Official Title of Study:

A Phase 2 Multicenter, Randomized, Double-Blinded, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of CC-99677 in Subjects With Active Ankylosing Spondylitis

NCT Number: NCT04947579

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A PHASE 2 MULTICENTER, RANDOMIZED, DOUBLE-BLINDED, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY TO EVALUATE THE EFFICACY AND SAFETY OF CC-99677 IN SUBJECTS WITH ACTIVE ANKYLOSING SPONDYLITIS

PROTOCOL NUMBER:	**CC-99677-AS-001**
COMPOUND NUMBER:	**CC-99677 (BMS-986371)**
DATE FINAL:	**14 FEB 2020**
DATE AMENDMENT 1.0 FINAL	**06 NOV 2020**
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SPONSOR NAME/ ADDRESS:	Celgene Corporation 86 Morris Avenue Summit, NJ 07901

MEDICAL MONITOR / EMERGENCY CONTACT INFORMATION

Contact Information: Medical Monitor
Name: [redacted]
Title: Medical Director
Address: [redacted]
Phone: [redacted]
E-mail: [redacted]

Note: The back-up 24-hour global emergency contact call center should only be used if you are not able to reach the Clinical Research Physician(s) or Medical Monitor or designee for emergency calls.

Back-up 24-hour Global Emergency Contact Call Center: [redacted] (global reachable number)

[redacted] provides a list of country-specific contact numbers. Countries not listed here need to dial the global reachable number as indicated above. There may be restrictions when dialling a country-specific number from a mobile phone.

CELGENE THERAPEUTIC AREA HEAD SIGNATURE PAGE

SITE PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Signature of Site Principal Investigator	**dd mmm yyyy**
Printed Name of Site Principal Investigator **Institution Name:**_____ By my signature, I agree to personally supervise the conduct of this study at my study site and to ensure its conduct is in compliance with the protocol, informed consent, Institutional Review Board (IRB)/Ethics Committee (EC) procedures, instructions from Celgene representatives, the Declaration of Helsinki, International Council for Harmonisation (ICH) Good Clinical Practices Guidelines, and local regulations governing the conduct of clinical studies.	

OVERALL RATIONALE FOR PROTOCOL AMENDMENT 3.0:

The primary purpose of this protocol amendment is to provide updated results from drug-drug interaction studies resulting in changes to permitted and prohibited concomitant medications, including allowance of hormonal contraceptives.

Additional revisions, including to sections of the Protocol Summary, have been made to align the protocol with respect to these changes.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 3.0		
Section Number & Title	**Description of Change**	**Brief Rationale**
Medical Monitor/ Emergency Contact Information	• Updated contact information.	• Updated due to administrative changes.
Section 1.4: Clinical Experience	• Results of drug-drug interaction studies have been included.	• To provide context for the permission of the following concomitant medications: metformin, statins, and oral contraceptives. • To provide context for the continued prohibition of moderate to strong cytochrome P450 (CYP) 3A4/5 and P-glycoprotein (P-gp) inhibitors and exclusion of moderate to strong CYP3A4/5 and P-gp inducers.
Section 2: Study Objectives and Endpoints	• Removed tender joints from the exploratory endpoint of peripheral arthritis.	• For alignment with established guidelines for evaluating peripheral joint disease in ankylosing spondylitis (AS).
Section 2.1: Study Endpoints	Exploratory pharmacokinetic (PK) endpoints modified as follows: • AUC(TAU) for CC-99677 and CC-0782951 included as PK parameters. • MR_Cmax, MR_AUC(TAU), and MR_AUC(0-T) for CC-0782951 included as PK parameters.	• PK parameters modified to accurately reflect the those that can be calculated or reported based on the PK sampling, observed PK properties of CC-99677 and CC-0782951, and Bristol-Myers Squibb Company (BMS) standards for reporting PK parameters. • CL/F modified to CLT/F to correct a typographical error.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 3.0		
Section Number & Title	**Description of Change**	**Brief Rationale**
	• $AUC_{(0-\infty)}$, $t_{1/2z}$, and V_z/F removed as PK parameters. • C_{trough} removed as a PK parameter for sparse PK collection. • CL/F corrected to CLT/F.	
Section 3.1.5: Primary Analysis	• Clarified that following primary analysis of both the biologic-naive main study and the biologic failure substudy, the remainder of the Long-term Extension Period will be performed in a Sponsor-unblinded fashion.	• No need to continue Sponsor blinding following primary analysis.
Section 4.2: Inclusion Criteria for the Biologic-naive Main Study	• Inclusion of hormonal contraceptives as an acceptable method of contraception. • Removal of requirement to have statins dose modified.	• Oral contraceptives are now permitted following oral contraceptive drug-drug interaction (DDI) study. • Statins are now permitted following results from completed DDI studies.
Section 4.3: Exclusion Criteria for Biologic-naive Main Study	• Revision to exclusion criterion 8 to add Janus kinase (JAK) inhibitors to list of prohibited medications. • Revised exclusion criterion 14 to include use of any medications known to be either a moderate or strong inhibitor or a moderate or strong inducer of CYP3A4/5. • Revised exclusion criterion 15 to include use of any medication known to be either a moderate or strong inhibitor or a moderate or strong inducer of P-gp.	• JAK inhibitors are now approved for treatment of AS and therefore are included as a prohibited medication. • Added strong inducers of CYP3A4/5 due to availability of DDI data. • Added strong inducers of P-gp to exclusion criterion due to availability of DDI data.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 3.0		
Section Number & Title	**Description of Change**	**Brief Rationale**
	• Separated use of any medication known to be either a moderate or strong P-gp or a strong breast cancer resistance protein inhibitor into 2 standalone criteria (exclusion criteria 16 and 17). • Clarified exclusion criterion 22 to indicate that hemoglobin A1C (HbA1c) should only be drawn in subjects with a known history of diabetes.	• Revised for ease of understanding. • To avoid the unnecessary or inappropriate collection of HbA1c in subjects without a known history of diabetes.
Section 7.2.2: Dose Modifications/ Interruptions	• Clarified that dose interruptions are allowed in the context of an adverse event. • Added that temporary interruption of IP is allowed in the context of clinical suspicion for SARS-CoV-2 or a positive diagnostic test for SARS-CoV-2.	• Updated to allow dose interruptions in the context of adverse events including suspicion for SARS-CoV-2 or a positive diagnostic test for SARS-CoV-2.
Section 8.1: Permitted Concomitant Medications and Procedures	• Removal of statement that statin dose will require adjustment during the study.	• Dose adjustment and associated monitoring of statins are no longer required following rosuvastatin drug-drug interaction studies.
Section 8.2: Permitted Medications That Require Careful Monitoring	• Updated section to reflect results of completed DDI studies involving CC-99677. • Removal of mention of medications that are substrates of CYP3A4/5 (eg, midazolam).	• A clinically significant interaction is unlikely with drugs that are substrates of BCRP, P-gp, OATP1B1, OATP1B3 and OCT1 transporters AND that have a wide therapeutic index. • CYP3A4/5 substrates no longer require careful monitoring following the drug-drug interaction study with midazolam.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 3.0		
Section Number & Title	**Description of Change**	**Brief Rationale**
	• Removal of mention of statins and metformin.	• Routine monitoring of statins and metformin are now permitted based on drug-drug interaction studies.
Section 9.0: Statistical Considerations	• Clarified that following primary analysis of both the biologic-naive main study and the biologic failure substudy, the remainder of the Long-term Extension Period will be performed in a Sponsor-unblinded fashion.	• No need to continue Sponsor blinding following primary analysis.
Section 9.2: Study Population Definitions	• PK population definition modified and PK Evaluable population definition added.	• To accurately capture the BMS process for reporting listings, summaries, and statistical analyses of PK data.
Section 9.9.3: Pharmacokinetic Analyses	• PK parameters modified.	• PK parameters modified to accurately reflect those that can be calculated or reported based on PK sampling, observed PK properties of CC-99677 and CC-0782951, and BMS standards for reporting PK parameters.
Appendix C: Examples of Drugs That Are Excluded Based on Potential Drug-Drug Interactions	• Expansion of the list of moderate or strong inhibitors and moderate or strong inducers of CYP3A4/5 (Table 7). • Expansion of the list of moderate or strong inhibitors or moderate or strong inducers of P-gp (Table 8).	• To provide clarity for investigators as to which medications should be avoided.
Appendix D: Examples of Drugs That Are Substrates for Selected	• Combined Tables 10 and 11. • Removed mention of statins and metformin.	• Combined for ease of readability. • Statins and metformin are now permitted following DDI studies.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 3.0		
Section Number & Title	**Description of Change**	**Brief Rationale**
Transporters and Should Be Used with Caution	• Removed Table 12.	• CYP3A4/5 substrates now permitted following DDI studies.
All	• Minor formatting and typographical corrections.	• Minor, therefore, these have not been summarized.

PROTOCOL SUMMARY

Study Title

A Phase 2 Multicenter, Randomized, Double-Blinded, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of CC-99677 in Subjects with Active Ankylosing Spondylitis

Indication

Ankylosing Spondylitis (AS)

Objectives

Primary Objective

To evaluate the dose dependent efficacy of oral CC-99677 (also known as BMS-986371), administered every day (QD) compared to placebo, as determined by the attainment of the Assessment in SpondyloArthritis International Society Response Criteria (ASAS20) after 12 weeks of treatment, in subjects with radiologically confirmed AS and inadequate response to nonsteroidal anti-inflammatory drugs (NSAIDs).

Secondary Objectives

To evaluate the effects of oral CC-99677, administered QD, compared to placebo, after 12 weeks of treatment in subjects with AS, on:

- The signs and symptoms of AS, as assessed by attainment of Assessment in SpondyloArthritis International Society 40% Response Criteria (ASAS40), a composite measure of clinical improvement in axial spondyloarthritis, Ankylosing Spondylitis Disease Activity Score (ASDAS) with C-reactive protein (CRP) as the acute-phase reactant (ASDAS-CRP), and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)
- Measures of physical function, as assessed by Bath Ankylosing Spondylitis Functional Index (BASFI)
- Spinal and sacroiliac joint inflammation as measured by Spondyloarthritis Research Consortium of Canada (SPARCC) magnetic resonance imaging (MRI) score of sacroiliac joints and spine
- Percent change from baseline in high-sensitivity C-reactive protein (hsCRP)
- Safety and tolerability

Exploratory Objectives

To evaluate the effects of oral CC-99677, administered QD in subjects with AS, on:

- The signs and symptoms of AS, as assessed by the attainment of ASAS20 and ASAS40 (excluding Week 12)
- The signs and symptoms of AS, as assessed by ASDAS-CRP (excluding Week 12), achievement of a clinically important improvement (ASDAS-CRP $\geq$ 1.1), a major improvement (ASDAS-CRP $\geq$ 2.0) and attainment of inactive disease (ASDAS-CRP $<$ 1.3)
- The signs and symptoms of AS, as assessed by BASDAI (excluding Week 12)
- Measures of physical function, as assessed by BASFI (excluding Week 12)

- Spinal mobility, as assessed by Bath Ankylosing Spondylitis Metrology Index-Linear (BASMI-Linear), Chest expansion, and Occiput to wall distance at Weeks 4 through Week 64
- High-sensitivity C-reactive protein (hsCRP) level at Weeks 2 through 64
- Enthesitis as assessed by Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) at Weeks 4 through 64
- Peripheral arthritis, as determined by swollen joint count at Weeks 4 through 64
- Quality of life, as assessed by Ankylosing Spondylitis Quality of Life (ASQoL), Short Form-36 (SF-36), and ASAS Health Index (ASAS HI) at Weeks 12, 24 and 64
- Pharmacokinetics (PK) of CC-99677 at Weeks 4 through 12
- Target Engagement of CC-99677 at Weeks 4 through 12
- Relationship between CC-99677 exposure and serum pharmacodynamic (PD) biomarkers at Weeks 4 through 64
- Whole blood messenger ribonucleic acid (mRNA) gene expression profiling in relationship to treatment response at Weeks 4 through 64
- Relationship between CC-99677 exposure and osteoclast precursors with ex vivo osteoclastogenesis at Week 12
- Bone turnover markers at Weeks 12, 24 and 64
- Pharmacogenetic (PG) markers and their relationship to treatment response at Baseline Visit
- Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) serology (anti-SARS-CoV-2) total or immunoglobulin-G [IgG], Immunoglobulin-M [IgM]) at Week 64

Biologic-Naïve Main Study Design

This is a Phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group efficacy and safety study. This study is designed to assess response to CC-99677 treatment by measuring signs and symptoms of AS, objective measures of disease activity, quality of life assessments, safety, and tolerability over a 12-week double-blind period. This study will also assess the efficacy and long-term safety of CC-99677 in a 52-Week Long-term Extension Period.

In the biologic-naïve main study, approximately 147 adult male and female subjects with a diagnosis of AS (Sieper, 2009) fulfilling the modified New York criteria for AS (van der Linden, 1984) (APPENDIX B) and no prior exposure to biologic treatments for AS will be randomized with equal allocation to receive either CC-99677 150 mg PO QD, CC-99677 60 mg PO QD, or matching placebo for a duration of 12 weeks. Randomization to treatment groups will be stratified by Screening hsCRP concentration (≤ upper limit of normal/ > upper limit of normal of the reference lab).

At Week 12 subjects originally randomized to receive placebo will be re-randomized 1:1 to blinded CC-99677 (150 mg or 60 mg PO QD) through Week 64. Subjects originally randomized to CC-99677 (150 mg or 60 mg PO QD) will continue to receive the same dose through Week 64. At Week 16 subjects who do not achieve an ASAS20 will be discontinued from CC-99677 and the study.

An interim analysis (IA) will be conducted when approximately 30 subjects in the biologic-naïve main study complete 12 weeks of treatment. A Steering Committee comprised of unblinded Bristol Myers Squibb (BMS) committee members independent of the Study Team and external AS expert(s) will review the data from the IA and will convey one of the following decisions to the blinded study team:

- Continue the study without modification
- Terminate the study for futility
- Discontinue a treatment group based on preliminary assessment of dose-dependent risk-benefit
- Add an additional dose cohort (dose not to exceed 150 mg)

If the Steering Committee determines that an additional dose cohort is needed, then the additional dose cohort will be initiated as part of the biologic-naïve main study, only, as described in Section 3.1.2.

The study team responsible for managing the study will remain blinded. Details and timing of the interim analysis will be described in a Steering Committee charter. The Steering Committee charter will further describe any potential future interim analyses.

The primary analysis will be performed when all subjects in the biologic-naïve cohort have completed 12 weeks of treatment or have discontinued early, and all expected data are collected. Following the database lock, the remainder of the Long-term Extension Period will be conducted in a Sponsor-unblinded fashion. All subjects and site personnel will remain blinded throughout the duration of the trial.

The exposure-response analyses, along with observed efficacy and safety results from the primary analysis may support the selection of a single efficacious dose of CC-99677 or dropping a dose due to insufficient benefit-risk. In either of these events, subjects in the Long-term Extension may be reallocated to the selected CC-99677 dose(s) through Week 64.

Assessments for efficacy, safety, tolerability, quality of life, PK, PD and PG will be performed at specified timepoints as outlined in Table of Events, Table 3 and Table 4. Subjects who discontinue prematurely from the study at any time will be required to enter the 4-week Post-treatment Observational Follow-up Period.

The study will be conducted in compliance with the International Council for Harmonisation (ICH) Technical Requirements for Registration of Pharmaceuticals for Human Use/Good Clinical Practice (GCP) and applicable regulatory requirements.

Biologic-failure Substudy

Approximately 50 subjects with AS who have failed not more than 1 biologic agent taken for AS due to inadequate efficacy response to an approved dose for at least 12 weeks and/or unacceptable safety/tolerability of a biologic agent (in the opinion of the Investigator) will be recruited into a substudy, conducted concurrently with the biologic-naïve main study. Subjects will be randomized 2:2:1 to receive treatment with CC-99677 150 mg PO QD, CC-99677 60 mg PO QD, or matching placebo respectively and will enter into 12-Week Placebo-controlled period. At Week

12 subjects originally randomized to receive placebo will be re-randomized 1:1 to blinded CC-99677 (150 mg or 60 mg PO QD) through Week 64. Subjects originally randomized to CC-99677 (150 mg or 60 mg PO QD) will continue to receive the same dose through Week 64.

Internal Safety Monitoring Team

In addition to daily safety monitoring conducted by Investigators and individual study personnel, cumulative and interval blinded adverse events (AEs), serious adverse events (SAEs), discontinuations and laboratory findings will be reviewed by a Safety Management Team (SMT) internally at Celgene. The SMT is comprised of lead representatives from multiple Celgene functions. The scope, conduct, processes, and accountabilities of the SMT are specified by Celgene Standard Operating Procedure (SOP).

Independent External Data Monitoring Committee

Although the Celgene study staff will monitor safety on an ongoing basis throughout the study, formal unblinded safety and efficacy assessments of the study data will be performed by an independent external Data Monitoring Committee (DMC). The DMC will include physician experts with experience in treating subjects with AS and a statistician, all of whom are not otherwise involved in the study conduct and in whom there is no identified conflict of interest. The external DMC may make a recommendation to stop the study at any time based on an assessment of the overall Benefit/Risk of clinical data. Operational details for the DMC will be detailed in a separate DMC charter.

Steering Committee

A Steering Committee (SC), comprised of both unblinded BMS committee members independent of the study team and external AS expert(s) will review the data from the IA and will convey decisions to the blinded study team. The SC may oversee additional IAs. Operational details for the SC will be detailed in a separate SC charter.

Study Population

Adult male and female subjects ≥ 18 years of age with a diagnosis of AS fulfilling the modified New York criteria for AS (van der Linden, 1984) (APPENDIX B), symptoms of active disease based on a BASDAI score ≥ 4, and a Total Back Pain Numerical Rating Scales (NRS) score ≥ 4 will be recruited. Subjects can receive NSAID therapies, or low-dose corticosteroids, provided they are in accordance with eligibility criteria and permitted concomitant medications. Subjects in the biologic-naïve main study must not have had prior treatment with a biologic therapy (eg, tumor necrosis factor (TNF) blocker or anti-IL-17 agent) for AS. Subjects with AS who have failed not more than one biologic agent taken for AS due to inadequate response to an approved dose for at least 12 weeks and/or unacceptable safety/tolerability with at least one dose of a biologic agent (in the opinion of the Investigator) will be recruited into a separate biologic-failure substudy.

Length of Study

The study consists of multiple periods:

- Screening Period (up to 6 weeks)
- Double-blind, Placebo-controlled Treatment Period (12 weeks)
- Long-term Extension Period (52 Weeks)
- Post-treatment Observational Follow-Up Period (4 weeks)

Subjects will remain in the study for a maximum of 74 weeks and will be requested to attend a total of 16 study visits (from Screening Visit to Observational Follow-up Visit). Subjects who discontinue treatment early (after randomization) are required to have an Early Termination Visit and will be requested to enter the Observational Follow-up Period.

The End of Trial is defined as either the date of the last visit of the last subject to complete the post-treatment follow-up, or the date of receipt of the last data point from the last subject that is required for primary, secondary and/or exploratory analysis, as prespecified in the protocol, whichever is the later date.

Study Treatments

Subjects will be randomized (1:1:1 in the biologic-naïve main study, 2:2:1 in the biologic-failure substudy) to one of the following 3 treatment groups at Baseline (Day 1; Week 0):

1) CC-99677 150 mg PO QD
2) CC-99677 60 mg PO QD
3) Placebo PO QD

If the additional dose cohort is initiated (Section 3.1.4) in the biologic-naïve main study, then subjects will be randomized in a 5:1 ratio to receive either CC-99677 (additional dose) or matching placebo at Baseline (Day 1, Week 0):

4) Additional dose cohort (dose not to exceed 150 mg), (Section 3.1.2)
5) Placebo PO QD

Randomization and treatment assignment will be managed by an Interactive Web Response System (IWRS).

Overview of Key Efficacy Assessments

- ASAS20
- ASAS40
- ASDAS-CRP
- BASDAI
- BASFI-Linear
- SPARCC MRI assessments of the spine and sacroiliac joints

Overview of Key Pharmacodynamic Assessments

- hsCRP
- Serum levels of other proinflammatory cytokines relevant to AS pathophysiology and disease evolution may include, but are not limited to, TNF-α, IL-6, IL-17A, and IL-23
- mRNA expression will be analyzed. This is set to explore the relationship between clinical response and change in gene expression with CC-99677

- Markers of bone turnover (including but not limited to serum carboxy terminal cross-linked telopeptide of type 1 collagen [CTX] and procollagen Type I N-terminal pro-peptide [P1NP])
- Mitogen-activated protein kinase-activated protein kinase 2 (MK2) target engagement in peripheral blood mononuclear cells (PBMCs)
- Osteoclast precursors in PBMCs

Overview of Key Safety Assessments

- Adverse Events (type, frequency, severity, seriousness, and relationship of AEs to Investigational Product [IP])
- Number of subjects who discontinue IP due to any AE
- Clinically significant changes in laboratory findings
- Physical examination, vital signs, and weight
- Pregnancy testing and pregnancy education
- 12-lead electrocardiogram

Statistical Methods

With 147 total subjects and an equal allocation ratio, the study will randomize 49 subjects to each treatment group. This sample size will provide 80% power, calculated by nQuery Advisor version 7 and without accounting for multiplicity, to detect a treatment difference of 25% in ASAS20 response rate at Week 12 between either active treatment group and placebo, using a chi-square test at a two-sided significance level of 0.10, and assuming the response rates of 59% for both CC-99677 treatment groups and 34% for placebo (the latter based on historical studies), with dropouts considered as nonresponders in these assumed response rates. Applying the Hochberg procedure to adjust for the multiplicity of the comparisons of two active treatment groups with placebo, the study will provide 81% power to achieve statistical significance at the two-sided significance level of 0.10 for at least 1 treatment group, with the same response rate assumptions stated above.

An additional 50 subjects will be enrolled in the biologic-failure substudy. Primary analysis of efficacy of subjects enrolled in the biologic-failure substudy will be separate from that of the biologic-naive main study although an exploratory pooled analysis of efficacy will also be performed.

The full analysis set (FAS) will be the primary population for the efficacy analysis. The FAS will consist of all subjects who are randomized and receive at least 1 dose of IP.

Binary endpoints will be analyzed by the Cochran-Mantel-Haenszel (CMH) test stratified by the randomization stratification factor hsCRP concentration (≤ upper limit of normal/ > upper limit of normal) obtained at Screening Visit 1. The primary missing data handling approach for binary endpoints will be nonresponder imputation (NRI), by which a subject will be considered a nonresponder at a given time point if the subject does not have sufficient data (including the baseline data for the endpoints assessing the change from baseline) assessed within the analysis window of the time point for response determination. The Hochberg procedure will be applied to the primary efficacy endpoint analysis to adjust for multiplicity.

The continuous endpoints will be analyzed by an adaptive approach (Mehrotra, 2012) that uses either a longitudinal data analysis (LDA) model (Liu, 2009) (in the absence of severe departures from normality) or robust regression model/nonparametric methods (in the presence of severe departures from normality). The LDA model assumes a common mean across treatment groups at baseline and a different mean for each treatment group at each of the postbaseline time points. In this model, the response vector consists of the baseline and postbaseline values. Time is treated as a categorical variable so that no restriction is imposed on the trajectory of the means over time. The model will also adjust for the randomization stratification factor hsCRP concentration (≤ upper limit of normal/ > upper limit of normal) and its interaction with time.

Summary statistics will be provided over time for the Long-term Extension Period.

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1 INTRODUCTION

1.1 Disease Background

Ankylosing spondylitis (AS) is a chronic, systemic inflammatory disease of indeterminate etiology that affects the axial spine (spondylitis), with sacroiliitis as its hallmark. Other manifestations include involvement of peripheral joints, digits, and entheses. The most common presenting symptom is chronic back pain and progressive spinal stiffness, a result of inflammation affecting the spine and sacroiliac joints (Feld, 2018). The most common extraarticular manifestations of AS include uveitis (~33%) (Zeboulon, 2008), inflammatory bowel disease (~7%), and psoriasis (~9%) (Stolwijk, 2015). Ankylosing spondylitis is typically diagnosed in people younger than 40 years and about 80% of patients develop first symptoms when they are younger than 30 years (Hanson, 2017). It is estimated that approximately 70% of patients with AS are males (de Winter, 2016).

Recent studies reported the prevalence of AS to range from 9 to 30 per 10,000 in the general population, depending on geographic area, study population or data source, case definition, and ascertainment methods (Wang, 2018). In general, there is a clear correlation between the prevalence of AS in a given population and the prevalence of HLA-B27 in that group, with the prevalence of AS being approximately 5 to 6 percent among people who are HLA-B27-positive (Reveille, 2013). Approximately 94% of individuals with AS are HLA-B27-positive (Brown, 1996).

Although HLA-B27 is the largest single genetic contributor to disease pathophysiology, many other genetic loci, including those associated with the interleukin (IL)-17A pathway, have been associated with AS (Brown, 2016; Costantino, 2018). Chronic inflammation in AS is thought to be driven by CD4+ and/or CD8+ T lymphocytes, including innate-like lymphocytes, and cytokines such as tumor necrosis factor (TNF)-α and IL-17A (Ranganathan, 2017). Classification criteria for AS were proposed based on clinical grounds in the 1960s and later modified to include radiological criteria, known as the modified New York criteria for diagnosis of AS (van der Linden, 1984) (APPENDIX B). More recently, the Assessment of SpondyloArthritis international Society (ASAS) formulated classification criteria for axial spondyloarthritis (axSpA), of which AS is considered the prototype disease, based on imaging, clinical, and laboratory criteria (Rudwaleit, 2009a; Rudwaleit 2009b). Disease classification of axSpA is established in persons with a history of back pain for 3 or more consecutive months before reaching 45 years of age, the presence of sacroiliitis confirmed on magnetic resonance imaging (MRI) or plain radiography, and with at least one clinical or laboratory finding that is characteristic of spondyloarthritis (SpA). Alternatively, persons with this history who have a positive test result for HLA-B27 and ≥ 2 clinical or laboratory features of SpA also fulfill the classification criteria for axSpA. Individuals with axSpA who have established radiographic evidence of sacroiliitis are considered to have met the definition for AS (Rudwaleit, 2009a; Rudwaleit 2009b).

The treatment goal in patients with AS is to optimize long-term health-related quality of life and social participation through control of signs and symptoms, prevention of structural damage, normalization or preservation of function, avoidance of toxicities and minimization of

comorbidities (Smolen, 2018). Current treatment guidelines for active AS (Bath Ankylosing Spondylitis Disease Activity Index [BASDAI] of at least 4 or Ankylosing Spondylitis Disease Activity Score – C-reactive protein [ASDAS-CRP] of at least 2.1) strongly recommend the use of nonsteroidal anti-inflammatory drugs (NSAIDs) and conditionally recommend their continuous use, based on very low-quality evidence (van der Heijde D, 2017a). Tumor necrosis factor (TNF) blockers and anti-IL-17A monoclonal antibody (mAb) agents have become standard of care for patients who are unresponsive or intolerant to NSAIDs. Based on results of pivotal trials of currently approved biologics in AS, about 30% to 40% of patients treated with biologics do not achieve an Assessment of SpondyloArthritis International Society Response Criteria with an improvement of at least 20% (ASAS20) and up to 64% of patients do not achieve an Assessment of SpondyloArthritis International Society Response Criteria with an improvement of at least 40% (ASAS40) (Sieper 2017; Deodhar 2019). Although biologics can reduce inflammation and improve symptoms, there is only indirect evidence that currently available biologic TNF blockers influence spinal radiographic progression (Haroon, 2014; Maas, 2017; Molnar, 2018), which continues to occur in spite of treatment (Poddubnyy, 2016). Biologics require parenteral administration and are associated with development of auto-antibodies, which may be neutralizing and limit drug effectiveness. In addition, profound TNF inhibition by currently available TNF-directed biologics is associated with increased risks of serious infections and malignancies.

In summary, AS patients who fail or cannot tolerate NSAIDs, and those who have also failed therapy with biologic agents, represent a patient population with high unmet medical need and there are currently no approved oral medications available to treat the underlying disease.

1.2 Compound Background

CC-99677 (also known as BMS-986371) is a novel, orally bioavailable, small-molecule covalent inhibitor of mitogen-activated protein (MAP) kinase-activated protein kinase 2 (MK2). The MK2 enzyme is a serine/threonine protein kinase that is regulated through direct phosphorylation by p38 MAP kinase. Inflammation mediated by MK2 is a consequence of an increase in the stability and translation of messenger ribonucleic acid (mRNA) of proinflammatory cytokines, such as TNF-α, IL-17 and IL-6. This is accomplished by phosphorylation and inhibition of the mRNA destabilizing function of tristetraprolin, which leads to cytokine translation (Hitti, 2006; Ronkina, 2010).

CC-99677 is a potent and selective covalent inhibitor of MK2 in biochemical and cellular assays. The mean (standard deviation) half maximal effective concentration (EC50) in cellular assays was 89 (2.6) nM. Please refer to the Investigator's Brochure for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and known adverse event profile.

1.3 Nonclinical Experience

CC-99677 inhibited production of proinflammatory cytokines, including TNF-α, IL-6, monocyte chemoattractant protein-1 (MCP-1), and IL-17A in vitro. CC-99677 showed pharmacologic activity in a human leukocyte antigen (HLA)-B27 transgenic rat model of AS; this model is considered to be relevant to the study of human HLA-B27-associated diseases (O'Neill 1997;

Turner, 2005). A dose of CC-99677 corresponding to MK2 engagement (target engagement [TE]) of approximately 70% was associated with greater decrease in paw swelling than etanercept, tofacitinib, or a lower (approximately 40%) level of TE. The benefit of CC-99677 (mean 65% inhibition of paw swelling compared to vehicle control) was highly statistically significant. Following oral doses, CC-99677 formed an active metabolite, CC-0782951, by O-deethylation which also formed a covalent bond with MK2.

Based on in vitro studies, cytochrome P450 (CYP) 3A4/5 is the major isozyme involved in oxidative metabolism of CC-99677. CC-99677 is a weak to moderate inhibitor of multiple CYPs and a weak inducer of CYP2B6. Given the expected exposures at the planned doses, CC-99677 is unlikely to alter the levels of coadministered drugs due to inhibition or induction of hepatic CYP enzymes; however, there is potential for inhibition of gut CYP3A4/5 as CC-99677 concentrations may be higher in the intestinal lumen.

In vitro transporter studies indicate that at clinical doses CC-99677 has the potential to inhibit multiple drug transporters (p-glycoprotein [P-gp], breast cancer resistance protein [BCRP], organic cation transporter [OCT] 1, organic anion transporting polypeptide [OATP] 1B1, and OATP1B3), in addition, CC-99677 and its metabolite, CC-0782951, are substrates of P-gp and BCRP. Compared to CC-99677, the major metabolite CC-0782951 has lower in vitro inhibitory potencies toward CYP enzymes and drug transporters. With a lower maximum plasma concentration (C_{max}) than CC-99677 in humans, CC-0782951 is not expected to increase the potential in vivo CYP and drug transporter inhibition profile and therefore is not expected to alter the clinical drug-drug interaction (DDI) profile of CC-99677. Based on the pharmacokinetic (PK) properties in animal models, CC-99677 is predicted to have an acceptable pharmacokinetic profile in humans (CC-99677 IB).

1.3.1 Nonclinical Toxicology

CC-99677 has been evaluated in a battery of oral repeat-dose toxicity studies with up to 26-weeks of dosing in mice and 39- weeks of dosing in the monkey. In addition, dose range-finding prenatal development studies (rabbits and mice), a fertility and early embryonic development study in mice, and genetic toxicity studies (in vitro and in vivo) were conducted. The phototoxic potential of CC-99677 was evaluated in vitro, and in vivo using mice. The oral route of administration was used for all in vivo toxicity studies as it is the route of clinical administration. The main circulating components in animal plasma were CC-99677 and its active metabolite CC-0782951.

In the Good Laboratory Practice (GLP)-compliant repeat-dose toxicity studies, heart muscle, skeletal muscle, liver, duodenum, stomach, adrenal gland, bone marrow, spleen and thymus were identified as target organs for CC-99677.

In mice, adverse effects noted in 28- and 91-day studies were minimal to mild myofiber degeneration or cardiomyopathy at 750 mg/kg/day. No microscopic findings were noted in the hearts of recovery mice in the 91-day study. In a 26-week study in mice, there was mortality at 750 mg/kg/day that was associated with adverse clinical observations. Some of these animals had microscopic changes where stress may be a contributing factor, including decreased hematopoietic cellularity in the bone marrow and decreased lymphocytes and/or lymphoid necrosis in the spleen

and thymus. Surviving animals exhibited similar clinical observation that were less severe. In contrast to the shorter term studies, there were no effects noted in the hearts of early decedents or surviving mice in the 26-week study. Based upon adverse findings and mortality at 750 mg/kg/day, the no observed adverse effect level (NOAEL) in mice after 26 weeks of dosing was 100 mg/kg/day, corresponding to a mean area under the concentration-time curve from time zero to the last measurable time point (AUC_{LST}) of 23,500 and 30,600 ng·hr/mL for CC-99677 in males and females, respectively and a mean AUC_{LST} of 2,030 and 4,620 ng·hr/mL for CC-0782951 in males and females, respectively.

In monkeys, administration of CC-99677 once daily for up to 39-weeks to male and female monkeys was well tolerated at doses up to 375 mg/kg/day. No adverse findings were noted in any study. Test article-related but nonadverse microscopic findings were limited to degenerative changes in the skeletal muscle at ≥ 150 mg/kg/day in the 28-day study; no findings in skeletal muscle were noted after 91 days or 39 weeks using the same dose levels. There were no associated changes in clinical pathology parameters for the findings in skeletal muscle in the 28-day study. In the 39-week study, minimal to mild increases in platelets were noted at ≥ 50 mg/kg/day, which were most pronounced on Day 181, and were partially or fully resolved at the terminal collection on Day 272, despite continued dosing.

Based upon the lack of adverse changes in any parameter evaluated at up to 39-weeks of dosing, the NOAEL for CC-99677 was 375 mg/kg/day, the highest dose tested corresponding to an exposure (AUC_{LST}) of 10,800 ng·hr/mL for males and 6,350 ng·hr/mL for females and for the metabolite CC-0782951 was 7,470 ng·hr/mL for males and 5,650 ng·hr/mL for females. The lowest NOAEL exposures were achieved in female monkeys in the 39-week study. These exposures are approximately 4.7- and 8.4-fold higher for parent and metabolite, respectively, than the expected exposures in humans at 150 mg.

CC-99677 was negative in the bacterial mutagenicity assay, the in vitro micronucleus assay in human peripheral blood lymphocytes (HPBL), and the in vivo micronucleus assay in mice. In prenatal development studies in mated female mice, all mice given 750 mg/kg/day, the highest dose tested, were euthanized due to poor clinical condition. In mice given 15 and 100 mg/kg/day, no developmental toxicity or adverse maternal effects were observed. In prenatal development studies in time-mated female rabbits, severe maternal toxicity was observed at 375 mg/kg/day, the highest dose tested. Heart malformations and Tetralogy of Fallot were noted in rabbit fetuses at ≥ 15 mg/kg/day, the lowest dose tested. The NOAEL for developmental toxicity in rabbits was determined to be < 15 mg/kg/day.

CC-99677 reduced fertility and fecundity indices in male and female mice and adverse ovarian and uterine parameters in females at 750 mg/kg/day. The NOAEL for reproductive performance and fertility was 100 mg/kg/day in mice.

There was no evidence of cutaneous phototoxicity in hairless mice administered 15 mg/kg/day and subsequently exposed to light; however, cutaneous phototoxicity (erythema, edema, and/or skin flaking) was observed in mice administered doses ≥ 100 mg/kg/day.

Please refer to the Investigator's Brochure for detailed information toxicity studies.

1.4 Clinical Experience

As of May 17, 2021, CC-99677 has been administered to 162 healthy subjects in 3 completed clinical pharmacology studies (CC-99677-CP-001, CC-99677-CP-002, and CC-99677-CP-003).

In the clinical pharmacology study CC-99677-CP-002, CC-99677 was administered to healthy volunteers (N = 16) in an open-label study to evaluate effects of cytochrome P450 inhibition and induction of the pharmacokinetics of CC-99677 and effects of CC-99677 on the pharmacokinetics of digoxin, metformin, methotrexate, midazolam, rosuvastatin, and sulfasalazine (Data on file from Celgene Corporation; Section 1.4.1 and Section 1.4.2).

Study CC-99677-CP-003 was designed to investigate whether the coadministration of CC-99677 would affect the PK of combined oral contraceptives Ortho Tri-Cyclen containing 0.035 mg ethinyl estradiol and 0.180 mg/0.215 mg/0.250 mg norgestimate (Data on file from Celgene Corporation; Section 1.4.1 and Section 1.4.2).

Study CC-99677-CP-004 is an additional ongoing clinical pharmacology study to evaluate the safety, tolerability, PK, pharmacodynamics (PD) and pharmacogenomics of CC-99677 in healthy adult Japanese volunteers. The data will be used to support the inclusion of Japanese subjects in future CC-99677 Phase 2 and 3 clinical trials. No clinical data are available yet for CC-99677-CP-004 to inform the clinical experience with CC-99677.

1.4.1 Efficacy and Safety

CC-99677-CP-001 was a Phase 1, three-part study with a double-blind, placebo-controlled, single ascending dose (SAD) phase, a double-blind multiple ascending dose (MAD) phase, and an open-label cross-over food effect phase. The study enrolled a total of 97 healthy adult subjects.

Part 1 (SAD phase) evaluated the safety, tolerability, and PK of CC-99677 following single oral doses of 3 mg to 400 mg. In Part 1, 48 subjects were randomized and enrolled into 6 cohorts. Each cohort consisted of 8 subjects: 6 subjects received CC-99677, and 2 subjects received placebo. The most common treatment-emergent adverse events (TEAEs) in this part were in the categories of musculoskeletal and connective tissue disorders, skin and subcutaneous tissue disorders, and infections and infestations. In Part 1, 5 of the 22 total TEAEs were suspected to be related to CC-99677. The most common TEAEs suspected of being related to CC-99677 were in the skin and subcutaneous tissue disorder category with 2 TEAEs in 2 subjects who had a mild, transient, pruritic, erythematous rash without other organ involvement at the 400-mg dose level. The majority of TEAEs were mild in nature. Only one TEAE was moderate in nature (gastroenteritis lasting less than 24 hours in the 30 mg cohort). There were no severe TEAEs or serious adverse events (SAEs).

Part 2 (MAD phase) evaluated the safety, tolerability, and PK of CC-99677 following multiple daily oral doses of 10, 30, 60, 120, and 150 mg. In Part 2, 37 subjects were randomized and enrolled and received 14 days of dosing. The most common TEAEs in Part 2 were categorized under nervous system disorders (headache and dizziness) and gastrointestinal disorders (nausea, constipation, diarrhea, abdominal pain, dyspepsia, and rectal bleeding). In Part 2, 9 of the 42 total TEAEs were suspected to be related to CC-99677. The most common TEAEs suspected of being

related to CC-99677 in Part 2 were in the vascular disorders class with 2 TEAEs in 2 subjects (skin flushing in 1 subject and hot flush in 1 subject). In the 120-mg dose cohort there was an observation in 3 of 6 subjects on active treatment with an increase in serum transaminase levels (alanine aminotransferase [ALT] in particular) above the upper limit of the normal reference range (ULN). The ALT elevation in one of these subjects, which peaked at 2.3 X ULN at Day 17, was judged by the Investigator to be a TEAE suspected to be related to CC-99677. This adverse event (AE) resolved without intervention when the ALT returned toward the normal reference range by day 28. The other 2 subjects had ALT elevations less than 2x above the upper limit of normal. All subjects in the 120-mg cohort with ALT values crossing above the ULN were asymptomatic, and on follow-up laboratory testing after completion of dosing, all transaminase levels began to return toward the baseline values without intervention. No other liver chemistry abnormalities were noted. In the subsequent 150-mg dose cohort, no transaminase level changes were observed in any subject during the 14-day dosing period. One subject in the 150-mg dose cohort was found to have an elevated aspartate transaminase (AST) level on outpatient follow up 14 days after the end of dosing (Day 28). This was determined to be the result of increased exercise undertaken by the normally sedentary subject after leaving the site at the end of the confinement period. There was no apparent trend towards increasing liver transaminase concentrations (ALT and AST) in any subject in that dose cohort.

The PK of CC-99677 was assessed in 48 healthy human subjects in Study CC-99677-CP-002. Study CC-99677-CP-002 was a Phase 1, three-part, open-label, DDI study to assess the safety, tolerability, and PK of BMS-986371 administered alone or in combination with methotrexate and sulfasalazine; itraconazole; rifampin; midazolam; or a cocktail of digoxin, metformin, and rosuvastatin in healthy subjects. CC-99677, administered alone; coadministered with methotrexate and sulfasalazine; or coadministered with itraconazole, rifampin, midazolam, or a cocktail of digoxin, metformin, and rosuvastatin, was generally safe and well tolerated by the healthy adult subjects in this study. Overall, 13 of 48 subjects (27.1%) experienced at least 1 TEAE. With the exception of 1 severe TEAE of increased transaminases experienced by 1 subject, all other TEAEs were considered mild in severity. No TEAEs were suspected of being related to any study drug. No deaths or other serious TEAEs were reported, and no subjects discontinued due to a TEAE (CC-99677 IB).

Study CC-99677-CP-003 was a Phase 1, open-label, fixed-sequence, cross-over study on the effects of BMS-986371 on the PK of an oral contraceptive (OC) in healthy female subjects. There were no deaths or SAEs in the study. Overall, 13 of 28 subjects (46.4%) experienced at least 1 TEAE (total of 26 TEAEs). With the exception of 3 moderate TEAEs and 1 severe TEAE, all other TEAEs were considered mild in severity. Overall, 7 subjects (25.0%) reported TEAEs that were suspected of being related to the study drug: 6 subjects (21.4%) after receiving the OC and prior to CC-99677 dosing on Cycle 2 Day 15, and 3 subjects (12.5%) after receiving the OC and/or CC-99677 on or after Cycle 2 Day 15 and throughout the 28-day follow-up. After receiving the OC, 4 subjects (14.3%) reported TEAEs that led to discontinuation from the study. In this study, of note, asymptomatic self-limited elevations of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were reported as TEAEs in 2 subjects per the study protocol based on the

degree of elevation above the laboratory reference range. Both increased hepatic enzyme TEAEs occurred after the last day of OC+CC-99677 dosing and during the 28-day follow-up period, when only OC was being dosed. In the first subject, this was noted 29 days after the last CC-99677 dose (ALT: 1.78× above the upper limit of the reference range; AST: 1.05× above the upper limit of the reference range), and the investigator did not suspect a relationship, as there was no clear temporal relationship. In the second subject, elevation in levels began during the OC-only treatment phase and peaked 27 days after the last dose of CC-99677 (ALT: 9.94× above the upper limit of normal; AST: 2.73× above the upper limit of normal). The investigator felt there was a reasonable possibility that the study drug was the cause of the event. However, this subject had additional risk factors of prior biliary disease, fatty liver, and an overweight body mass index of 29.8. Therefore, the Sponsor deemed the precise etiology of these abnormal hepatobiliary laboratory results to be unknown. Bilirubin levels remained within normal limits for both subjects (please refer to CC-99677 IB for additional details).

Based upon review of the safety data, including physical examinations, vital sign measurements, clinical laboratory assessments, electrocardiograms (ECGs), and TEAEs, CC-99677 appears to be well tolerated when administered as a single dose up to 400 mg and when administered for 14 days up to 150 mg.

1.4.2 Pharmacokinetics

The PK of CC-99677 in healthy human volunteers was assessed in study CC-99677-CP-001. This clinical pharmacology study evaluated single doses of CC-99677 ranging from 3 to 400 mg and also repeat daily doses (QD x 14 days) of CC-99677 ranging from 10 mg to 150 mg.

Following single oral dosing, CC-99677 was rapidly absorbed with a median time to observed maximum plasma concentration (T_{max}) of 1 to 3 hours across the dose range of 3 mg to 400 mg. The systemic exposure (maximum plasma concentration [C_{max}] and area under the curve [AUC]) of CC-99677 increased in an approximately dose proportional manner across this range. The terminal elimination half-life ($t_{½}$) ranged from (geometric mean) 1.66 to 6.95 hours.

After multiple daily doses, CC-99677 was absorbed rapidly with a T_{max} of 1 to 2.5 hours across the dose range of 10 mg to 150 mg. The systemic exposures (C_{max} and AUC) on Day 14 of CC-99677 increased in an approximately dose-proportional manner. The $t_{½}$ on Day 14 was similar across studied doses, ranging from (geometric mean) 1.96 to 4.39 hours. There was limited accumulation of CC-99677 (range of accumulation ratio for AUC_{0-t} was 1.1 to 1.2 from 10 to 150 mg, respectively) upon repeated daily doses.

CC-99677 forms a pharmacologically active metabolite, CC-0782951 (formed by O-deethylation). Following single oral doses of CC-99677, CC-0782951 was formed with a T_{max} of approximately 1 to 3 hours across the dose range of 3 mg to 400 mg. With increasing dose, C_{max} and AUC_{0-t} increased in an approximately dose-proportional manner from 3 mg to 400 mg of single doses. The geometric mean $t_{½}$ of CC-0782951 ranged from 1.60 to 6.59 hours.

After multiple daily doses of CC-99677, CC-0782951 formed rapidly at a median T_{max} of approximately 1 to 3 hours across the dose range of 10 mg to 150 mg. The $t_{½}$ of CC-0782951 was similar after multiple daily doses (QD x 14 days), ranging from 2.13 to 4.4 hours across the studied

dose groups. There was limited accumulation of CC-0782951 (range of accumulation ratio for AUC_{0-t} was 0.9 to 1.2 from 10 to 150 mg, respectively) upon repeated daily doses.

Food has limited effect on the PK of the current formulation of CC-99677. Therefore, CC-99677 can be taken with or without food.

In Part 1 of Study CC-99677-CP-002, the effect of CC-99677 as a potential perpetrator of BCRP transporter based DDI was evaluated. To achieve this objective, methotrexate and sulfasalazine, both BCRP substrates and important concomitant medications in the rheumatologic indications for which CC-99677 is being studied, were administered in a cocktail approach to adult healthy male volunteers. The cocktail consisted of 7.5 mg of methotrexate and 1000 mg of sulfasalazine; CC-99677 was administered at a dose of 150 mg between Day 3 to Day 8. Serial PK samples were collected to characterize PK of methotrexate and sulfasalazine when administered without and with CC-99677. Pharmacokinetics of CC-99677 and its metabolite CC-0782951 was also collected during the combination phase with methotrexate and sulfasalazine.

The effect of CC-99677 on the plasma exposure of methotrexate and sulfasalazine was minimal with an approximate 50% increase in exposures in the presence of CC-99677 between the respective single administration of methotrexate or sulfasalazine and co-administered with CC-99677. The minimal change in PK exposure suggests a limited clinically relevant drug-drug interaction with BCRP. For narrow therapeutic index drugs, BCRP substrates should be used with caution. Concomitant dosing of methotrexate and sulfasalazine did not impact the PK exposures of CC-99677 and CC-0782951 based on comparison of historical PK data from PK data of CP-001, and consistent with a minimal extent of biliary secretion of CC-99677. These data indicate that coadministration of methotrexate or sulfasalazine would have limited impact on exposures of CC-99677 and CC-0782951.

In Part 2 of Study CC-99677-CP-002, coadministration of CC-99677 with itraconazole increased CC-99677 exposure by 150%. Coadministration of CC-99677 with rifampin reduced CC-99677 exposure by 92.4%. Therefore, concomitant use of strong or moderate CYP3A4/5 and/or P-gp inhibitors or inducers is prohibited.

In Part 3 of Study CC-99677-CP-002, coadministration of CC-99677 did not have a clinically meaningful effect on midazolam or metformin exposure. Therefore, concomitant use of CC-99677 with either CYP3A4/5 or OCT2 substrates is permitted. Coadministration of CC-99677 with rosuvastatin increased rosuvastatin exposure modestly by 41%. Based on this result with rosuvastatin and the lack of effect on the CYP3A4/5 substrate midazolam, coadministration of CC-99677 with statins is allowed with routine monitoring (eg, hepatic enzyme elevations and muscle soreness) of statin-associated adverse events (AEs).

In Study CC-99677-CP-003, coadministration of CC-99677 and Ortho Tri-Cyclen did not have a clinically meaningful effect on ethinyl estradiol, norgestrel, or 17-desacetyl norgestimate exposure. Therefore, concomitant administration of CC-99677 and oral contraceptives is allowed.

1.4.3 Pharmacodynamics

The pharmacodynamics (PD) of CC-99677 were assessed during Parts 1 and 2 of Study CC-99677 CP-001 by evaluating the effect of ascending dose levels of CC-99677 on target engagement (TE) with MK2 protein and on levels of proinflammatory cytokines using a whole-blood ex vivo assay in which blood isolated from subjects treated with CC-99677 or placebo was incubated with lipopolysaccharide stimulation (LPS) for 24 hours. A dose dependent increase in TE and TNF inhibition in the ex vivo assay was observed by 4 hours with single oral doses ranging from 10 mg to 400 mg in Part 1 of Study CC-99677-CP-001. Daily dosing of CC-99677 in Part 2 of the study resulted in a dose-dependent increases in TE following doses between 10 mg and 120 mg and plateauing at the 120 mg and 150 mg dose levels. This was accompanied by sustained reductions in TNF-α over 14 days of dosing, at doses greater than 10 mg, with maximal inhibition at 150 mg.

Please refer to the Investigator's Brochure for detailed information concerning the available pharmacology, drug metabolism, clinical studies, and known adverse event profile.

1.5 Rationale

1.5.1 Rationale for the Study Design

CC-99677-AS-001 is a Phase 2, randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of 2 dose groups of CC-99677 in subjects with active AS. The main study population comprises AS subjects who have failed therapy with at least 2 NSAIDs; an additional substudy will recruit AS subjects who have failed therapy with 2 NSAIDs and who have also failed 1 biologic agent. These patient populations were chosen to represent AS patients most likely to derive clinical benefit from CC-99677. Since biologic-failure subjects are expected to be less responsive to anti-inflammatory treatments, in general, the benefit-risk profile of CC-99677 will be evaluated separately for the main study population and the substudy population.

Efficacy assessment in this study will be based on patient and physician-reported outcomes, and objective measures of inflammation and disease activity. The ASAS Response Criteria are based on a disease assessment tool that utilizes results from a subject self-administered survey. The ASAS20 and ASAS40 criteria have been widely validated as tools to measure symptomatic improvement in the context of AS clinical trials (Anderson, 2001; Brandt, 2004). The ASAS20 is the primary endpoint in this study and has been used extensively in most Phase 2 and 3 clinical trials in AS. Several other disease activity measures will be assessed to corroborate the efficacy evaluation of CC-99677 during the study. These include ASAS40, ASDAS-CRP (van der Heijde, 2009), BASDAI, Bath Ankylosing Spondylitis Functional Index (BASFI) and Bath Ankylosing Spondylitis Metrology Index-Linear (BASMI-Linear) (Sieper, 2009).

Magnetic resonance imaging of the spine and sacroiliac joints using the Spondyloarthritis Research Consortium of Canada (SPARCC) scoring system (Maksymowych, 2005; Maksymowych, 2010) will be performed to assess the effect of CC-99677 on spinal and sacroiliac joint inflammation. Magnetic resonance imaging provides an objective assessment of inflammation and evidence of sacroiliitis and predicts radiographic progression of disease (reviewed in Schwartzman, 2019). In clinical trials of AS, clinical improvements are accompanied by rapid (within 12 weeks) reduction in bone marrow edema, as measured by MRI (Lambert, 2007; Braun, 2017; van der Heijde, 2017b;

van der Heijde, 2018). Therefore, MRI provides a rapid, responsive PD measure of inflammation and will yield supportive evidence of efficacy of CC-99677.

The 12 weeks treatment duration of this trial is considered adequate to assess potential clinical benefits and improvements in spinal and sacroiliac joint inflammation, as assessed by MRI. This duration is consistent with other trials of biological agents in AS (Mease, 2019). In 24-week, placebo-controlled trials of biologics in AS, maximal clinical benefits were already apparent after 12 weeks of treatment (Davis, 2003; Inman, 2008; Landewé, 2014), suggesting that 12 weeks of treatment is the optimal duration to demonstrate the maximal benefit of an anti-inflammatory agent while minimizing the duration of treatment with placebo.

The 52-week Long-term Extension Period following Week 12 will provide additional exploratory long-term safety and efficacy information and enable those subjects randomized to placebo in the placebo-controlled period the opportunity to receive CC-99677 during the extension period. The 16-week timepoint to assess subject eligibility to continue in the Long-term Extension provides the shortest duration to reasonably assess efficacy of CC-99677 in those subjects receiving placebo through Week 12. In other trials of AS, attainment of ASAS20 was observed in a high proportion of subjects as early as 4 weeks following onset of treatment (Landewé, 2014; van der Heijde, 2018). Therefore, it is anticipated that clinical benefits of CC-99677 should already be apparent following 4 weeks of treatment. Discontinuing treatment in nonresponders ensures that subjects who are unlikely to derive benefits from CC-99677 do not remain in the study beyond 16 weeks.

The planned Interim Analysis (IA) (see Section 3.1.4) will provide additional information on observed safety and efficacy of CC-99677. A Steering Committee (see Section 3.1.8) will review the Interim Analysis data and determine whether to add an additional dose. For example, if 60 mg and 150 mg dose groups demonstrate similar robust efficacy an additional low-dose cohort will be added to potentially define a lower efficacious dose.

1.5.1.1 COVID-19 Pandemic-related Risk Assessment

While the global coronavirus disease 2019 (COVID-19) pandemic has been identified as a potential risk to clinical trial subjects in general, and it may particularly affect individuals with underlying chronic diseases, the overall benefit-risk for participation in this AS study with CC-99677 is considered favorable. The individual benefit-risk considerations regarding COVID-19 infection remains the responsibility of the Investigator. Testing to exclude COVID-19 infection prior to enrollment and to inform decisions about subject care during the study should follow local standard practice and requirements. Based on the mechanism of action, pharmacological modulation of the MK2 pathway by CC-99677 may alter the host response to infection and potentially predispose to infections, including COVID-19.

1.5.2 Rationale for Dose, Schedule and Regimen Selection

Daily doses of 60 mg and 150 mg CC-99677 were selected for this trial based on preclinical and clinical data in addition to simulation that supports adequate target engagement at clinically tolerated doses.

In the CC-99677-CP-001 study of healthy volunteers, daily doses between 60 mg and 150 mg were associated with exposures of CC-99677 that were sufficient to achieve levels of the TE in humans that correlate with efficacy in multiple preclinical animal models. In multiple animal models of arthritis and skin inflammation, TE of 40% and above were associated with efficacy, and greater levels of TE were associated with greater improvements in disease activity. In the human leukocyte antigen - B27 transgenic (HLA-B27Tg) model of AS in rats, TE of approximately 70% was associated with a greater decrease in paw swelling as compared to therapeutic doses of etanercept, a biologic TNF-α inhibitor, and tofacitinib, a Janus kinase (JAK) inhibitor (CC-99677 IB). In ex vivo studies of peripheral blood mononuclear cells (PBMCs) from healthy volunteers, TE of 60% achieved approximately 70% inhibition of TNF-α secretion. The relationship between CC-99677 exposure and TE was explored using a maximum effect (Emax) model with clinical data from study CC-99677-CP-001. The 60 mg and 150 mg doses correspond to exposures with a predicted median TEs of approximately 67% and 79%, respectively. These two doses represent a distribution across a range of target engagement levels that can be expected to lead to clinical benefits in AS.

In a 91-day repeat-dose toxicology study with mice, the NOAEL was determined to be 100 mg/kg/day, corresponding to a mean AUC_{LST} of 28800 and 3590 ng·hr/mL for CC-99677 and CC-0782951, respectively. In humans, the highest dose tested in this study will be 150 mg, which corresponds to an observed AUC_{LST} of 1361 ng·hr/mL and 670.3 ng·hr/mL for CC-99677 and CC-0782951, respectively. These represent 21-fold and 5.4-fold margins below the mouse NOAEL for CC-99677 and CC-0782951, respectively. The NOAEL in mice was based on microscopic findings in the heart at a dose of 750 mg/kg/day (mean AUC_{LST} of 144000 ng·hr/mL and 39900 ng·hr/mL for CC-99677 and CC-0782951, respectively). This adverse finding was not observed in the 28- and 91-day studies in cynomolgus monkeys, which resulted in AUC_{LST} at the NOAEL corresponding to the highest dose tested, 375 mg/kg/day, of 9115 and 6470 ng·hr/mL for CC-99677 and CC-0782951, respectively. The exposures in monkeys represent 6.7-fold and 9.7-fold margins for CC-99677 and CC-0782951, respectively, based on the 150-mg dose.

Safety and tolerability data from study CC-99677-CP-001, which included single-dose and multiple-dose testing in healthy volunteers, support the proposed doses. In addition, there was limited to no observed accumulation of CC-99677 and limited accumulation of the major metabolite, CC-0782951, with daily dosing for 14 days (CC-99677 IB). In summary, the nonclinical and clinical safety, tolerability, exposure, PD, and preclinical efficacy data indicate that the proposed doses are appropriate for this study.

1.5.3 Rationale for Placebo Comparator

A placebo arm is needed in this Phase 2 trial to accurately determine the benefit-risk profile of CC-99677. Placebo ASAS20 response rates in AS clinical trials have been highly variable, ranging from 28.3% (van der Heijde, 2018) to 41.2% (van der Heijde, 2017b). The relatively high and variable placebo response rate has a significant impact on interpretation of efficacy in therapeutic AS trials and justifies the need to determine the placebo-adjusted response rate to adequately assess the treatment benefit of CC-99677 in AS. The use of placebo for 12 weeks is deemed acceptable by the AS research community as evidenced by multiple recently published

AS studies with other compounds. In addition, the European Union guidance on the clinical investigation of medicinal products for the treatment of axial spondyloarthritis also recommends placebo-controlled studies (European Medicines Agency [EMA], 2017).

1.5.4 Rationale for Pharmacodynamics and Potential Predictive Biomarkers

CC-99677 is a potent and selective inhibitor of MK2 in biochemical and cellular assays; moreover, it is an effective inhibitor of inflammation in vivo in animal models and of pro-inflammatory cytokines in vitro in patient-derived cells. These pro-inflammatory cytokines and chemokines include TNF-α, monocyte chemoattractant protein-1 (MCP-1), and IL-17A and have been shown to be increased in AS patients (Braun, 2002; West, 2017; Romero-Sanchez, 2011). Additionally, increased serum levels of TNF-α have been correlated with increased CRP levels in AS patients (Wagner, 2012). Thus, endogenous levels of TNF-α, IL-17A, and MCP-1 (among other soluble factors) in serum, as well as CRP, will serve as PD biomarkers. Reduction in CRP will provide evidence of modulation of a disease-relevant biomarker and establish a link to a clinical endpoint, as measured by ASDAS-CRP. The effect of CC-99677 administration on endogenous TNF-α and other circulating inflammatory factors will provide additional evidence of pathway modulation and proof of mechanism.

MK2 target engagement will be measured at each dose level and will allow for determination of PK/TE/PD/efficacy correlations and comparisons to previous studies and support dose selection in future studies.

In AS, several bone remodeling processes take place simultaneously: pathologic new bone formation in the form of syndesmophytes and bone loss in the form of bone erosion, osteolysis, and bone mineral density (BMD) loss leading to osteoporosis (Klingberg, 2012). CC-99677 has been shown to reduce bone resorption activity in vitro. Bone formation markers, such as procollagen type 1 N-terminal propeptide (P1NP) and bone resorption markers, such as carboxy terminal cross-linked telopeptide of type 1 collagen (CTX-1), are released from osteoblasts and osteoclasts, respectively (Arends, 2014). These biomarkers will be assessed in the study, providing an early evaluation of CC-99677 effect on bone remodeling.

Bone destruction is mediated by the recruitment of osteoclast precursors (OCPs) into the inflamed tissue and their differentiation into mature osteoclasts. TNF inhibition has resulted in sustained loss of circulating OCPs that can differentiate into osteoclasts (Lam, 2000; Li, 2004). CC-99677 was found to inhibit osteoclast differentiation in vitro, suggesting that MK2 inhibition may result in a similar reduction in osteoclast precursors in AS subjects.

Although TNF and IL-17 blockers as well as other emerging therapies are efficacious in patients with AS, not all patients derive benefits from these treatments. To identify biomarkers that potentially stratify subjects based on disease characteristics and response to CC-99677 treatment, pharmacogenetic and PD analyses will be incorporated in this study.

The analysis of variations or mutations in genes thought to be relevant to the drug's target pathway, and/or to the pathogenesis of the disease, may provide information relevant to differential responses of subjects to CC-99677. Genetic markers to be assessed include, but are not limited to, those involved in MK2 signaling, such as regulatory variants associated with circulating protein

levels of MK2 and other members of the MK2 pathway (Sun, 2018), CC-99677 metabolism (functional variants in CYP3A4, CYP3A5, CYP3A7, CYP2C8, and CYP2C9), and those shown to be associated with AS, including individual genetic variants such as HLA-B27 as well as polygenic risk scores built using public AS data (Rostami, 2019).

Whole genome ribonucleic acid (RNA) sequencing will be used to examine the quantity and sequences of RNA in blood, and to explore pharmacodynamics and opportunities for AS patient stratification with respect to response to CC-99677 special attention will be given to previously reported markers of AS in whole blood transcriptomics (Pimentel-Santos, 2011) and sexual dimorphism in AS (Gracey, 2016). Additionally, experiments are in progress to establish the signature of CC-99677 treatment on immune cells; such signatures, if identified, may be explored in the RNA sequencing data. Protein expression of cytokines and chemokines that we have shown to be modulated by CC-99677, including but not limited to TNF-α, IL-17A and MCP-1, will be monitored for stratification purposes as well. It is anticipated that the above biomarkers will be useful in monitoring disease course, predicting therapeutic response, and guiding population selection for future studies. In addition, serum samples will be biobanked at specified timepoints (Table 3 and Table 4) for SARS COV-2 serology.

2 STUDY OBJECTIVES AND ENDPOINTS

Table 1: Study Objectives

Primary Objective
The primary objective of the study is to evaluate the dose dependent efficacy of oral CC-99677, administered every day (QD), compared to placebo, as determined by the attainment of ASAS20 response after 12 weeks of treatment, in subjects with radiologically confirmed ankylosing spondylitis (AS) and inadequate response to nonsteroidal anti-inflammatory drugs (NSAIDs).
Secondary Objectives
To evaluate the effects of oral CC-99677, administered QD, compared to placebo, after 12 weeks of treatment in subjects with AS, on: • The signs and symptoms of AS, as assessed by attainment of ASAS40 response, ASDAS-CRP, and BASDAI • Measures of physical function, as assessed by BASFI • Spinal and sacroiliac joint inflammation as measured by Spondyloarthritis Research Consortium of Canada (SPARCC) MRI score of sacroiliac joints and spine • Percent change from baseline in C-reactive protein (hsCRP) • Safety and tolerability
Exploratory Objectives
To evaluate the effects of oral CC-99677, administered QD in subjects with AS, on: • The signs and symptoms of AS, as assessed by the attainment of ASAS20 and ASAS40 (excluding Week 12) • The signs and symptoms of AS, as assessed by ASDAS-CRP (excluding Week 12), achievement of a clinically important improvement (ASDAS-CRP $\geq$ 1.1), a major improvement (ASDAS-CRP $\geq$ 2.0) and attainment of inactive disease (ASDAS-CRP $<$ 1.3) • The signs and symptoms of AS, as assessed by BASDAI (excluding Week 12) • Measures of physical function, as assessed by BASFI (excluding Week 12) • Spinal mobility, as assessed by BASMI-Linear, Chest expansion, and Occiput to wall distance at Weeks 4 through Week 64 • High-sensitivity C-reactive protein (hsCRP) level at Weeks 2 through 64 • Enthesitis, as assessed by Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) at Weeks 4 through 64 • Peripheral arthritis, as determined by swollen joint count at Weeks 4 through 64 • Quality of life, as assessed by Ankylosing Spondylitis Quality of Life (ASQoL), Short Form-36 (SF-36), and ASAS Health Index (ASAS HI) at Weeks 12, 24 and 64 • Pharmacokinetics (PK) of CC-99677 at Weeks 4 through 12 • Target Engagement of CC-99677 at Weeks 4 through 12

Table 1: Study Objectives

• Relationship between CC-99677 exposure and serum pharmacodynamic (PD) biomarkers (including but not limited to TNF-α, IL-6, IL-17A, IL-23) at Weeks 4 through 64 • Whole blood mRNA gene expression profiling in relationship to treatment response at Weeks 4 through 64 • Relationship between CC-99677 exposure and osteoclast precursors with ex vivo osteoclastogenesis at Week 12 • Bone turnover markers (including but not limited to P1NP and CTX-1 in serum) at Weeks 12, 24 and 64 • Pharmacogenetic (PG) markers and their relationship to treatment response at Baseline Visit • SARS-CoV-2 serology (anti-SARS-CoV-2 total or IgG, IgM)a at Baseline and Week 64

[a] Study objectives are the same for the biologic-naive main study and for the biologic-failure substudy.

2.1 Study Endpoints

Table 2: Study Endpoints

Endpoint	Name	Description	Time-frame
Primary	ASAS20	Proportion of subjects who achieve an improvement in disease activity from baseline of ≥ 20% and ≥ 1 unit in at least 3 of the 4 ASAS domains on a scale of 0 to 10, and no worsening from baseline of ≥ 20% and ≥ 1 unit in the remaining domain on a scale of 0 to 10 Four ASAS Domains: – Patient Global Assessment of Disease (0 to 10 unit Numerical Rating Scale [NRS]); – Total Back Pain NRS; – Function (the Bath Ankylosing Spondylitis Functional Index [BASFI] score NRS); – Inflammation (mean of Bath Ankylosing Spondylitis Disease Activity Index [BASDAI] NRS Questions #5 and #6 for morning stiffness).	Week 12

Table 2: Study Endpoints

Endpoint	Name	Description	Time-frame
Secondary	ASAS40	Proportion of subjects who achieve an improvement in disease activity from baseline of ≥ 40% and ≥ 2 unit in at least 3 of the 4 ASAS domains on a scale of 0 to 10, and no worsening at all from baseline in the remaining domain	Week 12
	ASDAS-CRP	Change from baseline in ASDAS-CRP. ASDAS is score of disease activity comprising 3 items from BASDAI: 1. Back pain (question 2); 2. Peripheral pain/swelling (question 3); and 3. Duration of morning stiffness (question 6). *ASDAS-CRP Formula:* 0.12 x Back Pain + 0.06 x Duration of Morning Stiffness + 0.11 x Patient Global + 0.07 x Peripheral Pain/Swelling + 0.58 x ln (CRP+1)	Week 12
	BASDAI	Change from baseline in BASDAI	Week 12
	BASFI	Change from baseline in BASFI	Week 12
	SPARCC score for the total spine and sacroiliac joints	Change from baseline in the SPARCC scores of the total spine and of the sacroiliac joints	Week 12
	hsCRP	Percent change from baseline in high-sensitivity C-reactive protein (hsCRP)	Week 12
Exploratory	Safety and tolerability	AE Type	Signing of informed consent form through 4-week post-treatment observational follow-up period
		AE Frequency	
		AE Severity	
		Relationships of treatment emergent AEs to IP	
		Number of subjects who discontinue IP due to any treatment emergent AE	
		Clinically significant changes in vital signs, ECGs and/or laboratory findings	
	ASAS20	Proportion of subjects who achieve an improvement in disease activity from baseline of ≥ 20% and ≥ 1 unit in at least three ASAS domains on a scale of 10, and no worsening from baseline of ≥ 20% and ≥ 1 unit in the remaining domain on a scale of 0 to 10	Week 4 through Week 8 and Week 16 through Week 64
	ASAS40	Proportion of subjects who achieve an improvement in disease activity from baseline of ≥ 40% and ≥ 2 unit in at least three ASAS domains on a scale of 0 to 10, and no worsening at all from baseline in the remaining domain	Week 4 through Week 8 and Week 16 through Week 64

Table 2: Study Endpoints

Endpoint	Name	Description	Time-frame
	ASDAS-CRP	Change from baseline in ASDAS-CRP	Week 4 through Week 8 and Week 16 through Week 64
	BASDAI	Proportion of subjects achieving a ≥ 50% improvement from baseline in BASDAI	Week 4 through Week 8 and Week 16 through Week 64
	BASFI	Change from baseline in BASFI	Week 4 through Week 8 and Week 16 through Week 64
	BASMI - Linear	Change from baseline in spinal mobility	Week 4 through Week 64
	Chest expansion	Change from baseline in spinal mobility	Week 4 through Week 64
	Occiput to wall distance	Change from baseline in spinal mobility	Week 4 through Week 64
Exploratory	MASES Score	Change from baseline in MASES score in subjects with pre-existing enthesopathy	Week 4 through Week 64
	Peripheral Joint Count (44 swollen joint count)	Change from baseline in subject's swollen joint counts	Week 4 through Week 64
	Ankylosing Spondylitis Quality of Life (ASQoL)	Change from baseline in the ASQoL Questionnaire	Week 12, Week 24, and Week 64
	Short Form-36 (SF-36) v2	Change from baseline in SF-36 quality of life questionnaire	Week 12, Week 24, and Week 64
	ASAS Health Index (HI)	Change from baseline in ASAS Health Index quality of life questionnaire	Week 12, Week 24, and Week 64
	Exploratory Pharmacokinetic/Pharmacodynamic Endpoints		
	PK	Plasma PK parameters, such as Cmax, Tmax, AUC(0-T), AUC(TAU), and CLT/F for CC-99677 and Cmax, Tmax, AUC(0-T), AUC(TAU), MR_Cmax, MR_AUC(0-T), and MR_AUC(TAU) for CC-0782951, will be calculated for intense PK sampling at Week 4 if data permit. For sparse PK at Weeks 0, 4, 8, 12, 16, 20, and 24, concentrations of CC-99677 and CC-0782951 will be reported.	Intense PK: Week 4 Sparse PK: Baseline, Weeks 4, 8, 12, 16, 20, and 24
	Pharmacodynamics (PD)	Absolute change from baseline in high-sensitivity C-reactive protein (hsCRP)	Week 2 through Week 64

Table 2: Study Endpoints

Endpoint	Name	Description	Time-frame
		Percent change from baseline in high-sensitivity C-reactive protein (hsCRP)	Weeks 2 through 8 and Weeks 16 through 64
		Change from baseline in serum bone turnover markers, including but not limited to carboxy terminal cross-linked telopeptide of type 1 collagen (CTX) and procollagen type 1 N-terminal propeptide (P1NP)	Week 4 through Week 64
Exploratory	Pharmacodynamics (PD)	Change from baseline in target engagement measured by percent of MK2 bound to CC-99677 vs percent of free MK2 in peripheral blood mononuclear cells (PBMCs)	Weeks 4, 8, and 12
		Change from baseline in serum cytokines and other proteins by proteomics	Week 4 through Week 64
		Change from baseline in serum TNF-α and IL-17A	Week 4 through Week 64
		Change from baseline in osteoclast precursor frequency with ex vivo osteoclastogenesis in PBMCs	Week 12
		Change from baseline in whole blood RNA gene expression	Week 4 through Week 64
	Pharmacogenetics (PG)	Deoxyribonucleic acid (DNA) single nucleotide polymorphism (SNP) chip to detect AS associated polymorphisms and polymorphisms in the MK2 pathway	Baseline
	Biobanking for SARS-CoV-2 serologic status	SARS-CoV-2 serology (anti-SARS-CoV-2 total or IgG, IgM)	Baseline and Week 64

Abbreviations: Tmax = time to peak (maximum) serum concentration; AUC(0-T) = area under the plasma concentration-time curve from time zero to last measurable concentration; AUC(TAU) = area under the plasma concentration-time curve within a dosing interval; CLT/F = apparent total clearance; Cmax = maximum serum concentration of drug; Tmax = time to peak (maximum) serum concentration.

3 OVERALL STUDY DESIGN

3.1 Study Design

This is a phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group, efficacy and safety study in subjects with active AS. This study is designed to assess response to CC-99677 treatment by measuring signs and symptoms of AS, objective measures of disease activity, quality of life assessments, safety, and tolerability over a 12-week Double-blind Period. This study will also assess the efficacy and long-term safety of CC-99677 in a 52-week Long-term Extension Period.

The study consists of multiple periods (Figure 1):

- Screening Period (up to 6 weeks)
- Double-blind, Placebo-controlled Treatment Period (12 weeks)
- Long-term Extension Period (52 weeks)
- Post-treatment Observational Follow-up Period (4 weeks)

3.1.1 Biologic-Naïve Main Study

Approximately 147 adult male and female subjects with a diagnosis of AS fulfilling the modified New York criteria for AS (van der Linden, 1984) (APPENDIX B), symptoms of active disease based on a BASDAI score ≥ 4, a Total Back Pain Numerical Rating Scales (NRS) score ≥ 4, and no prior exposure to biologic treatment of AS, will be randomized 1:1:1 (49 subjects per arm) to receive either CC-99677 150 mg PO QD, CC-99677 60 mg PO QD, or matching placebo for a duration of 12 weeks (Figure 1). Randomization and treatment assignment will be managed by an Interactive Web Response System (IWRS). Randomization to treatment groups will be stratified by hsCRP concentration, (≤ upper limit of normal/ > upper limit of normal) obtained at initial Screening Visit 1.

Subjects will be treated for 12 Weeks in a Double-blind, Placebo-controlled Treatment Period, followed by a 52-week Long-term Extension Period and a 4-Week Post-treatment Observational Follow-up Period. At Week 12, subjects originally randomized to receive placebo will be re-randomized 1:1 to blinded CC-99677 (150 mg or 60 mg PO QD) through Week 64 or until early discontinuation. Subjects originally randomized to CC-99677 (150 mg or 60 mg PO QD) will continue to receive the same dose through Week 64 or until early discontinuation. Subjects who do not achieve an ASAS20 at Week 16 will be discontinued from the study.

An additional dose cohort may be added (Section 3.1.2) on the basis of the outcome of a planned Interim Analysis (IA) (Section 3.1.4).

The primary analysis (Section 3.1.5) for the biologic-naive cohort will be performed when all subjects in this cohort have completed 12 weeks of treatment, or have discontinued early, and all expected data are collected (Section 9). Following the database lock, the remainder of the Long-term Extension Period will be conducted in a Sponsor-unblinded fashion. All subjects and site personnel will remain blinded throughout the duration of the trial. The results may support the selection of a single efficacious dose of CC-99677 or dropping a dose due to insufficient benefit-

risk. In either of these events, subjects in the Long-term Extension may be reallocated to the selected CC-99677 dose(s) through Week 64.

Subjects will remain in the study for a maximum of 74 weeks and will be required to attend a total of 16 study visits (from Screening Visit to Observational Follow-up Visit). Assessments for efficacy, safety, tolerability, quality of life, PK and PD will be performed at specified timepoints as outlined in Table of Events, Table 3. Subjects who discontinue prematurely from the study at any time will be required to complete an Early Termination Visit (ET) and enter the 4-week Post-treatment Observational Follow-up Period.

The blind will be maintained for persons responsible for the ongoing conduct of the study. Blinded persons may include but are not limited to subjects, site personnel, Clinical Research Physician, Clinical Research Scientist, Clinical Trial Manager, Study Statistician, Data Manager, Programmers, and Clinical Research Associates.

The study will be conducted in compliance with the International Council for Harmonisation (ICH) Technical Requirements for Registration of Pharmaceuticals for Human Use/Good Clinical Practice (GCP) and applicable regulatory requirements.

3.1.2 Additional Dose Cohort

Approximately 59 eligible subjects will be randomized in a ~5:1 ratio (49 subjects in the CC-99677 dose cohort and 10 subjects in the placebo arm). Refer to Section 4 for specific inclusion and exclusion criteria. Randomized subjects will be treated for 12 Weeks in a Double-blind, Placebo-controlled Treatment period, followed by a 52-week long-term extension period and a 4-week Post-treatment Observational Follow-up Period (Figure 1).

At Week 12, all subjects originally randomized to receive placebo will be re-allocated to receive CC-99677 through Week 64 or until early discontinuation. All subjects originally randomized to CC-99677 will continue to receive the same dose through Week 64 or until early discontinuation. Subjects who do not achieve an ASAS20 at Week 16 will be discontinued from the study.

3.1.3 Biologic-Failure Substudy

Approximately 50 subjects with AS who have failed not more than 1 biologic agent taken for AS due to inadequate efficacy response to an approved dose for at least 12 weeks and/or unacceptable safety/tolerability of a biologic agent (in the opinion of the Investigator) will be recruited into a separate substudy, conducted concurrently with the biologic-naïve main study (Section 3.1.1). A minimum of 50% of biologic failure subjects will be recruited due to inadequate efficacy response. Subjects will be randomized with 2:2:1 ratio to have 20 subjects each to receive either treatment with CC-99677 150 mg PO QD, CC-99677 60 mg PO QD, and 10 subjects to receive matching placebo, for 12 weeks in a Double-blind, Placebo-controlled Treatment Period followed by a 52-week Long-term Extension Period, and a 4-week Post-treatment Observational Follow-up Period (Figure 2).

At Week 12, subjects originally randomized to receive placebo will be re-randomized 1:1 to blinded CC-99677 (150 mg or 60 mg PO QD) through Week 64 or until early discontinuation. Subjects originally randomized to CC-99677 (150 mg or 60 mg PO QD) will continue their current

dose through Week 64) or until early discontinuation. Subjects who do not achieve an ASAS20 at Week 16 will be discontinued from the study.

Subjects will remain in the study for a maximum of 74 weeks and will be required to attend a total of 16 study visits (from Screening Visit to Observational Follow-up Visit). Subjects who discontinue prematurely from the study at any time will be required to complete an Early Termination Visit and enter the 4-week Post-treatment Observational Follow-up Period. Other aspects of the substudy will be carried out as described in Section 6 for subjects recruited into the biologic-naïve main study.

3.1.4 Interim Analysis

An interim analysis (IA) will be conducted when approximately 30 subjects in the biologic-naïve main study complete 12 weeks of treatment. A Steering Committee (SC) comprised of both unblinded BMS committee members independent of the Study Team and external AS expert(s) will review the data from the IA and will convey one of the following decisions to the blinded study team:

- Continue the study without modification
- Terminate the study for futility
- Discontinue a treatment group based on preliminary assessment of dose-dependent risk-benefit
- Add an additional dose cohort (dose not to exceed 150 mg)

If the SC determines that an additional dose cohort is needed, then the additional dose cohort will be initiated in the biologic-naïve main study only as described in Section 3.1.2.

The SC will not play a role in the study conduct and the blind will be maintained for persons responsible for the ongoing conduct and management of the study. The SC may oversee additional IAs. Operational details for the SC will be detailed in a separate SC charter. Additional interim analyses may be conducted.

3.1.5 Primary Analysis

The primary analysis for the biologic-naive cohort will be performed when all subjects in this cohort have completed 12 weeks of treatment, or have discontinued early, and all expected data are collected (Section 9). The primary analysis for the biologic-failure cohort will be performed when all subjects in this cohort have completed 12 weeks of treatment, or have discontinued early, and all expected data are collected (Section 9). Following the database lock, the remainder of the Long-term Extension Period will be conducted in a Sponsor-unblinded fashion. All subjects and site personnel will remain blinded throughout the duration of the trial.

The primary analysis may support the selection of a single efficacious dose of CC-99677 or dropping a dose due to insufficient benefit-risk. In either of these events, subjects in the Long-term Extension may be reallocated to the selected CC-99677 dose(s) through Week 64.

Primary analysis of efficacy of subjects enrolled in the biologic-failure substudy will be separate from that of the biologic-naive main study.

3.1.6 Safety Monitoring Team

In addition to daily safety monitoring conducted by Investigators and individual study personnel, cumulative and interval blinded AEs, SAEs, discontinuations and laboratory findings will be reviewed by a Safety Management Team (SMT) internally at Celgene. The SMT is comprised of lead representatives from multiple Celgene functions. The scope, conduct, processes, and accountabilities are specified by Celgene Standard Operating Procedure (SOP).

3.1.7 Independent External Data Monitoring Committee

Although the Celgene study staff will monitor safety on an ongoing basis throughout the study, formal unblinded safety and efficacy assessments of the study data will be performed by an independent external Data Monitoring Committee (DMC). The DMC will include physician experts with experience in treating subjects with AS and a statistician, all of whom are not otherwise involved in the study conduct and in whom there is no identified conflict of interest. The external DMC may make a recommendation to stop the study at any time based on an assessment of the overall Benefit/Risk based on clinical data. Operational details for the DMC will be detailed in a separate DMC charter.

3.1.7.1 Study Stopping Criteria (Criteria for Urgent Review of Clinical Data by the DMC)

The study enrollment will be stopped, and the clinical data will be reviewed by the DMC if any of the following occur:

- If 1 subject experiences a drug-related Grade 5 AE by Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 grading system
- If 2 subjects develop drug-related Grade 4 AEs by CTCAE Version 5.0 grading system
- If 3 subjects develop the same drug-related Grade 3 AEs by CTCAE Version 5.0 grading system

Following urgent review by the DMC, the overall risk-benefit of continuing the trial will be assessed and a decision on whether to terminate the trial will be made.

Note: In the case of Grade 3 or 4 safety laboratory AEs that are considered at least possibly drug-related, repeat all abnormal safety laboratory assessments within 48 to 72 hours to refute or confirm the findings. The decision to temporarily interrupt the IP will be based on the Investigator's clinical judgment.

3.1.8 Steering Committee

A SC, comprised of both unblinded BMS committee members independent of the Study Team and external AS expert(s) who are not member(s) of the DMC, will review the data from the IA and will convey decisions to the blinded study team, as described in Section 3.1.4. The SC may oversee additional IAs. Operational details for the SC will be detailed in a separate SC charter.

Figure 1: Biologic-naïve Main Study Design

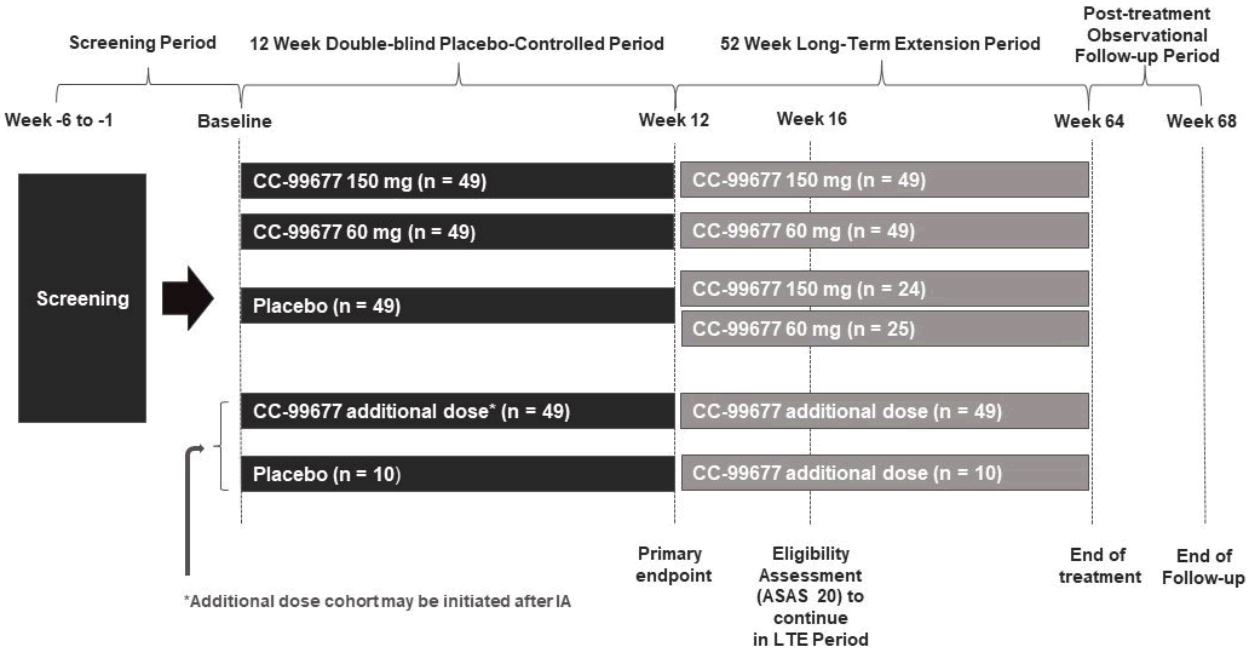
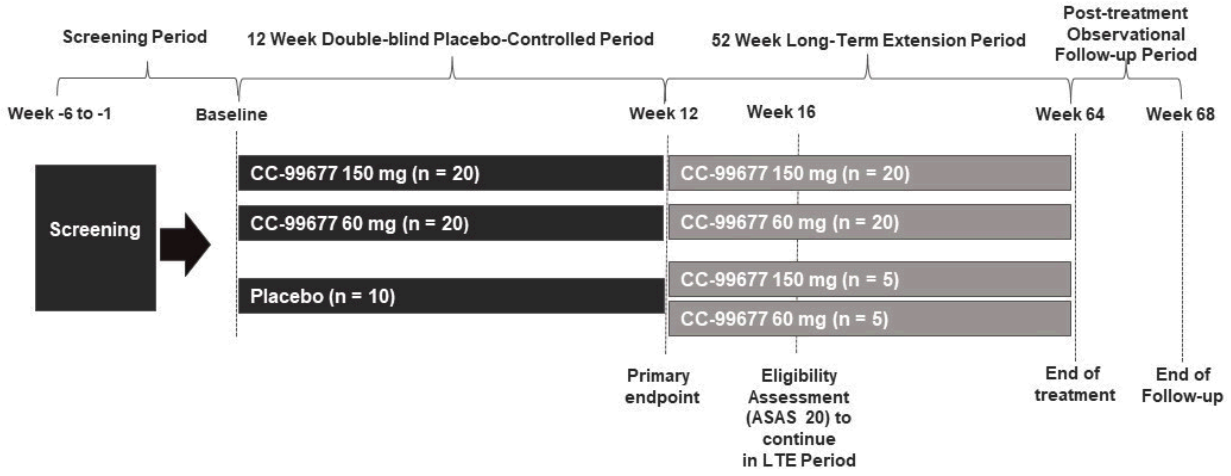


Figure 2: Biologic-failure Substudy Design



3.2 Study Duration for Subjects

The study will have a total duration of up to 74 weeks. The study will consist of up to a 6-week Screening Period; 12-Week Double-blind Placebo-controlled Treatment Period; a 52-Week Long-term Extension; and a 4-Week Post-treatment Observational Follow-up Period.

3.3 End of Trial

The End of Trial is defined as either the date of the last visit of the last subject to complete the Post-treatment Follow-up, or the date of receipt of the last data point from the last subject that is required for primary, secondary and/or exploratory analysis, as prespecified in the protocol, whichever is the later date.

4 STUDY POPULATION

4.1 Number of Subjects

Approximately 147 subjects diagnosed with AS will be recruited for the biologic-naïve main study. If an additional dose cohort is initiated after the interim analysis, an additional 59 subjects will be recruited for the biologic-naïve main study, yielding a total of approximately 206 subjects for the biologic-naïve main study. Approximately 50 subjects will be recruited for the biologic-failure substudy.

4.2 Inclusion Criteria for the Biologic-naïve Main Study

Subjects must satisfy the following criteria to be enrolled in the study:

General Patient Population:

1) Subject is ≥ 18 and ≤ 65 years of age at the time of signing the informed consent form (ICF)
2) Subject must understand and voluntarily sign an ICF prior to any study-related assessments/procedures being conducted
3) Subject is willing and able to adhere to the study visit schedule and other protocol requirements
4) Females of childbearing potential (FCBP) must either commit to true abstinence* from heterosexual contact (which must be reviewed on a monthly basis and source documented) or agree to use one highly effective method of contraception and be able to comply with highly effective contraception without interruption, 28 days prior to starting IP, during the study therapy (including dose interruptions), and for 28 days after discontinuation of IP. Highly effective methods of contraception are those that alone or in combination result in a failure rate based on a Pearl index of less than 1% per year when used consistently and correctly. Approved options for birth control are:
   - Any one of the following highly effective methods: combined (estrogen- and progestogen-containing) hormonal contraceptives; progestogen-only hormonal contraceptives associated with inhibition of ovulation; intrauterine device (IUD); tubal ligation (tying your tubes); or a partner with a vasectomy

     Note: A female of childbearing potential (FCBP) is a female who: 1) has achieved menarche, 2) has not undergone a hysterectomy or bilateral oophorectomy or salpingectomy, or 3) has not been naturally postmenopausal for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months), amenorrhea following cancer therapy does not rule out childbearing potential.
5) Females of childbearing potential (FCBP) must not be pregnant and must have two negative pregnancy tests as verified by the Investigator prior to starting investigational product (IP). She must agree to ongoing pregnancy testing during the course of the study, and after end of study treatment. This applies even if the subject practices true abstinence* from heterosexual contact
6) Male subjects must:
   a) Practice true abstinence* (which must be reviewed on a monthly basis) or agree to use condoms not made out of natural [animal] membrane during sexual contact with a pregnant female or a female of childbearing potential while participating in the study, during dose interruptions and for 28 days after the last dose of IP, even if he has undergone a vasectomy. Any nonpregnant FCBP partner of a male subject must use an approved method of effective

contraception, without interruption, during the study (including any dose interruptions) and for at least 28 days after the last dose of IP

* *True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject and is accepted as a contraceptive method per local guidelines or practice. Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception*

7) Subjects agrees to limit ultraviolet (UV) exposure during the study and for at least 3 days after final dose of IP by adhering to the photoprotection guidelines below:
   a) Avoid being outdoors when the sun is at maximal intensity
   b) Avoid tanning beds or sunbathing
   c) Wear clothing that would protect from the sun such as long-sleeves, sunglasses, and a hat
   d) Use sunscreen lotion in accordance with local guidance

Disease Specific Parameters:

8) Subject has a diagnosis of AS fulfilling the modified New York criteria for AS (van der Linden, 1984) (APPENDIX B) with radiologic entry criteria documented by central reading (historical radiographs up to 12 months old are considered acceptable)
9) Subject has active axial disease at Screening and Baseline defined by a BASDAI score ≥ 4 (0 to 10 scale) and Total Back Pain, as measured by a NRS ≥ 4 (0 to 10 scale)

Prior and Current Treatment:

10) Subject must have failed prior treatment with at least 2 NSAIDs (at the maximum tolerated dose) for at least 4 weeks each, with documented inadequate response

    Note: Concomitant use of one NSAID or cyclooxygenase 2 inhibitor for AS is permitted provided that the subject is receiving a stable dose 2 weeks prior to Baseline and subject agrees to maintaining this dose until Week 64, unless dose is reduced, or treatment is discontinued due to safety and/or tolerability concerns.
11) Subject has never received a biologic therapy (eg, TNF antagonist or monoclonal antibody [mAb] against IL-17A) for the treatment of AS
12) Concomitant use of sulfasalazine is permitted provided it is used at a stable dose for at least 4 weeks prior to Baseline (Day 1 of study)

4.3 Exclusion Criteria for Biologic-naïve Main Study

Disease Specific Requirements:

1) Subject has radiographic evidence of total ankylosis of the spine
2) Subject has uncontrolled severe psoriasis (defined as Body Surface Area > 10%)
3) Subject has active inflammatory bowel disease (eg, ulcerative colitis, Crohn's disease) within 6 months of Screening Visit based on clinical assessment
4) Presence of acute anterior uveitis within 4 weeks prior to Screening Visit
5) Autoimmune diseases such as, but not limited to: systemic lupus erythematous, mixed connective tissue disease, multiple sclerosis, rheumatoid arthritis, gout, reactive arthritis, vasculitis

6) Subject has concomitant fibromyalgia, which symptoms or therapy for, in the opinion of the Investigator, will significantly impact the assessment of AS disease manifestations and activity
7) Subject has clinically significant back pain caused by diseases other than AS (eg, degenerative disc disease, osteoarthritis) which symptoms or therapy for, in the opinion of the Investigator, will significantly impact the assessment of AS disease manifestations and activity

Prior and/or Current Medications/Therapies:

8) Concurrent treatment or treatment within the 6 months prior to Baseline with JAK inhibitors, cell depleting biologic agents (eg, anti-CD20 [eg, rituximab], anti-CD4, anti-CD3), denosumab, anti-IL-6 [eg, tocilizumab, sarilumab], and anti-IL-23 (eg, ustekinumab)
9) Use of oral corticosteroids (prednisone or equivalent) > 10 mg/day for ≥ 2 weeks prior to Baseline Visit

   Note: Concomitant use of prednisone ≤ 10 mg is permitted provided it is taken at a stable dose within 4 weeks of Baseline Visit.

10) Use of any intramuscular, intravenous or intraarticular corticosteroid treatment within 4 weeks of the Baseline Visit
11) Use of vitamin K antagonists (eg, warfarin)
12) Use of diclofenac or sulindac
13) Treatment with isoniazid within 4 weeks of the Baseline Visit and at any time during the Screening Period, up through the first dose of IP
14) Use of any medication known to be either a moderate or strong inhibitor or a moderate or strong inducer of CYP3A4/5 (see APPENDIX C, Table 7) until study completion. There must be a washout period of 5 PK half-lives of any such drug used by the subject prior to Baseline Visit. The Medical Monitor or designee should be queried in case of uncertainty.
15) Use of any medication known to be either moderate or strong inhibitor or moderate or strong inducer of P-gp until study completion (see APPENDIX C, Table 8). There must be a washout period of 5 PK half-lives of any such drug used by the subject prior to Baseline Visit. The Medical Monitor or designee should be queried in case of uncertainty.
16) Use of any medication known to be a strong BCRP inhibitor until study completion (see APPENDIX C, Table 8). There must be a washout period of 5 PK half-lives of any such drug used by the subject prior to Baseline Visit. The Medical Monitor or designee should be queried in case of uncertainty.
17) Use of any medications that are substrates of one or more of the transporters P-gp, OCT1, OATP1B1, and OATP1B3 **and** have a narrow therapeutic index (eg, methotrexate, digoxin, cyclosporine, mycophenolic acid, and leflunomide). Additional examples can be found in APPENDIX C, Table 9.

Note:

- *BCRP substrates with a narrow therapeutic index (eg, prazosin) should be used with caution (APPENDIX D Table 10). Sulfasalazine is not excluded based on results from CC-99677-CP-002 (see Section 1.4.2).*
- *At least 1-month washout period prior to randomization is required for the conventional synthetic disease-modifying antirheumatic drugs (DMARDs), except for leflunomide, which has to be discontinued for 15 weeks prior to randomization unless a cholestyramine*

washout has been performed. Subjects should not discontinue any of the above synthetic DMARDS for the sole purpose of participating in this trial.

18) Participation in any study of an investigational drug, including those for COVID-19, may not participate in BMS clinical trials until the protocol specific washout period is achieved (one month or 5 PK or PD [if known] half-lives of the investigational drug, whichever is longer prior to Screening Visit), or have participated in more than one study with an investigational agent for AS within one year prior to Screening Visit

19) If a study participant has received a COVID-19 vaccine prior to screening, enrollment must be delayed until the biologic impact of the vaccine is stabilized, as determined by discussion between the investigator and the BMS clinical trial physician, (See Section Section 8.4)

20) Any botanical preparations (eg, herbal supplements or traditional Chinese medicines derived from plants, minerals, or animals) intended to treat AS or other immunological diseases within 4 weeks prior to Study Day 1

General Health:

21) Major surgery performed within 8 weeks prior to Screening Visit or planned within 64 weeks after Screening Visit

22) Evidence of significant cardiac, renal, neurologic, psychiatric, endocrinologic (including uncontrolled diabetes, defined as hemoglobin A1c (HbA1c) ≥ 9.5%), metabolic, hepatic disease or gastrointestinal disease

Note: HbA1c should only be collected in subjects with a known history of diabetes.

23) History or evidence of congenital and/or acquired immunodeficiencies (eg, common variable immunodeficiency, human immunodeficiency virus [HIV], etc.)

24) The subject has serologic tests during Screening (Table 3) consistent with infection with either hepatitis B or hepatitis C, and/or confirmed history of hepatitis B or hepatitis C infection. Subjects with isolated positive hepatitis B surface antibody are not excluded.

25) The subject has evidence on chest X-ray of lung pathology that, in the opinion of the Investigator, would pose an unacceptable safety risk in the event of further participation in the trial

Note: Examples of X-ray findings that would preclude further trial participation include active lower tract respiratory infection or suspected malignancy. If comparison with prior X-rays demonstrates unchanged findings, subject may be eligible for further participation following discussion with medical monitor.

26) History of active or latent tuberculosis (TB) infection, unless there is medical record documentation of successful completion of a standard course of treatment considered appropriate

Note: Documentation of adequate treatment for TB must be obtained and reviewed by the Medical Monitor prior to randomization. In such subjects, the QuantiFERON-TB Gold test is not needed. Instead, a chest radiograph, obtained within the 12 weeks prior to Screening or during Screening, without changes suggestive of active TB infection as determined by a qualified radiologist, is sufficient to permit further participation in the study for these subjects.

If the subject lives in, or has emigrated from, a TB high burden country (APPENDIX E, then further study participation requires documentation of adequate treatment for either active or

latent TB infection within 2 years of the Screening Visit. For subjects residing in, or emigrating from, a TB high burden country and treated for TB more than 2 years prior to the Screening Visit, further trial participation requires a negative QuantiFERON-TB Gold test during screening.

27) History of active or latent TB infection, and subject lives in, or has emigrated from, a multidrug-resistant (MDR) TB high burden country (APPENDIX F)

28) Subject has had a household contact with a person with active TB and subject did not receive appropriate and documented prophylaxis for TB

Note: Household contact is a person who shared the same enclosed living space as the index case for one or more nights or for frequent or extended daytime periods during the 3 months before the start of current treatment

29) Active or history of recurrent bacterial, viral, fungal, mycobacterial or other infections (including, but not limited to, atypical mycobacterial disease and herpes zoster), or any major episode of infection requiring hospitalization or treatment with intravenous or oral antibiotics within 4 weeks of the Screening Visit and at any time during the Screening Period, up through the first dose of IP.

Note: Additionally, in the case of prior SARS-CoV-2 infection, symptoms must have completely resolved and based on investigator assessment in consultation with the clinical trial physician, there are no sequelae that would place the participant at a higher risk of receiving investigational treatment. In addition, subject may not participate in the trial if participation is deemed inconsistent with local guidelines related to SARS-CoV-2.

30) Administration of a live or attenuated vaccine within 4 weeks prior to Baseline

31) History of malignancy (exceptions: excised and cured basal/squamous cell skin carcinomas, and cervical carcinoma in situ with no recurrence in 5 years)

32) Subject has any other significant medical/psychiatric condition or laboratory abnormality that would prevent the subject from participating in the study or places him/her at unacceptable risk for participation in the study

33) Subject with any of the following laboratory criteria:

- White blood cell count (WBC) < $3500/mm^3$ (< 3.5 X 10^9/L) or > $14,000/mm^3$ (> 14 X 10^9/L)
- Neutrophil count < $1500/mm^3$ (< 1.5 X 10^9/L)
- Platelet count < $100,000/mm^3$ or > $500,000/mm^3$
- Serum creatinine > 1.5 mg/dL (> 132.6 µmol/L)
- Aspartate aminotransferase (AST) > 1.5 X upper limit of normal (ULN)
- Alanine aminotransferase (ALT) > 1.5 X ULN
- Total bilirubin > 2 X ULN
- Hemoglobin < 8.5 g/dL (< 85 g/L)

34) Subject engages in or has a history of systemic use (eg, smoking, ingestion) of marijuana, tetrahydrocannabinol (THC), cannabidiol (CBD oil), or cannabinoids within 4 weeks of randomization; or has a history of recreational drug abuse or significant alcohol consumption

for a period of more than 3 consecutive months within 1 year prior to Screening. Significant alcohol consumption is defined as more than 14 oz (420 mL) per week in females and more than 21 oz (630 mL) per week in males, on average (1 oz/30 mL of alcohol is present in one 12 oz/360 mL beer, one 4 oz/120 mL glass of wine, or a 1 oz/30 mL measure of 40% proof alcohol)

Subjects must also agree not to engage in recreational drug abuse, significant alcohol consumption as described above, or systemic use of marijuana, THC, CBD oil, or cannabinoids for the duration of the study.

35) Subject has history of drug-related photosensitivity
36) Subject has a known hypersensitivity to CC-99677 or any ingredient in the IP
37) Females of childbearing potential (FCBP) must not be lactating or breastfeeding during the study period.
38) Females of childbearing potential (FCBP) must not donate eggs during the study or within 28 days of the last dose of study drug
39) Males must not donate sperm or semen during the study or within 28 days of the last dose of study drug

4.4 Inclusion Criteria for Biologic-Failure Substudy

Subjects participating in the biologic-failure substudy must:

1) Meet all the inclusion criteria for subjects in the biologic-naïve main study except Inclusion Criterion 11
2) Have discontinued one and only one biologic (eg, TNF antagonist or monoclonal antibody [mAb] against IL-17A) for AS, either due to inadequate response to an approved biologic dose for at least 12 weeks and/or unacceptable safety/tolerability with at least one dose of a biologic agent (in the opinion of the Investigator). The following minimum washout periods prior to Baseline must be adhered to for the biologics or their corresponding biosimilars:
   - etanercept: 4 weeks
   - infliximab: 8 weeks
   - adalimumab, certolizumab pegol, golimumab, ixekizumab: 12 weeks
   - secukinumab: 24 weeks

   Note: Any questions regarding washout periods prior to Baseline should be directed to the Medical Monitor. Subjects should not discontinue any of the above biologics for the sole purpose of participating in this trial

4.5 Exclusion Criteria for Biologic-Failure Substudy

1) Subjects participating in the biologic-failure substudy must not meet any of the exclusion criteria listed for subjects in the biologic-naïve main study

5 TABLE OF EVENTS

Table 3: Table of Events, Screening, Baseline and 12-Week Placebo-Controlled Treatment Period

	Screening	Placebo-controlled Treatment Period					Early Termination (ET)
Visit Number	**1**	**2 (Baseline)**	**3**	**4**	**5**	**6**	**ET[a]**
Week	**-6 to -1**	**0 (Day 1)**	**2 (± 3 days)**	**4 (± 3 days)**	**8 (± 3 days)**	**12 (± 5 days)**	**NA**
General Assessments							
Informed Consent	X	-	-	-	-	-	-
Optional informed consent for PG	X	-	-	-	-	-	-
Inclusion/Exclusion criteria	X	X	-	-	-	-	-
Demographics	X	-	-	-	-	-	-
Complete medical history and disease history	X	-	-	-	-	-	-
Prior/concomitant medications	Continuous, starting after the informed consent form is signed through 28 days after end of treatment						
Prior AS therapies	X	-	-	-	-	-	-
Prior/concomitant procedures	Continuous, starting after the informed consent form is signed through 28 after end of treatment						
QuantiFERON®-TB Gold ELISA[b]	X	-	-	-	-	-	-
HLA-B27 testing	-	X	-	-	-	-	-
Chest radiograph[c]	X	-	-	-	-	-	-
Viral serologies[d]	X	-	-	-	-	-	-
Postmenopausal testing: estradiol and follicle-stimulating hormone (for women 50-55 years with undocumented status)	X	-	-	-	-	-	-
Hemoglobin A1c	X	-	-	-	-	-	-
Sacroiliac joint radiographs[e]	X	-	-	-	-	-	-

Table 3: Table of Events, Screening, Baseline and 12-Week Placebo-Controlled Treatment Period

	Screening	Placebo-controlled Treatment Period					Early Termination (ET)
Visit Number	**1**	**2 (Baseline)**	**3**	**4**	**5**	**6**	**ET[a]**
Week	**-6 to -1**	**0 (Day 1)**	**2 (± 3 days)**	**4 (± 3 days)**	**8 (± 3 days)**	**12 (± 5 days)**	**NA**
Safety and Laboratory Assessments							
Adverse events[f]	Continuous starting after the informed consent form is signed through 28 days after end of treatment						
Complete physical examination	X	-	-	-	-	-	X
Limited physical examination	-	X	X	X	X	X	-
Vital signs and weight	X	X	X	X	X	X	X
Height	X	-	-	-	-	-	-
12-lead ECG	X	X	-	X	X	X	X
Hematology laboratory evaluations	X	X	X	X	X	X	X
Chemistry laboratory evaluations	X	X	X	X	X	X	X
Lipid panel	X	X	-	X	X	X	X
PT/INR	-	X	X	X	X	X	X
Pregnancy testing[g]	X	X	X	X	X	X	X
Pregnancy counseling for FCBP and male subjects with female partners of childbearing potential	Continuous starting after the informed consent form is signed through 28 days after end of treatment						
Efficacy Assessments							
BASDAI	X	X	-	X	X	X	X
BASFI	-	X	-	X	X	X	X
Patient Global Assessment of Disease	-	X	-	X	X	X	X
Total Back Pain NRS	X	X	-	X	X	X	X

Table 3: Table of Events, Screening, Baseline and 12-Week Placebo-Controlled Treatment Period

	Screening	Placebo-controlled Treatment Period					Early Termination (ET)
Visit Number	**1**	**2 (Baseline)**	**3**	**4**	**5**	**6**	**ET[a]**
Week	**-6 to -1**	**0 (Day 1)**	**2 (± 3 days)**	**4 (± 3 days)**	**8 (± 3 days)**	**12 (± 5 days)**	**NA**
Nighttime back pain NRS	-	X	-	X	X	X	X
BASMI Linear	-	X	-	X	X	X	X
Occiput to wall measurement	-	X	-	X	X	X	X
Chest expansion	-	X	-	X	X	X	X
Enthesitis evaluation[h]	-	X	-	X	X	X	X
Peripheral joint count evaluation	-	X	-	X	X	X	X
MRI of sacroiliac joints AND spine (SPARCC method)[i]	-	X	-	-	-	X	X
Sparse Pharmacokinetic Assessments							
PK blood draw (sparse)[j]	-	X	-	X	X	X	-
Intense Pharmacokinetic, Biomarkers and Pharmacodynamic Assessments at Selected Sites							
PK blood draw (intense)[k]	-	-	-	X	-	-	-
Blood draw for PD (target engagement)[l]	-	X	-	X	X	X	-
Blood draw for PD (ex vivo osteoclastogenesis)[m]	-	**X**	-	-	-	**X**	-
Biomarkers and Pharmacodynamic Assessments at All Sites							
hsCRP[n]	X	X	X	X	X	X	X
Serum bone turnover markers[o]	-	X	-			X	-
Serum TNF-α and IL-17A	-	X	-	X	X	X	-
Serum cytokines and other proteins by proteomics	-	X	-	X	X	X	-

Table 3: Table of Events, Screening, Baseline and 12-Week Placebo-Controlled Treatment Period

	Screening	Placebo-controlled Treatment Period					Early Termination (ET)
Visit Number	**1**	**2 (Baseline)**	**3**	**4**	**5**	**6**	**ET[a]**
Week	**-6 to -1**	**0 (Day 1)**	**2 (± 3 days)**	**4 (± 3 days)**	**8 (± 3 days)**	**12 (± 5 days)**	**NA**
RNA gene expression analysis (whole blood sample)	-	X	-	X	X	X	-
SARS-CoV-2 serology for biobanking[p]		X	-	-	-	-	X
SARS-CoV-2 Serology for Documented or Suspected Infection [q]	Only collected approximately 4 weeks after SARS-CoV-2 infection						
DNA blood draw (whole blood)[r]	-	X	-	-	-	-	-
Health-Related Quality of Life Assessments							
ASQoL	-	X	-	-	-	X	X
SF-36	-	X	-	-	-	X	X
ASAS Health Index	-	X	-	-	-	X	X
Investigational Product							
Dispense IP	-	X	-	X	X	X	-
Return and count IP capsules	-	-	X	X	X	X	X

Abbreviations: AE = adverse event; AS = ankylosing spondylitis; ASAS Health Index = Assessment of SpondyloArthritis International Society Health Index; ASQoL = Ankylosing Spondylitis Quality of Life questionnaire; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; BASMI linear = Bath Ankylosing Spondylitis Metrology Index – Linear; β-hCG = beta human chorionic gonadotropin; CRF = case report form; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ET = early termination; EOT= end of treatment; FCBP = female of childbearing potential; HLA-B27 = human leukocyte antigen B27; hsCRP = high-sensitivity c-reactive protein; IL-17A = interleukin-17; IP = investigational product; MRI = magnetic resonance imaging; NA= not applicable; NRS = numerical rating scales; PD = pharmacodynamics; PG = pharmacogenetics; PK = pharmacokinetics; RNA = ribonucleic acid; SAE = serious adverse event; SF-36 = Short Form (36) Health Survey; SPARCC = Spondyloarthritis Research Consortium of Canada; TB = tuberculosis; TNF-α = tumor necrosis factor-alpha.

a. Subjects who discontinue the study prior to the Week 12 Visit will have an ET Visit.

b. QuantiFERON-TB Gold testing will be performed at Screening, only. Documentation of adequate treatment for TB must be obtained and reviewed by the Medical Monitor prior to randomization. In such subjects, the QuantiFERON-TB Gold test is not needed. Instead, a chest radiograph, obtained within the 12 weeks prior to Screening or during Screening, without changes suggestive of active TB infection as determined by a qualified radiologist, is sufficient to permit further participation in the study for these subjects. If the subject lives in, or has emigrated from, a TB high burden country then further study participation requires documentation of adequate treatment for either active or latent

TB infection within 2 years of the Screening Visit. For subjects residing in, or emigrating from, a TB high burden country and treated for TB more than 2 years prior to the Screening Visit, further trial participation requires a negative QuantiFERON-TB Gold test during screening.

c. Chest radiography (posterior anterior view) will be performed at Screening visit or obtained within 12 weeks prior to Screening for all subjects to determine eligibility.

d. Serology testing will be performed at Screening to determine the subject's immune status with respect to the following viruses: human immunodeficiency virus antibodies, hepatitis B surface antigen and core antibody, and hepatitis C virus antibody. Subjects who received hepatitis B vaccination and who test positive for hepatitis B surface antibody and negative for both hepatitis B surface antigen and hepatitis B core antibody are not excluded from the study.

e. Sacroiliac joint radiographs must be performed if not obtained within 12 months prior to Screening, to determine whether subjects fulfill the modified New York classification criteria. Sacroiliac joint films must be submitted for central reading to confirm eligibility. Images of the anterior-posterior lumbar spine will not be accepted for sacroiliac joint examination.

f. Adverse events collected from time of consent. All AEs (SAEs or non-serious AEs) related to SARS-CoV-2 infection are collected from time of consent and continuously during the study including at the safety follow up visit. After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and non-serious AEs, including SARS-COV-2 will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the participant is lost to follow-up. COVID-19 related AEs/SAEs will be captured in specific clinical safety program (CSP) case report form (CRF) pages

g. Females of childbearing potential must have a negative serum pregnancy test result at Screening, and negative urine and serum pregnancy test result at Baseline and all subsequent visits. A negative urine pregnancy test result is required prior to IP administration. If the urine pregnancy test is indeterminate, confirmation retesting on serum is required and IP must be held pending negative serum pregnancy test result. If the urine pregnancy test is positive IP must be discontinued and confirmation retesting on serum is required (see Section 10.4).

h. Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) should be obtained in all subjects.

i. MRI of sacroiliac joint AND spine – SPARCC methodology must be performed between Visits 1 and 2 inclusive, as well as at Visit 6 or Early Termination Visit. If Early Termination Visit occurs before Week 6, then MRI of sacroiliac joint should not be done. All images will be submitted for central reading.

j. Sparse PK samples will be collected in all subjects at pre-specified time points (See Section 6.7.1). For subjects who take IP in the evening, IP will be taken at 5 PM the day prior to the sparse PK collections. On the day of sparse PK sample collection, IP must be taken in the morning and at the study site. The actual times of drug administration and PK blood sample collections will be recorded in the source documents and CRF.

k. Intense PK samples will only be performed at selected sites and will be collected in subjects predose and 0.5, 1, 2, 3, 6, 8, and 12 hours postdose. IP must be taken at the study site after collection of the pre-dose PK blood sample. The actual times of drug administration and PK blood sample collections will be recorded in the source documents and CRF. This planned PK schedule may be modified; if modified, the total number of minimal time points per subject will not exceed 8 draws per visit.

l. Blood draw for PD (target engagement) will only be performed at selected sites and in a subset of subjects participating in the study.

m. Blood draw for PD (ex vivo osteoclastogenesis) will only be performed at selected sites and in a subset of subjects participating in the study

n. The subject's serum CRP will be measured using hsCRP. Post-baseline results are to be blinded.

o. Serum bone turnover marker samples will be collected under fasted conditions. Subjects must not have received high-dose biotin supplements (multivitamins are allowable) within 72 hours prior to sample collection.

p. Serum collected to be used for measurements of anti-SARS-CoV-2 serology (anti-SARS-CoV-2 total or IgG [see Section 6]) per national and local guidelines.

q. Serum should also be collected approximately 4 weeks after a documented or suspected SARS-CoV-2 infection (Section 6).

r. Pharmacogenetic testing will only be performed when an optional informed consent is provided from the subject.

Table 4: Table of Events, Long-term Extension Period (52- Weeks)

	Long-Term Extension Period (1 Year)									Early Termination (ET)	Observational Follow-up
Visit Number	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15 (EOT)**	**ET[a]**	**16**
Week	**14 (± 3 days)**	**16[b] (± 3 days)**	**20 (± 3 days)**	**24 (± 3 days)**	**32 (± 3 days)**	**40 (± 3 days)**	**48 (± 3 days)**	**56 (± 3 days)**	**64 (± 3 days)**	**NA**	**4 Weeks after Last Dose (± 3 days)**
General Assessments											
Concomitant medications	Continuous, starting after the informed consent form is signed through 28 days after end of treatment										
Prior/concomitant procedures	Continuous, starting after the informed consent form is signed through 28 days after end of treatment										
Safety and Laboratory Assessments											
Adverse events[c]	Continuous, starting after the informed consent form is signed through 28 days after end of treatment										
Complete physical examination	X	-	-	-	-	-	-	-	X	X	X
Limited physical examination	-	X	X	X	X	X	X	X		-	
Vital signs and weight	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X	X	-	X	X	X	X	X	X	X	X
Hematology laboratory evaluations	X	X	X	X	X	X	X	X	X	X	X
Chemistry laboratory evaluations	X	X	X	X	X	X	X	X	X	X	X
Lipid panel	-	X	X	X	X	X	X	X	X	X	X
PT/INR	X	X	X	X	X	X	X	X	X	X	X
Pregnancy testing[d]	X	X	X	X	X	X	X	X	X	X	X

Table 4: Table of Events, Long-term Extension Period (52- Weeks)

	Long-Term Extension Period (1 Year)									Early Termination (ET)	Observational Follow-up
Visit Number	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15 (EOT)**	**ET[a]**	**16**
Week	**14 (± 3 days)**	**16[b] (± 3 days)**	**20 (± 3 days)**	**24 (± 3 days)**	**32 (± 3 days)**	**40 (± 3 days)**	**48 (± 3 days)**	**56 (± 3 days)**	**64 (± 3 days)**	**NA**	**4 Weeks after Last Dose (± 3 days)**
Pregnancy counseling for FCBP and male subjects with female partners of childbearing potential	Continuous starting after the informed consent form is signed through 28 days after end of treatment										
Efficacy Assessments											
BASDAI	-	X	X	X	-	-	X	-	X	X	-
BASFI	-	X	X	X	-	-	X	-	X	X	-
Patient Global Assessment of Disease	-	X	X	X	-	-	X	-	X	X	-
Total Back Pain NRS	-	X	X	X	-	-	X	-	X	X	-
Nighttime back pain NRS	-	X	X	X	-	-	X	-	X	X	-
BASMI Linear	-	X	X	X	-	-	X	-	X	X	-
Occiput to wall measurement	-	X	X	X	-	-	X	-	X	X	-
Chest expansion	-	X	X	X	-	-	X	-	X	X	-
Enthesitis evaluation[e]	-	X	X	X	-	-	X	-	X	X	-
Peripheral joint count evaluation	-	X	X	X	-	-	X	-	X	X	-
Sparse Pharmacokinetic Assessments											
PK blood draw (sparse)[f]	-	X	X	X	-	-	-	-	-	-	-

Table 4: Table of Events, Long-term Extension Period (52- Weeks)

	Long-Term Extension Period (1 Year)									Early Termination (ET)	Observational Follow-up
Visit Number	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15 (EOT)**	**ET[a]**	**16**
Week	**14 (± 3 days)**	**16[b] (± 3 days)**	**20 (± 3 days)**	**24 (± 3 days)**	**32 (± 3 days)**	**40 (± 3 days)**	**48 (± 3 days)**	**56 (± 3 days)**	**64 (± 3 days)**	**NA**	**4 Weeks after Last Dose (± 3 days)**
Biomarkers and Pharmacodynamic Assessments at All Sites											
hsCRP[g]	X	X	X	X	-	-	X	-	X	X	-
Serum bone turnover markers[h]	-	-	-	X	-	-		-	X	-	-
Serum TNF-α and IL-17A	-	-	-	X	-	-	X	-	X	-	-
Serum cytokines and other proteins by proteomics	-	-	-	X	-	-	X	-	X	-	-
RNA gene expression analysis (whole blood sample)	-	-	-	X	-	-	-	-	X	-	-
SARS-CoV-2 serology[i]	-	-	-	-	-	-	-	-	X	X	-
SARS-CoV-2 serology for documented or suspected infection [j]	Only collected approximately 4 weeks after confirmed or suspected SARS-CoV-2 infection										
Health-Related Quality of Life Assessments											
ASQoL	-	-	-	X	-	-	-	-	X	X	-
SF-36	-	-	-	X	-	-	-	-	X	X	-
ASAS Health Index	-	-	-	X	-	-	-	-	X	X	-

Table 4: Table of Events, Long-term Extension Period (52- Weeks)

	Long-Term Extension Period (1 Year)									Early Termination (ET)	Observational Follow-up
Visit Number	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15 (EOT)**	**ET[a]**	**16**
Week	**14 (± 3 days)**	**16[b] (± 3 days)**	**20 (± 3 days)**	**24 (± 3 days)**	**32 (± 3 days)**	**40 (± 3 days)**	**48 (± 3 days)**	**56 (± 3 days)**	**64 (± 3 days)**	**NA**	**4 Weeks after Last Dose (± 3 days)**
Investigational Product											
Dispense IP	-	X	X	X	X	X	X	X	-	-	-
Return and count IP capsules	-	X	X	X	X	X	X	X	X	X	-

Abbreviations: AE = adverse event; AS = ankylosing spondylitis; ASAS Health Index = Assessment of SpondyloArthritis International Society Health Index; ASQoL = Ankylosing Spondylitis Quality of Life questionnaire; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; BASMI linear = Bath Ankylosing Spondylitis Metrology Index – Linear; β-hCG = beta human chorionic gonadotropin; CRF = case report form; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ET = early termination; EOT= end of treatment; FCBP = female of childbearing potential; HLA-B27 = human leukocyte antigen B27; hsCRP = high-sensitivity c-reactive protein; IL-17A = interleukin-17; IP = investigational product; MRI = magnetic resonance imaging; NA= not applicable; NRS = numerical rating scales; PD = pharmacodynamics; PG = pharmacogenetics; PK = pharmacokinetics; RNA = ribonucleic acid; SAE = serious adverse event; SF-36 = Short Form (36) Health Survey; SPARCC = Spondyloarthritis Research Consortium of Canada; TB = tuberculosis; TNF-α = tumor necrosis factor-alpha.

a. Subjects who discontinue the study prior to the Week 64 Visit will have an ET Visit.

b. Subjects who do not achieve an ASAS20 at Week 16 will be discontinued from the study

c. Adverse events collected from time of consent. All AEs (SAEs or non-serious AEs) related to SARS-CoV-2 infection are collected from time of consent and continuously during the study including at the safety follow up visit. After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and non-serious AEs, including SARS-COV-2 will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the participant is lost to follow-up. COVID-19 related AEs/SAEs will be captured in specific clinical safety program (CSP) case report form (CRF) pages.

d. Females of childbearing potential must have a negative urine and serum pregnancy test result at all visits. A negative urine pregnancy test result is required prior to IP administration. If the urine pregnancy test is indeterminate, confirmation retesting on serum is required and IP must be held pending negative serum pregnancy test result. If the urine pregnancy test is positive IP must be discontinued and confirmation retesting on serum is required (see Section 10.4). At home urine pregnancy test kits will be provided to maintain monthly pregnancy testing between Weeks 24 and 64.

e. Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) should be obtained in all subjects.

f. Sparse PK samples will be collected in all subjects at pre-specified time points (See Section 6.7.1). For subjects who take IP in the evening, IP will be taken at 5PM the day prior to the sparse PK collections. On the day of sparse PK sample collection, IP must be taken in the morning and at the study site. The actual times of drug administration and PK blood sample collections will be recorded in the source documents and CRF.

g. The subject's serum CRP will be measured using hsCRP. Post-baseline results are to be blinded.

h. Serum bone turnover marker samples will be collected under fasted conditions. Subjects must not have received high-dose biotin supplements (multivitamins are allowable) within 72 hours prior to sample collection.

i. Serum collected to be used for measurements of anti-SARS-CoV-2 serology (anti-SARS-CoV-2 total or IgG [see Section 6]).
j. Serum should also be collected approximately 4 weeks after a documented or suspected SARS-CoV-2 infection (see Section 6).

6 PROCEDURES

The following procedures will be conducted according to the schedule indicated in Table of Events, Table 3 and Table 4.

Any questions regarding the protocol should be directed to the Medical Monitor or designee.

Signed informed consent forms (ICFs) must be obtained before any study evaluations are performed per local regulations during the course of the study.

6.1 Screening Period

Screening evaluations will be performed for all subjects to determine study eligibility. These evaluations must be completed within 6 weeks of Screening (Visit 1) unless noted otherwise below. Subjects are permitted to be re-screened once should they fail to meet the study criteria; however all rescreened subjects must be re-consented for the study.

Note: Subjects who fail the entry criteria due to a positive hepatitis B, hepatitis C or TB test result should not be rescreened for the study. Subjects who received hepatitis B vaccination and who test positive for hepatitis B surface antibody and negative for both hepatitis B surface antigen and hepatitis B core antibody are not excluded from the study.

Waivers to the protocol will not be granted during the conduct of this trial, under any circumstances.

Safety laboratory analyses and all assessments will be performed centrally. Screening laboratory values must demonstrate subject eligibility but may be repeated within the Screening window, if necessary.

The following will be performed at screening as specified in Table of Events, Table 3 after informed consent has been obtained:

- The Screening Visit should be registered in the interactive web response system (IWRS).
- Pharmacogenomics: The pharmacogenetic substudy is optional, and a separate consent will be signed for this assessment at Screening.
- Inclusion/exclusion criteria: Subjects must meet all inclusion criteria (Section 4.2) and must not have any of the conditions specified in the exclusion criteria (Section 4.3) to qualify for participation in the study. The subject's source documents must support his/her qualifications for the study.
- Demographics: Including initials, date of birth, sex, race, and ethnicity if allowed by local regulations.
- Complete medical history: All relevant medical conditions diagnosed or occurring prior to Screening should also be included. Specific information regarding AS diagnosis should also be included.
- Prior and concomitant medication evaluation: Including all medication (prescription and non-prescription, including vitamins) taken by the subject ≤ 28 days before Screening, including stop dates for medications prohibited in the study. All medications taken by the subject at any time during the study must also be recorded. Other key medications and therapies, such as

tuberculosis or relevant diseases, should also be recorded. Additional instructions can be found in the electronic case report form (eCRF) Completion Guidelines.

- Prior AS therapies: Including all previous treatment for AS.
- Prior and concomitant procedures: Including surgery, systemic or any other therapy for AS.
- Chest Radiograph: A chest radiograph (posterior anterior view) will be performed at Screening visit or obtained within 12 weeks prior to Screening for all subjects to determine eligibility.

  *Note: Examples of X-ray findings that would preclude further trial participation include active lower tract respiratory infection or suspected malignancy. If comparison with prior X-rays demonstrates unchanged findings, subject may be eligible f*or further participation following discussion with medical monitor.

- QuantiFERON-TB Gold test: A positive test or 2 successive indeterminate tests will disqualify the subject from further participation in the study.

  QuantiFERON-TB Gold testing is not needed in subjects who have adequate documentation of successful treatment for either latent or active TB. In such subjects, a chest radiograph, obtained within the 12 weeks prior to Screening, without changes suggestive of active TB infection as determined by a qualified radiologist, will be sufficient to permit further participation in the study. Documentation of adequate treatment for TB must be obtained and reviewed by the Medical Monitor prior to randomization. If the subject lives in, or has emigrated from, a TB high burden country (APPENDIX E) then further study participation requires documentation of adequate treatment for either active or latent TB infection within 2 years of the Screening Visit. For subjects residing in, or emigrating from, a TB high burden country and treated for TB more than 2 years prior to the Screening Visit, further trial participation requires a negative QuantiFERON-TB Gold test during screening.

- Sacroiliac joint radiograph: One sacroiliac (SI) joint radiograph (anterior-posterior [AP] view) must be obtained if not performed in the previous 12 months prior to Screening, on all study subjects. This radiographic assessment needs to be carried out to ensure the diagnostic radiographic criterion has been met based on the modified New York criteria (van der Linden, 1984) (APPENDIX B). The SI joint radiograph (historical or newly obtained image) will be sent to a central reader for centralized scoring to determine if the subject has met the radiographic criterion of sacroiliitis grade ≥ 2 bilaterally, or sacroiliitis grade 3 to 4 unilaterally.
- Adverse Events: Adverse event assessment begins when the subject signs the informed consent form.
- Complete Physical Examination: Complete physical examinations will include evaluation of the skin, nasal cavities, eyes and ears, respiratory, cardiovascular, abdominal, neurological, lymphatic, and musculoskeletal systems (Section 6.5.1).
- Vital signs, height and weight: Vital signs, including seated blood pressure, body temperature, and heart rate will be taken. Height and weight (to be done in street clothes, no shoes) will also be measured and recorded.
- 12-lead electrocardiogram (ECG) (Section 6.5.2)
- Clinical laboratory evaluations: Clinical laboratory evaluations will be performed by a central laboratory to include the following laboratory assessments below. Subject eligibility and clinical laboratory criteria are provided in Section 4. One laboratory re-test is allowed after

obtaining Medical Monitor approval if the result is exclusionary during the Screening Period. Details pertaining to the central laboratory assessments and panels are included in Section 6.5.3.

  - QuantiFERON-TB Gold (see details above)
  - Hepatitis B and C tests
  - Human immunodeficiency virus (HIV) test
  - Postmenopausal tests
  - Hemoglobin A1c
  - Hematology panel
  - Chemistry panel
  - Lipid panel
  - Pregnancy test (serum beta human chorionic gonadotropin [β-hCG])
  - Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted
- Efficacy assessments (Section 6.6):
  - BASDAI
  - Total Back Pain NRS
- Biomarkers/Pharmacodynamic assessment (Section 6.8):
  - hsCRP
- SARS-CoV-2 serology is collected approximately 4 weeks after a documented or suspected SARS-CoV-2 infection. Unless required by local guidelines, testing for asymptomatic COVID-19 infection via molecular testing is not required. However, some subjects may develop suspected or confirmed symptomatic COVID-19 infection, or be discovered to have asymptomatic COVID-19 infection during the Screening Period. In such cases, subjects may be considered eligible for the study after meeting the following criteria:
  - At least 10 days (20 days for severe/critical illness) have passed since symptoms first appeared or positive test result, and
  - At least 24 hours have passed since last fever without the use of fever-reducing medications, and
  - Symptoms (eg, cough, shortness of breath) have resolved and
  - In the opinion of the investigator, there are no COVID-19 sequelae that may place the participant at a higher risk of receiving investigational treatment, and
  - Negative follow-up molecular test for COVID-19 based on institutional, local or regional guidelines
- Information to be collected on Screening Failures: At a minimum, the information to be collected should include the informed consent date, demographics, and reason why the subject did not qualify for the study will be collected for all subjects determined to be screen failures. Adverse events experienced by screen failure subjects will be collected from the date of signing consent to the day the subject is confirmed to be a screen failure. This information will be captured in the subject's source documents and appropriate case report forms (CRFs).

6.2 Treatment Period

The subject will begin treatment upon confirmation of eligibility. For all subsequent visits, an administrative window of ± 3 days is permitted.

The following evaluations will be performed at the frequency specified in Table of Events, Table 3 and Table 4. The evaluations should be performed prior to dosing on the visit day, unless otherwise specified.

- Inclusion/exclusion criteria: Subjects must meet all inclusion criteria (Section 4.2 or Section 4.4) and must not have any of the conditions specified in the exclusion criteria (Section 4.3 or Section 4.5) to qualify for participation in the study. The subject's source documents must support his/her qualifications for the study.
- Concomitant medications evaluation (continuously)
- Concomitant procedures evaluation (continuously)
- Adverse event evaluation (continuously)
- Limited physical examination (Section 6.5.1)
- Vital signs, including seated blood pressure, body temperature, and heart rate will be taken. Weight (to be done in street clothes, no shoes) will also be measured and recorded
- 12-lead ECG (Section 6.5.2)
- Clinical Laboratory Evaluations (Section 6.5.3)
  - Hematology panel
  - Chemistry panel
  - Lipid panel
  - Prothrombin time (PT) and international normalized ratio (INR)
  - HLA-B27
  - Serum and urine pregnancy test (prior to dosing)
  - Counseling about pregnancy precautions and the potential risks of fetal exposure (continuously)
- Efficacy assessments (Section 6.6)
  - BASDAI
  - BASFI
  - Patient Global Assessment of Disease
  - Total Back Pain NRS
  - Nighttime back pain NRS
  - BASMI-Linear
  - Occiput to wall measurement
  - Chest expansion
  - Enthesitis evaluation
  - Peripheral joint count

  - MRI of sacroiliac joint AND spine (SPARCC method)
- Pharmacokinetic (PK) assessments (Section 6.7)
  - Sparse pharmacokinetic assessment
  - Intense pharmacokinetic assessment (at selected sites)
- Biomarkers and Pharmacodynamic assessments (Section 6.8)
  - Target engagement (at selected sites)
  - Ex vivo osteoclastogenesis (at selected sites)
  - hsCRP
  - Serum bone turnover markers
  - Serum TNF-α and IL-17A
  - Serum cytokines and other proteins by proteomics
  - Whole blood RNA gene expression profiling for genes including but not limited to TNF-α, IL-17A, MCP-1, IL-6
  - SARS-CoV-2 serology for biobanking
  - SARS-CoV-2 serology for documented or suspected Infection
- Pharmacogenetics assessment (Section 6.8.2) at the Baseline Visit
- Patient-reported Outcomes/Quality of Life Questionnaires (Section 6.9)
  - ASQoL
  - SF-36
  - ASAS Health Index
- Investigational product (IP) dispensation: The Principal Investigator, Sub-investigator, or Study Coordinator should make an effort to witness subjects taking their first dose and record the date and time in the source document record.

6.3 Early Termination

An early termination (ET) evaluation will be performed for subjects who are withdrawn from treatment for any reason as soon as possible after the decision to permanently discontinue treatment has been made.

The following evaluations will be performed as specified in Table of Events, Table 3 and Table 4:

- Concomitant medications evaluation
- Concomitant procedures evaluation
- Adverse Events (monitored through 28 days after the last dose of IP, Section 10)
- Complete physical examination
- Vital signs, including seated blood pressure, body temperature, and heart rate will be taken. Weight (to be done in street clothes, no shoes) will also be measured and recorded
- 12-lead ECG
- Clinical Laboratory Evaluations (Section 6.5.3)
  - Hematology panel

  - Chemistry panel
  - Prothrombin time (PT) and international normalized ratio (INR)
  - Pregnancy test (Urine and serum β-hCG)
- Counseling about pregnancy precautions and the potential risks of fetal exposure (continuously)
- Efficacy assessment will be continued according to the schedule defined in Table of Events, Table 3 and Table 4.
- Pharmacodynamics assessment (Section 6.8)
  - hsCRP test
  - SARS-CoV-2 serology for biobanking
  - SARS-CoV-2 Serology for Documented or Suspected Infection
- Patient-reported Outcomes/ Quality of Life Questionnaires (Section 6.9)
- Investigational product (IP) return (all used and unused pill containers) and IP compliance assessment (Section 7.6)

6.4 Post-treatment Observational Follow-up Period

All subjects will be followed for 28 days after the last dose of IP for AE reporting, as well as SAEs made known to the Investigator at any time thereafter that are suspected of being related to IP, as described in Section 10.

- Concomitant medications evaluation (continuously)
- Concomitant procedures evaluation (continuously)
- Adverse event evaluation (continuously)
- Complete physical examination
- Vital, including seated blood pressure, body temperature, and heart rate will be taken. Weight (to be done in street clothes, no shoes) will also be measured and recorded
- 12-lead ECG (Section 6.5.2)
- Clinical Laboratory Evaluations (Section 6.5.3)
  - Hematology panel
  - Chemistry panel
  - Prothrombin time (PT) and international normalized ratio (INR)
  - Pregnancy test (Urine and serum β-hCG)
  - Counseling about pregnancy precautions and the potential risks of fetal exposure (continuously)
- Pharmacodynamics assessment (Section 6.8)
  - SARS-CoV-2 Serology for Documented or Suspected Infection

6.5 Safety Assessments

6.5.1 Physical Examination

Complete physical examinations will include evaluation of the skin, nasal cavities, eyes, ears, respiratory, cardiovascular, abdominal, neurological, lymphatic, and musculoskeletal systems. Gynecological, urogenital, and rectal examinations will not be performed unless needed. A limited physical examination includes evaluation of the respiratory, cardiovascular, abdominal systems. Gynecological, urogenital and rectal examinations will not be done unless needed. Results of the physical examination will be recorded only in the source documents. Clinically significant abnormal findings (with the exception of the disease under study [AS]) identified prior to first dose of IP will be recorded on the eCRF as medical history; clinically significant findings after the first dose of IP will be recorded as AEs.

6.5.2 Electrocardiogram

Subjects will have a 12-lead electrocardiogram (ECG) at the frequency specified in Table of Events, Table 3 and Table 4. The Investigator or designee will use his/her own ECG equipment. The same ECG equipment should be used throughout the entire study. A standard 12-lead ECG (reporting PR interval, QRS, QT and corrected QT [QTc] intervals) will be performed by the Investigator or qualified designee. For safety evaluation of the subject's ECG, the Investigator should utilize the QT correction method (ie, Bazett or Fridericia) routinely available at the study site. ECGs will be performed after the subject has been in the supine or near supine position for at least 10 minutes. An ECG tracing from each prespecified visit will be reviewed by the Investigator or medically qualified designee and any abnormal results will be classified as clinically significant (CS) or not clinically significant (NCS) for real-time safety monitoring. Clinically significant abnormal findings identified prior to first dose of IP will be recorded on the eCRF as medical history; clinically significant findings after the first dose of IP will be recorded as an AE and followed to resolution (ie, until it returns to baseline, stabilizes, or becomes NCS as judged by the Investigator or medically-qualified designee).

6.5.3 Clinical Laboratory Assessments

Clinical laboratory evaluations will be performed by a central laboratory to include the following laboratory assessments performed at the frequency specified in Table of Events, Table 3 and Table 4. "Abnormal, clinically significant" results should be recorded in the Medical History eCRF if found prior to first dose of IP, or in the AE eCRF if found after the first dose of IP.

Clinical laboratory evaluations are not required to be fasting; however, any unusual findings in serum glucose may be repeated with a subsequent fasting lab. In all cases, the site will record whether a clinical laboratory evaluation was fasting or non-fasting on the lab requisition form.

- Mycobacterium tuberculosis (TB) testing: testing will be done at the Screening Visit via QuantiFERON®-TB Gold.

  Note: A positive QuantiFERON-TB Gold test or 2 successive indeterminate QuantiFERON-TB Gold tests will disqualify the subject from further participation in the study.

If a subject has adequate documentation of successful treatment for either latent or active TB, the QuantiFERON-TB Gold test is not needed. Instead, a chest radiograph, obtained within the 12 weeks prior to Screening, without changes suggestive of active TB infection as determined by a qualified radiologist, will be sufficient to permit further participation in the study for these subjects. Documentation of adequate treatment for TB must be obtained and reviewed by the Medical Monitor prior to randomization.

If the subject lives in, or has emigrated from, a TB high burden country (APPENDIX E) then further study participation requires documentation of adequate treatment for either active or latent TB infection within 2 years of the Screening Visit. For subjects residing in, or emigrating from, a TB high burden country and treated for TB more than 2 years prior to the Screening Visit, further trial participation requires a negative QuantiFERON-TB Gold test during screening.

- Hepatitis B and hepatitis C testing: testing will be performed at Screening. The hepatitis screen includes testing for hepatitis B surface antigen (HBsAg) and antibody, hepatitis B core antibodies, and hepatitis C antibodies (HCV Ab). A positive result for one or more of these tests will disqualify the subject from further participation in the study (Section 4.3). The Investigator should refer the subject to his/her general practitioner or other appropriate healthcare provider for further follow-up.

  Note: Subjects who received hepatitis B vaccination and who test positive for hepatitis B surface antibody and negative for both hepatitis B surface antigen and hepatitis B core antibody are not excluded from the study.

- Human immunodeficiency virus (HIV) test: testing will be performed at Screening. A positive test result will disqualify the subject from participation in the study. The Investigator should refer any subject who tests positive for HIV to the appropriate HIV counsellor or Health Advisor (per the Investigator's medical practice procedure) for further follow-up.
- Postmenopausal tests: estradiol and follicle-stimulating hormone (FSH) levels are required for all females 50 to 55 years of age who do not have documentation confirming their postmenopausal status. Postmenopausal test will be performed at Screening.
- Hemoglobin A1c: test will be only be performed on subjects receiving metformin treatment at screening as indicated in Table of Events, Table 3 and Table 4.
- Hematology Panel: including complete blood count (CBC) with differential, including red blood cell (RBC) count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, white blood cell (WBC) count (with differential), neutrophil count (percent and absolute), and platelet count.
- Chemistry Panel: including total protein, albumin, calcium, phosphorous, glucose, uric acid, total bilirubin (TBL), alkaline phosphatase (ALP), AST/ serum glutamic oxaloacetic transaminase (SGOT), ALT/ serum glutamic pyruvic transaminase (SGPT), sodium, potassium, chloride, carbon dioxide, blood urea nitrogen (BUN), serum creatinine, creatine phosphokinase (CPK), troponin-T and lactic dehydrogenase (LDH).
- Lipid panel: including total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides will be assessed as indicated in Table of Events, Table 3 and Table 4. As described above, clinical laboratory evaluations are not required to be fasting; however, any unusual findings in lipids may be repeated with a

subsequent fasting lab. In all cases, the site will record whether a clinical laboratory evaluation was fasting or non-fasting on the lab requisition form.

- Prothrombin time (PT) and international normalized ratio (INR) will be assessed as indicated in Table of Events, Table 3 and Table 4.
- HLA-B27: a DNA test for the presence of HLA-B27 gene variant will be completed at Baseline in all subjects for AS diagnostic purposes (Reveille, 2006). This is the only DNA test that will be done on the subject's blood, as part of the main study informed consent, and is different from the DNA blood draw for the pharmacogenetic substudy, which requires a separate informed consent.
- Pregnancy testing is required for all female subjects of childbearing potential as indicated in Table of Events, Table 3 and Table 4:
  - Urine β-hCG pregnancy test will be performed at the Baseline Visit and prior to the first administration of IP. A negative urine pregnancy test result is required prior to IP administration.
  - Urine β-hCG pregnancy test will be performed at all other visits as indicated in the Table of Events, Table 3 and Table 4. If the urine β-hCG pregnancy test is indeterminate IP must be held pending negative serum β-hCG pregnancy test result. If the urine β-hCG pregnancy test is positive IP must be discontinued and confirmation retesting on serum β-hCG is required (refer to Section 10.4).
  - Serum beta human chorionic gonadotropin (β-hCG) pregnancy test will be performed at all visits.

6.6 Efficacy Assessment

The following sections describe the efficacy measures and assessments obtained or completed directly from the subject, or efficacy evaluations completed by the Investigator (or authorized site staff member) on the subject. Every effort must be made to ensure the same assessor completes the clinical efficacy assessments for each participant at all visits at approximately the same time throughout the study, according to the Table of Events (Table 3 and Table 4). The timeframes for all clinical efficacy measures obtained from the subject are indicated in Table of Events, Table 3 and Table 4.

6.6.1 Assessment of SpondyloArthritis International Society Response Criteria

The ASAS20 and ASAS40 are validated response criteria widely used in the evaluation of efficacy of agents used in the treatment of axSpA (Sieper, 2009).

The ASAS20 is defined as improvement ≥ 20% and ≥ 1 unit on a scale of 0 to 10 in each of the 3 domains, with no worsening in the fourth, where the domains are physical function, total back pain, patient global assessment of disease, and inflammation (mean of BASDAI NRS Questions #5 and #6 for morning stiffness) (Anderson, 2001).

The ASAS40 is defined as improvement ≥ 40% and ≥ 2 units on a scale of 0 to 10 in each of the 3 domains, with no worsening in the fourth, where the domains are physical function, total back pain, patient global assessment of disease, and inflammation (mean of BASDAI NRS Questions #5 and #6 for morning stiffness) (Brandt, 2004).

6.6.2 Ankylosing Spondylitis Disease Activity Score with CRP

The ASDAS–CRP is a validated disease activity index in AS that combines patient reported assessments of back pain (BASDAI question 2), duration of morning stiffness (BASDAI question 6), peripheral joint pain and/or swelling (BASDAI question 3), general wellbeing, and CRP, in a weighted manner (van der Heijde, 2009). The cut-off values for disease activity states and improvement scores are defined as follows: < 1.3 inactive disease, ≥ 1.3 and < 2.1 low disease activity, ≥ 2.1 and ≤ 3.5 high disease activity and, 3.5 very high disease activity. The minimum clinically important difference (MCID), are defined as: change of at least 1.1 unit for 'clinically important improvement' and change of at least 2.0 units for 'major improvement' (Machado, 2011; Machado, 2018).

6.6.3 Bath Ankylosing Spondylitis Disease Activity Index

The BASDAI is a composite score based on a subject self-administered survey of six questions using a 0 to 10 unit numerical rating scale (NRS) that assesses the subject's five major symptoms of AS during the last week: 1) fatigue; 2) spinal pain; 3) peripheral joint pain/swelling; 4) areas of localized tenderness; 5a) morning stiffness severity upon wakening; 5b) morning stiffness duration upon wakening (Calin, 1999; Sieper, 2009). The subject will be asked to mark the box with an X on a 0 to 10 unit NRS for each of the 6 questions. To give each of the five symptoms equal weighting, the mean of the two scores relating to morning stiffness is taken. The resulting 0 to 50 score is divided by 5 to give a final 0 to 10 BASDAI score. A BASDAI score of 4 or greater is considered to be indicative of active AS disease.

6.6.4 Bath Ankylosing Spondylitis Functional Index

The BASFI is a composite score based on a subject self-administered survey of ten questions using a 0 to 10 unit numerical rating scale (NRS) that assesses a subject's degree of mobility and functional ability (Calin, 1994; Sieper, 2009) during the last week. The questionnaire consists of eight questions regarding function in AS and the two last questions reflecting the subject's ability to cope with everyday life. The subject will be asked to mark the box with an X on a 0 to 10 unit NRS for each of the 10 questions, on which the left-hand box of 0 represents "easy," and the right-hand box represents impossible." The resulting 0 to 100 score is divided by 10 to give a final 0 to 10 BASFI score. A higher BASFI score correlates to reduced functional ability.

6.6.5 Patient Global Assessment of Disease Activity

The Patient Global Assessment of Disease Activity is the subject's assessment of how active their spondylitis was on average during the last week. The subject will be asked to mark the box with an X on a 0 to 10 unit NRS in which the left-hand box of 0 represents "not active" and the right-hand box represents "very active" (Sieper, 2009).

6.6.6 Total Back Pain

The Total Back Pain NRS is the subject's assessment of, on average last week, how much pain they have in their spine due to AS. The subject will be asked to mark the box with an X on a 0 to 10 unit NRS in which the left-hand box of 0 represents "no pain" and the right-hand box represents "most severe pain" (Sieper, 2009).

6.6.7 Nighttime Back Pain

The nighttime back pain NRS is the subject's assessment of, on average last week, how much pain they have in their spine due to AS at night. The subject will be asked to mark the box with an X on a 0 to 10 unit NRS in which the left-hand box of 0 represents "no pain" and the righthand box represents "most severe pain" (Sieper, 2009).

6.6.8 Bath Ankylosing Spondylitis Metrology Index - Linear

The BASMI - Linear was designed to assess axial status (ie, cervical, dorsal and lumbar spine, hips, and pelvic soft tissue) and to define clinically significant changes in spinal movement (Jenkinson, 1994; Sieper, 2009). Five dimensions of movement (lateral lumbar flexion, tragus to wall, forward lumbar flexion, maximal intermalleolar distance, and cervical rotation) are measured and normalized on 0 to 10 unit NRS. The average of these scores is the total BASMI - Linear score, with a higher value indicating more severe limitation in spinal mobility.

6.6.9 Occiput to Wall Measurement

Occiput to wall measurement is the distance measured between the occiput located on the back of the subject's skull and the wall. The subject stands with heels and shoulder against the wall with the back straight. The chin is at the usual carry level. The maximal effort to touch the head against the wall is asked of the subject. The distance between the occiput and the wall is measured in centimeters (cm) (Sieper, 2009).

6.6.10 Chest Expansion Measurement

When ankylosing spondylitis affects the mid-back region (thoracic spine), normal chest expansion may be compromised. The chest expansion measurement is the difference between the circumference of the chest in maximal inspiration and maximal expiration. To conduct the test, the subject has his/her hands resting on or behind the head. The amount of chest expansion is measured from deep expiration to full inspiration and is measured at the level of the fourth intercostal space anteriorly in males and just below the breasts in females (Sieper, 2009).

6.6.11 Enthesitis Evaluation

Enthesitis, or the swelling of the sites where tendons or ligaments insert into the bone, is a prominent clinical manifestation in subjects with AS. The Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) will be used in this study to measure the severity of a subject's enthesitis (Heuft-Dorenbosch, 2003).

6.6.12 Peripheral Joint Count

An ASAS joint evaluation which includes the "44 tender and 44 swollen" joint counts (Sieper, 2009) will be performed on all subjects to monitor peripheral joint involvement. Non weighted measures will be used to assess tender and swollen joints. In order to maintain consistency throughout the study, preferably the same evaluator should perform the peripheral joint assessments at the study site at each study visit.

6.6.13 MRI of Sacroiliac Joint and Spine (SPARCC Method)

The MRI assessments will be conducted at all sites. Details regarding the MRI specific procedures and the consistent acquisition of MRI images will be outlined in a separate image acquisition document.

MRI assessment will be performed on the sacroiliac joints and the entire spine (cervical, thoracic, and lumbar). The Baseline MRI must be performed between Visits 1 and 2 inclusive. Subsequent MRIs should be completed at Visit 6 (the final treatment visit) or at the Early Termination Visit. If the Early Termination Visit occurs before Week 6, then MRI of sacroiliac joint should not be done.

All MRI visits should be scheduled well in advance to allow for proper planning. In addition, it is strongly recommended to schedule two MRI visits (an initial and a repeat visit) for each MRI time point in order to be assured of a high-quality MRI scan at each protocol-specified time point. The initial and repeat MRI visits should be scheduled approximately 7 to 14 days apart to allow enough time for confirmation of quality scans from the initial MRI. If the initial MRI scans are of acceptable quality, then the scheduled repeat MRI session can be cancelled. The scoring of the standardized MRIs will be conducted by well-trained, independent, central readers.

6.7 Pharmacokinetics

Blood samples will be collected at prespecified times for measurement of CC-99677 and CC-0782951 in plasma. Concentrations of CC-99677 and CC-0782951 in plasma will be measured using a validated liquid chromatography tandem mass spectrometry assay.

On all PK visits, subjects must bring their IP to the study center and IP must be administered to subjects at the study center after the collection of the predose PK blood sample. Subjects will be asked to report the date and time of their last IP dose (dose from the day before visit) to the study staff during their visit at the study center. The IP dosing time on the day of the PK sample collection should also be documented by the study staff. Dosing and sample collection information including dosing date, dosing time, and actual PK blood sampling time should be accurately documented on the appropriate eCRF pages.

Pharmacokinetic blood sampling should be performed at the nominal time(s) specified in this clinical protocol. All actual PK blood sample collection times will be recorded in the source documents and CRF. Explanation should be provided in the source documents and CRF for missed or mishandled samples and for samples collected outside the following time windows:

- Predose (0 hour) sample: - 60 minutes;
- Samples between 0.25 to 1 hour postdose, inclusive: ± 3 minutes;
- Samples between 2 to 4 hours postdose, inclusive: ± 15 minutes;
- Samples between 6 to 12 hours postdose, inclusive: ± 20 minutes;

See the Laboratory Manual for specific sample collection, handling and processing instructions.

6.7.1 Sparse Pharmacokinetics Blood Draw

All subjects in the study will have sparse PK samples collected (~3 ml) at the following time points:

- Visit 2 (Week 0): 3 hours post dose
- Visit 4 (Week 4): 2 hours post dose
- Visit 5 (Week 8): 1 hour post dose
- Visit 6 (Week 12): pre-dose and 3 hours post dose
- Visit 8 (Week 16): 2 hours post dose
- Visit 9 (Week 20): 1 hour post dose
- Visit 10 (Week 24): pre-dose

Note: For subjects who take IP in the evening, IP should be taken at approximately 5 PM the day prior to sparse PK collections. On the day of sparse PK sample collection, IP must be taken and witnessed at the study site.

6.7.2 Intense Pharmacokinetics Blood Draw

A subset of sites will be selected for participation in the intensive PK study. In addition to the sparse PK sampling in these subjects, intensive PK blood samples will be collected (~3 ml) at the following time points:

- Visit 4 (Week 4): pre-dose and 0.5, 1, 2, 3, 6, 8, and 12 hours post dose.

The actual times of drug administration and PK blood sample collections will be recorded in the source documents and CRF. On the day of intense PK sample collection, IP must be taken at the study site after collection of the pre-dose PK blood sample. This planned PK schedule may be modified; if modified, the total number of minimal time points per subject will not exceed 8 draws per visit and blood sample volume will remain approximately 3 mL for each nominal time point.

6.8 Biomarkers, Pharmacodynamics, Pharmacogenomics

Blood samples will be collected as specified in Table of Events, Table 3 and Table 4 for measurement of various PD and PG biomarkers. Specific details regarding the collection, processing, storage, and shipment of all PD and PG samples are provided in a separate Laboratory Manual.

For those biomarkers that require approval from national health authorities, biomarker samples cannot be collected in those countries until approval is received (See Section 6.8.1 and Section 6.8.2). *Note: Assays for some biomarkers may not be available in all countries.*

6.8.1 Biomarkers/Pharmacodynamics

All sites will be expected to participate in biomarker studies, except for pharmacodynamic measurement of target engagement and ex vivo osteoclastogenesis, which will be performed at selected sites, only.

Biospecimen operations will ensure that all sites are qualified to handle biomarker logistic requirements, including sample collection, processing and shipping, and image acquisition procedures. The following assessments will be explored:

High-sensitivity C-reactive protein (hsCRP)

Blood samples will be collected as specified in Table of Events, Table 3 and Table 4 to measure hsCRP levels since it is required for calculating the ASDAS efficacy variables, and it is also an important disease-relevant biomarker (Section 1.4.3).

Serum bone turnover markers

Blood samples will be collected under fasted conditions. Subjects must not have received high-dose biotin supplements (multivitamins are allowable) within 72 hours prior to sample collection as specified in Table of Events, Table 3 and Table 4. Specific serum bone turnover markers including but not limited to C terminal telopeptide (CTX) and procollagen I intact N terminal peptide (P1NP) will be measured.

Blood Collection for Pharmacodynamic Measurement of Target Engagement, at selected sites only

Blood samples will be collected as specified in Table of Events, Table 3, to measure target engagement. Samples will be evaluated for percent of MK2 bound to CC-99677 versus percent of free MK2 in PBMCs.

Blood Collection for Measurement of Serum TNF-α and IL-17A

Blood samples will be collected as specified in Table of Events, Table 3 and Table 4, to measure serum TNF-α and IL-17A by an ultra-sensitive enzyme-linked immunosorbent assay (ELISA) method.

Blood Collection for Measurement of Serum Cytokines and Proteins by Proteomics

Effects of CC-99677 on serum proteins such as serum cytokines, chemokines and other inflammatory factors will be evaluated. Blood samples will be collected as specified in Table of Events, Table 3 and Table 4.

Blood Collection for Markers of ex vivo osteoclastogenesis (at selected sites only)

Osteoclast precursors in PBMCs will be assessed as specified in Table of Events, Table 3.

Whole blood RNA for gene expression profiling

Effects of CC-99677 on gene expression will be evaluated by RNAseq analysis as specified in Table of Events, Table 3 and Table 4.

SARS-CoV-2 serology

Serum will be collected at times indicated in Table 3 and Table 4 for biobanking and possible measurements of SARS-CoV-2 serology (anti-SARS-CoV-2 total or IgM and/or IgG antibodies), and documented or suspected infection.

6.8.2 Pharmacogenomics

The pharmacogenetic substudy is optional, and a separate consent will be signed for this assessment at Screening.

Pharmacogenetic testing will be conducted using DNA isolated from a single blood sample at Baseline, as specified in Table of Events, Table 3. DNA polymorphisms will be investigated for their ability to stratify patient subsets or response to CC-99677. Genetic markers to be assessed include, but are not limited to, those involved in MK2 signaling, CC-99677 metabolism, and those shown to be associated with ankylosing spondylitis.

Detailed instructions for sample preparation and handling will be provided in a separate lab manual.

6.9 Patient Reported Outcomes

The timeframes for all health-related quality of life measures are indicated in Table of Events, Table 3 and Table 4.

6.9.1 Ankylosing Spondylitis Quality of Life

The ASQoL is a validated disease specific patient reported outcomes instrument to assess the impact of ankylosing spondylitis (AS) on the quality of life of individuals with emphasis on the ability of the person to fulfill his or her needs (Doward, 2003). It consists of 18 items requesting a yes (score=1) or no (score=0) response to questions related to the impact of pain on sleep, mood, motivation, ability to cope, activities of daily living (ADL), independence, relationships, and social life. The summary score ranges 0–18 with higher scores indicating worse quality of life. The MCID was defined as a 1.8-point change for ASQoL (van der Heijde, 2007a).

6.9.2 Medical Outcome Study Short Form 36-Item Health Survey, Version 2

The SF-36 (Ware, 1992) is a validated, self-administered 36-item general health status instrument often used in clinical trials and health services research. It consists of 8 scales: physical function (PF), role limitations–physical (RP), vitality (VT), general health perceptions (GH), bodily pain (BP), social function (SF), role limitations–emotional (RE), and mental health (MH) (Ware, 1992). Scale scores range from 0 to 100, with higher scores indicating better health. Two overall summary scores can also be obtained—a Physical Component Summary score (PCS) and a Mental Component Summary score (MCS). The PCS and MCS scores are transformed to have a mean of 50 and standard deviation of 10, with higher scores indicating better health. The concepts measured by the SF-36 are not specific to any age, disease, or treatment group, allowing comparison of relative burden of different diseases and the relative benefit of different treatments. Version 2 of the SF-36 will be used in this study.

6.9.3 ASAS Health Index

The ASAS Health Index is a validated linear composite measure and includes 17 items and is intended to capture relevant information on functioning and health of patients with AS (Kiltz, 2014).

7 DESCRIPTION OF STUDY TREATMENTS

CC-99677 is available for clinic use in Swedish orange, opaque, hard hydroxypropyl methylcellulose (HPMC) capsules. In addition to drug substance, the formulated capsules will contain HPMCAS, microcrystalline cellulose, croscarmellose sodium, silicon dioxide, and magnesium stearate. Refer to the Investigator's Brochure for information regarding CC-99677.

CC-99677 will be supplied by the Sponsor and labeled appropriately as IP for this study.

CC-99677 will be provided by the sponsor as 30 mg and 60 mg formulated capsules and will be labeled appropriately as investigational material. In addition, the sponsor will provide matching placebo identical in appearance to CC-99677 30 mg and 60 mg formulated capsules labeled appropriately as investigational material.

7.1 Description of Investigational Product

- Sufficient quantities of CC-99677 and equivalent placebo will be supplied by Celgene (or designee) and labeled appropriately as IP for this study. Celgene as the sponsor will label the IP as appropriate and will include all required information following local regulations and/or regulatory requirements in each participating country.
- CC-99677 and equivalent placebo will be provided in the relevant strength(s) as capsules for oral administration. The dosing schedule and dose adjustments to be followed for this study are described in Section 7.2.
- All IP must be stored according to the package label and in a secure, limited-access location and may be dispensed only by the Investigator or by a member of the staff specifically authorized by the Investigator.

7.2 Treatment Administration and Schedule

Subjects are instructed to take 3 capsules once daily, approximately the same time of day (preferably in the morning), with or without food.

12-Week Double-blind, Placebo-controlled Treatment Period: Baseline to Week 12

- CC-99677 150 mg QD PO
- CC-99677 60 mg QD PO
- Placebo QD PO

If the additional dose cohort is initiated (Section 3.1.4) in the biologic-naïve main study, then additional IP will be provided as follows:

- Additional dose cohort (dose not to exceed 150 mg) (Section 3.1.2)
- Placebo PO QD

Table 5: Study Treatment Administration (Number of Capsules)

Treatment Allocation	30 mg	60 mg	Placebo Matching 30 mg	Placebo Matching 60 mg	Total Number of Capsules per Day
CC-99677 150 mg	1	2	0	0	3
CC-99677 60 mg	0	1	1	1	3
Placebo	0	0	1	2	3

Note: An additional dose cohort (dose not to exceed 150 mg) may be added following results from the planned IA (Section 3.1.4). In this event, this will not result in subjects receiving an increased number of capsules per day.

To maintain the blind at the site and subject level, the original individual subject treatment assignments at randomization will not be revealed to the Investigators until after the 12-Week database lock and after all final analyses are completed and the final results have been released.

Capsules of CC-99677 will be counted at every visit starting at Visit 3 through the completion of the study. If a dose of IP is missed for the entire day, the subject should not take an extra dose the next day or take an unscheduled dose. Subjects who take more than the prescribed dose of IP should be instructed to contact study staff immediately and seek emergency medical care if needed.

Any interruption in the IP will not alter the current dose or dose interval, nor will the length of the study be extended to account for days of missed IP.

7.2.1 Overdose

Overdose, as defined for this protocol, applies to protocol-required dosing of the IP, only. Other medications are excluded from this definition. Overdose for this protocol is defined as the accidental or intentional administration of any dose of IP that is considered both excessive and medically important. Adverse events associated with an overdose must be collected on the adverse events page of the CRF for all overdosed subjects but the overdose itself is not considered an AE.

Detailed information about any CC-99677 overdose in this study, regardless of whether the overdose was accidental or intentional, should be reported on the drug exposure CRF page.

7.2.2 Dose Modification/Interruptions

Because this is a dose-finding study no dose reductions will be permitted. However, in the event the subject experiences an adverse event, a temporary IP interruption is permitted anytime during the study. The Sponsor should be notified in advance of the dosage interruption; however, the decision to interrupt IP dosing will be based on the Investigator's clinical judgment. If the subject misses 4 or more consecutive days of dosing, Celgene must be contacted to decide whether dosing should resume or whether the subject should be terminated from the study IP and enter the Post-treatment Observational Follow-up Period.

If a dose of IP is missed, it should be taken as soon as possible on the same day, provided it occurs within 36 hours of the previous dose. The dose should be skipped if the timing of the dose occurs > 36 hours of the previous dose.

Temporary interruption of IP is allowed in the context of clinical suspicion for SARS-CoV-2 or a positive diagnostic test for SARS-CoV-2 if deemed necessary by the investigator. Temporary interruption of IP may also be considered in the event of SARS-CoV-2 vaccination according to local guidelines. In order to facilitate reporting of SARS-CoV-2 events that occur during the study, all AEs and SAEs related to SARS-CoV-2 must be reported from the time of consent. In addition, such AEs or SAEs will trigger additional data collection through dedicated eCRF pages, which will allow the Sponsor to further evaluate these events.

Note: If the dose is missed for the entire day, the subject should not take an extra dose the next day or take an unscheduled dose.

7.3 Method of Treatment Assignment

Randomization, stratification and treatment assignment will be managed by an Interactive Web Response System (IWRS).

Designated study personnel at the investigational sites will be assigned password-protected, coded identification numbers, which give them authorization to access the IWRS to randomize subjects. The system will present a menu of questions by which the study personnel will identify the subject and confirm eligibility. When all questions have been answered, the IWRS will assign a randomization identification number. Confirmation of the randomization will be sent via fax to the investigational site, Celgene and/or its representative.

During the study visits, the pharmacy or authorized study personnel at the investigational site will dispense coded IP kits in accordance with the randomization number assigned by the IWRS.

7.4 Packaging and Labeling

The label(s) for IP will include, but not limited to Sponsor name, address and telephone number, the protocol number, IP name, dosage form and strength (where applicable), amount of IP per container, lot number, expiry date (where applicable), medication identification/kit number, dosing instructions, storage conditions, and required caution statements and/or regulatory statements as applicable. Additional information may be included on the label as applicable per local regulations.

7.5 Investigational Product Accountability and Disposal

The Investigator(s) or a qualified designee(s) is/are responsible for taking an inventory of each shipment of IP received, and comparing it with the accompanying accountability form. The Investigator(s) or qualified designee(s), will verify the accuracy of the information on the form, sign and date it, retain a copy in the study file, and return a copy to Celgene, where it will be maintained in the trial master file.

At the study site, all IP will be stored in a secure, locked area to prevent unauthorized access. IP must be stored at the correct temperature as directed on the bottle label(s). Any expired IP must

be stored separately before they are returned or destroyed to prevent them from being accidentally administered to study subjects. Accurate recording of all IP administration will be made, at minimum, in the appropriate section of the subject's source documents.

The Investigator(s) or qualified designee(s) is responsible for the accountability of all IP issued to the site during the course of the study.

Celgene (or designee) will review with the Investigator and relevant site personnel the process for IP return, disposal, and/or destruction including responsibilities for the site versus Celgene (or designee).

7.6 Investigational Product Compliance

The study staff will maintain an ongoing record of the dispensing and administration of CC-99677 for each subject via an accountability record or equivalent document that will be verified by Celgene's study monitor.

For CC-99677 dispensed to the subject for outpatient administration, study personnel will review the instructions printed on the package with the study subject prior to dispensing CC-99677. IP will be dispensed as noted in Table of Events, Table 3 and Table 4.

The subjects will be instructed to return the CC-99677 containers, including any unused medication, to the study site at each visit for capsule counts and reconciliation. Subjects will be asked whether they have taken their CC-99677 as instructed at each study visit. Any problems with CC-99677 compliance will be reviewed with the subject.

If a subject misses 4 or more consecutive days of dosing or is taking less than 80% of the doses between study visits Celgene should be contacted to decide whether dosing should resume or whether the subject should be terminated from the treatment period of the study.

Gross compliance problems (eg, missing 4 or more consecutive days of dosing or taking less than 80% of the doses between study visits) should be discussed with Celgene. Compliance will be categorized into 4 classes: $< 50\%$, $\geq 50\%$ to $\leq 80\%$, $> 80\%$ to $\leq 120\%$, $> 120\%$.

Accurate recording of all CC-99677 administration (including dispensing and dosing) will be made in the appropriate section of the subject's eCRF and source documents.

8 CONCOMITANT MEDICATIONS AND PROCEDURES

Over the course of this study, additional medications may be required to manage aspects of the disease state of the subjects, including side effects from trial treatments or disease progression. All concomitant medications (prescription and non-prescription), treatments, and therapies taken by the subject from Screening until 28 days after the last dose of IP, must be reported on the CRF.

All concomitant medications (prescription and non-prescription) will be commercially sourced by the clinical site responsible for use in this trial and in accordance with local guidelines. Please refer to local prescribing and package insert information for more details on available formulations, preparation, storage conditions (eg, refrigeration), approved indications, known precautions, warnings, and adverse reactions for these drugs (see current version of prescribing information).

Non-drug therapies for AS (including physical therapies) should be kept stable during the study.

For information regarding other drugs that may interact with IP and affect its metabolism, pharmacokinetics, or excretion, please see the Investigators Brochure.

8.1 Permitted Concomitant Medications and Procedures

- Concomitant use of one NSAID or cyclooxygenase (COX)- 2 inhibitor on a regular basis up to the maximum recommended dose as per local guidelines is permitted, provided the drug is for treatment of AS and is used at a stable dose for at least 2 weeks prior to Baseline (Day 1 of study). The dose and frequency of the medication must be maintained stable until conclusion of study treatment (end of Week 64), even if subject experiences improvement in disease activity. If the subject experiences an adverse event (eg, gastrointestinal bleed) then dose reduction, stopping or switching to another NSAID or COX-2 inhibitor, or discontinuation of the agent is allowed. As needed (PRN) use of NSAIDs or COX-2 inhibitors is not recommended during the study and is not permitted within the 24 hours prior to a study visit.
- Concomitant use of sulfasalazine is permitted, provided sulfasalazine is used at a stable dose for at least 4 weeks prior to Baseline (Day 1 of study); dose must be stably maintained until conclusion of study treatment (end of Week 64) unless dose adjustments are required for safety and/or tolerability concerns.
- In case the subject requires PRN medication for pain, acetaminophen/paracetamol and/or low-strength opioid analgesics up to the maximum recommended doses per local guidelines may be used but cannot be taken within 24 hours prior to a study visit with disease activity assessment.
- Acetylsalicylic acid at a dose of ≤ 325 mg /day for cardiac prophylaxis is allowed.
- Bisphosphonate therapy is allowed if stable for at least 1 year prior to randomization and must be maintained stable until conclusion of study treatment (end of Week 64).
- Concomitant use of systemic corticosteroids at or up to 10 mg/day of prednisone or equivalent is permitted, provided the drug is used at a stable dose for at least 4 weeks prior to Baseline. The dose and frequency of the medication must be maintained stable until conclusion of study treatment (end of Week 64).

- Subjects may receive statins (3-hydroxy-3-methyl-glutaryl-coenzyme A reductase [HMG-CoA reductase] inhibitors) during the study; however, routine monitoring for statin-related AEs (eg, hepatic enzyme elevations and muscle soreness) is recommended.

8.2 Permitted Medications That Require Careful Monitoring

Studies examining drug-drug interactions involving CC-99677 in humans have been completed (see Section 1.4.2). CC-99677 may potentially inhibit the transporters BCRP, P-gp, OATP1B1, OATP1B3 and OCT1 (Section 1.3). Based on data from these studies, there is unlikely to be a clinically significant interaction with drugs that are substrates of these transporters AND that have a wide therapeutic index. Drugs that are substrates of these transporters AND that have a narrow therapeutic index, however, should be used with caution, and subjects receiving such drugs should be closely monitored for potential toxicities during participation in the study. A partial list of these drugs, including those that are therapeutically relevant to common comorbidities in the AS population, are listed in APPENDIX D, Table 10. Questions regarding potential co-administration of CC-99677 with drugs that are substrates of BCRP, P-gp, OATP1B1, OATP1B3 or OCT1 (APPENDIX D, Table 10) should be discussed with the medical monitor.

8.3 Prohibited Concomitant Medications

The following medications cannot be administered for the specified times prior to the initiation of study IP and for the duration of the study:

- Use of Vitamin K antagonists (eg, warfarin) during the study
- Use of diclofenac or sulindac
- Use of any medication known to be either a moderate or strong inhibitor or a moderate or strong inducer of CYP3A4/5 until study completion (See APPENDIX C, Table 7). There must be a washout period of 5 PK half-lives of any such drug used by the subject prior to Baseline Visit. The Medical Monitor or designee should be queried in case of uncertainty.
- Use of any medication known to be either a moderate or strong inhibitor or a moderate or strong inducer of P-gp until study completion (see APPENDIX C, Table 8). There must be a washout period of 5 PK half-lives of any such drug used by the subject prior to Baseline Visit. The Medical Monitor or designee should be queried in case of uncertainty.
- Use of any medication known to be a strong BCRP inhibitor until study completion (see APPENDIX C, Table 8). There must be a washout period of 5 PK half-lives of any such drug used by the subject prior to Baseline Visit. The Medical Monitor or designee should be queried in case of uncertainty.
- Use of any medications that are substrates of one or more of the transporters P-gp, OATP1B1, OATP1B3, and OCT1 **and** have a narrow therapeutic index (eg, methotrexate, digoxin, cyclosporine, mycophenolic acid, and leflunomide). Additional examples can be found in APPENDIX C, Table 9.

  Note:

- *BCRP substrates with a narrow therapeutic index (eg, prazosin) should be used with caution (*APPENDIX D, Table 10). *Sulfasalazine is not excluded based on results from* CC-99677-CP-002 *(see Section* 1.4.2).
- *At least a 1-month washout period prior to randomization is required for the conventional synthetic disease-modifying antirheumatic drugs (DMARDs), except for leflunomide, which has to be discontinued for 15 weeks prior to randomization unless a cholestyramine washout has been performed. Subjects should not discontinue any of the above synthetic DMARDs for the sole purpose of participating in this trial.*

- Use of high potency opioid analgesics (eg, methadone, hydromorphone, morphine or oxycodone)
- Treatment with any biologic indicated for AS (eg, anti-TNF or anti-IL-17A mAb)
- Introduction of a JAK inhibitor or immunomodulating therapy including but not limited to 6-mercaptopurine, azathioprine, cyclosporine or other calcineurin inhibitors (eg, sirolimus, tacrolimus), gold therapies
- Treatment with any systemic, intravenous, intramuscular or intra-articular corticosteroid within 4 weeks of the Baseline visit
- Use of any other investigational drug
- Any botanical preparation (eg, herbal supplements or traditional Chinese medicines derived from plants, minerals, or animals) intended to treat AS or other immunological diseases.

8.4 Vaccination Guidelines

Currently, there are no available data on the use of CC-99677 and its impact on immune responses following vaccination. Based on the mechanism of action, pharmacological modulation of the MK2 pathway by CC-99677 may reduce the effectiveness of vaccines.

Administration of live and live-attenuated vaccines, such as varicella, oral polio and inhaled flu vaccine, is prohibited during the study and for 4 weeks after the last dose of study drug. Routine household contact with persons vaccinated with live vaccine components should be avoided.

Vaccination with non-live vaccines should be performed based on local guidelines (eg, COVID-19 vaccine, seasonal influenza vaccine).

All routine vaccinations should be administered prior to the study. If vaccination is performed near the expected enrollment date, it is suggested that enrollment is delayed until the vaccination series is completed and any symptoms related to vaccination have resolved. If vaccination becomes available only after enrollment, vaccination can proceed at discretion of the investigator. These include genetic, protein-based, replication incompetent, or inactivated vaccine as approved by local authorities.

COVID-19 vaccination, when available, is recommended prior to enrollment. If a participant receives a COVID-19 vaccine during the study, the Week 12 visit should not take place within 5 days after vaccine administration so that any acute reaction to the vaccine will not potentially confound study assessments. Please contact the Medical Monitor with any questions related to COVID-19 vaccines.

8.5 Required Concomitant Medications and Procedures

There are no required concomitant medications for inclusion in this study. However, subjects must have undergone prior treatment with at least 2 NSAIDs (at the highest dose tolerable) for at least 4 weeks (each) with documented inadequate response.

9 STATISTICAL CONSIDERATIONS

9.1 Overview

Key elements of the statistical analysis of this study are described in this section; details, including the estimands for the primary and secondary objectives, will be documented in a Statistical Analysis Plan (SAP). The statistical analysis of this study will be the responsibility of the Biostatistics department of the Sponsor or its designee.

This study will initially be conducted as a double-blind study with in-house blinding procedures. Following primary analysis of both the biologic-naïve main study and the biologic-failure susbstudy, the remainder of the Long-term Extension Period will be conducted in a Sponsor-unblinded fashion. For the primary data analysis, the Week 12 database will not be unblinded until medical/scientific review has been conducted, protocol deviations have been identified, the data have been declared final and complete, and an SAP has been written and approved. The randomization schedule will be generated and implemented by the external vendor of the study IWRS.

9.2 Study Population Definitions

The full analysis set (FAS) will be the primary population for the efficacy analysis. The FAS will consist of all subjects who are randomized and receive at least 1 dose of IP.

Primary analysis of efficacy of subjects enrolled in the substudy will be separate from that of the main cohort.

A supportive analysis using the per-protocol (PP) Population will be performed for the primary endpoint. The PP population will consist of all subjects included in the FAS who have no protocol deviations that may substantially affect the efficacy results. The final determination on protocol deviations, and thereby the composition of the PP population, will be made prior to the unblinding of the database and will be separately documented.

Subjects will be included in the treatment group to which they were randomized for the analysis using the FAS and PP populations.

The safety analysis will be based on the safety population, which will consist of all subjects who are randomized and receive at least 1 dose of IP. Subjects will be included in the treatment group corresponding to the IP they actually received for the analysis using the safety population.

The PK Population will include all subjects who receive at least 1 dose of CC-99677 and have at least 1 measurable concentration datum. Subjects will be included in the treatment group corresponding to the IP they actually receive. The PK Population will be used for all listings.

The PK Evaluable Population will include all subjects who have at least 1 evaluable PK parameter. Subjects will be included in the treatment group corresponding to the IP they actually receive. The PK Evaluable Population will be the population used for all summaries and statistical analyses.

9.3 Sample Size and Power Considerations

With 147 total subjects and an equal allocation ratio, the study will randomize 49 subjects to each treatment group. This sample size will provide 80% power, calculated by nQuery Advisor version

7 and without accounting for multiplicity, to detect a treatment difference of 25% in ASAS20 response rate at Week 12 between either active treatment group and placebo, using a chi-square test at a two-sided significance level of 0.10, and assuming the response rates of 59% for both CC-99677 treatment groups and 34% for placebo (the latter based on historical studies), with dropouts considered as nonresponders in these assumed response rates. Applying the Hochberg procedure to adjust for the multiplicity of the comparisons of two active treatment groups with placebo, the study will provide 81% power to achieve statistical significance at the two-sided significance level of 0.10 for at least 1 treatment group, with the same response rate assumptions stated above.

An additional 50 subjects will be enrolled in the biologic-failure substudy. The purpose of this substudy is to estimate the treatment effect of CC-99677 in subjects who have received not more than one biologic for AS, due to inadequate efficacy response to an approved biologic dose for at least 12 weeks and/or unacceptable safety/tolerability of a biologic agent (in the opinion of the Investigator). A minimum of 50% of biologic failure subjects will be recruited due to inadequate efficacy response to treatment. Subjects enrolled in the substudy will be randomized using a 2:2:1 allocation ratio (20 subjects each to receive either CC-99677 150 mg PO QD or CC-99677 60 mg PO QD and 10 subjects to receive matching placebo).

9.4 Background and Demographic Characteristics

Subject's age, height, weight, and baseline characteristics will be summarized using descriptive statistics, while sex, race and other categorical variables will be provided using frequency tabulations. Medical history data will be summarized using frequency tabulations by Medical Dictionary for Drug Regulatory Activities (MedDRA) system organ class and preferred term.

9.5 Subject Disposition

Subject disposition (analysis population allocation, entered, completed, discontinued, along with primary reason for discontinuation) will be summarized using frequency and percent. A summary of subjects enrolled by site will be provided. Important protocol deviations will be summarized using frequency tabulations.

9.6 Efficacy Analysis

The primary efficacy endpoint is the ASAS20 assessment at Week 12 (Visit 6) of the Double-blind, Placebo-controlled Period (for the comparison between CC-99677 150 mg PO QD, CC-99677 60 mg PO QD and placebo.

9.6.1 Statistical Methods

Binary endpoints will be analyzed by the Cochran-Mantel-Haenszel (CMH) test stratified by the randomization stratification factor hsCRP concentration (≤ upper limit of normal/ > upper limit of normal). The primary missing data handling approach for binary endpoints will be nonresponder imputation (NRI), by which a subject will be considered a nonresponder at a given time point if the subject does not have sufficient data (including the baseline data for the endpoints assessing the change from baseline) are assessed within the analysis window of the time point for response determination.

The continuous endpoints will be analyzed by an adaptive approach (Mehrotra, 2012) that uses either a longitudinal data analysis (LDA) model (Liu, 2009) (in the absence of severe departures from normality) or robust regression model/nonparametric methods (in the presence of severe departures from normality).The LDA model assumes a common mean across treatment groups at baseline and a different mean for each treatment group at each of the postbaseline time points. In this model, the response vector consists of the baseline and postbaseline values. Time is treated as a categorical variable so that no restriction is imposed on the trajectory of the means over time. The model will also adjust for the randomization stratification factor hsCRP concentration (≤ upper limit of normal/ > upper limit of normal) and its interaction with time.

Summary statistics will be provided over time for the Long-term Extension Period.

9.6.2 Multiplicity

Multiplicity adjustment by the Hochberg procedure will be made in this study for the primary efficacy endpoint analysis.

9.6.3 Subgroup Analyses

Subgroup analyses of the primary endpoint by the randomization stratification factor, baseline demographic and disease characteristics will be provided to explore the consistency of the treatment effect across various subgroups. Details of the analysis will be provided in the SAP.

9.7 Safety Analysis

Safety will be assessed by clinical review of all relevant parameters including treatment-emergent adverse events (TEAEs), laboratory tests, vital signs, weight, and ECGs. No inferential testing for statistical significance will be performed.

TEAEs will be classified using the MedDRA classification system. All TEAEs will be summarized by system organ class, preferred term, severity, and relationship to IP. TEAEs leading to death or to discontinuation from treatment and serious TEAEs will also be tabulated. In the by-subject analysis, a subject having the same event more than once will be counted only once and by greatest severity.

Laboratory, vital signs, weight, and ECG data will be summarized descriptively by time point. In addition, shift tables showing the number of subjects with low, normal, and high values compared to the normal ranges at baseline versus postbaseline will be provided for laboratory tests.

9.8 Interim Analysis

An interim analysis (IA) will be conducted when approximately 30 subjects in the biologic-naïve main study complete 12 weeks of treatment. A Steering Committee (SC) comprised of independent BMS committee members independent of the Study Team and external AS expert(s) will review the data from the IA and will convey one of the following decisions to the blinded study team:

- Continue the study without modification
- Terminate the study for futility
- Discontinue a treatment group based on preliminary assessment of dose-dependent risk-benefit

- Add an additional dose cohort (dose not to exceed 150 mg)

If the SC determines that an additional dose cohort is needed, then the additional dose cohort will be initiated in the biologic-naïve main study only as described in Section 3.1.2.

The SC will not play a role in the study conduct. The study team responsible for managing the study will remain blinded. Details and timing of the interim analysis will be described in a Steering Committee charter. Additional interim analyses may be conducted.

9.9 Other Topics

9.9.1 Internal Safety Management Team

In addition to ongoing safety monitoring conducted by Investigators and individual study personnel, cumulative and interval blinded AEs, SAEs, discontinuations due to AEs, and abnormal laboratory findings will be reviewed internally by the Celgene Safety Management Team (SMT). The SMT is comprised of lead representatives from multiple Celgene functions engaged in the CC-999677 development program. The scope, conduct, processes, and accountabilities are specified by Celgene Standard Operating Procedure (SOP).

9.9.2 Independent External Data Monitoring Committee

Formal unblinded safety and efficacy assessments of the study data will be performed by an external, independent DMC. The external DMC will not be involved in any decision making at the IA but may make a recommendation to stop the study based on their assessment of the overall Benefit/Risk of clinical data. A DMC will be convened that will include physician experts with experience in treating subjects with AS and a statistician, all of whom are not otherwise involved in the study conduct and in whom there is no identified conflict of interest. Operational details for the DMC will be detailed in a separate DMC charter.

9.9.3 Pharmacokinetic Analyses

The pharmacokinetic analysis will be performed using the PK population as defined in Section 9.2.

Intense PK collection: Pharmacokinetic parameters of CC-99677 (Cmax, Tmax, AUC[0-T], AUC[TAU] and CLT/F) and CC-0782951 (Cmax, Tmax, AUC[0-T], AUC[TAU], MR_Cmax, MR_AUC[0-T], and MR_AUC[TAU]) in plasma may be estimated from concentration-time data using noncompartmental analysis, as appropriate.

Sparse PK collection: At Weeks 0, 4, 8, 12, 16, 20, and 24, concentrations of CC-99677 and CC-0782951 will be reported.

Descriptive statistics will be provided for CC-99677 concentrations and PK parameters, and the results will be presented in tabular and graphic form as appropriate. PK parameters for both intense and sparse PK will be reported as per the *BMS PK Harmonization Document Guidance for Contract Research Organizations for Analysis and Reporting of Pharmacokinetic (PK) Data in Clinical Studies.*

The relationship between plasma exposure of CC-99677 and selected clinical endpoints (eg, toxicities, efficacy and/or biomarkers) may be explored.

10 ADVERSE EVENTS

10.1 Monitoring, Recording and Reporting of Adverse Events

An AE is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a subject during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values (as specified by the criteria in Section 10.3), regardless of etiology. Any worsening (ie, any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be considered an AE. A diagnosis or syndrome should be recorded on the AE page of the CRF rather than the individual signs or symptoms of the diagnosis or syndrome.

Abuse, withdrawal, sensitivity or toxicity to an IP should be reported as an AE. Overdose, accidental or intentional, whether or not it is associated with an AE should be reported on the overdose CRF. (See Section 7.2 for the definition of overdose.) Any sequela of an accidental or intentional overdose of an IP which meets the definition of an adverse event, should be reported as an AE on the AE CRF. If the sequela of an overdose meets serious criteria, then it must be marked as serious on the CRF. The overdose itself should not be reported as an AE.

In the event of overdose, the subject should be monitored as appropriate and should receive supportive measures as necessary. There is no known specific antidote for CC-99677 overdose. Actual treatment should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

All subjects will be monitored for AEs during the study. Assessments may include monitoring of any or all of the following parameters: the subject's clinical symptoms, laboratory, pathological, radiological or surgical findings, physical examination findings, or findings from other tests and/or procedures.

All AEs including AEs related to SARS-CoV-2 infection, will be recorded by the Investigator from the time the subject signs informed consent until 28 days after the last dose of IP as well as those SAEs made known to the Investigator at any time thereafter that are suspected of being related to IP. All adverse events (serious/non-serious) will be recorded on the CRF and in the subject's source documents. In addition, all SARS-CoV-2 infection-related AEs or SAEs will trigger additional data collection through specialized clinical safety program (CSP) eCRF pages, which will allow the Sponsor to further evaluate these events. All SAEs must be reported to Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event.

The SAE is recorded within the eCRF and the data is transmitted electronically to Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event. In the event electronic transmission is not available, a paper SAE Report Form will be completed and sent directly to Celgene Drug Safety, ensuring the event is recorded on the CRF as well.

10.2 Evaluation of Adverse Events

A qualified Investigator will evaluate all adverse events as to:

10.2.1 Seriousness

An SAE is any AE occurring at any dose that:

- Results in death;
- Is life-threatening (ie, in the opinion of the Investigator, the subject is at immediate risk of death from the AE);
- Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay);
- Results in persistent or significant disability/incapacity (a substantial disruption of the subject's ability to conduct normal life functions);
- Is a congenital anomaly/birth defect;
- Constitutes an important medical event.

Important medical events are defined as those occurrences that may not be immediately life-threatening or result in death, hospitalization, or disability, but may jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed above. Medical and scientific judgment should be exercised in deciding whether such an AE should be considered serious.

Events **not considered** to be SAEs are hospitalizations for:

- a standard procedure for protocol therapy administration. However, hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as an SAE.
- routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- the administration of blood or platelet transfusion as routine treatment of studied indication. However, hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable SAE.
- a procedure for protocol/disease-related investigations (eg, surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling). However, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE.
- hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE.
- a procedure that is planned (ie, planned prior to start of treatment on study); must be documented in the source document and the CRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.
- an elective treatment of or an elective procedure for a pre-existing condition, unrelated to the studied indication, that has not worsened from baseline.
- emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

For each AE, the Investigator will provide information on severity, start and stop dates, relationship to the IP, action taken regarding the IP, and outcome.

10.2.2 Severity/Intensity

For each AE the Investigator must assess the severity/ intensity of the event.

The severity/intensity of AEs will be graded based upon the subject's symptoms according to the current active minor version of the Common Terminology Criteria for Adverse Events (CTCAE, Version 5.0)

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

AEs that are not defined in the CTCAE should be evaluated for severity/intensity according to the following scale:

- Grade 1 = Mild – transient or mild discomfort; no limitation in activity; no medical intervention/therapy required
- Grade 2 = Moderate – mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required
- Grade 3 = Severe – marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization is possible
- Grade 4 = Life-threatening – extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable
- Grade 5 = Death - the event results in death

The term "severe" is often used to describe the intensity of a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This criterion is *not* the same as "serious" which is based on subject/event *outcome* or *action* criteria associated with events that pose a threat to a subject's life or functioning.

Seriousness, not severity, serves as a guide for defining regulatory obligations.

10.2.3 Causality

The Investigator must determine the relationship between the administration of the IP and the occurrence of an AE as Not Suspected or Suspected as defined below:

Not suspected:	a causal relationship of the adverse event to IP administration is **unlikely or remote**, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.
Suspected:	there is a **reasonable possibility** that the administration of IP caused the adverse event. 'Reasonable possibility' means there is evidence to suggest a causal relationship between the IP and the adverse event.

Causality should be assessed and provided for each AE based on currently available information. Causality is to be reassessed and provided as additional information becomes available.

If an event is assessed as suspected of being related to a comparator, ancillary or additional IP that has not been manufactured or provided by Celgene, please provide the name of the manufacturer when reporting the event.

10.2.4 Duration

For each AE, the Investigator will provide a record of the start and stop dates of the event. After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, non-serious AEs of special interest (as defined in Section 10.5) and SARS-CoV-2 related AEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the participant is lost to follow-up.

10.2.5 Action Taken

The Investigator will report the action taken with IP as a result of each AE as applicable (eg, discontinuation, interruption, or dose reduction of IP, as appropriate) and report if concomitant and/or additional treatments were given for the event.

10.2.6 Outcome

The Investigator will report the outcome of the event for both AEs and SAEs.

All SAEs that have not resolved upon discontinuation of the subject's participation in the study must be followed until recovered (returned to baseline), recovered with sequelae, or death (due to the SAE).

10.3 Abnormal Laboratory Values

An abnormal laboratory value is considered to be an AE if the abnormality:

- results in discontinuation from the study;
- requires treatment, modification/ interruption of IP dose, or any other therapeutic intervention; or
- is judged to be of significant clinical importance, eg, one that indicates a new disease process and/or organ toxicity or is an exacerbation or worsening of an existing condition.

Regardless of severity grade, only laboratory abnormalities that fulfill a seriousness criterion need to be documented as a serious adverse event.

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded as the AE. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE. If possible, the laboratory abnormality should be recorded as a medical term and not simply as an abnormal laboratory result (eg, record thrombocytopenia rather than decreased platelets).

10.4 Pregnancy

All pregnancies or suspected pregnancies occurring in either a female subject of childbearing potential or partner of childbearing potential of a male subject are immediately reportable events.

In the event of a pregnancy occurring in a female subject of childbearing potential or female partner of a male subject, Celgene will follow up with the clinical Investigator each trimester of pregnancy

and for 1 year following the birth of the infant (if applicable). Please reference the pregnancy information consent (permission) forms for data collection for additional information.

10.4.1 Females of Childbearing Potential

Pregnancies and suspected pregnancies (including elevated β-hCG or positive pregnancy test in a female subject of childbearing potential regardless of disease state) occurring while the subject is on IP, or within 28 days of the subject's last dose of IP, are considered immediately reportable events. Investigational product is to be discontinued immediately and the subject instructed to return any unused portion of the IP to the Investigator. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by email, phone or facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent form.

The female subject may be referred to an obstetrician-gynecologist or another appropriate healthcare professional for further evaluation.

The Investigator will follow the female subject until completion of the pregnancy and must notify Celgene Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form or approved equivalent form.

If the outcome of the pregnancy was abnormal (eg, spontaneous abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as an SAE. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to the IP should also be reported as an SAE to Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event.

10.4.2 Male Subjects

If a female partner of a male subject taking IP becomes pregnant, the male subject taking IP should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.

10.5 Adverse Events of Special Interest

Investigators should identify AEs that meet the following criteria for adverse events of special interest (AESIs).

10.5.1 Photosensitivity Reactions

A toxicology study in mice suggests that CC-99677 has the potential for photosensitivity. Therefore, subjects should take precautions to limit light exposure while receiving CC-99677 (Section 4.2). In the event of a suspected photosensitivity rash, the adverse event should be discussed with the Medical Monitor. At the Investigator's discretion, in consultation with the Medical Monitor, a skin biopsy and/or consultation with a dermatologist may be obtained to further

characterize the rash. Please refer to Section 11 for discontinuation of IP based on potential photosensitivity reactions.

10.5.2 Hepatic Enzyme Elevations

In the 120-mg dose cohort of the MAD part of CC-99677-CP-001, 3 out of 6 subjects experienced an increase in serum transaminase levels above the ULN, (Section 1.4). All subjects were asymptomatic, no interventions were required, and hepatic enzymes returned to normal. There were no treatment interruptions. A plan to closely monitor hepatic enzyme elevations is outlined in APPENDIX G, Hepatotoxicity Monitoring Criteria for Interruption and Discontinuation of IP, based on liver function test abnormalities.

10.5.3 Monitoring, Recording and Reporting of Adverse Events of Special Interest

To better characterize and understand any potential AEs for hepatic enzyme elevations and photosensitivity the severity/intensity of AEs will be graded based upon the subject's symptoms according to the current active minor version of the Common Terminology Criteria for Adverse Events (CTCAE, Version 5.0):

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

10.6 Reporting of Serious Adverse Events

Any AE that meets serious criterion requires reporting as an SAE within 24 hours of the Investigator's knowledge of the event. This instruction pertains to initial SAE reports as well as any follow-up reports.

This requirement applies to all SAEs (regardless of relationship to IP) that occur during the study (from the time the subject signs informed consent until 28 days after the last dose of IP) or any SAE made known to the Investigator at any time thereafter that are suspected of being related to IP. Serious adverse events occurring prior to treatment (after signing the ICF) are to be recorded within the CRF, but do not require reporting to Celgene Drug Safety.

Where required by local legislation, the Investigator is responsible for informing the Institutional Review Board/Ethics Committee (IRB/EC) of the SAE and providing them with all relevant initial and follow-up information about the event. The Investigator must keep copies of all SAE information on file including correspondence with Celgene and the IRB/EC.

The SAE is recorded within the eCRF, and the data is transmitted electronically to Celgene Drug Safety. In the event electronic transmission is not available, a paper SAE Report Form will be completed and sent directly to Celgene Drug Safety, ensuring the event is recorded on the CRF as well.

10.7 Expedited Reporting of Adverse Events

For the purpose of regulatory reporting, Celgene Drug Safety will determine the expectedness of events suspected of being related to CC-99677 based on the IB.

In the United States, all suspected unexpected serious adverse reactions (SUSARs) will be reported in an expedited manner in accordance with 21 Code of Federal Regulations (CFR) 312.32.

For countries within the European Economic Area (EEA), Celgene or its authorized representative will report in an expedited manner to Regulatory Authorities and Ethics Committees concerned, suspected unexpected serious adverse reactions (SUSARs) in accordance with Directive 2001/20/EC and the Detailed Guidance on collection, verification and presentation of adverse reaction reports arising from clinical trials on investigational products for human use (ENTR/CT3) and also in accordance with country-specific requirements.

Celgene or its authorized representative shall notify the Investigator of the following information:

- Any AE suspected of being related to the use of IP in this study or in other studies that is both serious and unexpected (ie, SUSAR);
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

Where required by local legislation, the Investigator shall notify his/her IRB/EC promptly of these new serious and unexpected AE(s) or significant risks to subjects.

The Investigator must keep copies of all pertinent safety information on file including correspondence with the IRB/EC. See Section 14.3 for record retention information.

11 DISCONTINUATIONS

11.1 Individual Stopping Criteria

The subject will be discontinued from the investigational product:

- If 1 subject develops a Grade 3 AE or higher (according to CTCAE Version 5.0 grading system) considered to be at least possibly drug-related
- If the subject meets discontinuation criteria outlined in APPENDIX G (Hepatotoxicity Monitoring Criteria for Interruption and Discontinuation of Investigational Product)

  Note: In the case of Grade 3 or 4 safety laboratory AEs that are considered at least possibly drug-related, repeat all abnormal safety laboratory assessments within 48 to 72 hours to refute or confirm the findings. The decision to temporarily interrupt the IP will be based on the Investigator's clinical judgment.
- Pregnancies and suspected pregnancies (including elevated β-hCG or positive pregnancy test in a female subject of childbearing potential regardless of disease state) occurring while the subject is receiving IP (Section 10.4.1)

11.2 Treatment Discontinuation

The following events are considered sufficient reasons for **discontinuing** a subject from the **investigational product**:

- Adverse Event
- Withdrawal by subject
- Death
- Lost to follow-up
- Other (to be specified on the CRF)

The reason for discontinuation of treatment should be recorded in the CRF and in the source documents.

The decision to discontinue a subject from treatment remains the responsibility of the treating physician, which will not be delayed or refused by the Sponsor. However, prior to discontinuing a subject, the Investigator may contact the Medical Monitor and forward appropriate supporting documents for review and discussion.

11.3 Study Discontinuation

The following events are considered sufficient reasons for discontinuing a subject from the study:

- Screen failure
- Adverse event
- Withdrawal by subject
- Death
- Lost to follow-up
- Other (to be specified on the CRF)

The reason for study discontinuation should be recorded in the CRF and in the source documents.

12 EMERGENCY PROCEDURES

12.1 Emergency Contact

In emergency situations, the Investigator should contact the responsible Clinical Research Physician/Medical Monitor or designee by telephone at the number(s) listed on the Emergency Contact Information page of the protocol (after title page).

In the unlikely event that the Clinical Research Physician/Medical Monitor or designee cannot be reached, please contact the global Emergency Call Center by telephone at the number listed on the Emergency Contact Information page of the protocol (after title page). This global Emergency Call Center is available 24 hours a day and 7 days a week. The representatives are responsible for obtaining your call-back information and contacting the on-call Celgene/contract research organization Medical Monitor, who will then contact you promptly.

Note: The back-up 24-hour global emergency contact call center should only be used if you are not able to reach the Clinical Research Physician(s) or Medical Monitor or designee for emergency calls.

12.2 Emergency Identification of Investigational Products

The blind must not be broken during the course of the study **unless** in the opinion of the Investigator, it is absolutely necessary to safely treat the subject. If it is medically imperative to know what IP the subject is receiving, IP should be temporarily discontinued if, in the opinion of the Investigator, continuing IP can negatively affect the outcome of the subject's treatment.

The decision to break the blind in emergency situations remains the responsibility of the treating physician, which will not be delayed or refused by the Sponsor. However, the Investigator may contact the Medical Monitor prior to breaking the blind to discuss unblinding, mainly in the interest of the subject.

The Investigator should ensure that the code is broken only in accordance with the protocol. The Investigator should promptly notify the Medical Monitor of the emergency unblinding and the reason for breaking the blind, which should be clearly documented by the Investigator in the subject's source documentation.

Emergency unblinding should only be performed by the Investigator through the Interactive Web Response System (IWRS).

13 REGULATORY CONSIDERATIONS

13.1 Good Clinical Practice

The procedures set out in this study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that Celgene, its authorized representative, and Investigator abide by Good Clinical Practice (GCP), as described in International Conference for Harmonisation (ICH) Guideline E6 and in accordance with the general ethical principles outlined in the Declaration of Helsinki. The study will receive approval from an IRB/EC prior to commencement. The Investigator will conduct all aspects of this study in accordance with applicable national, state, and local laws of the pertinent regulatory authorities.

13.2 Investigator Responsibilities

Investigator responsibilities are set out in the ICH Guideline for Good Clinical Practice and in the local regulations. Celgene staff or an authorized representative will evaluate and approve all Investigators who in turn will select their staff.

The Investigator should ensure that all persons assisting with the study are adequately informed about the protocol, amendments, study treatments, as well as study-related duties and functions, including obligations of confidentiality of Celgene information. The Investigator should maintain a list of Sub-investigators and other appropriately qualified persons to whom he or she has delegated significant study-related duties.

The Investigator is responsible for keeping a record of all subjects who sign an informed consent form (ICF) and are screened for entry into the study. Subjects who fail screening must have the reason(s) recorded in the subject's source documents.

The Investigator, or a designated member of the Investigator's staff, must be available during monitoring visits to review data, resolve queries and allow direct access to subject records (eg, medical records, office charts, hospital charts, and study-related charts) for source data verification. The Investigator must ensure timely and accurate completion of CRFs and queries.

The information contained in the protocol and amendments (with the exception of the information provided by Celgene on public registry websites) is considered Celgene confidential information. Only information that is previously disclosed by Celgene on a public registry website may be freely disclosed by the Investigator or its institution, or as outlined in the Clinical Trial Agreement. Celgene protocol, amendment and IB information is not to be made publicly available (for example on the Investigator's or their institution's website) without express written approval from Celgene. Information proposed for posting on the Investigator's or their institution's website must be submitted to Celgene for review and approval, providing at least 5 business days for review.

At the time results of this study are made available to the public, Celgene will provide Investigators with a summary of the results that is written for the lay person. The Investigator is responsible for sharing these results with the subject and/or their caregiver as agreed by the subject.

13.3 Subject Information and Informed Consent

The Investigator must obtain informed consent of a subject and/or a subject's legal representative prior to any study related procedures.

Documentation that informed consent occurred prior to the study subject's entry into the study and of the informed consent process should be recorded in the study subject's source documents including the date. The original ICF signed and dated by the study subject and by the person consenting the study subject prior to the study subject's entry into the study, must be maintained in the Investigator's study files and a copy given to the study subject. In addition, if a protocol is amended and it impacts on the content of the informed consent, the ICF must be revised. Study subjects participating in the study when the amended protocol is implemented must be reconsented with the revised version of the ICF. The revised ICF signed and dated by the study subject and by the person consenting the study subject must be maintained in the Investigator's study files and a copy given to the study subject.

13.4 Confidentiality

Celgene affirms the subject's right to protection against invasion of privacy and to be in compliance with ICH and other local regulations (whichever is most stringent). Celgene requires the Investigator to permit Celgene's representatives and, when necessary, representatives from regulatory authorities, to review and/or copy any medical records relevant to the study in accordance with local laws.

Should direct access to medical records require a waiver or authorization separate from the subject's signed ICF, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

13.5 Protocol Amendments

Any amendment to this protocol must be approved by the Celgene Clinical Research Physician/Medical Monitor. Amendments will be submitted to the IRB/EC for written approval. Written approval must be obtained before implementation of the amended version occurs. The written signed approval from the IRB/EC should specifically reference the Investigator name, protocol number, study title and amendment number(s) that is applicable. Amendments that are administrative in nature do not require IRB/EC approval but will be submitted to the IRB/EC for information purposes.

13.6 Institutional Review Board/Independent Ethics Committee Review and Approval

Before the start of the study, the study protocol, ICF, and any other appropriate documents will be submitted to the IRB/EC with a cover letter or a form listing the documents submitted, their dates of issue, and the site (or region or area of jurisdiction, as applicable) for which approval is sought. If applicable, the documents will also be submitted to the authorities in accordance with local legal requirements.

IP can only be supplied to an Investigator by Celgene or its authorized representative after documentation on all ethical and legal requirements for starting the study has been received by

Celgene or its authorized representative. This documentation must also include a list of the members of the IRB/EC and their occupation and qualifications. If the IRB/EC will not disclose the names, occupations and qualifications of the committee members, it should be asked to issue a statement confirming that the composition of the committee is in accordance with GCP. For example, the IRB General Assurance Number may be accepted as a substitute for this list. Formal approval by the IRB/EC should mention the protocol title, number, amendment number (if applicable), study site (or region or area of jurisdiction, as applicable), and any other documents reviewed. It must mention the date on which the decision was made and must be officially signed by a committee member. Before the first subject is enrolled in the study, all ethical and legal requirements must be met.

The IRB/EC and, if applicable, the authorities, must be informed of all subsequent protocol amendments in accordance with local legal requirements. Amendments must be evaluated to determine whether formal approval must be sought and whether the ICF should also be revised.

The Investigator must keep a record of all communication with the IRB/EC and, if applicable, between a Coordinating Investigator and the IRB/EC. This statement also applies to any communication between the Investigator (or Coordinating Investigator, if applicable) and regulatory authorities.

Any advertisements used to recruit subjects for the study must be reviewed by Celgene and the IRB/EC prior to use.

13.7 Ongoing Information for Institutional Review Board/ Ethics Committee

If required by legislation or the IRB/EC, the Investigator must submit to the IRB/EC:

- Information on serious or unexpected adverse events as soon as possible;
- Periodic reports on the progress of the study;
- Deviations from the protocol or anything that may involve added risk to subjects.

13.8 Termination of the Study

Celgene reserves the right to terminate this study prematurely at any time for reasonable medical or administrative reasons. Any premature discontinuation will be appropriately documented according to local requirements (eg, IRB/EC, regulatory authorities, etc).

In addition, the Investigator or Celgene has the right to discontinue a single site at any time during the study for medical or administrative reasons such as:

- Unsatisfactory enrollment;
- GCP noncompliance;
- Inaccurate or incomplete data collection;
- Falsification of records;
- Failure to adhere to the study protocol.

14 DATA HANDLING AND RECORDKEEPING

14.1 Data/Documents

The Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the IP are complete, accurate, filed and retained. Examples of source documents include: hospital records; clinic and office charts; laboratory notes; memoranda; subject's diaries or evaluation checklists; dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiche; X-ray film and reports; and records kept at the pharmacy, and the laboratories, as well as copies of CRFs or CD-ROM.

14.2 Data Management

Data will be collected via CRF and entered into the clinical database per Celgene SOPs. This data will be electronically verified through use of programmed edit checks specified by the clinical team. Discrepancies in the data will be brought to the attention of the clinical team, and investigational site personnel, if necessary. Resolutions to these issues will be reflected in the database. An audit trail within the system will track all changes made to the data.

14.3 Record Retention

Essential documents must be retained by the Investigator according to the period of time outlined in the clinical trial agreement. The Investigator must retain these documents for the time period described above or according to local laws or requirements, whichever is longer. Essential documents include, but are not limited to, the following:

- Signed ICFs for all subjects;
- Subject identification code list, screening log (if applicable), and enrollment log;
- Record of all communications between the Investigator and the IRB/EC;
- Composition of the IRB/EC;
- Record of all communications between the Investigator, Celgene, and their authorized representative(s);
- List of Sub-investigators and other appropriately qualified persons to whom the Investigator has delegated significant study-related duties, together with their roles in the study, curriculum vitae, and their signatures;
- Copies of CRFs (if paper) and of documentation of corrections for all subjects;
- IP accountability records;
- Record of any body fluids or tissue samples retained;
- All other source documents (subject records, hospital records, laboratory records, etc.);
- All other documents as listed in Section 13 of the ICH consolidated guideline on GCP (Essential Documents for the Conduct of a Clinical Trial).

The Investigator must notify Celgene if he/she wishes to assign the essential documents to someone else, remove them to another location or is unable to retain them for a specified period. The Investigator must obtain approval in writing from Celgene prior to destruction of any records.

If the Investigator is unable to meet this obligation, the Investigator must ask Celgene for permission to make alternative arrangements. Details of these arrangements should be documented.

All study documents should be made available if required by relevant health authorities. Investigator or institution should take measures to prevent accidental or premature destruction of these documents.

15 QUALITY CONTROL AND QUALITY ASSURANCE

All aspects of the study will be carefully monitored by Celgene or its authorized representative for compliance with applicable government regulations with respect to current GCP and SOPs.

15.1 Study Monitoring and Source Data Verification

Celgene ensures that appropriate monitoring procedures are performed before, during and after the study. All aspects of the study are reviewed with the Investigator and the staff at a study initiation visit and/or at an Investigators' Meeting. Prior to enrolling subjects into the study, a Celgene representative will review the protocol, CRFs, procedures for obtaining informed consent, record keeping, and reporting of AEs/SAEs with the Investigator. Monitoring will include on-site visits with the Investigator and his/her staff as well as any appropriate communications by mail, email, fax, or telephone. During monitoring visits, the facilities, IP storage area, CRFs, subject's source documents, and all other study documentation will be inspected/reviewed by the Celgene representative in accordance with the Study Monitoring Plan.

Accuracy will be checked by performing source data verification that is a direct comparison of the entries made onto the CRFs against the appropriate source documentation. Any resulting discrepancies will be reviewed with the Investigator and/or his/her staff. Any necessary corrections will be made directly to the CRFs or via queries by the Investigator and/or his/her staff. Monitoring procedures require that informed consents, adherence to inclusion/exclusion criteria and documentation of SAEs and their proper recording be verified. Additional monitoring activities may be outlined in a study-specific monitoring plan.

15.2 Audits and Inspections

In addition to the routine monitoring procedures, a Good Clinical Practice Quality Assurance unit exists within Celgene. Representatives of this unit will conduct audits of clinical research activities in accordance with Celgene SOPs to evaluate compliance with Good Clinical Practice guidelines and regulations.

The Investigator is required to permit direct access to the facilities where the study took place, source documents, CRFs and applicable supporting records of study subject participation for audits and inspections by IRB/ECs, regulatory authorities (eg, FDA, EMA, Health Canada) and company authorized representatives. The Investigator should make every effort to be available for the audits and/or inspections. If the Investigator is contacted by any regulatory authority regarding an inspection, he/she should contact Celgene immediately.

15.3 Product Quality Complaint

A Product Quality Complaint (PQC) is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, purity, or performance of any drug product manufactured by or on behalf of Celgene Corporation after it is released for distribution. PQCs may reduce the usability of the product for its intended function or affect performance of the product and therefore pose a significant risk to the subject. Examples of PQCs include (but are not limited to): mixed product, mislabeling, lack of effect, seal/packaging breach, product missing/short/overage, contamination, suspected falsified, tampered, diverted or

stolen material, and general product/packaging damage. If you become aware of a suspected PQC, you are obligated to report the issue immediately. You can do so by emailing [redacted] or by contacting the Celgene Customer Care Center [redacted]

16 PUBLICATIONS

As described in Section 13.2, all protocol- and amendment-related information, with the exception of the information provided by Celgene on public registry websites, is considered Celgene confidential information and is not to be used in any publications. Celgene protocol-related information proposed for use in a publication must be submitted to Celgene for review and approval and should not be utilized in a publication without express written approval from Celgene, or as described in the Clinical Trial Agreement.

Celgene will ensure Celgene-sponsored studies are considered for publication in the scientific literature in a peer-reviewed journal, irrespective of the results. At a minimum, this applies to results from all Period 3 clinical studies, and any other study results of significant medical importance. This also includes results relating to investigational medicines whose development programs have been discontinued.

Study results may also be presented at one or more medical congresses and may be used for scientific exchange and teaching purposes. Additionally, this study and its results may be submitted for inclusion in all appropriate health authority study registries, as well as publication on health authority study registry websites, as required by local health authority regulations.

Eligibility for external authorship, as well as selection of first authorship, will be based on several considerations, including, but not limited to, contribution to protocol development, study recruitment, data quality, participation in data analysis, participation in study Steering Committee (when applicable) and contribution to abstract, presentation and/or publication development.

17 REFERENCES

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18 APPENDICES

APPENDIX A TABLE OF ABBREVIATIONS

Table 6: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ADL	Activity of daily living
AE	Adverse event
ALT	Alanine aminotransferase (SGPT)
ALP	Alkaline phosphatase
AS	Ankylosing spondylitis
ASAS	Assessment In Spondyloarthritis International Society
ASAS HI	Assessment of Spondyloarthritis International Society Health Index
ASDAS	Ankylosing Spondylitis Disease Activity
ASDAS-CRP	Ankylosing Spondylitis Disease Activity with C-reactive protein as the acute-phase reactant
AP	Anterior-Posterior
ASQOL	Ankylosing Spondylitis Quality of Life questionnaire
AST	Aspartate aminotransferase (SGOT)
AUC	Area under the curve
AUC(0-T)	Area under the plasma concentration-time curve from time zero to last measurable concentration
AUC_{LST}	Area under the concentration-time curve from time zero to the last measurable time point
AUC(TAU)	Area under the concentration-time curve over the dosing interval
axSpA	Axial Spondyloarthritis
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
BASMI	Bath Ankylosing Spondylitis Metrology Index
BASMI-Linear	Bath Ankylosing Spondylitis Metrology Index-Linear
BCRP	Breast cancer resistance protein
β-CTX	β-subunit of C-terminal telopeptide
β-hCG	β-subunit of human chorionic gonadotropin
BMD	Bone mineral density
BMS	Bristol Myers Squibb
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
CLT/F	Apparent total body clearance

Table 6: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
C_{max}	Maximum plasma concentration of drug
CMH	Cochran-Mantel-Haenszel
COVID-19	Coronavirus disease 2019
COX	Cyclooxygenase
CRF	Case report form
CRP	C-reactive protein
CS	Clinically significant
CSP	Clinical safety program
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DMARDS	Disease modifying anti-rheumatic drugs
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EEA	European Economic Area
EMA	European Medicines Agency
EOT	End of treatment
ET	Early termination
EudraCT	European Union Drug Regulating Authorities Clinical Trials (ie, European Clinical Trials Database)
FAS	Full analysis set
FCBP	Female of childbearing potential
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
HbA1c	Hemoglobin A1C
HBsAg	Hepatitis B surface antigen
hCG	Human chorionic gonadotropin
HDL	High-density lipoprotein
hsCRP	High- sensitivity C-reactive protein

Table 6: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
HIV	Human immunodeficiency virus
HLA-B 27	Human leukocyte antigen - B27
HLAB27Tg	Human leukocyte antigen - B27 transgenic
hr	Hour
ICF	Informed consent form
ICH	International Council for Harmonisation
IB	Investigators Brochure
IgG	Immunoglobulin-G
Ig-M	Immunoglobulin-M
IL-2	Interleukin-2
IL-6	Interleukin-6
IL-17	Interleukin-17
IL-23	Interleukin-23
IMPD	Investigational Medicinal Product Dossier
IND	Investigational New Drug
INR	International normalized ratio
IP	Investigational product
IRB	Institutional Review Board
IUD	Intrauterine device
IWRS	Interactive web response system
JAK	Janus kinase
LDA	Longitudinal data analysis
LDL	Low-density lipoprotein
LFT	Liver function test
LPS	Lipopolysaccharide stimulation
mAb	Monoclonal antibody
MAD	Multiple-ascending dose
MAPK	Mitogen activated protein kinase
MASES	Maastricht Ankylosing Spondylitis Enthesitis Score
MCID	Minimum clinically important difference
MCP-1	Monocyte chemoattractant protein-1
MCS	Mental Component Summary

Table 6: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
MedDRA	Medical Dictionary for Drug Regulatory Activities
MK2	Mitogen-activated protein (MAP) kinase-activated protein kinase 2
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
MR_AUC(0-T)	Metabolite to parent molar ratio of AUC(0-T)
MR_AUC(TAU)	Metabolite to parent molar ratio of AUC(TAU)
MR_Cmax, OC	Metabolite to parent molar ratio of Cmax Oral Contraceptive
NCS	Not clinically significant
NOAEL	No observed adverse effect level
NOEL	No observed effect level
NRI	Nonresponder imputation
NRS	Numerical Rating Scales
NSAIDS	Nonsteroidal anti-inflammatory drug
OATP	Organic anion transporting polypeptide
OCP	Osteoclast precursors
OCT	Organic cation transporter
P1NP	Procollagen I intact N-terminal peptide
PBMC	Peripheral blood mononuclear cell
PCS	Physical Component Summary
PD	Pharmacodynamics
PG	Pharmacogenomics
P-gp	P-glycoprotein
PK	Pharmacokinetics
PP	Per-protocol
PQC	Product quality complaint
PRN	As needed
PT	Prothrombin time
QD	Once daily
RBC	Red blood cell count
RNA	Ribonucleic acid
SAE	Serious adverse event
SAD	Single Ascending Dose

Table 6: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SF-36	Short Form-36
SI	Sacroiliac
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SMT	Safety Management Team
SNP	Single nucleotide polymorphism
SOP	Standard operating procedure
SpA	Spondyloarthritis
SPARCC	Spondyloarthritis Research Consortium of Canada
SUSAR	Suspected unexpected serious adverse reaction
$t_{½}$	Terminal elimination half-life
TB	Tuberculosis
TBL	Total bilirubin
TE	Target engagement
TEAEs	Treatment-emergent adverse events
T_{max}	Time to C_{max}
TNF	Tumor necrosis factor
TNF-α	Tumor necrosis factor-alpha
ULN	Upper limit of normal
UV	Ultraviolet
WBC	White blood cell count

APPENDIX B MODIFIED NEW YORK CRITERIA FOR ANKYLOSING SPONDYLITIS (1984)

Clinical Criteria

- Low back pain and stiffness for more than 3 months that improves with exercise, but is not relieved by rest
- Limitation of motion of the lumbar spine in the sagittal and frontal planes
- Limitation of chest expansion relative to normal values correlated for age and sex

Radiological Criterion

- Sacroiliitis grade ≥ 2 bilaterally or grade 3 to 4 unilaterally

A designation of "definite AS" requires the radiological criterion to be met in association with at least one clinical criterion

Source: van der Linden, 1984.

APPENDIX C EXAMPLES OF DRUGS THAT ARE EXCLUDED BASED ON POTENTIAL DRUG-DRUG INTERACTIONS

Table 7: Examples of Moderate or Strong Inhibitors and Moderate or Strong Inducers of CYP3A4/5 That are Excluded

Category	Inhibitors	Inducers
Antibiotic	ciprofloxacin, clarithromycin, elithromycin, erythromycin	rifampin, rifabutin, rifapentin, nafcillin
Anticonvulsant		phenytoin, carbamazepine, phenobarbital, cenobamate
Antiviral		lopinavir, efavirenz, asunaprevir/beclabuvir/daclatasvir, tipranavir/ritonavir
Antidepressant	fluvoxamine, nefazodone	thioridazine
Antifungal	fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole	
Cardiovascular drug	diltiazem, dronedarone, verapamil	
Other	aprepitant, conivaptan, cyclosporine, grapefruit juice, tofisopam	

Source: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers.

Note: This list of CYP3A4/5 inhibitors is not exhaustive, for questions please consult the Medical Monitor. The Indiana University (2016) "Cytochrome P450 Drug Interaction Table" should be utilized to determine inhibitors of CYP3A4/5. (http://medicine.iupui.edu/clinpharm/ddis/table.aspx).

Table 8: Examples of Moderate or Strong Inhibitors of P-gp, Moderate or Strong Inducers of P-gp, and Strong Inhibitors of BCRP That are Excluded

Transporter	Category	Inhibitors	Inducers
P-gp	Antibiotic	clarithromycin	rifampin, rifabutin
	Antifungal	itraconazole	
	Anticonvulsant		Carbamazepine, phenytoin
	Antiviral		efavirenz, ritonavir
	Cardiovascular drug	amiodarone, carvedilol, dronedarone, propafenone, quinidine, ranolazine, verapamil	
BCRP	Chemotherapy	eltrombopag	
	Herbal supplement	curcumin	
	Immunosuppressive drug	cyclosporine A	

Abbreviations: P-gp = P-glycoprotein; BCRP = Breast cancer resistance protein.

Source: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers.

Note: This list is not exhaustive, for questions please consult the Medical Monitor.

Table 9: Examples of Substrates of One or More Potentially Affected Transporters with a Narrow Therapeutic Index and Should be Excluded

Category	Substrate
Blood thinner	dabigatran etexilate
Cardiovascular drug	digoxin, procainamide
Immunosuppressive drug	cyclosporine, leflunomide, mycophenolic acid, methotrexate, sirolimus

Note: This list is not comprehensive. The investigator should consult the product insert for any concomitant medication and use best clinical judgement or contact the study Medical Monitor if there are questions.

APPENDIX D EXAMPLES OF DRUGS THAT ARE SUBSTRATES FOR SELECTED TRANSPORTERS AND SHOULD BE USED WITH CAUTION

Table 10: Examples of Drugs That Are Substrates for BCRP, P-gp, OATP1B1/3, and OCT1 With a Narrow Therapeutic Index and Should be Used With Caution

Transporter	Category	Substrate
BCRP	Cardiovascular drug	prazosin
P-gp	Antidiabetes	saxagliptin, sitagliptin
	Blood thinner	rivaroxaban, ticagrelor
	Cardiovascular drug	aliskiren, ambrisentan, talinolol
	Other	colchicine, fexofenadine, tolvaptan
OATP1B1/3	Anti-diabetes	repaglinide, glyburide
	Cardiovascular drug	ambrisentan, telmisartan, valsartan, olmesartan
	Lipid lowering agent	atorvastatin, ezetimibe, fluvastatin, simvastatin acid, pitavastatin
OCT1	Analgesic	tramadol
	Neurologic drug	gabapentin, pramipexole
	Other	varenicline

Abbreviations: BCRP = breast cancer resistance protein; OATP = organic anion transporting polypeptide; OCT = organic cation transporter; P-gp = p-glycoprotein.

Note: This list is not comprehensive. The investigator should consult the product insert for any concomitant medication and use best clinical judgement or contact the study Medical Monitor if there are questions. Substrates of these transporters that have a narrow therapeutic index are excluded.

APPENDIX E TUBERCULOSIS HIGH BURDEN COUNTRY LIST

1) Angola
2) Bangladesh
3) Brazil
4) Cambodia
5) Central African Republic
6) China
7) Congo
8) Democratic People's Republic of Korea
9) Democratic Republic of Congo
10) Ethiopia
11) India
12) Indonesia
13) Kenya
14) Lesotho
15) Liberia
16) Mozambique
17) Myanmar
18) Namibia
19) Nigeria
20) Pakistan
21) Papua New Guinea
22) Philippines
23) Russian Federation
24) Sierra Leone
25) South Africa
26) Tanzania
27) Thailand
28) United Republic of Viet Nam
29) Zambia
30) Zimbabwe

APPENDIX F MULTI-DRUG RESISTANT TUBERCULOSIS HIGH BURDEN COUNTRY LIST

1) Angola
2) Azerbaijan
3) Bangladesh
4) Belarus
5) China
6) Democratic People's Republic of Korea
7) Democratic Republic of Congo
8) Ethiopia
9) India
10) Kazakhstan
11) Kenya
12) Kyrgyzstan
13) Indonesia
14) Moldova
15) Mozambique
16) Myanmar
17) Nigeria
18) Pakistan
19) Papua New Guinea
20) Peru
21) Philippines
22) Russian Federation
23) South Africa
24) Thailand
25) Ukraine
26) United Republic of Viet Nam
27) Uzbekistan
28) Republic of Somalia
29) Tajikistan
30) Zimbabwe

APPENDIX G HEPATOTOXICITY MONITORING CRITERIA FOR INTERRUPTION AND DISCONTINUATION OF INVESTIGATIONAL PRODUCT*

Table 11: Hepatotoxicity Monitoring Criteria**

Laboratory Test	Action
ALT or AST > 3 x ULN but ≤ 8 x ULN And TBL ≤ 2 x ULN and INR ≤ 1.5	Continue with IP treatment Repeat all LFTs within 48-72 hours to refute or confirm the findings* If abnormal findings are confirmed, close observation is required (repeat LFTs 2-3 times per week) for at least 2 weeks Subject is to be followed until the laboratory value(s) return to baseline.
Any of the following: ALT or AST > 3 x ULN and (TBL > 2 x ULN or INR > 1.5) ALT or AST > 8 x ULN ALT or AST > 5 x ULN for more than 2 weeks ALT or AST > 3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	Interrupt IP treatment Repeat all LFTs within 48-72 hours to confirm or refute the abnormal findings* If abnormal findings are confirmed and cannot be attributed to causes other than IP treatment, study drug should be permanently discontinued and close observation is required (repeat LFTs 2-3 times per week) for at least 2 weeks; subject is to be followed until the laboratory value(s) return to baseline If abnormal findings are not confirmed and/or findings can be attributed to causes other than IP treatment, close observation is required (repeat LFTs to be based on results on repeat testing) and discussion with MM should take place to determine whether IP can be re-started

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BLM = baseline measurement(s); INR = international normalized ratio; IP = investigational product; LFT = liver function test; MM = Medical Monitor; TBL = total bilirubin; ULN = upper limit of normal.

* All LFTs refer to the following tests: ALT, AST, total bilirubin, alkaline phosphatase, prothrombin time (to determine INR). Other causes of LFT elevation should be ruled out: a history of alcohol use and biliary colic as potential causes of abnormal liver function tests should be elicited. Tests for other causes of increased AST or ALT include those for infections (hepatitis A, hepatitis B, hepatitis C, hepatitis E), acetaminophen toxicity, toxicology screen, and autoimmune diseases (antinuclear antibodies, anti-smooth muscle antibodies, anti-liver/kidney microsomal antibodies type 1, immunoglobulin G [IgG]). Additional tests and evaluations may be requested by the and include right upper quadrant ultrasonogram.

** Based on Guidance for Industry Drug-induced Liver Injury: Premarketing Clinical Evaluation; (*http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm* [FDA, 2009])

1. JUSTIFICATION FOR AMENDMENT

The primary purpose of this amendment is:

- In response to Health Authority feedback, include mitigation measures in the protocol for potential Drug-Drug Interactions (DDIs) where CC-99677 could be a victim
- In response to Health Authority feedback, specify revised washout periods for prohibited medications
- In response to Health Authority feedback, for Females of child-bearing potential (FCBP):
  - List pregnancy and breastfeeding as specific exclusion criteria
  - Add monthly home urine pregnancy tests, considered acceptable on days in which the subject will not be attending study visits on-site
- In response to Health Authority feedback, provide rationale for the planned interim analysis and provide examples of criteria that may be used to trigger an additional dose group
- In response to Health Authority feedback, include individual and study stopping criteria appropriate for the study population

Significant changes included in this amendment are summarized below:

- Section 1.4 Clinical Experience
  - Data cut-off for administration of CC-99677 was updated to September 23, 2020 to align with Investigator's Brochure (Edition 7.0)
  - Added additional wording to introduce an ongoing Phase 1 CC-99677 DDI study to evaluate effects of cytochrome P450 inhibition and induction of the pharmacokinetics (PK) of CC-99677 and effects of CC-99677 on the pharmacokinetics of digoxin, metformin, methotrexate, midazolam, rosuvastatin, and sulfasalazine (CC-99677-CP-002)
  - Added additional wording to introduce Study CC-99677-CP-003, an ongoing clinical pharmacology study in female healthy volunteers to assess the effects of CC-99677 on the PK of an oral contraceptives (OC)
  - Added additional wording to introduce Study CC-99677-CP-004, an additional ongoing clinical pharmacology study to evaluate the safety, tolerability, PK, pharmacodynamics (PD) and pharmacogenomics of CC-99677 in healthy adult Japanese volunteers
- Section 1.4.2 Pharmacokinetics
  - Added section to provide results from CP-002 DDI study:
    - The effect of CC-99677 on methotrexate and sulfasalazine was minimal, suggesting a limited clinically relevant DDI with breast cancer resistance protein (BCRP)

  - For narrow therapeutic index drugs, BCRP substrates should be used with caution
  - Concomitant dosing of methotrexate and sulfasalazine did not impact the pharmacokinetic (PK) parameters of CC-99677 and CC0782951 based on comparison of historical data of PK data from CP-001 and consistent with a minimal extent of biliary secretion of CC-99677, suggesting that coadministration of methotrexate or sulfasalazine would have limited impact on exposures of CC-99677 and CC0782951

- Section 1.5.1 Rationale for the Study Design
  - Added a paragraph to describe planned Interim Analysis (IA) and the decision process and an example of criteria for the introduction of an additional dose cohort
- Section 1.5.1.1 COVID-19 Pandemic-related Risk Assessment
  - Added additional wording "*Based on the mechanism of action, pharmacological modulation of the MK2 pathway by CC-99677 may alter the host response to infection and potentially predispose to infections, including COVID-19*"
- Section 2.1 Study Endpoints
  - Added additional secondary endpoint for high-sensitivity C-reactive protein (hsCRP) to support secondary endpoint Ankylosing Spondylitis Disease Activity with C-reactive protein as the acute-phase reactant
  - Revised timepoints for exploratory endpoint, "*Change from baseline in ASDAS-CRP,*" to Week 4 through Week 8 and Week 16 through Week 64
- Section 3.1.7.1 Study Stopping Criteria
  - Added study stopping criteria (criteria for Urgent Review of Clinical Data by the Data Monitoring Committee [DMC]) specifying the number and type of adverse events (AEs) (utilizing the standardized Common Terminology Criteria for Adverse Events [CTCAE] grading system for severity)
- Section 4.2 Inclusion Criteria
  - Combined criteria for FCBP as follows: FCBP must either commit to true abstinence from heterosexual contact (which must be reviewed on a monthly basis and source documented) or agree to use one highly effective method of contraception.
  - Revised criterion for FCBP to specify that they must not be pregnant and must have two negative pregnancy tests
  - Added criterion to allow concomitant use of sulfasalazine based on results from DDI study summarized in Section 1.4.2.
- Section 4.3 Exclusion Criteria, Prior and/or Current Medications/Therapies
  - Added exclusion criterion for moderate or strong cytochrome P450 (CYP)3A4/5 inhibitors: "*Use of any medications known to be a moderate or strong CYP3A4/5 inhibitor until study completion*."

- Added exclusion criterion for moderate or strong p-glycoprotein (P-gp) and strong BCRP inhibitors: "*Use of any medications that are known to be either moderate or strong P-gp or strong BCRP inhibitors until study completion*".
- Based on data from study CC-99677-CP-002, there is unlikely to be a clinically significant interaction with BCRP substrates that have a wide therapeutic index. Therefore, revised criterion for medications that are substrates of one or more transporters P-gp, organic cation transporter (OCT)1, organic anion transporting polypeptide (OATP)1B1, and OATP1B3 and have a narrow therapeutic index: "*Use of any medications that are substrates of one or more of the transporters P-gp, OCT1, OATP1B1, and OATP1B3 and have a narrow therapeutic index (eg, methotrexate, digoxin, cyclosporine, and mycophenolic acid and leflunomide). Note: BCRP substrates with a narrow therapeutic index (e.g., prazosin) should be used with caution. Sulfasalazine is not excluded based on results from* CC-99677-CP-002 *(see Section 1.4.2)."*
  - Additional data related to other transporters and CYP3A4/5 are forthcoming.
- Revised criterion for investigational SARS-CoV-2 vaccination, "*If a study participant has received a COVID-19 vaccine prior to screening, enrollment must be delayed until the biologic impact of the vaccine is stabilized, as determined by discussion between the investigator and the BMS clinical trial physician, (See Section 8.4)"*
- Added criterion related to botanical preparations: "*Any* botanical *preparations (eg, herbal supplements or traditional Chinese medicines derived from plants, minerals, or animals) intended to treat AS or other immunological diseases within 4 weeks prior to Study Day 1.*"

- Section 4.3 Exclusion Criteria, General Health
  - Added exclusion criterion, "*Females of childbearing potential (FCBP) must not be lactating or breastfeeding during the study period*."
  - Added exclusion criterion, "*Females of childbearing potential (FCBP) must not donate eggs during the study or within 28 days of the last dose of study drug.*"
  - Added exclusion criterion, "*Males must not donate sperm or semen during the study or within 28 days of the last dose of study drug*" to be consistent with contraceptive requirements for CC-99677
- Section 4.4 Inclusion Criteria for Biologic-Failure Substudy
  - Revised minimum washout periods prior to Baseline for biologics or their corresponding biosimilars:
    - etanercept: 4 weeks
    - infliximab: 8 weeks
    - adalimumab, certolizumab pegol, golimumab, ixekizumab: 12 weeks
    - secukinumab: 24 weeks

- Section 5 Table 3 and Table 4
  - Table 3, added lipid panel at Early Termination Visit
  - Table 4, added lipid panel at Early Termination Visit and Observational Follow-up Visit
  - Updated footnote to include negative serum pregnancy test at every visit. In Table 4, updated footnote to specify that monthly pregnancy testing is required, and that at home pregnancy test kits will be provided to maintain monthly pregnancy testing between Weeks 24 and 64
- Section 6 Procedures
  - Updated entire section to include reference to Table 4, "*Table of Events, Long-term Extension Period (52- Weeks)*"
- Section 6.1 Screening Period
  - Added wording for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); serology collection after a documented or suspected SARS-CoV-2 infection
- Section 6.2 Treatment Period
  - Updated pregnancy test requirements to include serum pregnancy test prior to dosing
  - Updated biomarkers and pharmacodynamic assessments for SARS-CoV-2 serology to specify sample is for biobanking
  - Added SARS-CoV-2 serology sample taken for documented or suspected infection
- Section 6.3 Early Termination
  - Updated pregnancy test requirements to include serum pregnancy test
  - Added Lipid panel
  - Updated biomarkers and pharmacodynamic assessments for SARS-CoV-2 serology to specify sample is for biobanking
  - Added SARS-CoV-2 serology sample taken for documented or suspected infection
- Section 6.4 Post-treatment Observational Follow-up Period
  - Updated pregnancy test requirements to include serum pregnancy test prior to dosing
  - Added wording for SARS-CoV-2 serology collection after a documented or suspected SARS-CoV-2 infection
- Section 6.5.3, Clinical Laboratory Assessments
  - Revised testing for hepatitis B and hepatitis C to include B surface antigen (HBsAg) and antibody, hepatitis B core antibodies only
  - Chemistry panel revised to remove duplicate wording for lipid panel and to include serum creatinine and troponin-T

- Section 6.6 Efficacy Assessment
  - Added wording, "*Every effort must be made to ensure the same assessor completes the clinical efficacy assessments for each participant at all visits at approximately the same time throughout the study, according to the Table of Events (Table 3 and Table 4*)."
- Section 6.6.3 Bath Ankylosing Spondylitis Disease Activity Index
  - Added wording for the recall period, "*during the last week*"
- Section 6.6.4 Bath Ankylosing Spondylitis Functional Index
  - Added wording for the recall period, "*during the last week*"
- Section 6.8 Biomarkers, Pharmacodynamics, Pharmacogenetics
  - Added wording, "*For those biomarkers that require approval from national health authorities, biomarker samples cannot be collected in those countries until approval is received (See Section 0 and Section 0). Note: Assays for some biomarkers may not be available in all countries."*
- Section 6.8.1 Biomarkers/Pharmacodynamics
  - Added wording for SARS-CoV-2 serology collection after a documented or suspected SARS-CoV-2 infection
- Section 6.9, Patient Reported Outcomes
  - Updated Section 6.9 header from subject to patient reported outcomes.
- Section 8.1 Permitted Concomitant Medications and Procedures:
  - Updated list of medications to include concomitant use of sulfasalazine
- Section 8.2 Permitted Medications That Require Careful Monitoring
  - Added cross-reference to revised appendix that list permitted medications that should be used with caution
- Section 8.3 Prohibited Concomitant Medications
  - Removed use of sulfasalazine from the list
  - Added moderate or strong CYP3A4/5 inhibitors
  - Added moderate or strong P-gp and strong BCRP inhibitors
  - Added any botanical preparations
- Section 8.4 Vaccination Guidelines
  - Updated to provide additional guidance on SARS-CoV-2 vaccination
- Section 10.1, Monitoring, Recording and Reporting of Adverse Events
  - Added wording for data collection of adverse events (AEs) related to SARS-CoV-2 infection

- Section 11 Discontinuations
  - Added Section 11.1 Individual Stopping Criteria
  - Revised Section 11.2 Treatment Discontinuation
- Section 18 Appendices
  - Revised Appendix C to include the following tables with excluded medications:
    - Table 7: Examples of drugs that are moderate or strong CYP3A4/5 inhibitors that are excluded
    - Table 8: Examples of drugs that are moderate or strong inhibitors of P-gp and strong inhibitors of BCRP that are excluded
    - Table 9: Examples of substrates of one or more potentially affected transporters with a narrow therapeutic index and should be excluded
  - Revised Appendix D to include the following tables with examples of drugs that are substrates for selected transporters and should be used with caution:
    - Table 10: Examples of drugs that are substrates of BCRP with a narrow therapeutic index and should be used with caution
    - Table 11: Examples of drugs that are substrates for P-gp, OATP1B1/3 and OCTs with a narrow therapeutic index and should be used with caution
    - Table 12: Examples of drugs that are substrates for CYP3A4/5 and should be used with caution

1. JUSTIFICATION FOR AMENDMENT

The primary purpose of this amendment is to include a planned Interim Analysis (IA), the addition of a Steering Committee (SC) who will assist in decision making from the IA results, provide the option of adding an additional dose cohort at the (IA), and the addition of a 1-year Long-term Extension (LTE) Period.

Significant changes included in this amendment are summarized below:

- Protocol Summary and Section 2, Study Objectives and Endpoints

  Primary objective updated to reflect dose dependent evaluation of CC-99677. Secondary and exploratory objectives updated to include timepoints for placebo-controlled and long-term extension period.

- Protocol Summary, Section 3.1.4 and Section 9.8, Interim Analysis (IA)

  A planned IA will be conducted when approximately 30 subjects in the biologic-naïve main study complete 12 weeks of treatment and will offer the option of adding an additional dose cohort (not to exceed 150 mg). Results from the IA will support one of the following decisions:

  - Continue the study without modification
  - Terminate the study for futility
  - Discontinue a treatment group based on preliminary assessment of dose-dependent risk-benefit
  - Add an additional dose cohort (dose not to exceed 150 mg)

- Protocol Summary, Section 3.1.8 and Section 9.9.2, Steering Committee (SC)

  The SC will convey a decision to the blinded Study Team to terminate study for futility or add an additional dose. The SC will be composed of both unblinded BMS committee members independent of the Study Team and external AS expert(s) to provide objectivity on decision making.

  Note: The External DMC will not be involved in any decision making at the IA but can make a recommendation to stop the study at any time based on their assessment of the overall Benefit/Risk.

- Protocol Summary, Section 3.1.2, and Section 7.2, Additional Dose Cohort

  If the SC conveys a decision to include an additional dose cohort, then the additional dose cohort will offer an opportunity to explore dose ranging within this study after proof of concept has been established, and also eliminates the need for a separate dose ranging study. If a decision is made to add an additional dose this dose will not exceed 150 mg.

- Protocol Summary, Section 1.1.5, Section 3.1 and Section 3.2, Study Duration for Subjects (52-week Long-term Extension Period) and Table 4, Table of Events, Long-term Extension Period (52-Weeks)

  The 52-week long-term extension period following Week 12 is added to provide additional exploratory long-term safety and efficacy information and enable those

subjects randomized to placebo in the placebo-controlled period the opportunity to receive CC-99677 during the extension period.

- Protocol Summary, Section 1.1.5, and Section 3.1.3, Biologic-failure Substudy, Study Duration for Subjects (52-week Long-term Extension Period) and Table 4, Table of Events, Long-term Extension Period (52-Weeks)

  The 52-week long-term extension period following Week 12 is added to provide additional exploratory long-term safety and efficacy information and enable those subjects randomized to placebo in the placebo-controlled period the opportunity to receive CC-99677 during the extension period.

- Section 3.1.1, Biologic-Naïve Main Study and Section 3.1.3, Biologic-failure Substudy (Week 16 eligibility criteria to continue in LTE period)

  The primary purpose of the Week 16 efficacy assessment (ASAS 20) is to help determine who may obtain benefit from long-term treatment. The 16-week timepoint provides the shortest duration to reasonably assess efficacy of CC-99677 in those subjects receiving placebo through Week 12. In other trials of AS, attainment of ASAS 20 was observed in a high proportion of subjects as early as 4 weeks following onset of treatment. Therefore, it is anticipated that clinical benefits of CC-99677 should already be apparent following 4 weeks of treatment. Discontinuing treatment in nonresponders ensures that subjects who are unlikely to derive benefits from CC-99677 do not remain in the study beyond 16 weeks.

This amendment also includes other administrative, corrective and/or minor changes, including but not limited to those summarized below:

- Section 1.3 Nonclinical Experience was updated to include major metabolite (CC0782951) data that is not expected to alter the clinical Drug-drug-interaction profile of CC-99677.
- Section 1.3.1 Nonclinical toxicology was updated to include long term chronic toxicity data.
- Section 1.5.11 COVID-19 Pandemic-related Risk Assessment was added to describe benefit-risk for participation in this AS study with CC-99677
- Section 1.5.4 Rationale for Pharmacodynamics and Potential Predictive Biomarkers was updated to include rationale for biobanking of SARS COV-2 serology samples
- Section 3.1.5 Primary Analysis description added
- Section 3.1.6 and Section 9.9.1, Internal Safety Management Team description of Council for International Organizations of Medical Sciences, Working Group VI (CIOMS VI) was removed as the scope, conduct, processes, and accountabilities of the Safety Management Team (SMT) are specified by Celgene Standard Operating Procedure (SOP).
- Section 3.1.7 description of the External Data Monitoring Committee (DMC) was updated to reflect roles and responsibilities of DMC in respect to review of safety and efficacy study related data.

- Section 4.1, Number of subjects revised to a sample size of approximately 147 subjects.
- Sections 4.1, 9.3, 9.6, and 9.6.2, Sample Size and Power Considerations, sample size calculation adjusted to 147 based on nonresponder imputation. Power considerations updated to include Hochberg procedure to test two active treatment groups versus placebo in order to be more statistically rigorous. This methodology will protect the overall type 1 error as the alpha value. The primary efficacy endpoint still maintains 81% power (which is defined as declaring at least one dose with statistical significance).
- Section 4.2 Inclusion Criterion #4 updated to more accurately reflect highly effective method of contraception
- Section 4.2 Inclusion Criterion #6 updated to include additional photoprotection guidelines to avoid ultraviolet exposure with use of tanning beds or sunbathing
- Section 4.3 Exclusion Criterion # 12 and Section 8.3 updated to exclude use of diclofenac or sulindac due to potential for transporter-related drug-drug interaction with CC-99677 and potential increased risk of liver toxicity
- Section 4.3 Exclusion Criterion # 15 updated to include investigational drugs for COVID-19
- Section 4.3 Exclusion Criterion # 16 added to include investigational vaccine for SARS-CoV-2
- Section 4.3 Exclusion Criterion # 25 updated to include note for prior SARS-CoV-2 infection
- Section 4.3 Exclusion Criterion # 29 updated to include platelet count < 100,000/mm^3 or > 500,000/mm^3
- Section 4.5 Exclusion Criteria for Biologic-Failure Substudy Criterion #1 updated to correctly reflect that subjects participating in biologic failure substudy must **not** meet any of the exclusion criteria listed for subjects in the biologic-naïve main study.
- Section 5 Table of Events, Section 6.2, Section 6.3, Section 6.4 and Section 6.5.3 added PT/INR testing to more closely align with Food and Drug Administration (FDA) Drug-Induced Liver Injury (DILI) Guidance.
- Section 5 Table of Events, Sections 6.1, 6.2, 6.3, 6.4 and 6.5.3 added COVID 19 serology per new BMS guidance for banking of serum sample at Baseline and at study exit, added assessments for long-term extension period
- Section 6.7.1, Sparse Pharmacokinetics Blood Draw added visits 8, 9 and 10.
- Section 6.8.1, Biomarkers/Pharmacodynamics added SARS-CoV-2 serology sample for biobanking.
- Section 8.2, Permitted Medications that Require Careful Monitoring, added information on CC-99677-CP-002 and CC-99677-CP-003 drug-drug interaction studies.

- Section 10.1 and Section 10.2.4 Adverse Events (AEs), updated to include AEs related to SARS-CoV-2 infection.
- Section 11.3, Criteria for Urgent Review of Clinical Data by the Data Monitoring Committee (DMC), removed as DMC-related text will be outlined in a separate DMC Charter.
- Appendix F, Hepatotoxicity Monitoring Criteria, table simplified to provide clear guidance to investigators for liver enzyme monitoring.