's pericarditis

(7) Renal

Urine protein–to-creatinine ratio (or 24-hour urine protein) representing 500 mg protein/24 hours OR red blood cell casts

(8) Neurologic

Seizures, psychosis, mononeuritis multiplex (in the absence of other known causes such as primary vasculitis), myelitis, peripheral or cranial neuropathy (in the absence of other known causes such as primary vasculitis, infection, and diabetes mellitus), acute confusional state (in the absence of other causes, including toxic/metabolic, uremia, drugs)

(9) Hemolytic anemia

(10) Leukopenia (<4000/mm^3) OR Lymphopenia (<1000/mm^3)

Leucopenia at least once: In the absence of other known causes such as Felty's syndrome, drugs, and portal hypertension.

Lymphopenia at least once: in the absence of other known causes such as corticosteroids, drugs, and infection

(11) Thrombocytopenia (<100,000/mm^3)

At least once in the absence of other known causes such as drugs, portal hypertension, and thrombotic thrombocytopenic purpura

IMMUNOLOGIC CRITERIA

(1) ANA level above laboratory reference range

(2) Anti-dsDNA antibody level above laboratory reference range (or 2-fold the reference range if tested by enzyme-linked immunosorbent assay [ELISA])

(3) Anti-Sm: presence of antibody to Sm nuclear antigen

(4) Antiphospholipid antibody positivity, as determined by

- Positive test for lupus anticoagulant
- False-positive test result for rapid plasma regain (RPR)
- Medium- or high-titer anticardiolipin antibody level (IgA, IgG, or IgM)
- Positive test result for anti–2-glycoprotein I (IgA, IgG, or IgM)

(5) Low complement (C3, C4, or CH50)

(6) Direct Coombs' test (in the absence of hemolytic anemia)

Source:

Petri M, Orbai AM, Alarcon GS, et al. Derivation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum 2012 Aug;64(8):2677-86.

APPENDIX 6 SYSTEMIC LUPUS INTERNATIONAL COLLABORATING CLINICS/AMERICAN COLLEGE OF RHEUMATOLOGY DAMAGE INDEX (SDI)

SLICC/ACR Damage Index

System Lupus International Collaborating Clinics/American College of Rheumatology Damage Index for Systemic Lupus Erythematosus

Item	Score
Ocular (either eye, by clinical assessment)	
Any cataract ever	1
Retinal change or optic atrophy	1
Neuropsychiatric	
Cognitive impairment (eg memory deficit, difficulty with calculation, poor concentration, difficulty in spoken or written language, impaired performance levels) or major psychosis	1
Seizures requiring therapy for 6 months	1
Cerebrovascular accident ever (score 2 if > 1)	1(2)
Cranial or peripheral neuropathy (excluding optic)	1
Transverse myelitis	1
Renal	
Estimated or measured glomerular filtration rate < 50% Proteinuria >= (greater than or equal to) 3.5 gm/24 hours **OR** End-stage renal disease (regardless of dialysis or transplantation)	1 1 3
Pulmonary	
Pulmonary hypertension (right ventricular prominence, or loud P2)	1
Pulmonary fibrosis (physical and radiograph)	1
Shrinking lung (radiograph)	1
Pleural fibrosis (radiograph)	1
Pulmonary infarction (radiograph)	1
Cardiovascular	
Angina or coronary artery bypass	
Myocardial infarction ever (score 2 if > 1)	1(2)
Cardiomyopathy (ventricular dysfunction)	1
Valvular disease (diastolic murmur, or systolic murmur > 3/6)	1
Pericarditis for 6 months, or pericardiectomy	1
Peripheral vascular	
Claudication for 6 months	1
Minor tissue loss (pulp space)	1
Significant tissue loss ever (eg loss of digit or limb)(score 2 if > 1 site)	1(2)
Venous thrombosis with swelling, ulceration, or venous stasis	1
Gastrointestinal	
Infarction or resection of bowel below duodenum, spleen, liver, or gall bladder ever, for cause any (score 2 if > 1 site)	1(2)
Mesenteric insufficiency	1
Chronic peritonitis	1
Stricture or upper gastrointestinal tract surgery ever	1
Pancreatic insufficiency requiring enzyme replacement or with a pseudocyst	1
Musculoskeletal	
Muscle atrophy or weakness	1
Deforming or erosive arthritis (including reducible deformities, excluding avascular necrosis)	1
Osteoporosis with fracture or vertebral collapse (excluding avascular necrosis)	1
Avascular necrosis (score 2 if > 1)	1(2)
Osteomyelitis	1
Tendon rupture	1
Skin	
Scarring chronic alopecia	1
Extensive scarring or panniculum other than scalp and pulp space	1
Skin ulceration (excluding thrombosis) for > 6 months	1
Premature gonadal failure	1
Diabetes (regardless of treatment)	1
Malignancy (exclude dysplasia) (score 2 if > 1 site)	1(2)

(From the Systemic Lupus International Collaborating Clinics (SLICC) and the American College of Rheumatology Diagnostic and Therapeutic Criteria Committee, 1996)
Gladman EM, Ginzler E, Goldsmith C et al. SLICC/ACR damage index for SLE. Arthritis Rheum 1996;39(3):363

APPENDIX 7 BRITISH ISLES LUPUS ASSESSMENT GROUP (BILAG)-2004 INDEX

BILAG-2004 INDEX Centre: Date: Initials/Hosp No:

- **Only record manifestations/items due to SLE Disease Activity**
- **Assessment refers to manifestations occurring in the last 4 weeks (compared with the previous 4 weeks)**
- **TO BE USED WITH THE GLOSSARY**

Record: **ND** Not Done
0 Not present
1 Improving
2 Same
3 Worse
4 New
Yes/No OR Value (where indicated)
***Y/N Confirm this is due to SLE activity (Yes/No)**

CONSTITUTIONAL
1. Pyrexia - documented > 37.5°C ( )
2. Weight loss - unintentional > 5% ( )
3. Lymphadenopathy/splenomegaly ( )
4. Anorexia ( )

MUCOCUTANEOUS
5. Skin eruption - severe ( )
6. Skin eruption - mild ( )
7. Angio-oedema - severe ( )
8. Angio-oedema - mild ( )
9. Mucosal ulceration - severe ( )
10. Mucosal ulceration - mild ( )
11. Panniculitis/Bullous lupus - severe ( )
12. Panniculitis/Bullous lupus - mild ( )
13. Major cutaneous vasculitis/thrombosis ( )
14. Digital infarcts or nodular vasculitis ( )
15. Alopecia - severe ( )
16. Alopecia - mild ( )
17. Peri-ungual erythema/chilblains ( )
18. Splinter haemorrhages ( )

NEUROPSYCHIATRIC
19. Aseptic meningitis ( )
20. Cerebral vasculitis ( )
21. Demyelinating syndrome ( )
22. Myelopathy ( )
23. Acute confusional state ( )
24. Psychosis ( )
25. Acute inflammatory demyelinating polyradiculoneuropathy ( )
26. Mononeuropathy (single/multiplex) ( )
27. Cranial neuropathy ( )
28. Plexopathy ( )
29. Polyneuropathy ( )
30. Seizure disorder ( )
31. Status epilepticus ( )
32. Cerebrovascular disease (not due to vasculitis) ( )
33. Cognitive dysfunction ( )
34. Movement disorder ( )
35. Autonomic disorder ( )
36. Cerebellar ataxia (isolated) ( )
37. Lupus headache - severe unremitting ( )
38. Headache from IC hypertension ( )

MUSCULOSKELETAL
39. Myositis - severe ( )
40. Myositis - mild ( )
41. Arthritis (severe) ( )
42. Arthritis (moderate)/Tendonitis/Tenosynovitis ( )
43. Arthritis (mild)/Arthralgia/Myalgia ( )

Weight (kg): **Serum urea (mmol/l):**
African ancestry: Yes/No **Serum albumin (g/l):**

CARDIORESPIRATORY
44. Myocarditis - mild ( )
45. Myocarditis/Endocarditis + Cardiac failure ( )
46. Arrhythmia ( )
47. New valvular dysfunction ( )
48. Pleurisy/Pericarditis ( )
49. Cardiac tamponade ( )
50. Pleural effusion with dyspnoea ( )
51. Pulmonary haemorrhage/vasculitis ( )
52. Interstitial alveolitis/pneumonitis ( )
53. Shrinking lung syndrome ( )
54. Aortitis ( )
55. Coronary vasculitis ( )

GASTROINTESTINAL
56. Lupus peritonitis ( )
57. Abdominal serositis or ascites ( )
58. Lupus enteritis/colitis ( )
59. Malabsorption ( )
60. Protein losing enteropathy ( )
61. Intestinal pseudo-obstruction ( )
62. Lupus hepatitis ( )
63. Acute lupus cholecystitis ( )
64. Acute lupus pancreatitis ( )

OPHTHALMIC
65. Orbital inflammation/myositis/proptosis ( )
66. Keratitis - severe ( )
67. Keratitis - mild ( )
68. Anterior uveitis ( )
69. Posterior uveitis/retinal vasculitis - severe ( )
70. Posterior uveitis/retinal vasculitis - mild ( )
71. Episcleritis ( )
72. Scleritis - severe ( )
73. Scleritis - mild ( )
74. Retinal/choroidal vaso-occlusive disease ( )
75. Isolated cotton-wool spots (cytoid bodies) ( )
76. Optic neuritis ( )
77. Anterior ischaemic optic neuropathy ( )

RENAL
78. Systolic blood pressure (mm Hg) value ( ) **Y/N***
79. Diastolic blood pressure (mm Hg) value ( ) **Y/N***
80. Accelerated hypertension Yes/No ( )
81. Urine dipstick protein (+=1, ++=2, +++=3) ( ) **Y/N***
82. Urine albumin-creatinine ratio mg/mmol ( ) **Y/N***
83. Urine protein-creatinine ratio mg/mmol ( ) **Y/N***
84. 24 hour urine protein (g) value ( ) **Y/N***
85. Nephrotic syndrome Yes/No ( )
86. Creatinine (plasma/serum) µmol/l ( ) **Y/N***
87. GFR (calculated) ml/min/1.73 m^2 ( ) **Y/N***
88. Active urinary sediment Yes/No ( )
89. Active nephritis Yes/No ( )

HAEMATOLOGICAL
90. Haemoglobin (g/dl) value ( ) **Y/N***
91. Total white cell count (x 10^9/l) value ( ) **Y/N***
92. Neutrophils (x 10^9/l) value ( ) **Y/N***
93. Lymphocytes (x 10^9/l) value ( ) **Y/N***
94. Platelets (x 10^9/l) value ( ) **Y/N***
95. TTP ( )
96. Evidence of active haemolysis Yes/No ( )
97. Coombs' test positive (isolated) Yes/No ( )

Revision: 1/Sep/2009

Sources:

Isenberg, DA, Rahman A, Allen E, et al. BILAG 2004. Development and initial validation of an updated version of the British Isles Lupus Assessment Group's disease activity index for patients with systemic lupus erythematosus. Rheumatology (Oxford) 2005;44(7):902-6.

Yee CS, Farewell V, Isenberg DA, et al. Revised British Isles Lupus Assessment Group 2004 Index - A Reliable Tool for Assessment of Systemic Lupus Erythematosus Activity. Arthritis Rheum 2006;54:3300–05.

Yee CS, Farewell V, Isenberg DA, et al. British Isles Lupus Assessment Group 2004 index is valid for assessment of disease activity in systemic lupus erythematosus. Arthritis Rheum 2007;56(12):4113-19.

Yee CS, Cresswell L, Farewell V, et al: Numerical scoring for the BILAG-2004 index. Rheumatology (Oxford) 2010 Sep;49(9):1665-9.

APPENDIX 8 SYSTEMIC LUPUS ERYTHEMATOSUS DISEASE ACTIVITY INDEX 2000 (SLEDAI-2K)

For Assessment over a 30-Day Window (J. Rheumatol. Copyright©2002)

For Reference Use Only

SLEDAI 2K Weight	SCORE	Descriptor	Definition
8	_____	Seizure	Recent onset, exclude metabolic, infectious or drug causes.
8	_____	Psychosis	Altered ability to function in normal activity due to severe disturbance in the perception of reality. Include hallucinations, incoherence, marked loose associations, impoverished thought content, marked illogical thinking, bizarre, disorganized, or catatonic behavior. Exclude uremia and drug causes
8	_____	Organic brain syndrome	Altered mental function with impaired orientation, memory, or other intellectual function, with rapid onset and fluctuating clinical features, inability to sustain attention to environment, plus at least 2 of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, or increased or decreased psychomotor activity. Exclude metabolic, infectious, or drug causes.
8	_____	Visual disturbance	Retinal changes of SLE. Include cytoid bodies, retinal hemorrhages, serous exudate or hemorrhages in the choroid, or optic neuritis. Exclude hypertension, infection, or drug causes.
8	_____	Cranial nerve disorder	New onset of sensory or motor neuropathy involving cranial nerves.
8	_____	Lupus headache	Severe, persistent headache; may be migrainous, but must be nonresponsive to narcotic analgesia.
8	_____	CVA	New onset of cerebrovascular accident(s). Exclude arteriosclerosis.
8	_____	Vasculitis	Ulceration, gangrene, tender finger nodules, periungual infarction, splinter hemorrhages, or biopsy or angiogram proof of vasculitis
4	_____	Arthritis	≥ 2 joints with pain and signs of inflammation (i.e., tenderness, swelling or effusion).
4	_____	Myositis	Proximal muscle aching/weakness, associated with elevated creatine phosphokinase/aldolase or electromyogram changes or a biopsy showing myositis
4	_____	Urinary casts	Heme-granular or red blood cell casts.
4	_____	Hematuria	>5 red blood cells/high power field. Exclude stone, infection or other cause.
4	_____	Proteinuria	>0.5 gram/24 hours
4	_____	Pyuria	>5 white blood cells/high power field. Exclude infection.
2	_____	Rash	Inflammatory type rash.
2	_____	Alopecia	Abnormal, patchy or diffuse loss of hair.
2	_____	Mucosal ulcers	Oral or nasal ulcerations.
2	_____	Pleurisy	Pleuritic chest pain with pleural rub or effusion, or pleural thickening.
2	_____	Pericarditis	Pericardial pain with at least 1 of the following: rub, effusion, or electrocardiogram or echocardiogram confirmation.
2	_____	Low complement	Decrease in CH50, C3, or C4 below the lower limit of normal for testing laboratory
2	_____	Increased DNA binding	Increased DNA binding by Farr assay above normal range for testing laboratory.
1	_____	Fever	>38° C. Exclude infectious cause.
1	_____	Thrombocytopenia	<100,000 platelets / x10^9/L, exclude drug causes.
1	_____	Leukopenia	< 3,000 white blood cells / x10^9/L, exclude drug causes.

TOTAL SCORE: _____

Gladman DD, Ibanez D, Urowitz MB. Systematic lupus erythematosus disease activity index 2000. J Rheumatol. 2002:29:288-91.

Touma Z, Urowitz MB, Glasman DD. Sledai-2K 10 days versus 30 days in a longitudinal evaluation. Lupus. 2011. Jan:20(1): 67-70.)

APPENDIX 9 CUTANEOUS LUPUS ERYTHEMATOSUS DISEASE AREA AND SEVERITY INDEX (CLASI)

The CLASI is a sensitive, validated instrument developed by Victoria Werth, M.D. and her colleagues at the University of Pennsylvania in 2005 (copyright 2009 University of Pennsylvania, All Rights Reserved) for use in clinical studies to measure Cutaneous Lupus Erythematosus (CLE) disease activity and damage.

The modified (mCLASI) used in this study is defined as the activity portions of CLASI that describe skin erythema, scale/hypertrophy and inflammation of the scalp. Damage, oral ulcers, and alopecia without scalp inflammation are excluded from the mCLASI activity score.

Select the score in each anatomical location that describes the most severely affected cutaneous lupus-associated lesion

Extent

	activity		damage		
Anatomical Location	Erythema	Scale/ Hypertrophy	Dyspigmentation	Scarring/ Atrophy/ Panniculitis	Anatomical Location
	0-absent 1-pink; faint erythema 2- red; 3-dark red; purple/violaceous/ crusted/ hemorrhagic	0-absent; 1-scale 2-verrucous/ hypertrophic	0-absent, 1-dyspigmentaton	0 … absent 1 … scarring 2 … severely atrophic scarring or panniculitis	
Scalp				See below	Scalp
Ears					Ears
Nose (incl. malar area)					Nose (incl. malar area)
Rest of the face					Rest of the face
V-area neck (frontal)					V-area neck (frontal)
Post. Neck &/or shoulders					Post. Neck &/or shoulders
Chest					Chest
Abdomen					Abdomen
Back, buttocks					Back, buttocks
Arms					Arms
Hands					Hands
Legs					Legs
Feet					Feet

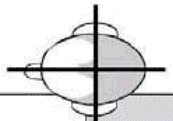
Mucous membrane

Mucous membrane lesions (examine if patient confirms involvement)	
0-absent; 1-lesion or ulceration	

Dyspigmentation

Report duration of dyspigmentation after active lesions have resolved (verbal report by patient … tick appropriate box)
☐ Dyspigmentation usually lasts less than 12 months (dyspigmentation score above remains) ☐ Dyspigmentation usually lasts at least 12 months (dyspigmentation score is doubled)

Alopecia



Recent Hair loss (within the last 30 days/as reported by patient)	
1-Yes 0-No	

NB: if scarring and non-scarring aspects seem to coexist in one lesion, please score both

Divide the scalp into four quadrants as shown. The dividing line between right and left is the midline. The dividing line between frontal and occipital is the line connecting the highest points of the ear lobe. A quadrant is considered affected if there is a lesion within the quadrant.

Alopecia (clinically not obviously scarred)		Scarring of the scalp (judged clinically)	
0-absent 1-diffuse; non-inflammatory 2-focal or patchy in one quadrant; 3-focal or patchy in more than one quadrant		0- absent 3- in one quadrant 4- two quadrants 5- three quadrants 6- affects the whole skull	

Total Activity Score (For the activity score please add up the scores of the left side i.e. for Erythema, Scale/Hypertrophy, Mucous membrane involvement and Alopecia)		Total Damage Score (For the damage score, please add up the scores of the right side, i.e. for Dyspigmentation, Scarring/Atrophy/Panniculitis and Scarring of the Scalp)	

Sources:

Albrecht J, Taylor L, Berlin JA, et al. The CLASI (Cutaneous Lupus Erythematosus Disease Area and Severity Index): An outcome instrument for cutaneous lupus erythematosus. J Invest Dermatol 2005;125:889 -94. Highlighted area indicates assessment by modified CLASI (mCLASI) criteria.

Bonilla-Martinez ZL, Albrecht J, Troxel, AB, et al. The Cutaneous Lupus Erythematosus Disease Area and Severity Index - A responsive instrument to measure activity and damage in patients with cutaneous lupus erythematosus. Arch Dermatol 2008;144(2):173-80.

Use of the modified CLASI assessment:

Merrill JT, Furie R, Werth VP, et al. Anifrolumab effects on rash and arthritis: impact of the type I interferon gene signature in the phase IIb MUSE study in patients with systemic lupus erythematosus. Lupus Science & Medicine 2018;5:e000284, doi:10.1136/lupus-2018-000284

APPENDIX 10 PHYSICIAN GLOBAL ASSESSMENT OF DISEASE ACTIVITY (PGA) (SLE; VAS)

The investigator will rate the overall status of the subject in response to the following statement:

"How do you assess your patient's (the subject's) current lupus disease activity as compared to the activity and Physician Global Assessment (PGA) at the last visit? Please indicate by placing a mark on the line below."

I _____I

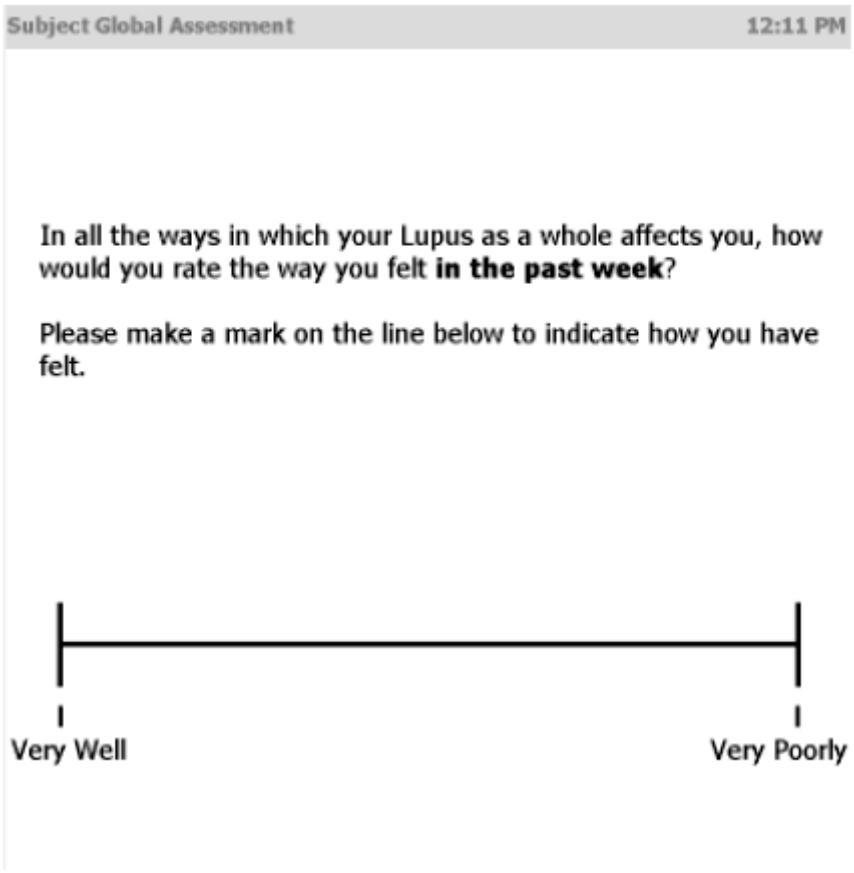
0 mm	100 mm
No disease activity	Worst possible disease activity

- 0 is 'no disease activity' indicating very good, asymptomatic, with no limitation of normal activities.
- 100 indicates 'the worst possible disease activity' and is at the very end of the scale. This refers to the most severe possible disease in SLE, and does not reflect the most severe disease ever seen in a particular subject, but the most severe disease ever seen in all SLE patients. This extreme level of disease activity would be expected to be seen only in hospitalized patients.
- When scoring the PGA, the assessor should always consider current activity as compared to the activity and PGA captured at the prior visit.

After marking the line on the yellow paper PGA Source Document, use the study-specific ruler provided to measure the length from 0 to your mark, to the nearest mm. Record this value on the paper PGA Source Document form printed on yellow paper and include signature of assessor and date assessed. Enter PGA (mm) on the PGA eCRF for the appropriate visit.

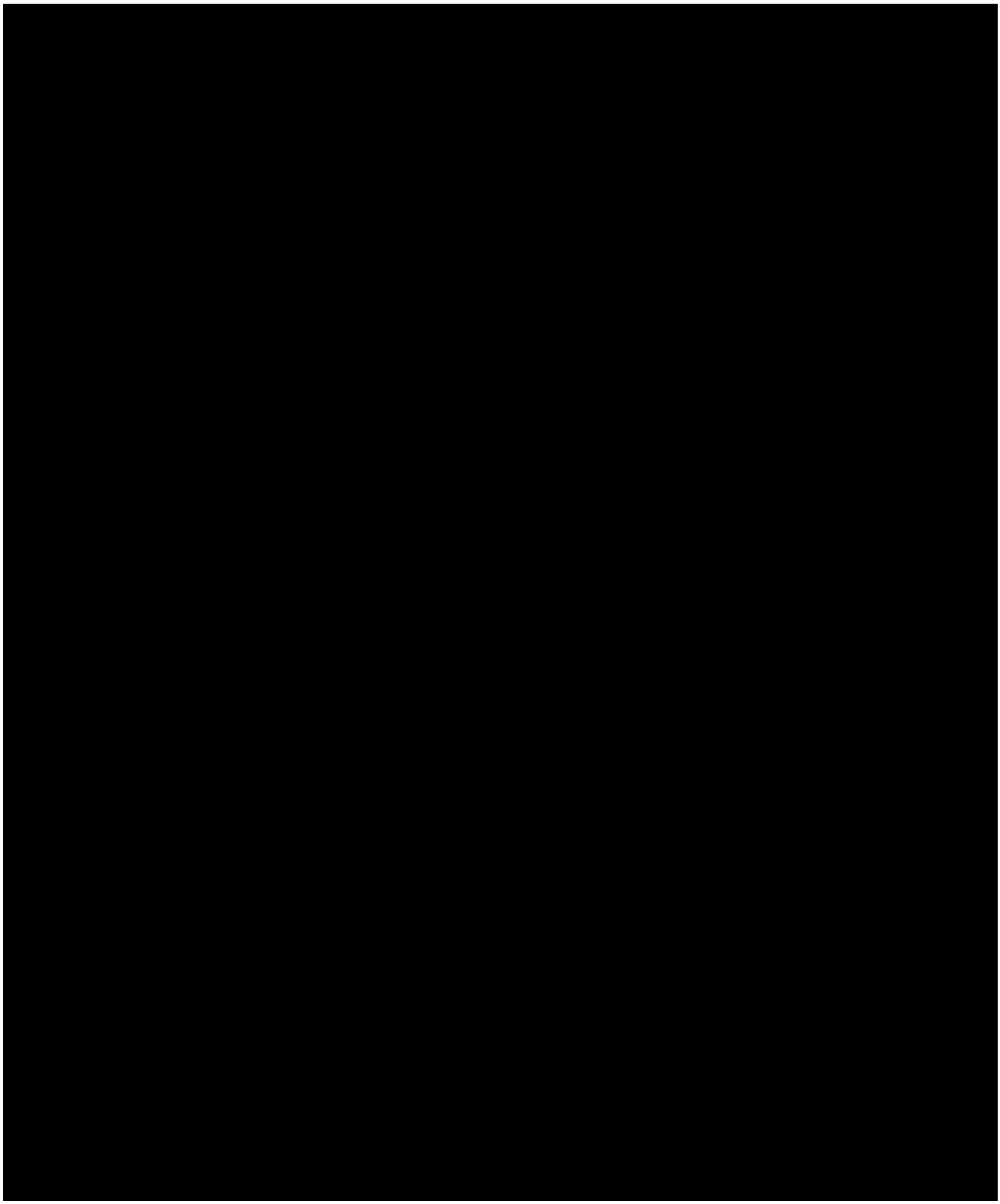
APPENDIX 11 SUBJECT GLOBAL ASSESSMENT OF DISEASE ACTIVITY (SGA) (SLE; VAS)

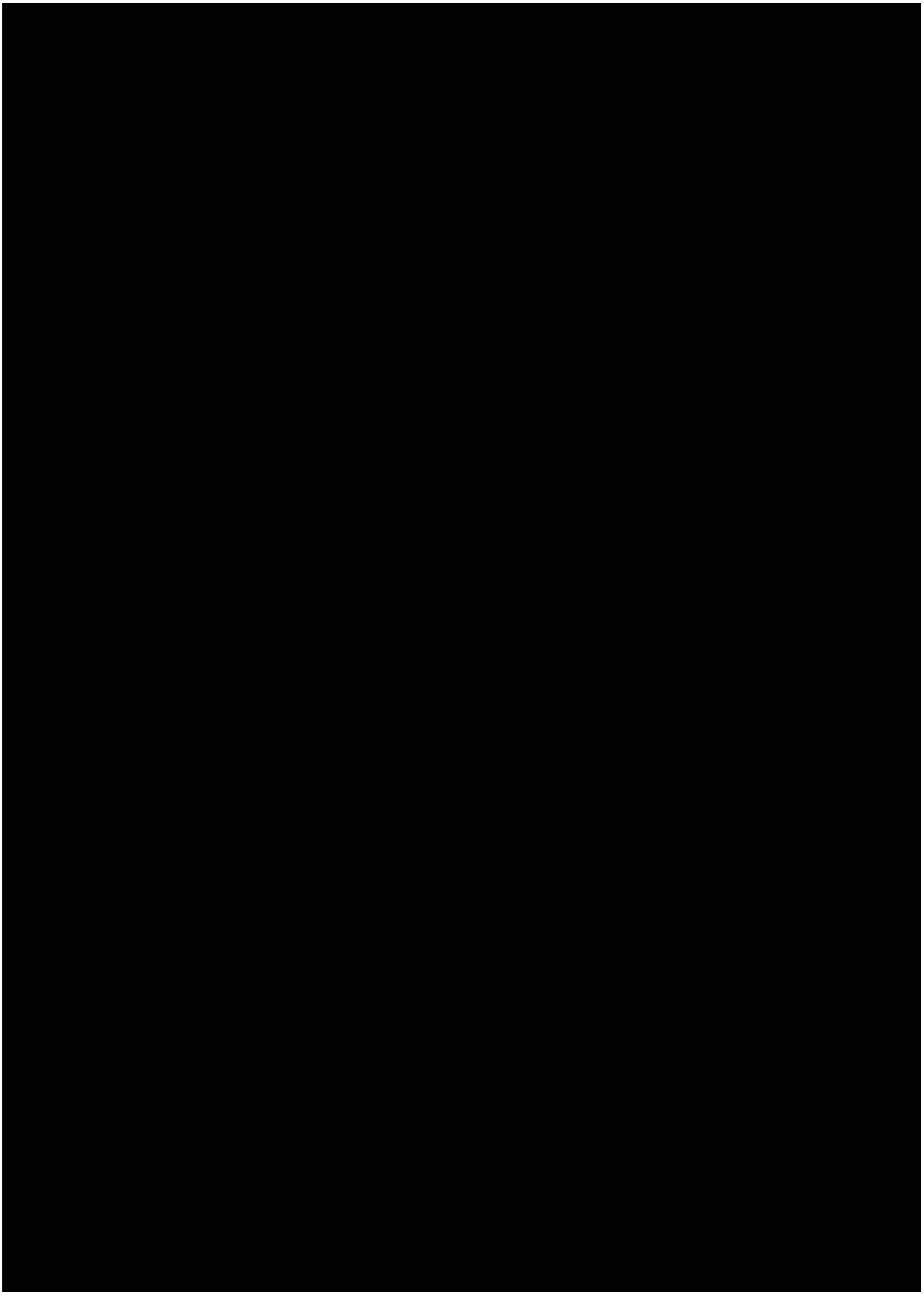
The Subject Global Assessment of Disease Activity will be captured on an eCOA device. The value will be stored as 0-100.

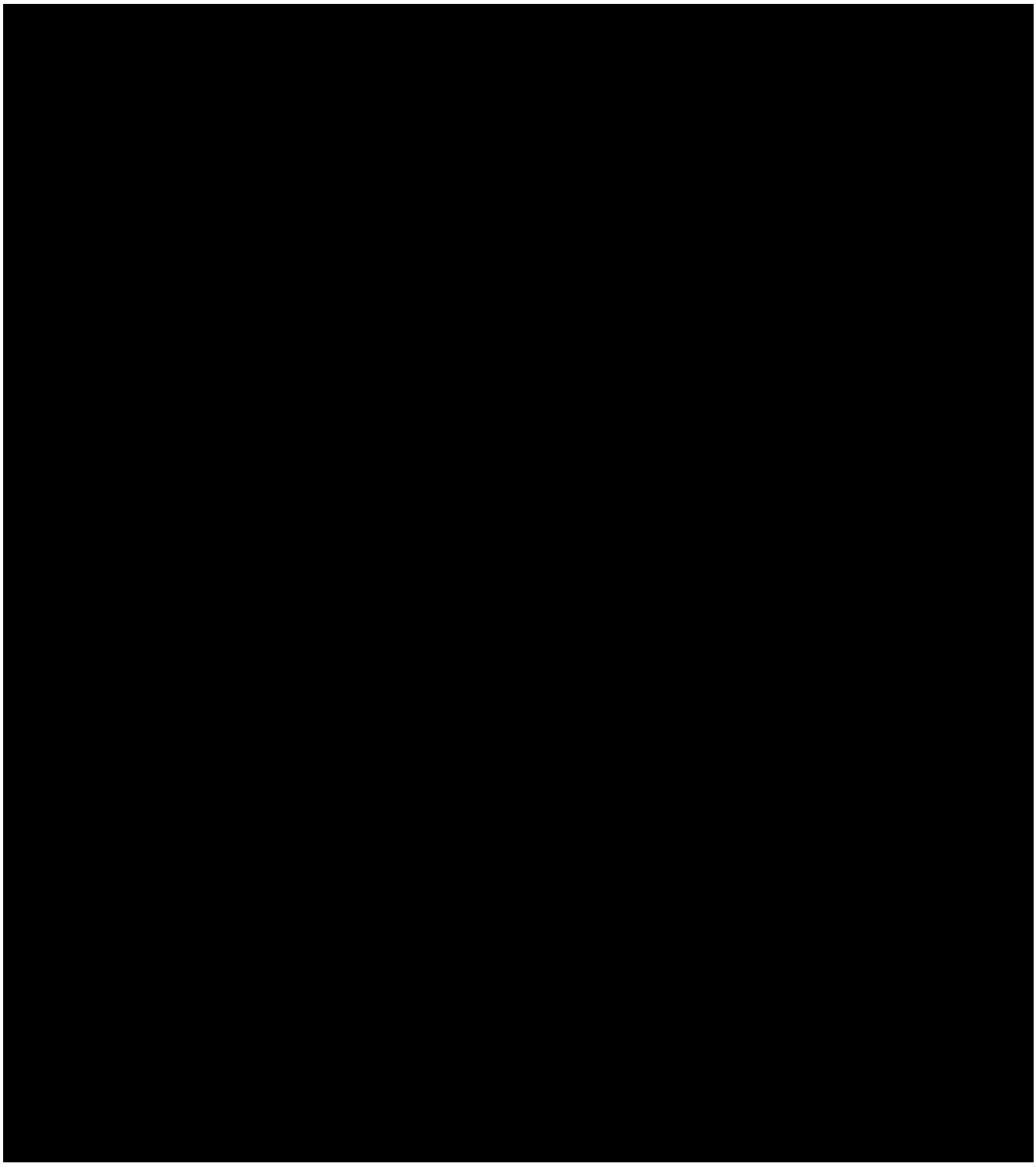


APPENDIX 12 PATIENT-REPORTED OUTCOMES MEASUREMENT INFORMATION SYSTEM-FATIGUE INSTRUMENT (PROMIS FATIGUE 6 A) (SLE; PSS; RA)

APPENDIX 13 EQ-5 D-5 L, EQ VAS (SLE; PSS, RA)







APPENDIX 14 SYSTEMIC LUPUS ERYTHMASTOSUS PAIN NUMERIC RATING SCORE (SLE, NRS)

APPENDIX 15 EUROPEAN LEAGUE AGAINST RHEUMATISM (EULAR) SJÖGREN'S SYNDROME DISEASE ACTIVITY INDEX (ESSDAI, PSS)

EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI)

Select one response from each domain.

Domains	Item Descriptions
1. Constitutional	**Exclusion of fever of infectious origin and voluntary weight loss**
No activity ☐0	Absence of the following symptoms
Low activity ☐3	Mild or intermittent fever (37.5-38.5°C)/night sweats and/or involuntary weight loss of 5-10% of body weight
Moderate activity ☐6	Severe fever (>38.5°C)/night sweats and/or involuntary weight loss of >10% of body weight
2. Lymphadenopathy	**Exclusion of infection**
No activity ☐0	Absence of the following features
Low activity ☐4	Lymphadenopathy ≥1 cm in any nodal region or ≥2 cm in inguinal region
Moderate activity ☐8	Lymphadenopathy ≥2 cm in any nodal region or ≥3 cm in inguinal region and/or splenomegaly (clinically palpable or assessed by imaging)
High activity ☐12	Current malignant B-cell proliferative disorder*
3. Glandular	**Exclusion of stone or infection**
No activity ☐0	Absence of glandular swelling
Low activity ☐2	Small glandular swelling with enlarged parotid (≤3 cm) or limited submandibular or lachrymal swelling
Moderate activity ☐4	Major glandular swelling with enlarged parotid (>3 cm), or important submandibular or lachrymal swelling

4. Articular		Exclusion of osteoarthritis
No activity	☐0	Absence of currently active articular involvement
Low activity	☐2	Arthralgias in hands, wrists, ankles, and feet accompanied by morning stiffness (>30 min)
Moderate activity	☐4	1-5 (of 28 total count) synovitis
High activity	☐6	≥6 (of 28 total count) synovitis
5. Cutaneous		**Rate as 'No activity' stable long-lasting features related to damage**
No activity	☐0	Absence of currently active cutaneous involvement
Low activity	☐3	Erythema multiforma
Moderate activity	☐6	Limited cutaneous vasculitis, including urticarial vasculitis, or purpura limited to feet and ankle, or subacute cutaneous lupus
High activity	☐9	Diffuse cutaneous vasculitis, including urticarial vasculitis, or diffuse purpura , or ulcers related to vasculitis

6. Pulmonary		Rate as 'No activity' stable long-lasting features related to damage, or respiratory involvement not related to the disease (tobacco use, etc.)
No activity	☐0	Absence of currently active pulmonary involvement
Low activity	☐5	Persistent cough or bronchial involvement with no radiographic abnormalities on radiography. Or radiological or HRCT evidence of interstitial lung disease.
Moderate activity	☐10	Moderately active pulmonary involvement, such as interstitial lung disease by HRCT with shortness of breath on exercise (NYHA II) or abnormal lung function tests restricted to: 70%>DL_{CO} ≥40% or 80% >FVC≥60%
High activity	☐15	Highly active pulmonary involvement, such as interstitial lung disease by HRCT with shortness of breath at rest (NYHA III, IV) or with abnormal lung function tests: DL_{CO} <40% or 80% >FVC<60%
7. Renal		**Rate as 'No activity' stable long-lasting features related to damage, and renal involvement not related to the disease. If biopsy has been performed, please rate activity based on histological features first**
No activity	☐0	Absence of currently active renal involvement with proteinuria <0.5 g/day, no haematuria, no leucocyturia, no acidosis, or long-lasting stable proteinuria due to damage
Low activity	☐5	Evidence of mild active renal involvement, limited to tubular acidosis without renal failure or glomerular involvement with proteinuria (between 0.5 and 1 g/day) and without haematuria or renal failure (GFR ≥60 mL/min)
Moderate activity	☐10	Moderately active renal involvement, such as tubular acidosis with renal failure (GFR <60 mL/min) or glomerular involvement with proteinuria between 1 and 1.5 g/day and without haematuria or renal failure (GFR ≥60 mL/min) or histological evidence of extra membranous glomerulonephritis or important interstitial lymphoid infiltrate
High activity	☐15	Highly active renal involvement, such as glomerular involvement with proteinuria between >1.5 g/day or haematuria or renal failure (GFR <60 mL/min), or histological evidence of proliferative membranous glomerulonephritis or cryoglobulinemia related renal involvement

ESSDA\003

8. Muscular		Exclusion of weakness due to corticosteroids
No activity	☐0	Absence of currently active muscular involvement
Low activity	☐6	Mild active myositis shown by abnormal EMG or biopsy with no weakness and creatine kinase (N<CK≤2N)
Moderate activity	☐12	Moderately active myositis shown by abnormal EMG or biopsy with weakness (maximal deficit of 4/5), or elevated creatine kinase (2N<CK≤4N)
High activity	☐18	Highly active myositis shown by abnormal EMG or biopsy with weakness (deficit of ≤3/5), or elevated creatine kinase (>4N)
9. Peripheral Nervous System (PNS)		**Rate as 'No activity' stable long-lasting features related to damage or PNS involvement not related to the disease**
No activity	☐0	Absence of currently active PNS involvement
Low activity	☐5	Mild active peripheral nervous system involvement, such as pure sensory axonal polyneuropathy shown by NCS or trigeminal (V) neuralgia
Moderate activity	☐10	Moderately active peripheral nervous system involvement shown by NCS, such as axonal sensory neuropathy with maximal motor deficit of 4/5, pure sensory neuropathy with presence of cryoglobulinemic vasculitis, ganglionopathy with symptoms restricted to mild/moderate ataxia, inflammatory demyelinating polyneuropathy (CIDP) with mild functional impairment (maximal motor deficit of 4/5 or mild ataxia), or cranial nerve involvement of peripheral origin (except trigeminal (V) neuralgia
High activity	☐15	Highly active PNS involvement shown by NCS, such as axonal sensory-motor neuropathy with motor deficit ≤3/5, peripheral nerve involvement due to vasculitis (mononeuritis multiplex, etc), severe ataxia due to ganglionopathy, inflammatory demyelinating polyneuropathy (CIDP) with severe functional impairment motor deficit ≤3/5 or severe ataxia

ESSDAI004

10. Central Nervous System (CNS)		Rate as 'No activity' stable long-lasting features related to damage or CNS involvement not related to the disease
No activity	☐0	Absence of currently active CNS involvement
Moderate activity	☐10	Moderately active CNS features, such as cranial nerve involvement of central origin, optic neuritis or multiple sclerosis-like syndrome with symptoms restricted to pure sensory involvement or proven cognitive impairment
High activity	☐15	Highly active CNS features, such as cerebral vasculitis with cerebrovascular accident or transient ischaemic attack, seizures, transverse myelitis, lymphocytic meningitis, multiple sclerosis-like syndrome with motor deficit
11. Haematological		**For anaemia, neutropenia, and thrombocytopenia, only autoimmune cytopenia must be considered** **Exclusion of vitamin or iron deficiency, drug induced cytopenia**
No activity	☐0	Absence of autoimmune cytopenia
Low activity	☐2	Cytopenia of autoimmune origin with neutropenia (1000<neutrophils<1500/mm^3), and/or anaemia (10<haemoglobin<12 g/dL), and/or thrombocytopenia (100,000<platelets<150,000/mm^3) or lymphopenia(500<lymphocytes<1000/mm^3)
Moderate activity	☐4	Cytopenia of autoimmune origin with neutropenia (500<neutrophils ≤1000/mm^3), and/or anaemia (8≤haemoglobin ≤10 g/dL), and/or thrombocytopenia (50,000≤platelets ≤100,000/mm^3) or lymphopenia (≤500/mm^3)
High activity	☐6	Cytopenia of autoimmune origin with neutropenia (neutrophils ≤500/mm^3), and/or anaemia (haemoglobin <8 g/dL), and/or thrombocytopenia (platelets <50,000/mm^3)

ESSDA005

12. Biological		
No activity	☐0	Absence of any of the following biological features
Low activity	☐1	Clonal component and/or hypocomplementemia (low C4 or C3 of CH50) and/or hypergammaglobulinemia or high IgG level between 16 and 20 g/L
Moderate activity	☐2	Presence of cryoglobulinemia and/or hypergammaglobulinemia or high IgG level >20 g/L, and or recent onset hypogammaglobulinemia or recent decrease of IgG level (<5 g/L)

*Defined as indolent not treated lymphoma or currently treated lymphoma or myeloma (or treatment ended from less than 6 months). Do not rate past treated lymphoma or myeloma in complete remission.

CIDP, chronic inflammatory demyelinating polyneuropathy; CK, creatine kinase; CNS, central nervous system; DLCO, diffusing CO capacity; EMG, electromyogram; FVC, forced vital capacity; GFR, glomerular filtration rate; Hb, haemoglobin; HRCT, high-resolution CT; IgG, immunoglobulin G; NCS, nerve conduction studies; NYHA, New York Heart Association Classification; Plt, platelet; PNS, peripheral nervous system.

Seror R, Theander E, Brun JG, et al. Validation of EULAR primary Sjogren's syndrome disease activity (ESSDAI) and patient indexes (ESSPRI). Ann Rheum Dis 2015;74(5):859-66.

APPENDIX 16 DISEASE ACTIVITY SCORE 28 C-REACTIVE PROTEIN (DAS28-CRP) (PSS; RA)

The DAS28-CRP score will be calculated programmatically using the 28 Tender Joint Count, the 28 Swollen Joint Count, the hsCRP, and the subject global assessment of disease activity VAS using the following formula.

Formula DAS28-4(crp) = 0.56*SQRT(TJC28) + 0.28SQRTSJC28) + 0.36*ln(CRP+1) + 0.014*GH + 0.96

APPENDIX 17 PHYSICIAN GLOBAL ASSESSMENT OF DISEASE ACTIVITY (PGA) (PSS)

The investigator will rate the overall status of the subject in response to the following statement:

"How do you assess your patient's (the subject's) current primary Sjögren's disease activity as compared to the activity and PGA at the last visit? Please indicate by placing a mark on the line below."

0 100

No disease activity Worst possible disease activity

- 0 is 'no disease activity' indicating very good, asymptomatic, with no limitation of normal activities.
- 100 indicates 'the worst possible disease activity' and is at the very end of the scale. This refers to the most severe possible disease in Sjögren's, and does not reflect the most severe disease ever seen in a particular subject, but the most severe disease ever seen in all SLE patients. This extreme level of disease activity would be expected to be seen only in hospitalized patients.
- When scoring the PGA, the assessor should always consider current activity as compared to the activity and PGA captured at the prior visit.

After marking the line on the paper PGA Source Document, use the study-specific ruler provided to measure the length from 0 to your mark, to the nearest mm. Record this value on the paper PGA Source Document form printed on green paper and include signature of assessor and date assessed. Enter PGA (mm) on the PGA eCRF for the appropriate visit.

APPENDIX 18 EUROPEAN LEAGUE AGAINST RHEUMATISM (EULAR) SJÖGREN'S SYNDROME PATIENT-REPORTED INDEX (ESSPRI) (PSS)

APPENDIX 19 SUBJECT GLOBAL ASSESSMENT OF DISEASE ACTIVITY (SGA) (PSS;VAS)

APPENDIX 20 SIMPLIFIED DISEASE ACTIVITY INDEX (SDAI) (RA)

The SDAI is the sum of the tender joint score (range 0 to 28), the swollen joint score (range 0 to 28), the subject global assessment (SGA) of disease activity (range 0 to 10 in increments of 0.5), the PGA of disease activity (range 0 to 10 in increments of 0.5), and C-reactive protein (CRP) test result.

The SDAI score will be calculated programmatically by the Sponsor or designee.

APPENDIX 21 CLINICAL DISEASE ACTIVITY INDEX (CDAI) (RA)

The CDAI is the sum of the tender joint score (range 0 to 28), the swollen joint score (range 0 to 28), the SGA of disease activity (range 0 to 10 in increments of 0.5), and the PGA of disease activity (range 0 to 10 in increments of 0.5)

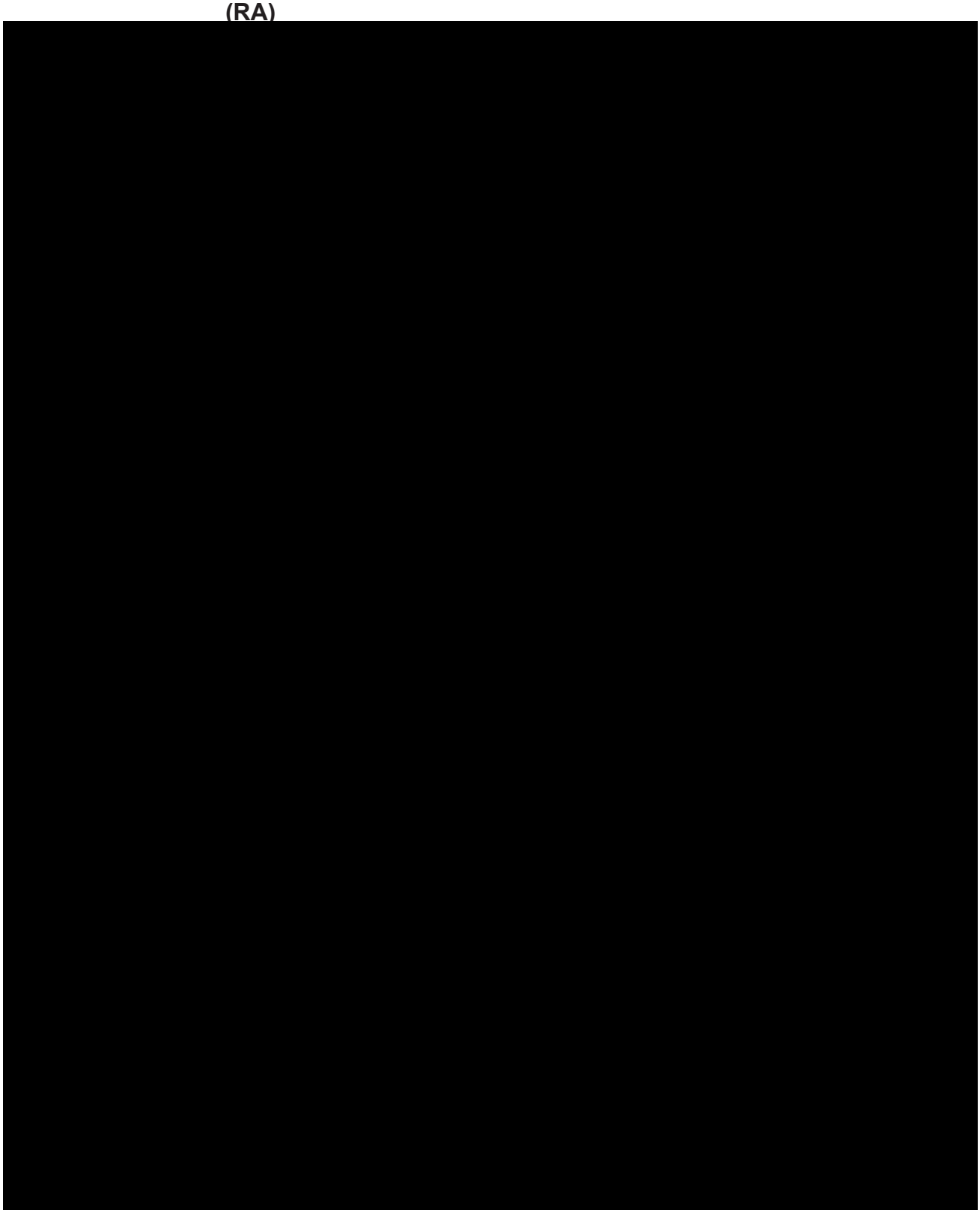
The CDAI composite score will be calculated programmatically by eCOA vendor.

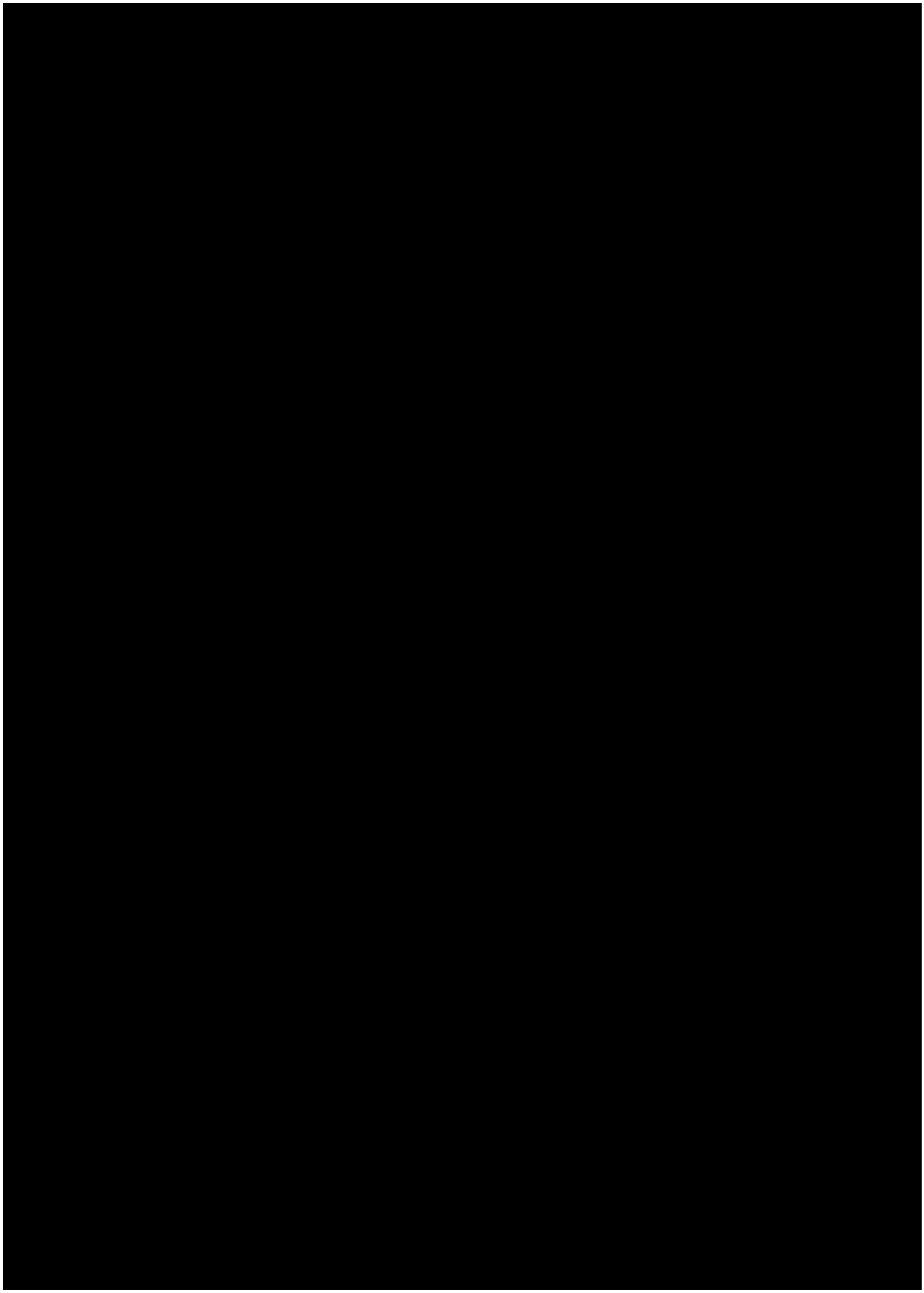
APPENDIX 22 AMERICAN COLLEGE OF RHEUMATOLOGY DISEASE ACTIVITY SCORE-28 ERYTHROCYTE SEDIMENTATION RATE (DAS28-ESR) (RA)

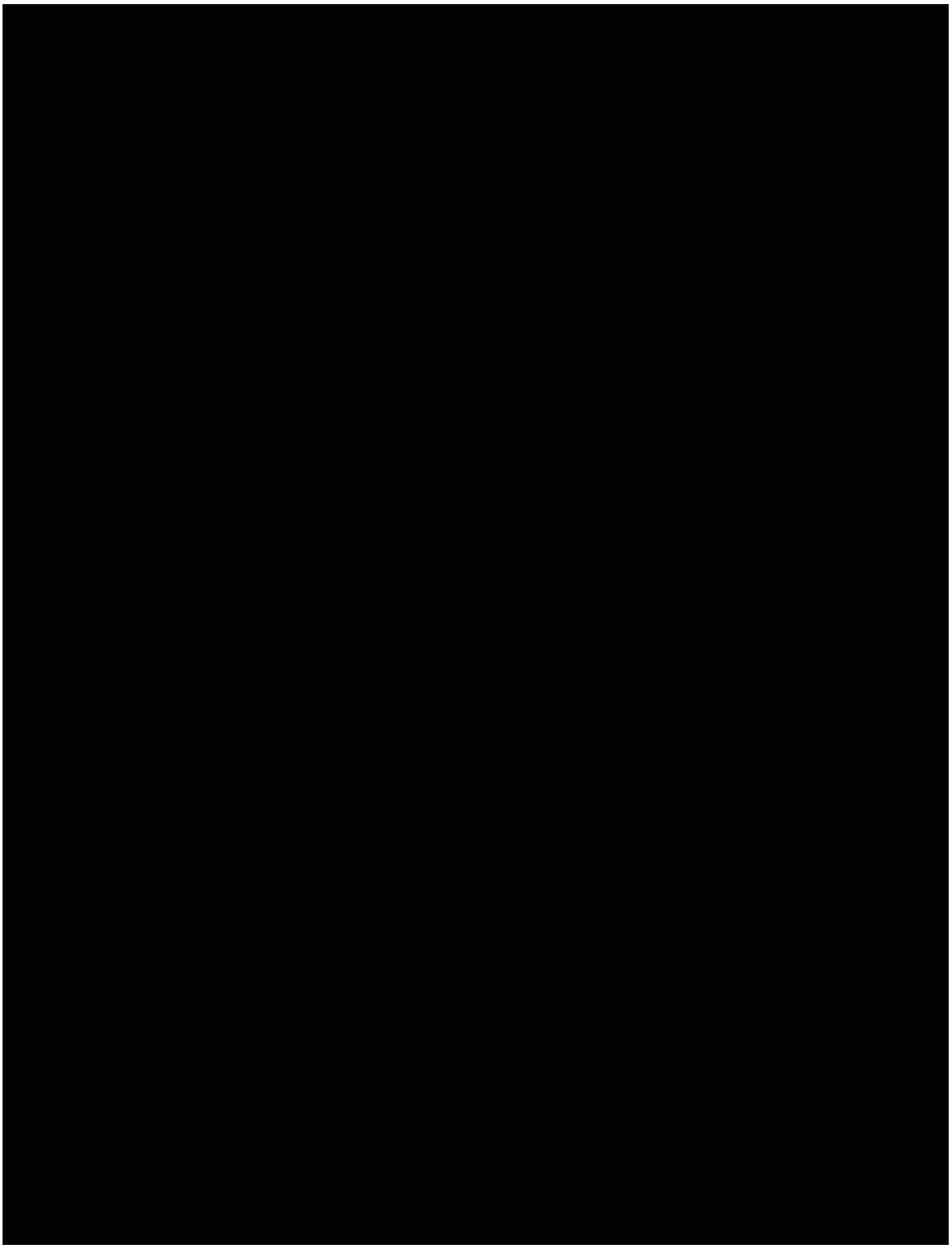
The DAS28-ESR score will be calculated programmatically using the 28 Tender Joint Count, the 28 Swollen Joint Count, the ESR, and the subject global assessment of disease activity VAS using the following formula.

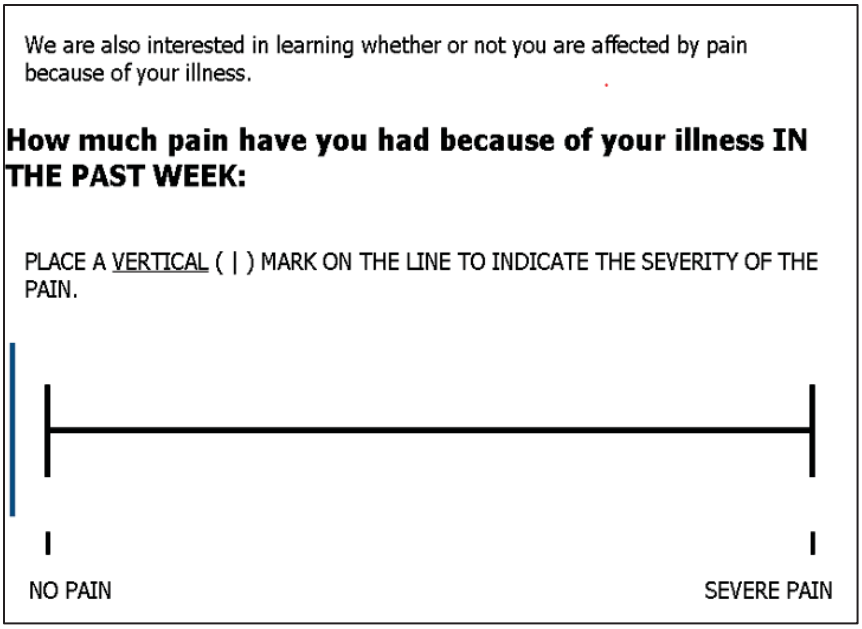
DAS28-ESR = 0.56*√(t28) + 0.28*√(sw28) + 0.70*Ln(ESR) + 0.014*VAS

APPENDIX 23 AMERICAN COLLEGE OF RHEUMATOLOGY HEALTH ASSESSMENT QUESTIONNAIRE DISABILITY INDEX (HAQ-DI) (RA)









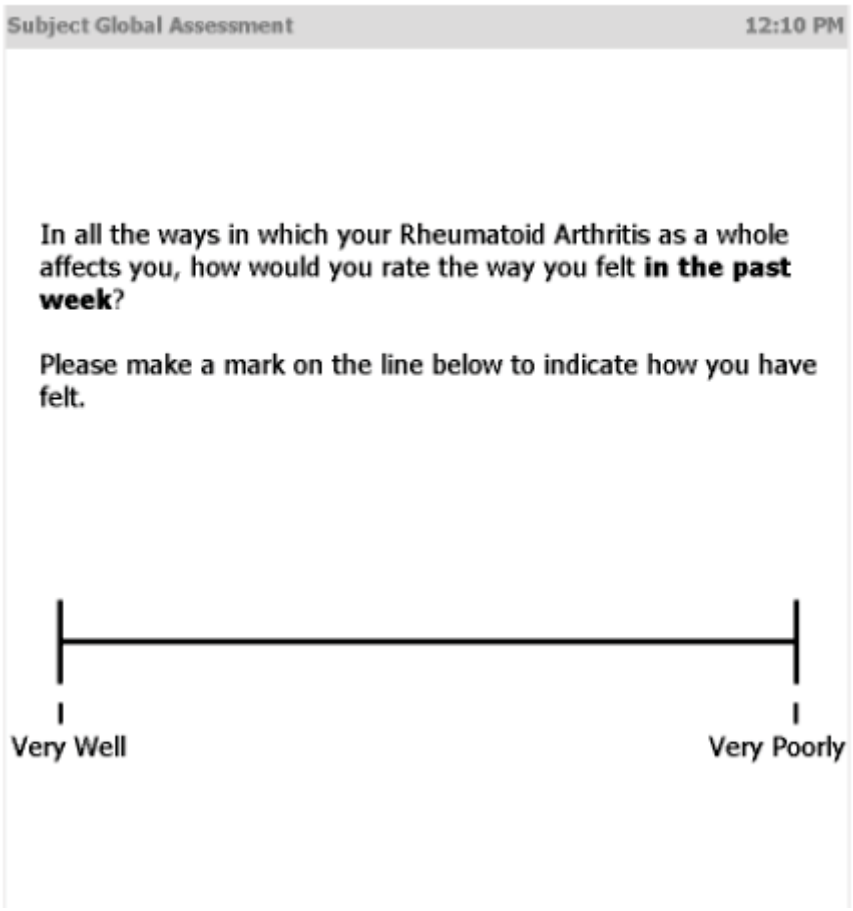
Sources:

Fries JF, Spitz PW, Young DY. The dimensions of health outcomes: the health assessment questionnaire, disability and pain scales. J Rheumatol 1982;9:789-93.

Fries JF, Spitz PW, Kraines G, Holman H. Measurement of patient outcome in arthritis. Arthritis Rheumatol 1980;23:137-45.

Ramey D, Raynauld JP, Fries JF. The health assessment questionnaire 1992: status and review. Arthritis Care Res 1992;5:199-29.

APPENDIX 24 SUBJECT GLOBAL ASSESSMENT OF DISEASE ACTIVITY (RA) (VAS)



APPENDIX 25 RHEUMATOID ARTHITIS MAGNETIC RESONANCE IMAGING SCORING SYSTEM (RAMRIS)

Score sheet for the OMERACT RAMRIS

using the EULAR-OMERACT RA MRI reference image atlas

WRIST JOINTS

MRI ID: _____ **Scorer's name:** _____

Centre where MRI was performed: _____

Image set (e.g. baseline or follow-up): _____

Sequences scored: _____

Scoring of synovitis

	Distal radio-ulnar joint	Radio-carpal joint	Intercarpal-CMCJ
Synovitis (0-3)			

Scoring of bone erosion and bone oedema

Bone erosion is scored 0-10, according to the proportion (in increments of 10%) of bone involved: 0: 0%, 1: 1-10%, 2: 11-20 %, ……., 10: 91-100%

Bone oedema is scored 0-3, according to the proportion (in increments of 33%) of bone involved: 0: 0%, 1: 1-33%, 2: 34-66 %, 3: 67-100%

For carpal bones, score the whole bone. For long bones, score from the articular surface (or its best estimated position if absent) to a depth of 1 cm.

	Base of metacarpal				
	1	2	3	4	5
Bone erosion (0-10)					
Bone oedema (0-3)					

	Trapezium	Trapezoid	Capitate	Hamate
Bone erosion (0-10)				
Bone oedema (0-3)				

	Scaphoid	Lunate	Triquetrum	Pisiform
Bone erosion (0-10)				
Bone oedema (0-3)				

	Distal radius	Distal ulna
Bone erosion (0-10)		
Bone oedema (0-3)		

Score sheet for the OMERACT RAMRIS

using the EULAR-OMERACT RA MRI reference image atlas

MCP JOINTS

MRI ID: _____Scorer's name: _____

Centre where MRI was performed: _____

Image set (e.g. baseline or follow-up): _____

Sequences scored: _____

Scoring of synovitis

	MCP-joints			
	2	**3**	**4**	**5**
Synovitis (0-3)				

Scoring of bone erosion and bone oedema

Bone erosion is scored 0-10, according to the proportion (in increments of 10%) of bone involved:
0: 0%, 1: 1-10%, 2: 11-20 %, ……., 10: 91-100%

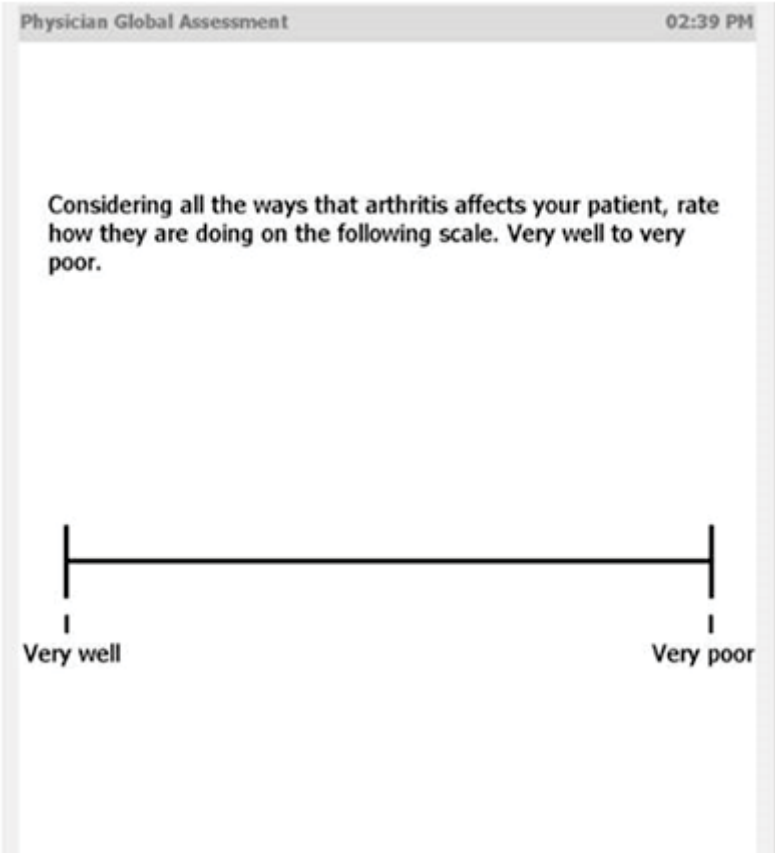
Bone oedema is scored 0-3, according to the proportion (in increments of 33%) of bone involved:
0: 0%, 1: 1-33%, 2: 34-66 %, 3: 67-100%

Score from the articular surface (or its best estimated position if absent) to a depth of 1 cm.

		MCP joints			
		2	**3**	**4**	**5**
Bone erosion 0-10	**Proximal**				
	Distal				
Bone oedema 0-3	**Proximal**				
	Distal				

APPENDIX 26 PHYSICIAN GLOBAL ASSESSMENT OF DISEASE ACTIVITY (RA) (VAS)

The investigator will rate the overall status of the subject in response to the following statement in eCOA device:



APPENDIX 27 ADME GENES

ADME Gene List (pharmaadme.org. accessed 09-Aug-2019)

Gene Symbol	Full Gene Name
Core ADME Gene List	
ABCB1	ATP-binding cassette, subfamily B (MDR/TAP), member 1
ABCC2	ATP-binding cassette, subfamily C (CFTR/MRP), member 2
ABCG2	ATP-binding cassette, subfamily G (WHITE), member 2
CYP1A1	cytochrome P450, family 1, subfamily A, polypeptide 1
CYP1A2	cytochrome P450, family 1, subfamily A, polypeptide 2
CYP2A6	cytochrome P450, family 2, subfamily A, polypeptide 6
CYP2B6	cytochrome P450, family 2, subfamily B, polypeptide 6
CYP2C19	cytochrome P450, family 2, subfamily C, polypeptide 19
CYP2C8	cytochrome P450, family 2, subfamily C, polypeptide 8
CYP2C9	cytochrome P450, family 2, subfamily C, polypeptide 9
CYP2D6	cytochrome P450, family 2, subfamily D, polypeptide 6
CYP2E1	cytochrome P450, family 2, subfamily E, polypeptide 1
CYP3A4	cytochrome P450, family 3, subfamily A, polypeptide 4
CYP3A5	cytochrome P450, family 3, subfamily A, polypeptide 5
DPYD	dihydropyrimidine dehydrogenase
GSTM1	glutathione S-transferase M1
GSTP1	glutathione S-transferase pi
GSTT1	glutathione S-transferase theta 1
NAT1	N-acetyltransferase 1 (arylamine N-acetyltransferase)
NAT2	N-acetyltransferase 2 (arylamine N-acetyltransferase)
SLC15A2	solute carrier family 15 (H+/peptide transporter), member 2
SLC22A1	solute carrier family 22 (organic cation transporter), member 1
SLC22A2	solute carrier family 22 (organic cation transporter), member 2
SLC22A6	solute carrier family 22 (organic anion transporter), member 6
SLCO1B1	solute carrier organic anion transporter family, member 1B1
SLCO1B3	solute carrier organic anion transporter family, member 1B3
SULT1A1	sulfotransferase family, cytosolic, 1 A, phenol-preferring, member 1

Gene Symbol	Full Gene Name
TPMT	thiopurine S-methyltransferase
UGT1A1	UDP glucuronosyltransferase 1 family, polypeptide A1
UGT2B15	UDP glucuronosyltransferase 2 family, polypeptide B15
UGT2B17	UDP glucuronosyltransferase 2 family, polypeptide B17
UGT2B7	UDP glucuronosyltransferase 2 family, polypeptide B7
Extended ADME Gene List	
ABCB8	ATP-binding cassette, subfamily B (MDR/TAP), member 8
ABCC12	ATP-binding cassette, subfamily C (CFTR/MRP), member 12
ABCC3	ATP-binding cassette, subfamily C (CFTR/MRP), member 3
ABCC4	ATP-binding cassette, subfamily C (CFTR/MRP), member 4
AHR	aryl hydrocarbon receptor
ALDH4A1	aldehyde dehydrogenase 4 family, member A1
ALDH5A1	aldehyde dehydrogenase 5 family, member A1
ALDH6A1	aldehyde dehydrogenase 6 family, member A1
CES1	carboxylesterase 1 (monocyte/macrophage serine esterase 1)
CES2	carboxylesterase 2 (intestine, liver)
CYP7A1	cytochrome P450, family 7, subfamily A, polypeptide 1
EPHX1	epoxide hydrolase 1, microsomal (xenobiotic)
FMO3	flavin containing monooxygenase 3
GSTA1	glutathione S-transferase A1
GSTA2	glutathione S-transferase A2
GSTA3	glutathione S-transferase A3
GSTA4	glutathione S-transferase A4
GSTA5	glutathione S-transferase A5
GSTM2	glutathione S-transferase M2 (muscle),glutathione S-transferase M4
GSTM3	glutathione S-transferase M3 (brain)
GSTM4	glutathione S-transferase M4
GSTO1	glutathione S-transferase omega 1,glutathione S-transferase omega 2
GSTO2	glutathione S-transferase omega 2
GSTT2	glutathione S-transferase theta 2
SLC10A1	solute carrier family 10 (sodium/bile acid cotransporter family), member 1
SLC15A1	solute carrier family 15 (oligopeptide transporter), member 1

Gene Symbol	Full Gene Name
SLC22A11	solute carrier family 22 (organic anion/cation transporter), member 11
SLC22A8	solute carrier family 22 (organic anion transporter), member 8
SLC7A5	solute carrier family 7 (cationic amino acid transporter, y+ system), member 5
SLCO1A2	solute carrier organic anion transporter family, member 1A2
SLCO2B1	solute carrier organic anion transporter family, member 2B1
SULT1A2	sulfotransferase family, cytosolic, 1 A, phenol-preferring, member 2
SULT1A3	sulfotransferase family, cytosolic, 1 A, phenol-preferring, member 3
SULT1B1	sulfotransferase family, cytosolic, 1B, member 1
UGT1A3	UDP glucuronosyltransferase 1 family, polypeptide A3
UGT1A6	UDP glucuronosyltransferase 1 family, polypeptide A6
UGT1A7	UDP glucuronosyltransferase 1 family, polypeptide A7
UGT1A8	UDP glucuronosyltransferase 1 family, polypeptide A8
UGT1A9	UDP glucuronosyltransferase 1 family, polypeptide A9
UGT2A1	UDP glucuronosyltransferase 2 family, polypeptide A1
UGT2B11	UDP glucuronosyltransferase 2 family, polypeptide B11
UGT2B28	UDP glucuronosyltransferase 2 family, polypeptide B28
UGT2B4	UDP glucuronosyltransferase 2 family, polypeptide B4
ABCA1	ATP-binding cassette, subfamily A (ABC1), member 1
ABCA4	ATP-binding cassette, subfamily A (ABC1), member 4
ABCB11	ATP-binding cassette, subfamily B (MDR/TAP), member 11
ABCB4	ATP-binding cassette, subfamily B (MDR/TAP), member 4
ABCB5	ATP-binding cassette, subfamily B (MDR/TAP), member 5
ABCB6	ATP-binding cassette, subfamily B (MDR/TAP), member 6
ABCB7	ATP-binding cassette, subfamily B (MDR/TAP), member 7
ABCC1	ATP-binding cassette, subfamily C (CFTR/MRP), member 1
ABCC10	ATP-binding cassette, subfamily C (CFTR/MRP), member 10
ABCC11	ATP-binding cassette, subfamily C (CFTR/MRP), member 11
ABCC5	ATP-binding cassette, subfamily C (CFTR/MRP), member 5
ABCC6	ATP-binding cassette, subfamily C (CFTR/MRP), member 6
ABCC8	ATP-binding cassette, subfamily C (CFTR/MRP), member 8
ABCC9	ATP-binding cassette, subfamily C (CFTR/MRP), member 9
ABCG1	ATP-binding cassette, subfamily G (WHITE), member 1
ADH1A	alcohol dehydrogenase 1 A (class I), alpha polypeptide

Gene Symbol	Full Gene Name
ADH1B	alcohol dehydrogenase IB (class I), beta polypeptide
ADH1C	alcohol dehydrogenase 1C (class I), gamma polypeptide
ADH4	alcohol dehydrogenase 4 (class II), pi polypeptide
ADH5	alcohol dehydrogenase 5 (class III), chi polypeptide,methionyl aminopeptidase 1
ADH6	alcohol dehydrogenase 6 (class V)
ADH7	alcohol dehydrogenase 7 (class IV), mu or sigma polypeptide
ALDH1A1	aldehyde dehydrogenase 1 family, member A1
ALDH1A2	aldehyde dehydrogenase 1 family, member A2
ALDH1A3	aldehyde dehydrogenase 1 family, member A3
ALDH1B1	aldehyde dehydrogenase 1 family, member B1
ALDH2	aldehyde dehydrogenase 2 family (mitochondrial)
ALDH3A1	aldehyde dehydrogenase 3 family, memberA1
ALDH3A2	aldehyde dehydrogenase 3 family, member A2
ALDH3B1	aldehyde dehydrogenase 3 family, member B1
ALDH3B2	aldehyde dehydrogenase 3 family, member B2
ALDH7A1	aldehyde dehydrogenase 7 family, member A1
ALDH8A1	aldehyde dehydrogenase 8 family, member A1
ALDH9A1	aldehyde dehydrogenase 9 family, member A1
AOX1	aldehyde oxidase 1
ARNT	aryl hydrocarbon receptor nuclear translocator
CBR1	carbonyl reductase 1
CBR3	carbonyl reductase 3
CDA	cytidine deaminase
CYB5R3	cytochrome b5 reductase 3
CYP11A1	cytochrome P450, family 11, subfamily A, polypeptide 1
CYP11B1	cytochrome P450, family 11, subfamily B, polypeptide 1
CYP11B2	cytochrome P450, family 11, subfamily B, polypeptide 2
CYP17A1	cytochrome P450, family 17, subfamily A, polypeptide 1
CYP1B1	cytochrome P450, family 1, subfamily B, polypeptide 1
CYP20A1	cytochrome P450, family 20, subfamily A, polypeptide 1
CYP20A1	cytochrome P450, family 20, subfamily A, polypeptide 1
CYP21A2	cytochrome P450, family 21, subfamily A, polypeptide 2
CYP24A1	cytochrome P450, family 24, subfamily A, polypeptide 1

Gene Symbol	Full Gene Name
CYP26A1	cytochrome P450, family 26, subfamily A, polypeptide 1
CYP27A1	cytochrome P450, family 27, subfamily A, polypeptide 1
CYP2A13	cytochrome P450, family 2, subfamily A, polypeptide 13
CYP2A7	cytochrome P450, family 2, subfamily A, polypeptide 7
CYP2C18	cytochrome P450, family 2, subfamily C, polypeptide 18
CYP2F1	cytochrome P450, family 2, subfamily F, polypeptide 1
CYP2J2	cytochrome P450, family 2, subfamily J, polypeptide 2
CYP39A1	cytochrome P450, family 39, subfamily A, polypeptide 1
CYP3A43	cytochrome P450, family 3, subfamily A, polypeptide 43
CYP3A7	cytochrome P450, family 3, subfamily A, polypeptide 7
CYP4B1	cytochrome P450, family 4, subfamily B, polypeptide 1
CYP4F11	cytochrome P450, family 4, subfamily F, polypeptide 11
CYP51A1	cytochrome P450, family 51, subfamily A, polypeptide 1
EPHX2	epoxide hydrolase 2, cytoplasmic
FMO1	flavin containing monooxygenase 1
FMO2	flavin containing monooxygenase 2
FMO4	flavin containing monooxygenase 4
FMO5	flavin containing monooxygenase 5
GPX2	glutathione peroxidase 2 (gastrointestinal)
GPX3	glutathione peroxidase 3 (plasma)
GPX7	glutathione peroxidase 7
GSR	glutathione reductase
GSTK1	glutathione S-transferase kappa 1
GSTM5	glutathione S-transferase M5
GSTZ1	glutathione transferase zeta 1 (maleylacetoacetate isomerase)
NNMT	nicotinamide N-methyltransferase
NR1I2	nuclear receptor subfamily 1, group I, member 2
NR1I3	nuclear receptor subfamily 1, group I, member 3
PNMT	phenylethanolamine N-methyltransferase
PON1	paraoxonase 1
PON2	paraoxonase 2
PON3	paraoxonase 3
POR	P450 (cytochrome) oxidoreductase

Gene Symbol	Full Gene Name
PPARD	peroxisome proliferative activated receptor, delta
PPARG	peroxisome proliferative activated receptor, gamma
RXRA	retinoid X receptor, alpha
SLC10A2	solute carrier family 10 (sodium/bile acid cotransporter family), member 2
SLC13A1	solute carrier family 13 (sodium/sulfate symporters), member 1
SLC13A2	solute carrier family 13 (sodium-dependent dicarboxylate transporter), member 2
SLC13A3	solute carrier family 13 (sodium-dependent dicarboxylate transporter), member 3
SLC16A1	solute carrier family 16 (monocarboxylic acid Transporter), member 1
SLC19A1	solute carrier family 19 (folate transporter), member 1
SLC22A10	solute carrier family 22 (organic anion/cation transporter), member 10
SLC22A12	solute carrier family 22 (organic anion/cation transporter), member 12
SLC22A13	solute carrier family 22 (organic cation transporter), member 13
SLC22A14	solute carrier family 22 (organic cation transporter), member 14
SLC22A15	solute carrier family 22 (organic cation transporter), member 15
SLC22A16	solute carrier family 22 (organic cation transporter), member 16
SLC22A17	solute carrier family 22 (organic cation transporter), member 17
SLC22A18	solute carrier family 22 (organic cation transporter), member 18
SLC22A18AS	solute carrier family 22 (organic cation transporter), member 18 antisense
SLC22A3	solute carrier family 22 (extraneuronal monoamine transporter), member 3
SLC22A4	solute carrier family 22 (organic cation transporter), member 4
SLC22A5	solute carrier family 22 (organic cation transporter), member 5
SLC22A7	solute carrier family 22 (organic anion transporter), member 7
SLC22A9	solute carrier family 22 (organic anion/cation transporter), member 9
SLC27A1	solute carrier family 27 (fatty acid transporter), member 1
SLC28A1	solute carrier family 28 (sodium-coupled nucleoside transporter), member 1
SLC28A2	solute carrier family 28 (sodium-coupled nucleoside transporter), member 2
SLC28A3	solute carrier family 28 (sodium-coupled nucleoside transporter), member 3
SLC29A1	solute carrier family 29 (nucleoside Transporter), member 1
SLC29A2	solute carrier family 29 (nucleoside Transporter), member 2
SLC2A4	solute carrier family 2 (facilitated glucose transporter), member 4
SLC2A5	solute carrier family 2 (facilitated glucose/fructose transporter), member 5
SLC5A6	solute carrier family 5 (sodium-dependent vitamin transporter)
SLC6A6	solute carrier family 6 (neurotransmitter transporter, taurine), member 6

Gene Symbol	Full Gene Name
SLC7A8	solute carrier family 7 (cationic amino acid transporter, y+ system), member 8
SLCO1C1	solute carrier organic anion transporter family, member 1C1
SLCO2A1	solute carrier organic anion transporter family, member 2A1
SLCO3A1	solute carrier organic anion transporter family, member 3A1
SLCO4A1	solute carrier organic anion transporter family, member 4A1
SLCO4C1	solute carrier organic anion transporter family, member 4C1
SLCO5A1	solute carrier organic anion transporter family, member 5A1
SLCO6A1	solute carrier organic anion transporter family, member 6A1
SULT1C1	sulfotransferase family, cytosolic, 1C, member 1
SULT1C2	sulfotransferase family, cytosolic, 1C, member 2
SULT1E1	sulfotransferase family 1E, estrogen-preferring, member 1
SULT2A1	sulfotransferase family, cytosolic, 2 A, DHEA preferring, member 1
SULT2B1	sulfotransferase family, cytosolic, 2B, member 1
TAP1	transporter 1, ATP-binding cassette, subfamily B (MDR/TAP)
UGT1A10	UDP glucuronosyltransferase 1 family, polypeptide A10
UGT1A4	UDP glucuronosyltransferase 1 family, polypeptide A4
UGT1A5	UDP glucuronosyltransferase 1 family, polypeptide A5
UGT2B10	UDP glucuronosyltransferase 2 family, polypeptide B10
ABCC13	ATP-binding cassette, subfamily C (CFTR/MRP), member 13
ARSA	arylsulfatase A
CAT	catalase
CHST8	carbohydrate (N-acetylgalactosamine 4-0) sulfotransferase 8
CYP19A1	cytochrome P450, family 19, subfamily A, polypeptide 1
CYP26C1	cytochrome P450, family 26, subfamily C, polypeptide 1
CYP27B1	cytochrome P450, family 27, subfamily B, polypeptide 1
CYP2R1	cytochrome P450, family 2, subfamily R, polypeptide 1
CYP2S1	cytochrome P450, family 2, subfamily S, polypeptide 1
CYP46A1	cytochrome P450, family 46, subfamily A, polypeptide 1
CYP4A11	cytochrome P450, family 4, subfamily A, polypeptide 11
CYP4F12	cytochrome P450, family 4, subfamily F, polypeptide 12
CYP4F2	cytochrome P450, family 4, subfamily F, polypeptide 2
CYP4F3	cytochrome P450, family 4, subfamily F, polypeptide 3
CYP4F8	cytochrome P450, family 4, subfamily F, polypeptide 8

Gene Symbol	Full Gene Name
CYP4Z1	cytochrome P450, family 4, subfamily Z, polypeptide 1
CYP7B1	cytochrome P450, family 7, subfamily B, polypeptide 1
CYP8B1	cytochrome P450, family 8, subfamily B, polypeptide 1
DHRS13	similar to dehydrogenase/reductase (SDR) family) member 13
DHRS2	dehydrogenase/reductase (SDR family) member 2
GPX1	glutathione peroxidase 1
GPX4	glutathione peroxidase 4 (phospholipid hydroperoxidase)
GPX5	glutathione peroxidase 5 (epididymal androgen-related protein)
GPX6	glutathione peroxidase 6 (olfactory)
GSS	glutathione synthetase
GSTCD	glutathione S-transferase, C-terminal domain containing
HNF4A	hepatocyte nuclear factor 4, alpha
HNMT	histamine N-methyltransferase
HSD11B1	hydroxysteroid (17-beta) dehydrogenase 11
HSD17B11	hydroxysteroid (17-beta) dehydrogenase 11
HSD17B14	hydroxysteroid (17-beta) dehydrogenase 14
LOC731356	SDR family) member 4 like 2
MGST1	microsomal glutathione S-transferase 1
MGST2	microsomal glutathione S-transferase 2
MGST3	microsomal glutathione S-transferase 3
MPO	myeloperoxidase
NOS1	nitric oxide synthase 1 (neuronal)
NOS2A	nitric oxide synthase 2 A (inducible, hepatocytes)
NOS3	nitric oxide synthase 3 (endothelial cell)
PPARA	peroxisome proliferator-activated receptor alpha
SERPINA7	serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 7
SLC7A7	solute carrier family 7 (cationic amino acid transporter, y+ system), member 7
SOD1	superoxide dismutase 1, soluble (amyotrophic lateral sclerosis 1 (adult))
SOD2	superoxide dismutase 2, mitochondrial
SOD3	superoxide dismutase 3, extracellular precursor
SULF1	sulfatase 1
SULT4A1	sulfotransferase family 4 A, member 1
TAP2	transporter 2, ATP-binding cassette, subfamily B (MDR/TAP)

Gene Symbol	Full Gene Name
UGT8	UDP glycosyltransferase 8 (UDP-galactose ceramide galactosyltransferase)
XDH	xanthine dehydrogenase
ADHFE1	alcohol dehydrogenase, iron containing, 1
CHST1	carbohydrate (keratan sulfate Gal-6) sulfotransferase 1
CHST10	carbohydrate sulfotransferase 10
CHST11	carbohydrate (chondroitin 4) sulfotransferase 11
CHST12	carbohydrate (chondroitin 4) sulfotransferase 12
CHST13	carbohydrate (chondroitin 4) sulfotransferase 13
CHST2	carbohydrate (N-acetylglucosamine-6-O) sulfotransferase 2
CHST3	carbohydrate (chondroitin 6) sulfotransferase 3
CHST4	carbohydrate (N-acetylglucosamine 6-O) sulfotransferase 4
CHST5	carbohydrate (N-acetylglucosamine 6-O) sulfotransferase 5
CHST6	carbohydrate (N-acetylglucosamine 6-O) sulfotransferase 6
CHST7	carbohydrate (N-acetylglucosamine 6-O) sulfotransferase 7
CHST9	carbohydrate (N-acetylgalactosamine 4-0) sulfotransferase 9
CYP2D7P1	cytochrome P450, family 2, subfamily D, polypeptide 7 pseudogene 1
DDO	D-aspartate oxidase
DHRS1	dehydrogenase/reductase (SDR family) member 1
DHRS12	dehydrogenase/reductase (SDR family) member 12
DHRS3	dehydrogenase/reductase (SDR family) member 3
DHRS4	dehydrogenase/reductase (SDR family) member 4
DHRS4L1	dehydrogenase/reductase (SDR family) member 4 like 1
DHRS4L2	dehydrogenase/reductase (SDR family) member 4 like 2
DHRS7	dehydrogenase/reductase (SDR family) member 7
DHRS7B	dehydrogenase/reductase (SDR family) member 7B
DHRS7C	dehydrogenase/reductase (SDR family) member 7C
DHRS9	dehydrogenase/reductase (SDR family) member 9
DHRSX	dehydrogenase/reductase (SDR family) X-linked
DPEP1	dipeptidase 1 (renal)
FMO6P	flavin containing monooxygenase 6
HAGH	hydroxyacylglutathione hydrolase
IAPP	islet amyloid polypeptide
KCNJ11	potassium inwardly-rectifying channel, subfamily J, member 11

Gene Symbol	Full Gene Name
LOC728667	SDR family) member 2 isoform 1
LOC731931	SDR family) member 2 isoform 1
MAT1A	methionine adenosyltransferase I, alpha
METAP1	methionyl aminopeptidase 1
PDE3A	phosphodiesterase 3A, cGMP-inhibited
PDE3B	phosphodiesterase 3B, cGMP-inhibited
PLGLB1	plasminogen-like B1
ATP7A	ATPase, Cu++ transporting, alpha polypeptide (Menkes syndrome)
ATP7B	ATPase, Cu++ transporting, beta polypeptide
CFTR	cystic fibrosis transmembrane conductance regulator