CLINICAL PROTOCOL

A PHASE 2B, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, MULTICENTER, DOSE-RANGING STUDY TO EVALUATE THE EFFICACY AND SAFETY PROFILE OF PF-06700841 IN PARTICIPANTS WITH ACTIVE SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

Study intervention Number:	PF-06700841
Study intervention Name:	Brepocitinib
United States (US) Investigational New Drug (IND) Number:	123650
European Clinical Trials Database (EudraCT) Number:	2018-004175-12
Protocol Number:	B7931028
Phase:	Phase 2b
Sponsor Legal Address:	Pfizer Inc. 66 Hudson Boulevard East New York, NY 10001

Short Title: A Phase 2b multicenter dose ranging study to evaluate efficacy and safety of PF-06700841 in systemic lupus erythematosus

Protocol Amendment Summary of Changes Table

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Non-substantial Modification(s)		
Amendment 8	15 June 2023	The driver for B7931028 Protocol Amendment 8 is to modify the key secondary endpoint of 'time to first severe SLE flare' CCI [redacted] ' Time to first severe SLE flare' will remain as a secondary endpoint, just not the 'key' secondary endpoint and the data will be summarized as a secondary endpoint. The estimands for the associated endpoints have been updated to reflect these changes. E2, has been updated to align with the revised 'Key' secondary endpoint of 'BICLA response at Week 52' as was E7, the estimand for 'time to first severe SLE flare'. Section 1.1 Synopsis, the table of Objectives and Estimands have been updated to reflect the change of key secondary endpoint to 'BICLA response at Week 52'. These changes have also been made throughout the OBJECTIVES, ESTIMANDS AND ENDPOINTS table in Section 3. Language has been added to Section 4.2 to describe the BICLA endpoint and the justification of its use. Language has been added to Section 9.1.1 Estimands to indicate that details regarding sensitivity analyses of the primary endpoint may be provided in the SAP. In Section 9.1.2 Hypotheses and Decision Rules, changes have been made throughout to replace time to first severe flare with BICLA response at Week 52 in the statistical hierarchy. The estimand for BICLA response at Week 52 is now described in Section 9.4.3.1, in place of the estimand which had previously described the analysis of time to first severe flare; the analysis of this endpoint will be performed in a manner which is entirely consistent with the primary analysis of the primary endpoint, SRI-4 response at Week 52. Subsequently, the

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		planned analysis for time to first severe flare is now described in Section 9.4.3.2. Rationale: The assumptions about the severe SLE flare rate in this study population have not been observed and thus the time to first severe flare endpoint would be substantially underpowered. Section 6.3.1 Allocation of Study Intervention has been updated to remove the following sentence, "Allocation to Study Intervention, In the event of a Quality Assurance audit, the auditor(s) will be allowed access to unblinded study intervention records at the site(s) to verify that randomization/dispensing has been done accurately". Rationale: This sentence was removed because the study was not set-up to allow study sites to have unblinded study intervention records. Therefore, the auditor would not have the ability to verify the accuracy of randomization and dispensing of study intervention as proposed in this sentence. Additionally, changes have been made throughout to ensure consistency of the protocol with the SAP. Typographical changes, and changes for grammar, have been made as they have been identified throughout the protocol and will not be summarized here. Rationale: Additional clarity regarding planned sensitivity analyses is provided. Section 9.1.2 Hypotheses and Decision Rules, Language has been added to indicate that any

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		future changes to the family-wise error control procedure would be detailed in the SAP. Rationale: This language is used to indicate how any additional changes to the statistical hierarchy will be addressed. Section 9.2 Sample Size Determination has been updated with power calculations for both the primary endpoint, SRI-4 response at Week 52, and the key secondary endpoint, BICLA response at Week 52 in a manner which is now consistent with the planned primary analyses of these endpoints. Rationale: Previously, the power calculations conducted and described in this section incorporated a 25% dropout rate even though these participants are counted as non-responders by the primary estimand. The calculations are now consistent with the estimand. This section is also updated to reflect the change in the key secondary endpoint.
Amendment 7	06 June 2022	The overall rationale for B7931028 Protocol Amendment 7 is to decrease the sample size for the study from 448 participants to 350 participants, and to allow eligibility of participants with latent TB (positive quantiferon gold tests) who agree to receiving treatment with INH and Vitamin B6. This amendment also includes the administrative changes made in Protocol Amendment 5 (requested during the EU Voluntary Harmonization Procedure (VHP) review of Amendment 4, countries submitting their initial clinical trial application with Amendment 5 (Italy and Argentina), and to any country requiring new protocol amendments to be submitted (Taiwan); and Protocol Amendment 6 (China only amendment) to be globally implemented. Furthermore, this change will allow specific safety

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		monitoring to be put into place to allow participants with latent TB (not active TB) to be eligible for the study provided the protocol inclusion/exclusion criteria can be met. Section 1.1 Synopsis, Section 3.0 Objectives, estimands and ENDPOINTS and Section 9.5 Interim Analysis –The Interim Analysis was updated to now read, "An Interim analysis may be conducted when sufficient number of participants completes Week 52 visits and before the interim analysis is instigated, the details of the objectives, decision criteria, dissemination plan and method of maintaining the study blind per Pfizer's SOPs will be documented and approved in the E-DMC charter. In addition, the analysis details must be documented and approved in an interim analysis plan (IAP)." Rationale: Since the sample size was modified from 448 to 350, there are already more than 50% subjects of the subjects that have completed Week 24 therefore, including a 'sufficient amount of participants' allows for the participants that meet the interim analysis requirements to all be included. In addition, the timepoint was updated from Week 24 to Week 52 to provide a more robust dataset. Section 1.1 Synopsis, Section 9.2 Sample Size Calculation - The Sample size has been modified from approximately 448 to approximately 350. Rationale: reduction of sample size to 350 patients provides at least 80% power for the primary endpoint and will allow more timely completion of this study. Section 1.3, Schedule of Activities, Section 8.2.1.2 Chest X-ray was added to the Week 56 visit, for subjects entering the study with latent TB. If a

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		subject is diagnosed with latent TB at Week 24 visit and follows the protocol requirements, a chest X-ray will be conducted at the Week 24 visit. The Schedule of Activities footnotes were reordered. Rationale: The Schedule of Activities was updated to collect the specific items required at each visit and to reorder the footnotes in chronological order. Section 2.2.2, Clinical Overview was updated to align the clinical trial data in this section with the latest version of IB. Section 2.2.2, Table 1 -Summary of Clinical Studies for Brepocitinib was replaced with Table 14 from the latest version of the PF-06700841 IB to ensure absolute alignment between the 2 documents. Section 5.2, Exclusion Criterion #27, Zostavax® was added as an example of a live herpes zoster virus vaccination that is prohibited in the study. Section 5.2, Exclusion Criterion #28, 'serological' was removed from the HIV criteria to broaden the HIV testing methodology. Section 5.2, Exclusion Criterion #32 and Section 8.2.6, Tuberculosis (TB) Screening and Monitoring: If a prospective participant is being treated for latent TB or is diagnosed during screening with latent TB and agrees to be treated – the requirements for a prospective participant to be eligible for the study were clarified. Rationale: To allow participants who have been diagnosed with latent TB and are currently receiving latent TB treatment or who are were diagnosed during screening and initiated latent TB treatment to be eligible for

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		the study. This scenario was not included in the previous versions of the protocol. Section 5.2, Exclusion Criterion #35, If the total bilirubin is ≥1.5 times the ULN, the subject may be eligible for the study if they have a history of Gilbert's syndrome and if their direct bilirubin was < ULN. Rationale: Participants with known Gilbert's syndrome have normal liver function despite elevated total bilirubin levels and do not need to be excluded from participation on the basis of the elevated bilirubin level. Sections 5.1, 5.3.1 and Appendix 10.4.1, Male participants are not required to use barrier contraception to minimize partner exposure to brepocitinib. Rationale: Based on calculated exposures in semen, Brepocitinib concentrations are predicted to have a safety margin ≥100 in male participants, and therefore female partners are not at teratogenicity/fetotoxicity risk. This was updated in the IB (version 7.0, dated November 2021). Section 6.1.1, Administration, Section 6.4, Study Intervention Compliance and Section 7.1.1, Temporary Discontinuation, the duration of study intervention interruption permitted was updated to 14 days. The updated text reads, "Participants interrupting study intervention for more than 14 days, should be discussed with the sponsor for possible withdrawal from the study." Rationale: To allow text alignment of study intervention interruptions.

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		Section 6.4, Study Intervention Compliance, was updated to include the upper bounds of the compliance range (>120%). Rationale: Both the upper and lower bounds of the study intervention should be included in the protocol to provide the comprehensive compliance situation. If compliance is outside these limits, Pfizer clinical should be contacted as soon as possible to determine if the participant should discontinue study medication due to non-compliance and if any additional safety assessments are needed. Section 9.3, Populations for Analysis, the 'full analysis set' was updated to read, "All participants randomly assigned to study intervention and **received at least one dose of study intervention**. Participants will be analyzed according to the product they were randomized." Previously the description was "All participants randomly assigned to study intervention **regardless of whether they have taken study intervention"**. Participants will be analyzed according to the product they were randomized. Rationale: This change was made to accurately define the full analysis set population. Appendix 10.13, List of Prohibited and Permitted Medications was updated to reflect accurate information on the following medications (updated text is bolded below): • Anti-malarials: Provided pre-existing **dose is stable for at least 12 weeks** and treatment **not** started/or stopped within 12 weeks of Day 1.

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		Throughout the protocol, the laboratory test, Coombs direct was updated to read, 'direct Coombs'. Rationale: This change was made to provide the accurate name of this laboratory test. Minor typographical errors and omissions were corrected.
Amendment 6	28 September 2021	Protocol Amendment 6 is only for use in China. If there is a global amendment in the future for this study, the changes in Amendment 6 will be implemented into the global amendment. The overall rationale for B7931028 protocol amendment 6 is to address the Quantiferon gold test results which are not negative. The amendment will allow specific safety monitoring to be put into place to allow participants with latent TB (not active TB) to be eligible for the B7931028 study provided the protocol criteria can be met. China is having the biggest impact on enrolling participants into the study because of this eligibility criteria; however, once the next global protocol amendment is required, this language will be added as well. Section 1.1. Synopsis, Overall Design; Intervention Groups and Duration Design; Section 1.2, Schema; Schedule of Activities, Footnote 'g'; Section 4.1 Study Design (twice); Section 5.2, Exclusion Criteria #32; Section 8, Study Assessments and Procedures, Screening - the screening period was increased from 5 weeks or 35-days to 7 weeks or 49 days. Rationale: These additional requirements would take additional time; therefore 2 weeks were added to the screening period. In addition, the following processes around TB testing and diagnosis of latent TB were added

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		to the protocol. Subjects diagnosed with latent TB were not previous permitted into the study; however, other investigation products with similar mechanisms of action permit subject with latent TB to be entered into their studies, but they also have processes to follow to monitor participant safety. Section 5.2, Exclusion Criteria #12: The following sentence was added to this exclusion criteria, "Prior Splenectomy is prohibited". Rationale: Splenectomy is associated with an increased risk of infection; therefore, it is prohibited from this study. Section 5.2, Exclusion Criteria #32 and Section 8.2.6, Tuberculosis (TB) Screening and Monitoring: Latent TB – Requirements for a prospective participant to be eligible for the study if the subject is diagnosed with latent TB (ie, visit to the infectious disease/pulmonary specialist for further investigation and agreement the participant can enroll into the study, only medication to treat latent TB permitted in the study is INH and Vitamin B6 therapy) was added to the protocol as it was not permitted in previous protocol versions. The main additions to Monitoring of TB on-study: • Week 24, if participant tests TB positive or TB indeterminant, they must discontinue study medication immediately, be seen the pulmonary/infectious disease specialist, once active TB is ruled out, then if the subject start INH and B6 latent TB treatment, they must be on that treatment at least 2-weeks prior to re-starting study medication. • Week 56, language to encourage the investigator to continue to follow-up with the

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		subject as appropriate after the conclusion of the study. Rationale: To allow prospective participants in the study to have the possibility of being eligible for the study (by having IGRA retest done, and the other protocol requirements completed by Day 1); whereas this was not permitted in the previous versions of the protocol. CCI [redacted] Section 5.2, Exclusion Criteria #24 and Appendix 13, Prohibited and Permitted Medications: The following exclusion criteria was added to ensure subjects on any of the bone marrow stimulants to improve cell counts is discontinued 12 weeks prior to Screening/Day 1. Rationale: In this study, a prospective participant was taking this medication. The team felt this was not an appropriate medication to be taken while participating in an investigational study due to unknown potential safety concerns. This exclusion criteria was added to avoid this situation in the future. Section 2.3 Benefit/Risk Assessments and Appendix 13 Permitted and Prohibited Concomitant Medications-In Section 2.3, the phrase 'inhibitors or' was removed. The list of prohibited CYP3A inhibitors were also removed from Appendix 13.

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		Rationale: To allow CYP3A inhibitors to be taken before and during the study, in order to align with the Brepocitinib IB dated September 2020. Appendix 15 Columbia Suicide Severity Rating Scale-The appendix was modified to align with Section 8.2.10, Suicidal Ideation and Behavior Risk Monitoring. Rationale: To avoid mishandling of participant safety data.
Amendment 5	28 April 2021	Summary of Changes in Amendment 4: Page 7; Appendix 14 Oral Corticosteroids, Systemic Equivalencies – will now include the following guidance: has been corrected to 'Appendix 13 List of Prohibited and Permitted Concomitant Medications – will now include the following guidance:' 'Rationale: This change adds the washout times to Appendix 14 to be consistent with the text in Section 5.2 Exclusion Criteria, #14' has been corrected to: 'Rationale: This change adds the washout times to Appendix 13 to be consistent with the text in Section 5.2 Exclusion Criteria, #14' Appendix 13 List of Prohibited and Permitted Concomitant Medications: Within the section on Topical, Permitted, Low potency topical steroids the following text "[class 6 (mild, such as desonide) or class 7 (least potent, such as hydrocortisone)]" has been added for completeness. In the row on Lower potency [opioid analgesics] the '£' symbols before the doses of Tramadol, Hydrocodone and Codeine were corrected to '≤'.
Amendment 4	02 March 2021	The driver for the initiation of protocol amendment 4 (PA4) was the FDA feedback from

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		the March 2020 Type C meeting. In the March 2020 Type C meeting, the FDA suggested to Pfizer statistical considerations for the protocol that have been implemented and the FDA suggested to Pfizer to consider anchoring the Facit-fatigue data changes in the study that were statistically significant in comparison to what the patient felt was clinically significant. • Section 1.1. Synopsis, Objectives and endpoints table, Section 3.0 Objectives, Estimands and Endpoints, Section 9.1 Estimands and Statistical Hypotheses and Section 9.4 Statistical Analysis were updated to reflect the feedback from the FDA Type C meeting. Primary endpoint edited for clarity and secondary endpoint criteria sub-divided in to "key secondary" and "other secondary". Analysis of the Primary Endpoint – Revised the primary analysis from a logistic regression model to the Cochran-Mantel-Haenszel (CMH) approach. Both approaches should produce similar results, but the former approach may be subject to convergence issue in some occasions. Updated all estimands with the five attributes to align with the finalized ICH9(R1) Estimands and Sensitivity Analysis Guidance. The five attributes are: Treatment, Population, Variable, Intercurrent events, and Population level summary. Updated the intercurrent events to make them specific. Removed the missing data from the Estimand statement per regulatory authority (FDA) comments on the Statistical Analysis

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		Plan (SAP) and updated relevant estimand descriptions in the synopsis. Incorporated new PRO scales into the secondary endpoints. Updated the estimands for the FACIT-F and LupusQoL into a hypothetical estimand. CCI  The following modifications were made to PA4 as a result of the PF-06700841 Investigational Brochure (IB). The following changes were added and/or modified to the overview of the MoA and the safety profile of the product: • Section 2.2.2. Clinical Overview Added study C2501007, an ongoing study in hidradenitis suppurativa. • Updated Table 1, Clinical Development Plan – the studies listed in this table were updated to reflect the updated information as well as the format of this table to be aligned with the September 2020 IB. • Section 2.3. Benefit/Risk Assessment -The following paragraph was added to the benefit/risk section of the protocol to be consistent with the language in the updated IB:

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		"In the brepocitinib development program, there have been thromboembolic events reported in ongoing blinded clinical studies, where relationship to treatment is uncertain. Suspected thromboembolic events will be subject to review by an external blinded adjudication committee. In this study, B7931028, participants with any history of pulmonary embolisms (unless these were caused by known antiphospholipid syndrome will be excluded from the protocol unless the participant has been adequately anticoagulated), exclusion criteria #5 and #6 have more detailed information". The following modifications from the 21Jan2020 PACL were incorporated into PA4: • Section 1.3 Schedule of Activities (SoA) footnote "s", Screening – will now state: SLE diagnosis using either the ACR SLE classification or SLICC criteria. Only one is to be used to perform the assessment; American College of Rheumatology Systemic Lupus Erythematosus Classification or Systemic Lupus International Collaborating Clinics Criteria. Rationale: This clarification will better align the (SoA footnote "s") with Section 5.1 Inclusion Criterion #3. • Section 5.2 Exclusion Criteria #20 – will now state: Participation in any studies with kinase inhibitors, other than JAK inhibitors such as those mentioned in #19 within 12 weeks of Day 1.

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		Rationale: The current text states #18 and represents a carry-over from Amendment 2. In Amendment 3, 1 exclusion criteria (#7) was split in to 2 separate criteria, which should have been addressed in Exclusion Criteria #20 by renumbering exclusion criteria #18 to exclusion criteria #19. This error in the criteria numbering has been corrected. • Section 5.2 Exclusion Criteria #31 – will now state: Chest radiograph taken at screening with changes suggestive of active TB infection, or previous inactive TB, general infections, heart failure or malignancy unless previously performed and documented within 12 weeks prior to Day 1. Rationale: The addition of the new text will make exclusion criterion #31 consistent with Section 8.2.2.1 Chest X-Ray. • Section 8.2.3 Vital Signs – will now state: Participants should refrain from smoking (or use any tobacco products) or ingesting caffeine during the 30 minutes prior to the measurements. Rationale: Per Amendment 3, Section 5.2 Exclusion Criteria, Other Exclusionary Criteria #38, “Participants who are currently vaping or using e-cigarettes” was added as a new exclusion criterion; the reference to e-cigarettes was erroneously NOT removed from Section 8.2.3 – this has now been corrected. • Various Sections – the listed typographical errors, which were introduced in Amendment 3, are corrected as follows:

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		• Section 1.1, Adjudication Committees, Section 3 Objectives, Estimands and Endpoints and Section 9.5.2 Adjudication Committees: thromboemblic was updated to thromboembolic. • Section 2.2.2, Clinical Overview-excertion as updated to excretion. • Table 1- mcirotracer was updated to microtracer; Peroid was updated to Period and unlabled was updated to unlabeled. • Section 3, Objectives, Estimands and Endpoints immunoimpressive was updated to immunosuppressive. • Section 3 and 9.5.2, Adjudication Committees- Malignacy was updated to Malignancy. • Section 5.1, Inclusion Criteria- monontherapy was updated to monotherapy. • Section 5.2, Exclusion Criteria- aematologic was updated to hematologic. • Section 10.12, Appendix 12- Comombs hmolytic was updated to Coombs haemolytic. • Appendix 9, Systemic Lupus International Collaborating Clinics (SLICC) Criteria (Immunological Criteria #4) – will now state: 4. Antiphospholipid antibody. Rationale: Deleted text was not removed previously.

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		• Appendix 13 List of Prohibited and Permitted Concomitant Medications was updated to reflect accurate information: Stable dose is defined as no new therapy or change in standard-of-care therapies as above within 12 weeks of Day 1 for immunosuppressives or within 2 weeks of Day 1 for corticosteroids (inserted after title of appendix). Rationale: This change will add a definition of stable dose to Appendix 13 for consistency with the definition of stable dose in Section 5.1 Inclusion Criteria, #5. • Appendix 13, List of Prohibited and Permitted Concomitant Medications – will now include the following guidance: Oral or parenteral (IV or IM) corticosteroids at doses <40 mg per day of prednisone (or equivalent) within 8 weeks of Day 1. Intra-articular corticosteroids or hyaluronic acid >4 weeks of Day 1. Topical corticosteroids, other than stable doses of class 6 (mild, such as desonide) or class 7 (least potent, such as hydrocortisone), >4 weeks of Day 1. <20 mg/day of prednisone or equivalent or have adjusted the dose of corticosteroids within 2 weeks of Day 1. Rationale: This change adds the washout times to Appendix 13 to be consistent with the text in Section 5.2 Exclusion Criteria, #14. • The following changes were implemented into PA4 from the PACL dated 04Feb2020:

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		An incorrect daily dose of chloroquine of 2.3 mg/kg/day was stated in the protocol; the maximum dose of chloroquine has been corrected to now be 250 mg/day to align with the standard maintenance dose used in practice for the treatment of SLE. • Modifications from the 03Aug2020 PACL were incorporated into PA4 were: Removal of Complement (Total) CH50 measurement from the protocol in the following sections: Section 1.3 Schedule of Activities – footnote "n". Section 3 Objectives Estimands and Endpoints. Section 8.8.4 Standard Complement Levels. Section 10.2 Appendix 2. Section 10.11 Appendix 11. Rationale: The central laboratory changed the kit for the CH50 assay during the study. No correlation could be achieved between the previous and new assays; therefore, it is not possible to compare the measurements between the previous and the new assay. The following changes were additional changes that incorporated into PA4: • Section 1.3 Schedule of Activities: • Weight was added to all visits in order to support BILAG scores which required the weight to be taken at every visit. • In order to better understand why investigators are not tapering steroids and

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		to remind investigators to taper the participant steroids, a new steroid tapering CRF was implemented to capture data for SLE Tapering Steroids as well as the reasons for not tapering steroids. • In order to provide support for the SLE activity on the assessments, the following data will now be collected on the brief PE CRF: general appearance, heart, lungs, skin, musculoskeletal and any other patient reported symptoms. • CCI [redacted] • Footnotes have been amended accordingly to support changes outlined. Section 4.1 Overall Design: • Updated to include additional guidance to the sites to encourage randomized participants to remain in the study at least through to the end of the double-blind period to complete safety and efficacy assessments. Section 4.2. Scientific Rationale for Study Design- This section was updated to provide accurate information in the protocol: • State the screening SLEDAI total score used for stratification from randomization was adjudicated.

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		• Remove the "attempt to taper" to "should taper" to emphasize tapering is not optional. Section 5.1. Inclusion Criteria: • Inclusion #2: The following sentence was added to this inclusion criteria, "All participants should be willing to remain in the study to the end of the double-blind period for safety and efficacy assessments." to emphasize, subjects in the study need to understand the study requirements for participating. • Inclusion #5: The following sentence was added to Inclusion 5 to allow for a minimum baseline dose of corticosteroids, "If receiving antimalarials in combination with corticosteroids, the minimum dose of corticosteroids permitted as part of this combination is 5 mg prednisone daily or an equivalent dose." • Inclusion #6: This inclusion criteria was updated to provide further clarity of the required inclusion for SLE disease activity at screening and baseline. Section 5.2. Exclusion Criteria: • Exclusion #1: This exclusion criteria was updated to provide more detailed information on renal exclusion in order to provide further clarity. • Exclusion #2: 'Active' was added in front of psychosis to clarify psychosis is at the time of the subject entering the study or 60 days prior to Day 1.

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		• Exclusion #3: This is the cancer exclusion criteria and the timepoint of 'within 5 years of screening' was added back into the exclusion criteria along with a statement that requires a note from the treating physician stating they are aware that their patient may participant in this study. Lastly, language added that Pfizer can determine if the subject should be excluded from the study for safety concerns based on their history of cancer. • Exclusion #5: Language added to provide further guidance to this exclusion criteria: "Any history of antiphospholipid syndrome associated with prior obstetrical loss with no prior thrombosis in women that does not require anticoagulation." • Exclusion #6: Language was added to provide further clarity of the process when Central ECG Review findings are reported as 'old MI'. • Exclusion #13: The following text in bold was added to this exclusion criteria to provide further clarity. Participation in other interventional studies within 12 weeks or 5 half-lives, if known, whichever is longer, prior to study entry and/or during study participation. Participation in any observational studies during study participation **which would require a participant to provide any study specific information including but not limited to the following: sponsor name of the study in which they are participating, the name of the study intervention, the indication being studied.**

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		• Exclusion #14: The addition of brief fluctuations in the dose prior to Day 1 were added to allow minor changes in the steroid at the beginning of the study. • Exclusion #17: The timeframe for the discontinuation of topical creams and ointments to be discontinued prior to Day 1 was updated from 12 weeks to 4 weeks to implement accurate requirements. • Exclusion #20: Combined exclusion criteria #20 with exclusion criteria #21 (now exclusion #20) to eliminate redundancy. The exclusion criteria #20 now reads, "Treatment with any non biologic investigational drug(s) including non-JAK kinase inhibitors, within 12 weeks of Day 1 or within 5 half-lives, if known, whichever is longer, and/or during study participation. • Exclusion #29: The following sentence was added to this exclusion criteria to allow for CT and MRI's to be collected in the study instead of chest radiograph, "(If the Investigator identifies a different diagnostic imaging study such as computed tomography [CT] or magnetic resonance imaging [MRI] with pre-approval from Pfizer clinical)". • Exclusion #31: First Bullet in this section was updated to provide more specific information on the IGRA preferred test, QFT-G and due to participants receiving corticosteroids or immunosuppressants having a false negative test. Therefore, the Mantoux ppd skin test is not an acceptable in this study.

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		• Exclusion #31: Bullet for Chest X-ray – Last bullet in this section was updated to provide more clarity of the expectations that, Chest radiograph taken at screening with changes suggestive of active or prior active or latent TB infection, other active or chronic pulmonary infections, heart disease, malignancy or other chronic, progressive pulmonary disease, unless previously performed and documented within 12 weeks prior to Day 1. • Exclusion #33, First bullet was updated from "Total immunoglobulins" to "IgG". Section 5.2.1. Screening: • For randomization of stratification, both the screening **(not the baseline visit)** SLEDAI score and the anti-dsDNA to reflect the actual data which are available. Section 5.3.2 Surgery: • Study intervention discontinuation from 28 days to 2 days was updated to allow for the appropriate amount of time for discontinuation prior to surgery. Section 5.3.3. Meals and Dietary Restrictions: • The following sentence was added to this section for further clarity "Diabetics who are taking antidiabetic medications or participants who cannot reasonably tolerate an 8-12 hour fast should not eat immediately prior to the visit as far as possible." Section 5.3.4 Other Requirements:

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		• The last bullet in this section provides information that all participants who are randomized should be encouraged to remain in the study through to the end of the double-blind period for safety and efficacy assessments, whether or not they continue to receive study intervention or are switched to non-protocol treatment; this is in order to reduce missing data as much as possible. Section 5.4. Screen Failures: • HIV test was added to this section (CXR and IGRA are already contained in this section) as it too does not need to be reobtained if the HIV test was already obtained within the protocol defined time period (12 weeks). Section 6.4. Study Intervention Compliance: • To provide more guidance to the site when a subject discontinues study intervention, the following sentence was added, "Subjects who are non-compliant with scheduled study visits or with study intervention should still be encouraged to return for all scheduled study visits." Section 6.5.2.1. Treatment Failures: • This section is not a required section in the protocol template. Therefore, this section was removed from the protocol and will be located in the SAP. Section 6.5.1.1. Use of Corticosteroids and Tapering Guidelines:

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		• Concise guidance on when to taper and when not to taper corticosteroids were updated for clarity. • New information which allows slight fluctuations of corticosteroids during Weeks 2-12 was added. Section 8. Study Assessments and Procedures, Screening: • For consistency purposes, participants who are screen failures may be rescreened one time in the study, the re-screening visit must occur at least ≥2 weeks (previously, the time between screen failure determination and re-screening was ≥1 month). The re-screen time period of 2 weeks or once month was inconsistent in the protocol and the study team felt that re-screening within at least 2 weeks was ample time for re-screening. For instance, if there was a lab result that was exclusionary, within 2 weeks, it is possible the result would not be exclusionary. Section 8.1.9. Joint Assessment (28 Swollen and Tender/Painful Joint Counts): • In this section, the joints of the ankles and feet were added to the 28 swollen and/or painful joints as these joints are representative to the SLE subjects. The following joints are examined along with the 28 joint count: temporomandibular joints, sternoclavicular joints, acromioclavicular joints, hip, ankle joints, transverse tarsal joints, metatarsophalangeal (MTP) joints (MTP 1, 2, 3, 4 and 5), interphalangeal joint 1 (foot)

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		CCI [redacted] Section 8.1.12. Patient Reported Outcome Measures (PROs): • CCI [redacted] CCI [redacted] [redacted] [redacted] Section 8.2.1.2. Chest X-Ray: • For consistency purposes, this section was updated to include: A chest CT or MRI may be obtained in place of the chest x-ray, PA and lateral view, only with advance permission of Pfizer (please note, this is not recommended for the screening assessment). Section 8.2.5. Hepatitis Screening and Monitoring: • For accuracy, the follow bullet was modified: Participants who have negative HBsAg, positive HBcAb and positive HBsAb, whether or not they have received prior HBV vaccination, and participants who have negative HBsAg, negative HBcAb and positive HBsAb without

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		documentation of prior HBV vaccination are required to undergo HBV cDNA testing monthly. Section 8.2.6.1 Interferon Gamma Release Assay (IGRA) Tuberculin Test: • To clarify the IGRA TB test preferred is the QUANTIFERON® Gold Test and the central laboratory is the preferred testing facility; however, it is allowed for a locally approved IGRA to be used per local guidelines. • To provide rationale to support the statement "The IGRA test is required since the Mantoux test skin test (tuberculin, purified protein derivative [PPD] skin test) may have false negative results in patients taking immunosuppression or corticosteroids". Section 9.1.2. Hypotheses and Decision Rules: • For consistency purposes, this section was updated to implement rewording of the treatment comparisons testings into one-sided hypothesis statements which were updated in other sections of the protocol per the FDA feedback. Section 10. Appendices: Section 10.13. Appendix 13: List of Prohibited and Permitted Concomitant Medications: • Added text to allow fluctuation in brief changes of permitted medications. • Updated the 'Oral prednisone or equivalent' row for accuracy purposes.

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		• Prednisone up to 20 mg/day (or equivalent) provided dose is stable for at least two weeks prior to Day 1 and corticosteroids were started at least 8 weeks prior to Day 1. If a participant is receiving antimalarials in combination with corticosteroids as background medication without an immunosuppressant, the minimum dose of corticosteroids allowed at baseline is 5 mg/day prednisone or equivalent. • Corticosteroids are permitted as clinically indicated for hypersensitivity reactions, insect bites or asthmatic exacerbations (up to 125 mg IV hydrocortisone or oral methylprednisolone dose pack with top dose of oral methylprednisolone 24 mg [or prednisone 30 mg or oral equivalent]) up to Week 12 and between Weeks 24 and 40. • Participants with active disease at baseline can receive the increased dose of corticosteroids as early as Day 1, up to the Week 4 visit and then the dose should be tapered back to the preceding dose. The maximum additional dose allowed is 10 mg/day prednisone equivalence above the Day 1 dose level, for a maximum of 14 days after which the previous dose must be resumed. • Antimalarials permitted row now read as follows, “Substitution of one antimalarial medication for another may be permitted for safety related issues after discussion with the sponsor. • High Potency opioids: Clarification that high opioids are prohibited for at home use by the participant was added to Appendix 13, List of Prohibited and Permitted Concomitant Medications.

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		• Low Potency opioids-Oxycodone is a high potency opioid and therefore removed from the low potency opioid section of Appendix 13. • Updated the list of 'moderate and strong CYP3A inducers prohibited information was updated to provide clarity that these medications as they are prohibited during treatment and within 12 weeks of Day 1. • CNIs (cyclosporine, tacrolimus, picrolimus, or voclosporin): • No systemic calcineurin inhibitors within 12 weeks of Day 1. • Optic; optic topical preparations (eye drops) are permitted on study. • Topical creams and ointments must be discontinued within 4 weeks of Day 1. • Other minor updates and edits for completion. Section 10.17 – Appendix 17 Guidelines for Participant Safety Monitoring and Discontinuation: The following clarifications were updated in this section: • For participants requiring a laboratory re-test between visits but not able to return to the site, the investigator must document this information in the subject source documents. • Pfizer Clinical can waive the re-test requirement if the principal investigator first discusses this situation with Pfizer

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		Clinical and if the participant is known to have intermittent abnormal labs. • When subjects discontinue study intervention, but continue in the study (do not withdraw consent) and later become a lost to follow-up participant, the process required by the site before declaring the participant to be a true lost to follow-up participant has been further detailed. • Updated second to last bullet to define that all participants whom experience a thromboembolic event must discontinue study intervention. • Other updates were included to provide further clarifications to safety monitoring and discontinuation. Global Changes made throughout the document include: • Updated the words, “subject” and “patient” to “participant” throughout the protocol, with the following exception, discussions of patient reported outcomes (PROs), statistical analysis and/or previous SLE patient data. Participant reflects the terminology used in the current protocol template. • The words, “investigational product” and “study drug” have been updated to “study intervention” as this is the terminology in the current protocol template. • Screening disease activity and anti-dsDNA is used to stratify randomization into the study and not the baseline disease activity and anti-dsDNA; therefore, the protocol

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		was updated to reflect the correct information. • For accuracy purposes, the reference to the SLE Flare CRF was updated to modified-SELENA-SLEDAI Flare Index (mSSFI). • Most references to completion of the CRFs was updated and instructions to reference the CRF completion guidelines was added. **Key Updates made to PA4 dated 02 March 2021 (P<u>A4 Second Update)</u>** • Section 1.2: Schema – Schema must show entirety of the text in the text boxes. • CCI [redacted] • Section 2.3 - Benefit Risk: This section was updated to reflect that participants who are screened for this study and whom have a history of thromboembolic events will be excluded from this study. • Section 5.1: Inclusion Criteria Inclusion #2- For further clarification, the following phrase was added to the text that describes that participants should return back to the study site monthly once they discontinue study intervention, “whether or not study intervention was discontinued”.

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		Inclusion #5, NOTE: The following text was added to the protocol, "brief fluctuations in therapy for toxicity are permitted (eg, holding a dose (≤7 days) or temporary reduction in corticosteroids of less than 3 mg/day." Inclusion Criteria #6, b, the following text in bold font was added for completeness, "On the day of randomization, a minimum of 3 joints that are both swollen and tender **is required if SLEDAI Arthritis is marked PRESENT.**" At the end of Inclusion #6, the following Note was added back into protocol: "Note: Data from the SLICC, SLEDAI and BILAG evaluations will be reviewed by the Sponsor and/or the Sponsor-selected independent reviewer(s). For participants to receive their first administration of study agent, approval must be received by the Sponsor and/or Sponsor-selected independent reviewers" was removed inadvertently on a previous draft of the protocol; therefore, in this version of the protocol, the Note was added back into the protocol. • Section 5.2: Exclusion Criteria Exclusion #5, NOTE: The following NOTE was inadvertently removed from the previous Protocol draft version and has been added back into the protocol: "Note: Any participant being treated for antiphospholipid syndrome or anticardiolipin antibodies must be adequately anticoagulated according to current local guidelines. Sites should make every effort to obtain a medical history of at least 3 years duration to document that

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		there have been no thrombotic events or an obstetrical history of repeat fetal losses. In the absence of this medical history information, a hematology consult may be required if antiphospholipid screening tests are positive." Exclusion #10, The following language was added for clarity. Participants that have had gastric bypass surgery are not permitted in this study; participants that have had the gastric sleeve procedure are permitted in the study. Exclusion #26 – The following herpes zoster vaccine was added to the protocol as it is permitted in the study, "the recombinant adjuvant herpes zoster vaccine (Shingrix®, GSK) is permitted prior to and on study. Exclusion #31- The following text was for completeness, "active infection, previous inactive TB infection, heart failure, suspected malignancy or any other clinically significant findings unless previously performed and documented within 12 weeks prior to Day 1. • Section 8.2.5 - Hepatitis Screening and Monitoring In the first bullet of this section, "unless previously vaccinated" was removed as it was incorrect. [redacted]

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		• Section 8.2.1.2: Chest X-Ray-For completeness, "or other approved diagnostic tests (ie, CT scan with or without contrast or MRI)." • Section 8.2.3-Vital Signs: The last sentence of this section was updated to be consistent with the SLE assessment requirements which requires oral temperatures to be collected (oral thermometers were used to validate these instruments). • Section 8.2.8 Clinical Safety Laboratory Tests. The following guidance was added to the third paragraph of this section. "All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 days after the last dose of study intervention should be repeated **at the central lab** until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor." • Section 10.2, Table 5 - This table was re-organized slightly and the 3 laboratory were added: cystatin, eGFR cystatin, eGFR creatinine. • Footnote "a" was removed causing all the other footnotes to move up one letter. • Section 10.13 Appendix 13- List of Prohibited and Permitted Concomitant Medications: Updated for accuracy with in the various sections of the protocol. Added the medication colchicine to this appendix. This medication must not exceed

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		0.6 mg BID for at least 8 weeks prior to Day 1 and throughout the study. • Miscellaneous formatting and typographical errors were modified.
Amendment 3	31 Oct 2019	Section 1.1. Synopsis Objectives and endpoint table: • Primary estimand edited for clarity and secondary endpoint criteria sub-divided in to “key secondary” and “other secondary”. • Health related quality of life estimands and endpoint were incorrectly outlined as “total domain score”. These have been updated to “individual domain scores”. • Added details of all planned adjudication committees. • Clarified the role of the eDMC. • Statistical methods updated to include assessment of dose groups and rejective closed testing procedures. Section 1.3. Schedule of activities • Footnote x added to specify that direct coombs should only be sent to a local laboratory only if the investigator suspects a clinically significant hemolytic anemia that will be scored on the BILAG and added to Appendix 12. • eGFR cystatin added at all visits • Urine microscopic exam added at all visits.

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		• ECG assessment added at Week 2 so as to assess cardiac function in combination with detailed PK assessments • CCI [redacted] • SLICC criteria added to make the SOA assessments consistent with the Inclusion Criteria. • MMF language updated removing the criteria for assessment to be performed at 12 hrs ± 30 mins. Participants are instead asked to refrain from taking a dose immediately prior to clinic visits where MMF levels are assessed. • Photographs are to be taken at US sites only; this has been made an optional assessment. • Abbreviations and footnotes have been amended accordingly to support changes outlined. Section 2.2.2., Table 1. Updated to include all completed/ongoing studies and to align with updates made in the latest version of the Investigator Brochure. Section 2.2.2.2. Clinical studies have been updated consistent with changes noted in IB. Section 2.2.2.3 updated to include draft results from definitive QTc study to support adding an ECG at week 2 and changes in Appendix 13 and stopping rules in Appendix 17 Section 2.3. Benefit Risk. Updated to include potential risk identified from the formal QT study

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		(B7931019) and to include more detailed risk language around thromboembolic events. Section 3. Objectives and estimands • Added additional clarifications on the primary endpoint estimand. [redacted] • Added details of all planned adjudication committees. • Clarified the role of the eDMC. Section 4.1. Overall design • MMF language updated removing the criteria for assessment to be performed at 12 hrs ± 30 mins. Participants are instead asked to refrain from taking a dose immediately prior to clinic visits where MMF levels are assessed. Section 5.1. Inclusion criteria Inclusion #5: Language updated to provide greater clarity around and specify permitted background therapy and all permitted combinations. Inclusion #6: To increase the baseline disease activity SLEDAI 2K ≥6 has been updated to ≥8 with a clinical score of ≥6 and clarification of BILAG disease activity criteria added" to the note in SOC. Inclusion #7. Updated to include a BMI criteria of <40, to prevent participants enrolling with significant co-morbidities and to allow accurate assessment of joint counts.

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		Section 5.2. Exclusion criteria. Please note that due to the deletion of some criteria in this amendment all references in this section to specific a exclusion number refers to the numbers as it will appear in the final version of this document. • Exclusion #1. The unit is incorrect and has been updated from mg/g to the correct unit of mg/mg. • Exclusion #3. Removed 5 year time frame for cancers prior to study entry such that current cancer or any history of cancer, other than the exceptions outlined, will be exclusionary. A requirement has also been added that if a participant has a cancer that has been treated and deemed cured, there must be documented evidence of the same from their oncologist or appropriate specialist. • Exclusion #5. Thrombosis exclusion has been broadened and exclusionary period increased from 6 to 12 months in response to potential risk outlined in the Investigator Brochure. • Exclusion #6. Added specific exclusion relating to pulmonary artery hypertension. • Exclusion #7/8. Split and clarification that participants with confounding autoimmune disorders are not eligible added. • Exclusion #10. Exclusion criteria removed as duplicate of a later exclusion criteria. • Exclusion #13. The exclusionary period has been increased from 4 to 12 Weeks for

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		participants taking part in other interventional studies. • Exclusion #14. Dose of prednisolone or equivalent has been updated from ≥20 mg/day to >20 mg/day to align with all other protocol references. • Exclusion #16. Added reference to 6-mercaptopurine to align with all other protocol sections. • Exclusion #17. Added sulfasalazine exclusion to prevent enrolment of subject with co-morbidities such as rheumatoid arthritis and Crohns disease. • Exclusion #19. Updated language to "Any prior treatment…." • Exclusion #20. Clarification added regarding prohibited prior Jak inhibitors. • Exclusion #21. The exclusionary period has been increased from 4 to 12 weeks prior to Day 1 for non-biologic investigation drugs to align with all other protocol sections. • Exclusion #22. The exclusionary period for exposure to live vaccine has been increased from 6 to 8 weeks prior to Day 1. • Exclusion #23. • Exclusion #30. Removed reference to CT and MRI which are being removed as alternate imaging modalities to monitor for tuberculosis.

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		• Exclusion #31. Clarified language to include any chronic infection and added specific reference to herpes simplex. • Exclusion #32 and all other relevant sections of the protocol. Removed preference for TB testing via T-spot as not available at the central lab. • Exclusion #34. Removed duplicate language around UPCR. • Exclusion #38 Added an exclusion for participant who are currently vaping. Section 5.3.3. Use of e-cigarettes or vaping is prohibited in new participants due to severe adverse events associated with this form of tobacco/nicotine use. Section 5.4. Clarifications for rescreening added. Section 6.5.1.1. Use of corticosteroids and tapering guidelines. Language simplified such that maximum additional dose is 10 mg/day above Day 1 dose level and for a maximum of 14 days. Section 6.5.2.2. Management of severe flare and/or worsening of disease. Language updated to clarify that participants should where possible remain in the study after discontinuation of study intervention, unless they also withdraw consent. They should, where possible, complete withdrawal procedures. Section 6.5.3. Rescue Medication. This section has been removed as use of additional therapies has been addressed in prior sections. Section 7.1. Updated to refer to Appendix 17 defined reasons for mandated discontinuation of study drug.

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		Section 8.1.6. Systemic Lupus International Collaborating Clinics. Appendix 9 is incorrectly referenced, updated to the correct reference to Appendix 10. Section 8.1.8. Photography. Made optional and restricted to participants with a CLASI-A score ≥10 at baseline. Section 8.1.11.2. Lupus QoL. Reference to "final score" updated to " individual domain score". Section 8.1.11.4. Administrative correction to PRO score name. CCI [redacted] Section 8.2.1.2. Chest x-ray. Reference to CT and MRI removed as these will no longer be used as alternate imaging modalities. Section 8.2.4 ECG. Wording clarified around which measurements will be single or triplicate readings and the use of central read. Section 8.2.5 Hepatitis screening and monitoring. The exclusion criteria and ongoing monitoring on study have been updated to provide clearer guidance to sites. Section 8.2.6.1. Interferon Gamma Release Assay (IGRA) Tuberculin Test. Language removed for participants who are positive for IGRA but are perceived at low risk of infection by PI. All positive tests will now be exclusionary. Section 8.2.7. Monitoring for infections. Parenteral antimicrobial updated to intravenous so as to only define the most severe infections.

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		Section 8.2.8. Clarification for handling of direct Coombs test. CCI [redacted]. Section 8.8.5. Coombs Direct Test. Updated to clearly outline that testing is only required if participant has evidence of hemolytic anemia. CCI [redacted] CCI [redacted] Section 9.1.1. Updated to be consistent with the clarifications made for the primary endpoint estimand in Section 3. Section 9.1.2. Hypothesis and decision rules and Section 12 References. Rationale: a new section added to predefine a sequentially rejective testing procedure for both the primary and the key secondary endpoints in order to control the family-wise type-I error rate. An associated reference added in the Reference section. Section 9.2. Sample size determination & Section 9.4.2. Analysis of Primary Endpoint. Updated to reflect the simulation results based on the sequentially rejective multiple testing procedure.

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		Section 9.4.3.2. Added the analysis method for the LupusQoL endpoint. Section 9.5.1. Clarified the eDMC's role in the interim analysis. Section 9.5.2. Adjudication Committees. Updated to add the details of all planned adjudication committees. Appendix 2. Table 5. Laboratory Testing • CCI [redacted] • Clarified requirements from complement assays • CCI [redacted] Appendix 4: Contraceptive Guidelines, Section 10.4.4. To remove the need for a country specific amendment the highly effective contraceptive methods that are user dependent, which are not approved in Japan have been highlighted. Appendix 7: ECG Findings of Potential Clinical Concern. QTcF criteria updated to 500 ms (absolute) to align with all other protocol references. Appendix 10: Systemic Lupus International Collaborating Clinics (SLICC)/American College of Rheumatology (ACR) Damage Index for SLE and Section 12 References. Reference incorrect, updated with the correct reference. Appendix 12: Footnote clarifying use of direct Coombs.

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		Appendix 13: List of Prohibited and Permitted Concomitant Medications. • Change in dose of permitted methylprednisolone for treatment of hypersensitivity • Immunosuppressive or immunomodulatory agents • 6-mercaptopurine and maximum permitted dose added. • Required period for stable dose updated from 30 days to 4 weeks to align with all other protocol references. Sulfasalazine added as a prohibited drug. Thymopetidum added as a prohibited drug. Herbal Medicine restriction added A list of common medications known to prolong the QT interval have been added. Appendix 17: Guidelines for Participant Safety Monitoring and Discontinuation. • Stopping rules added for decrease in eGFR cystatin and for increases in UPCr • Discontinuation criteria added around QT prolongation, eGFR, uPCR and thrombosis events to align with potential risks outlined in the Investigator Brochure. Where required typographical errors have been corrected. All new abbreviations have been added/removed from Appendix 23 as required.

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Amendment 2	11 June 2019	Title page: United States (US) Investigational New Drug (IND) Number: The IND number is incorrect and has been updated to 123650. Section 1.3 Schedule of Activities: Complete and Brief Physical Examination incorrectly referenced footnote "c", this has been corrected to footnote "d" Section 1.3 Schedule of Activities: *modified* SELENA-SLEDAI SLE flare index. The flare index measures changes since the last visit. As such measurements at screening and Baseline Day 1 are not required and have been removed. Section 5.1: Inclusion criteria #5, updated to remove reference to failed therapy and to include leflunomide and mizoribine. Section 5.2: Exclusion criteria #16, updated to include leflunomide and mizoribine. Section 6.5.1.1, Paragraph #5: Start of steroid taper window updated to Week 2 to make it consistent throughout the protocol Section 6.5.2.1, bullet #6, IM clarified as IM corticosteroids. Section 6.5.2.2, paragraph 1. Duplicate text referencing the use of rescue medication has been removed. Section 7.2 Patient discontinuation/ withdrawal from study: The following wording was removed so as to clarify participants right to withdraw: Participants should be questioned regarding their reason for withdrawal. Section 7.2 Withdrawal of consent: Wording regarding the need for participants to notify the investigator in writing of the decision to withdraw

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		consent removed so as to clarify participants right to withdraw. Section 8.1.9 Joint Assessments. Reference to medical marijuana removed and reference to narcotics replaced with lower potency opioid analgesics to make it consistent with Appendix 13. Section 8.2.3 Vital Signs, Paragraph 6, reference to tympanic assessment of body temperature removed as assessment instruments for SLE require an oral temperature. Section 8.2.4 Electrocardiograms. Paragraph 2, duplicate language has been removed. CCI  Section 9.5.1 Data Monitoring Committee. The section has been updated to outline that the external data monitoring committee (E-DMC) is a sponsor independent committee. Appendix 2, Table 4: References to Pneumococcal and tetanus antibodies have been removed as these are not assessed in this protocol. Section 10.4.4, Appendix 4: Contraceptive Methods. Section heading re-instated as missing from prior version. Only highly effective methods are permitted per protocol as such the following

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		contraceptive methods defined as "effective methods" have been removed. • Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action. • Male or female condom with or without spermicide. • Cervical cap, diaphragm, or sponge with spermicide. • A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods). 10.13, Appendix 13. Section referencing Thalidomide, lenalidomide, dapsone, adrenocorticotropic hormone (ACTH) by injection has been updated to remove incorrect wording and outline exclusion criteria prior to and during treatment and in the follow-up phase. 10.13 Appendix 13. CYP3A inhibitors (including drinks/foods): Updated to clarify these are permitted in the Follow-up period after a minimum of 48 hours (approximately 5 half-lives) following last dose of study intervention.
Amendment 1	04 Feb 2019	Section 1.3 Schedule of Events: The CLASI and 28 joint count will be performed at all scheduled visits including follow up (Visit 18). These additional assessments have been added to facilitate the adjudication of the primary endpoint assessments (BILAG, SLEDAI and Physician's Global Assessment) by an external adjudication committee. Section 10 Supporting Documentation and Operational Considerations. Patient reported outcome exemplars have been removed from the

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		amended protocol (formerly Appendices 22 to 28). Reference to these appendices in the body of the protocol have also been removed and replaced with reference to a separate PRO manual. Schedule of Activities. Visit day has been added to provide clarity on overall visit window. Footnote "q" of SOA and Section 6.5.1.2. Reference to the use of a daily diary have been removed. The text has been updated to outline that corticosteroid use will now be recorded in the participant's CRF. Section 3 and Section 8.1.4. CCI [redacted] Exclusion 12: Whilst this exclusion outlines that suicidal ideation is exclusionary, a reference to Section 8.2.10 has been added so that exclusion criteria at screening and discontinuation criteria are made explicit. Exclusion 32 and Table 4: Quantiferon GOLD plus has been added as an option to the TB testing. The appropriate abbreviation has also been added to Appendix 23 (Abbreviations). Section 6.1.1. Last sentence has been removed as this vaccine coadministered with 13vPnC does not apply to this protocol. Section 6.3.1: Reference to Third Party has been removed as there is no requirement for third party blinding in this study. Section 8.3.1: The active reporting period for adverse event collection was incorrectly stated as through and including a minimum of 30 calendar days. This has been corrected to 28 calendar days.

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		Section 10.1.6., Paragraph 8: The retention period for records pertaining to study conduct was missing. A 15 year retention period has been added. Section 10.1.7: Missing reference. The reference to study completion guidelines has now been added. Appendix 19 and References: The references outlined for the modified SELENA-SLEDAI Flare Index are incorrect. These sections have been updated with the correct reference. General: The following typographical and formatting errors have been corrected; Section 1.1 Synopsis: Statistical Methods and Section 9.1.1. • "non responder" has been updated to "a non-responder" Section 2: Introduction. • "with IC50 of…." has been updated to "with IC50 values of…." Section 8.1.8 Photography • "Photograph" corrected to "Photography" The last sentence in the second paragraph reading "These photographs will be reviewed as part of the participants eligibility criteria review by the sponsor and/or a consultant prior to randomization." is removed as photographs are not part of study eligibility criteria Appendix 8: 1997 Update on the 1982 Revised American College of Rheumatology (ACR) Criteria for the Classification of SLE • Bullets 10 and 11 formatting has been corrected

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		Appendix 10: Systemic Lupus International Collaborating Clinics (SLICC)/American College of Rheumatology (ACR) Damage Index for SLE • Renal section formatting has been corrected Appendix 13: List of Prohibited and Permitted Concomitant Medications • The typographical error "nvestigation" has been removed from Section 11.
Original protocol	12 Dec 2018	Not applicable (N/A)

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and institutional review boards (IRBs)/ethics committees (ECs).

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1. PROTOCOL SUMMARY

1.1. Synopsis

Rationale:

This is the first study of PF-06700841(brepocitinib) in participants with moderate to severe active, generalized Systemic Lupus Erythematosus (SLE) that have inadequate response to standard of care. The purpose of the study is to determine the safety and efficacy of PF-06700841 in SLE. The patient population selected for this study is participants who have active SLE (excluding active central nervous system [CNS] lupus or renal lupus with proteinuria (UPCr >3.0 mg/mg) and/or estimated glomerular filtration rate [eGFR] <50 mL/min/1.73 m^2) that usually require an increased level of immunosuppression. Such participants with SLE are currently being managed with multiple medications, including antimalarial drugs, immunosuppressives and corticosteroids. All these medications will be allowed as standard of care background treatment during the study. As study intervention will be adjunct therapy to participant's standard of care, no participants will receive placebo alone.

Objectives and Endpoints:

Objectives	Endpoints:	Estimands
Primary:	**Primary:**	**Primary:**
• To evaluate the efficacy of 3 QD dose levels of PF-06700841 compared to placebo in participants with active SLE.	• Proportion of participants achieving the Systemic Lupus Erythematosus Responder Index (SRI) change of 4 (SRI-4) at Week 52.	E1: This composite estimand is defined as a population average treatment difference between PF-06700841 and placebo in the proportion of participants with active SLE who achieved the binary SRI-4 endpoint at Week 52 and did not discontinue treatment prior to Week 52.
Key Secondary:	**Key Secondary:**	**Key Secondary:**
• To evaluate the efficacy of 3 QD dose levels of PF-06700841 compared to placebo in participants with active SLE.	• Proportion of participants achieving the British Isles Lupus Assessment Group-Based Composite Lupus Assessment (BICLA) at Week 52.	d between PF-06700841 and placebo in the proportion of participants with active SLE who achieved the binary BICLA endpoint at Week 52 and did not discontinue treatment prior to Week 52.

Objectives	Endpoints:	Estimands
• **Other Secondary:**	• **Other Secondary:**	**Other Secondary:**
• To assess attainment of low disease activity state of 3 QD dose levels of PF-06700841 compared to placebo in participants with active SLE.	• Proportion of participants achieving the Lupus Low Disease Activity State (LLDAS) at Week 52.	E3: This composite estimand is defined as a population average treatment difference between PF-06700841 and placebo in the proportion of participants with active SLE who achieved a LLDAS at Week 52 and did not discontinue treatment prior to Week 52.
• To compare the corticosteroid use (prednisone or equivalent) in PF-06700841 treated participants relative to placebo.	• Proportion of participants achieving a reduction in prednisone (or equivalent) dose to ≤7.5 mg/day at Week 52 and sustained for 12 weeks prior to Week 52, in the subset of participants on prednisone >7.5 mg/day (or equivalent) at baseline.	There is no defined estimand for this endpoint.
• To evaluate the efficacy of PF-06700841 compared to placebo in participants with active SLE and with sustained reduction of oral corticosteroids.	• Proportion of participants achieving SRI-4 response with dose of prednisone (or equivalent) reduced to ≤7.5 mg/day and sustained for 12 weeks at Week 52.	E4: This composite estimand is defined as a population average treatment difference between PF-06700841 and placebo in the proportion of participants who achieved the binary SRI-4 endpoint with sustained prednisone dose reduction to ≤7.5 mg/day (or equivalent) for 12 weeks at Week 52 and did not discontinue treatment prior to Week 52.
• To evaluate the Cutaneous Lupus Erythematosus Disease Area and Severity Index activity (CLASI-A) score in the subset of participants with baseline CLASI-A score ≥10 in PF-06700841 treated participants relative to placebo.	• Proportion of Participants with Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI-A) Total Activity Score ≥10 at Baseline with ≥50% Reduction in CLASI-A Total Activity Score at Week 52.	There is no defined estimand for this endpoint.
• To evaluate the effect on fatigue of PF-06700841 treated participants relative to placebo.	• Change from baseline in the total scores of Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) at Week 52.	E5: This hypothetical estimand is defined as a population average treatment difference between PF-06700841 and placebo in the FACIT-F score at Week 52 as if none of the specified intercurrent events have occurred.

Objectives	Endpoints:	Estimands
• To evaluate the effect on health-related quality of life of PF-06700841 treated participants relative to placebo.	• Change from baseline in the individual domain scores of the Lupus Quality of Life (LupusQoL) at Week 52.	E6: This hypothetical estimand is defined as a population average treatment difference between PF-06700841 and placebo in the LupusQoL individual domain scores at Week 52 as if none of the specified intercurrent events have occurred.
• To assess time to first severe flare in PF-06700841 treated participants relative to placebo.	• Time to first severe flare as measured by the modified Safety of Estrogen in Lupus: National Assessment (SELENA)-Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) Flare Index (m-SSFI).	E7: This estimand is defined as a population average treatment hazard ratio between PF-06700841 and placebo for the occurrence of the first severe flare event.
• To evaluate the safety and tolerability of PF06700841 dose levels versus placebo.	• Incidence of treatment-emergent adverse events (AEs). • Incidence of serious AEs (SAEs) and AEs leading to discontinuation. • The incidence of clinically significant abnormalities in vital signs and ECGs. • The incidence of clinically significant abnormalities in clinical laboratory values.	There is no defined estimand for these endpoints and they will be analyzed using Pfizer data standards as applicable.

Overall Design:

This is a Phase 2b, double-blind, randomized, placebo controlled, parallel design, multicenter, dose ranging study to assess the efficacy and safety of PF-06700841 in participants with active, moderate to severe generalized SLE. After an up to a 7-week screening period, eligible participants will be randomized in a 1:2:2:2 ratio such that participants will receive either 1 of three PF-06700841 once a day (QD) dose levels (15 mg, 30 mg and 45 mg) or placebo every day for 52 weeks.

Number of Participants

Approximately 350 randomized participants (100 participants per treatment group except 50 participants for the PF-06700841 15 mg QD dose group) will participate in this study at approximately 185 investigative sites worldwide. Randomization will be stratified by screening disease severity and anti-dsDNA status. The purpose of the stratified randomization is to achieve balanced treatment groups in these stratification factors.

Intervention Groups and Duration

For this study, the study intervention is PF-06700841. Blinded PF-06700841 and its matched placebo will be provided as tablets for oral administration. Participants will participate in this study for approximately 63 weeks. This includes up to a 7-week screening period, the 52-week treatment period, and the 4-week follow-up period.

Data Monitoring Committee

This study will use an independent external data monitoring committee (E-DMC). The E-DMC will be responsible for ongoing monitoring of the safety of participants in the study. This E-DMC will make recommendations with regard to continuing, stopping or altering the trial to a Sponsor Management Committee throughout the study. If an interim analysis is performed, the interim analysis results will also be provided to the E-DMC for review.

Adjudication Committees

This study will also use separate blinded adjudication committees consisting of independent external experts who will be responsible for the ongoing review of the following efficacy and safety endpoints:

1. BILAG, SLEDAI-2K and associated data.
2. Severe Flare.
3. Cardiovascular and thromboembolic events.
4. Malignancy.
5. Opportunistic infections.

Statistical Methods:

The primary estimand for the primary endpoint of Systemic Lupus Erythematosus Responder Index (SRI-4) response at Week 52 will be the population average treatment difference between PF-06700841 and placebo in the proportion of participants with active SLE who achieved SRI-4 endpoint at Week 52 and did not discontinue study intervention before Week 52. SRI-4 response is a composite endpoint where a responder must meet criteria in the assessment of SLEDAI-2K, BILAG and PhGA. Data post intercurrent events will be censored and any participant who experienced these intercurrent events will be considered as a non-responder at Week 52. The population-level summary will be the differences in the proportions of SRI-4 responder at Week 52 between each treatment dose arm of PF-06700841 and the placebo arm. For the primary endpoint, a treatment policy estimand will also be included in the SAP as a secondary estimand to estimate the treatment difference in the SRI-4 response rate at Week 52 regardless of occurrence of any intercurrent events prior to Week 52.

Each of the three dose groups of PF-06700841 will be compared with the placebo group for both the primary endpoint of SRI-4 response at Week 52 and the key secondary endpoint of BICLA response at Week 52 in 6 hypotheses. In order to control the overall family-wise type-I error rate, a sequentially rejective closed testing procedure is defined.

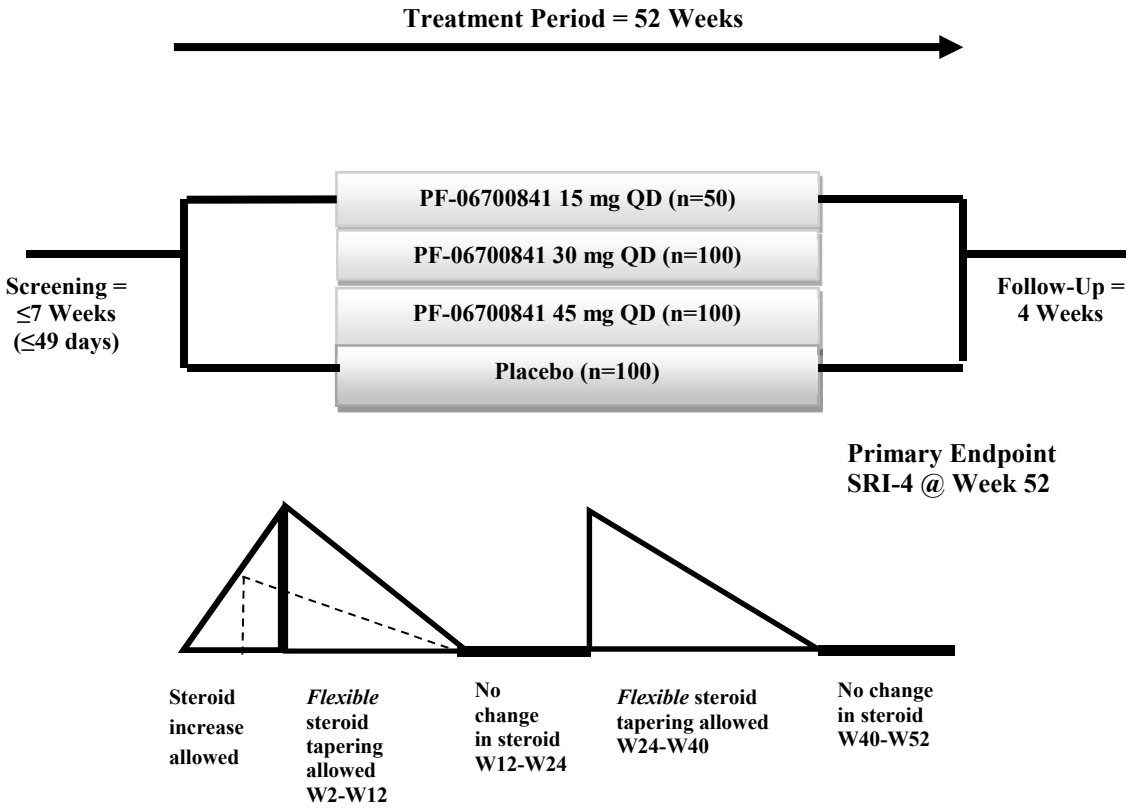
The primary endpoint is the proportion of SRI-4 responders at Week 52 and the primary analysis of this endpoint will be based on the Cochran-Mantel-Haenszel (CMH) approach adjusting for stratification factors. The hypothesis testing of this endpoint will be based on the p-values for pairwise treatment comparisons between each dose group of PF-06700841 and the placebo group. Treatment difference in the proportion of responders for the active treatment compared to the placebo will be estimated based on the CMH approach. These estimates will be reported with 95% confidence intervals and one-sided p-values.

The key secondary endpoint is the proportion of BICLA responders at Week 52 and the primary analysis of this endpoint will be conducted in the manner described above for the primary endpoint using the CMH approach adjusting for stratification factors. The hypothesis testing of this endpoint will be based on the p-values for pairwise treatment comparisons between each dose group of PF-06700841 and the placebo group. Treatment difference in the proportion of responders for the active treatment compared to the placebo will be estimated based on the CMH approach. These estimates will be reported with 95% confidence intervals and one-sided p-values.

An Interim analysis may be conducted when sufficient number of participants completes Week 52 visits and before the interim analysis is instigated, the details of the objectives, decision criteria, dissemination plan and method of maintaining the study blind per Pfizer's SOPs will be documented and approved in the E-DMC charter. In addition, the analysis details must be documented and approved in an interim analysis plan (IAP).

Further details of analyses in safety and efficacy will be specified in the statistical analysis plan.

1.2. Schema



1.3. Schedule of Activities

A table provides an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section of the protocol for detailed information on each procedure and assessment required for compliance with the protocol. The investigator may schedule visits (unplanned visits) in addition to those listed in the Schedule of Activities table, in order to conduct evaluations or assessments required to protect the well-being of the participant.

Protocol Activity	Screening	Treatment Period																Follow-up Period	Participant withdrawal or EW[b]	**Post-EW**
Study Identifier (Study Visit)	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18		
Visit Day/Week[a]	Days -49 to -1	Baseline Day 1	Wk 2 Day 15	Wk 4 Day 29	Wk 6 Day 43	Wk 8 Day 57	Wk 12 Day 85	Wk 16 Day 113	Wk 20 Day 141	Wk 24 Day 169	Wk 28 Day 197	Wk 32 Day 225	Wk 36 Day 253	Wk 40 Day 281	Wk 44 Day 309	Wk 48 Day 337	Wk 52 Day 365/ EOT	Week 56 /Day 393 EOS	N/A	EW +4 Weeks 28 days
Visit Window	None	None	±3 Days based on Day 1 Visit				±7 Days based on Day 1 Visit											±3 Days based on Day 1 Visit	N/A	EW +4 Weeks (±3 Days)
Enrollment Procedures																				
Informed consent	X																			
Inclusion/exclusion criteria	X	X																		
Demographics, medical history, SLE history, and smoking history	X																			
Prior SLE and non-SLE medications check	X	X																		
Medical Procedures																				
Vital signs (BP, HR [pulse], respirations and temperature)[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height[c]	X																			
Complete physical examination[d]	X									X								X	X	
Brief physical examination[d]		X	X	X	X	X	X	X	X		X	X	X	X	X	X	X			X
ECG (12-lead)[f]	X	X	X				X			X			X				X	X	X	X
Chest x-ray[e,bb]	X									X								X	X	

Protocol Activity	Screening	Treatment Period																Follow-up Period	Participant withdrawal or EW[b]	**Post-EW**
Study Identifier (Study Visit)	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18		
Visit Day/Week[a]	Days -49 to -1	Baseline Day 1	Wk 2 Day 15	Wk 4 Day 29	Wk 6 Day 43	Wk 8 Day 57	Wk 12 Day 85	Wk 16 Day 113	Wk 20 Day 141	Wk 24 Day 169	Wk 28 Day 197	Wk 32 Day 225	Wk 36 Day 253	Wk 40 Day 281	Wk 44 Day 309	Wk 48 Day 337	Wk 52 Day 365/ EOT	Week 56 /Day 393 EOS	N/A	EW +4 Weeks 28 days
Laboratory Safety Assessments																				
Blood chemistry, hematology, urinalysis[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Cystatin-based eGFR[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Lipid profile panel (fasting)[g]	X						X			X			X				X	X	X	X
Spot urine (Upr:Ucr)[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum FSH (WONCBP only)	X																			
Serum β-hCG[j]	X																			
Urine β-hCG (conducted at site)[j]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine microscopic exam[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HBsAg, HBcAb, and HCVAb (Hep B and Hep C reflex testing)[k]	X																			
HBV DNA to assess reactivation in high risk participants[k]		X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
HIV testing (per local regulations)[l]	X																			
TB testing (IGRA)[m]	X									X								X	X	
CCI																				
			[redacted]	[redacted]	[redacted]		[redacted]	[redacted]			[redacted]			[redacted]				[redacted]	[redacted]	[redacted]	
			[redacted]		[redacted]			[redacted]			[redacted]						[redacted]	[redacted]	[redacted]	[redacted]	

Protocol Activity	Screening	Treatment Period																Follow-up Period	Participant withdrawal or EW[b]	**Post-EW**
Study Identifier (Study Visit)	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18		
Visit Day/Week[a]	Days -49 to -1	Baseline Day 1	Wk 2 Day 15	Wk 4 Day 29	Wk 6 Day 43	Wk 8 Day 57	Wk 12 Day 85	Wk 16 Day 113	Wk 20 Day 141	Wk 24 Day 169	Wk 28 Day 197	Wk 32 Day 225	Wk 36 Day 253	Wk 40 Day 281	Wk 44 Day 309	Wk 48 Day 337	Wk 52 Day 365/ EOT	Week 56 /Day 393 EOS	N/A	EW +4 Weeks 28 days
CCI																				
Trial Treatment Procedures																				
IRT Registration	X																			
Randomization (after all screening procedures are completed/reviewed)		X																		
Study Intervention dispensing		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Study Intervention administration[s]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Study Intervention accountability			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Safety Assessments																				
SLE Steroid Tapering			X	X	X	X	X				X	X	X	X						
Concomitant corticosteroids[t]	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→

Protocol Activity	Screening	Treatment Period																Follow-up Period	Participant withdrawal or EW[b]	**Post-EW**
Study Identifier (Study Visit)	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18		
Visit Day/Week[a]	Days -49 to -1	Baseline Day 1	Wk 2 Day 15	Wk 4 Day 29	Wk 6 Day 43	Wk 8 Day 57	Wk 12 Day 85	Wk 16 Day 113	Wk 20 Day 141	Wk 24 Day 169	Wk 28 Day 197	Wk 32 Day 225	Wk 36 Day 253	Wk 40 Day 281	Wk 44 Day 309	Wk 48 Day 337	Wk 52 Day 365/ EOT	Week 56 /Day 393 EOS	N/A	EW +4 Weeks 28 days
Other concomitant medications & non-drug treatments	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Serious and non-serious AE monitoring	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Contraception check[u]	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Monitoring for Infections (skin swab for herpetiform rash, if suspected)	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Clinical Assessments																				
SLE diagnosis using either the ACR SLE classification or SLICC criteria[v]	X																			
BILAG history	X																			
Joint Assessment (28 tender/painful and swollen joint counts)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SLEDAI-2K	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
BILAG 2004	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physician Global Assessment (PhGA)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
modified SELENA-SLEDAI SLE flare index			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SLICC/ACR damage index for SLE		X															X		X	
CLASI	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Photography, if applicable[w]		X					X			X							X		X	
C-SSRS[x]	X									X										
Patient Reported Outcomes																				
FACIT-F		X	X	X		X	X			X			X				X	X	X	

Protocol Activity	Screening	Treatment Period																Follow-up Period	Participant withdrawal or EW[b]	**Post-EW**
Study Identifier (Study Visit)	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18		
Visit Day/Week[a]	Days -49 to -1	Baseline Day 1	Wk 2 Day 15	Wk 4 Day 29	Wk 6 Day 43	Wk 8 Day 57	Wk 12 Day 85	Wk 16 Day 113	Wk 20 Day 141	Wk 24 Day 169	Wk 28 Day 197	Wk 32 Day 225	Wk 36 Day 253	Wk 40 Day 281	Wk 44 Day 309	Wk 48 Day 337	Wk 52 Day 365/ EOT	Week 56 /Day 393 EOS	N/A	EW +4 Weeks 28 days
Lupus QoL		X		X		X	X			X							X	X	X	
CCI																				

Abbreviations: →= ongoing/continuous event; ACR = American College of Rheumatology; AE = adverse event; CCI ; anti-dsDNA = anti-double-stranded deoxyribonucleic acid; β-hCG = beta-human chorionic gonadotropin; BILAG = British Isles Lupus Assessment Group; CCI ; BP = blood pressure; CLASI = Cutaneous Lupus Erythematosus Disease Area and Severity Index; CLASI-A = CLASI activity score; CRF = Case Report Form; C-SSRS = Columbia-Suicide Severity Rating Scale; DNA = deoxyribonucleic acid; EC = ethics committee; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; CCI ; EOS = end of study; EOT = end of treatment;

Protocol Activity	Screening	Treatment Period																Follow-up Period	Participant withdrawal or EW[b]	**Post-EW**
Study Identifier (Study Visit)	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18		
Visit Day/Week[a]	Days -49 to -1	Baseline Day 1	Wk 2 Day 15	Wk 4 Day 29	Wk 6 Day 43	Wk 8 Day 57	Wk 12 Day 85	Wk 16 Day 113	Wk 20 Day 141	Wk 24 Day 169	Wk 28 Day 197	Wk 32 Day 225	Wk 36 Day 253	Wk 40 Day 281	Wk 44 Day 309	Wk 48 Day 337	Wk 52 Day 365/ EOT	Week 56 /Day 393 EOS	N/A	EW +4 Weeks 28 days

CCI n; EW = Early Withdrawal; FACIT-F = Functional Assessment of Chronic Illness Therapy-Fatigue; FSH = follicle stimulating hormone; HBV = hepatitis B virus; HEENT = head, eyes, ears, nose and throat; Hep B = Hepatitis B; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HCVAb = hepatitis C virus antibody; Hep C = Hepatitis C; HIV = human immunodeficiency virus; HR = heart rate; CCI IGRA = interferon gamma release assay; IP = study intervention; IRT = interactive response technology; *modified* SELENA-SLEDAI SLE Flare Index = Safety of Estrogen in Lupus: National Assessment-Systemic Lupus Erythematosus Disease Activity Index SLE Flare Index; CCI ; PBMC = peripheral blood mononuclear cells; PhGA = Physician Global Assessment; CCI ; CCI ; RNA = ribonucleic acid; CCI ; SLE = Systemic Lupus Erythematosus; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index-2000; SLICC/ACR Damage Index for SLE = Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index for SLE; TB = tuberculosis; Upr:Ucr = urine protein to urine creatinine ratio; WOCBP = women of childbearing potential; WONCBP = women of non-childbearing potential.

a. Day relative to start of study treatment (Day 1).

b. Please reference the B7931028 case report form completion guidelines to identify the appropriate CRFs to complete for any participant who discontinue study intervention early and/or prematurely withdraws from the study.

c. Vital Signs include blood pressure, pulse rate, respirations and temperature measured after approximately 5 minutes of rest. Weight and height will be measured without shoes. Since all clinical assessments were validated using oral temperatures, it is important to take oral temperatures ONLY on study; oral thermometers will be supplied by the Sponsor if requested.

d. A complete physical examination will include, at a minimum, head, ears, eyes, nose, mouth, skin, heart and lung examinations, lymph nodes, and gastrointestinal, musculoskeletal, and neurological systems. A brief physical, examination will include, at a minimum, assessments of general appearance, the heart, lungs, skin, musculoskeletal and participant-reported symptoms. Findings on the physical exam should support disease activity manifestations scored in SLEDAI, BILAG, CLASI and joint count.

e. Chest x-ray or other appropriate diagnostic imaging (ie, CT Scan with or without contrast or an MRI) may be performed up to 12 weeks prior to Day 1. All official reading must be located in the source documentation. Refer to Section 8.2.6.

f. A single ECG measurement will be collected at all scheduled visits except at baseline on Day 1 where ECG will be collected in triplicate approximately 2-4 minutes apart. At Week 2 visit, an ECG will be collected approximately 3 hours after dosing at the study site.

g. Samples for central laboratory evaluations (ie, hematology, blood chemistry, urinalysis, dipstick and microscopic) when performed for the lipid profile panel (total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides) must be collected after a minimum fast of 8 hours prior to the visit. Diabetics

Protocol Activity	Screening	Treatment Period																Follow-up Period	Participant withdrawal or EW[b]	**Post-EW**
Study Identifier (Study Visit)	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18		
Visit Day/Week[a]	Days -49 to -1	Baseline Day 1	Wk 2 Day 15	Wk 4 Day 29	Wk 6 Day 43	Wk 8 Day 57	Wk 12 Day 85	Wk 16 Day 113	Wk 20 Day 141	Wk 24 Day 169	Wk 28 Day 197	Wk 32 Day 225	Wk 36 Day 253	Wk 40 Day 281	Wk 44 Day 309	Wk 48 Day 337	Wk 52 Day 365/ EOT	Week 56 /Day 393 EOS	N/A	EW +4 Weeks 28 days

who are taking antidiabetic medications or participants who cannot reasonably tolerate an 8-12 hour fast should not eat immediately prior to the visit as far as possible. Laboratory tests may be repeated once during the 7-week screening period; the last value will be used to determine participant eligibility.

h. Cystatin-C based estimated glomerular filtration rate (eGFR) to be calculated by the central laboratory at all time points (with the exception of the Week 56 Visit).

i. Random spot urine samples will be collected after the first morning void.

j. Serum/urine pregnancy tests for WOCBP; serum pregnancy test must be performed at screening for all WOCBP as defined in the eligibility criteria urine pregnancy test must be performed at Day 1 for all WOCBP prior to dosing with study intervention and at all subsequent visits.

k. Reflex-testing (if necessary) consists of: participants at screening who are HBsAg negative but HBcAb positive will be reflex-tested for HBV DNA and, if HBV DNA is negative, may enroll; if HBV DNA is positive, they will be screen-failed. To assess for reactivations of HepB monthly, high risk participants are defined as follows: 1) HBsAg negative, HBcAb negative, HBsAb positive without documentation of prior HBV vaccination, 2) HBsAg negative, HBcAb positive, HBsAb positive whether or not they have received prior HBV vaccination.

l. Confirmation and documentation of negative HIV test result within 12 weeks prior to screening is acceptable.

m. Documented TB testing (IGRA) performed within 12 weeks prior to Study Day 1 is acceptable. Test results should be available in the source document. In this study therefore, a Mantoux skin test is not acceptable and an IGRA must be performed. An initial IGRA should be performed at the central laboratory so that at least one set of results will be available in the Pfizer database. If another test is required, it may be performed locally, and a T-SPOT® TB test (if available) would be preferred to another QuantiFERON® test.

n. Standard complement level measurements will include but are not limited to C3 and C4.

o. Direct Coombs should only be performed at a local lab and only if the investigator suspects a clinically significant hemolytic anemia is present that will be scored on the BILAG.

[redacted]

Protocol Activity	Screening	Treatment Period																Follow-up Period	Participant withdrawal or EW[b]	**Post-EW**
Study Identifier (Study Visit)	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18		
Visit Day/Week[a]	Days -49 to -1	Baseline Day 1	Wk 2 Day 15	Wk 4 Day 29	Wk 6 Day 43	Wk 8 Day 57	Wk 12 Day 85	Wk 16 Day 113	Wk 20 Day 141	Wk 24 Day 169	Wk 28 Day 197	Wk 32 Day 225	Wk 36 Day 253	Wk 40 Day 281	Wk 44 Day 309	Wk 48 Day 337	Wk 52 Day 365/ EOT	Week 56 /Day 393 EOS	N/A	EW +4 Weeks 28 days

s. On study visit days during the treatment period, participants should be instructed to refrain from dosing at home, and are instructed to take the study intervention at the investigator site.

t. A detailed history of corticosteroid use will be collected. Participants may receive a prescribed oral daily dose of prednisone (or equivalent see Appendix 14). The investigator/site staff will review the participant's corticosteroid usage and record in the CRF at each study visit.

u. WOCBP should have their method of contraception recorded in their source documentation.

v. SLE diagnosis using either the American College of Rheumatology Systemic Lupus Erythematosus Classification or Systemic Lupus International Collaborating Clinics Criteria.

w. US sites only (optional).

x. Participants who have recent or active suicidal ideation or behaviors will be excluded from study entry or after Day 1, would be discontinued from treatment and referred to a mental health professional for appropriate evaluation and treatment.

[redacted]

bb. Participants that enter the study with latent TB or develop newly positive QFT-G results during the study may be required to have additional chest X-Ray or chest CT at Weeks 24 and/or 56 (or End of study Visit). Refer to Section 8.2.6.

2. INTRODUCTION

PF-06700841(brepocitinib) is a potent tyrosine kinase (TYK)2/Janus kinase (JAK)1 inhibitor that is highly selective over the other human kinases and is being developed for the treatment of participants with active Systemic Lupus Erythematosus (SLE).

PF-06700841 is an orally bioavailable small molecule with a good selectivity profile over the other human kinases including JAK2 and JAK3. PF-06700841 inhibited the in vitro activities of TYK2, JAK1, JAK2 and JAK3 with IC50 values of 22.7, 16.8 nM, 76.6 nM and 6490 nM, respectively. PF-06700841 is capable of inhibiting the cytokines with signaling pathways mediated by JAK1 and/or TYK2, including type I IFNs, IL-6, IL-12, IL-15, IL-21, IL-22, IL-23, and IFNγ. Many of these cytokines are involved in the pathogenesis of SLE.

The inhibition of TYK2 and JAK1 will lead to modulation of multiple cytokines which play a critical role in the pathogenesis of SLE, including Type 1 interferons (IFNα,β; JAK1/TYK2 dependent), IFNγ (JAK1/JAK2 dependent), IL-6 (JAK1/JAK2/TYK2 dependent), and IL-21(JAK1/JAK3 dependent). In addition, IL-6 and IL-21 play a critical role in the development of Th17 cells and production of their signature cytokine IL-17, which has a critical role in a variety of autoimmune diseases including SLE.[1] Thus, key signaling molecules TYK2 and JAK1 are attractive therapeutic targets for diseases associated with widely dysregulated immune functions, such as SLE.

2.1. Study Rationale

This is the first study of PF-06700841 in participants with active, generalized SLE that have inadequate response to standard of care. The purpose of the study is to determine the safety and efficacy of PF-06700841 in SLE. The patient population selected for this study is participants who have active SLE (excluding active central nervous system [CNS] lupus or renal lupus with proteinuria (UPCr >3.0 mg/mg) and/or estimated glomerular filtration rate [eGFR] <50 mL/min/1.73 m^2) that usually require an increased level of immunosuppression. Such participants with SLE are currently being managed with multiple medications, including anti-malarial drugs, immunosuppressives and corticosteroids. All these medications will be allowed as standard of care background treatment during the study. As study intervention will be adjunct therapy to participant's standard of care, no participants will receive placebo alone.

2.2. Background

Systemic Lupus Erythematosus (SLE) is a chronic inflammatory disease of unknown etiology, which can affect the skin, joints, kidneys, lungs, nervous system, serous membranes and/or other organs of the body. Immunologic abnormalities, especially the production of [redacted] are a prominent feature of the disease.[2] The clinical course of SLE is variable and characterized by periods of remissions and relapses. Women, especially in their childbearing years, are affected more frequently than men.[3] SLE is more prevalent in certain racial and ethnic groups such as blacks (of African descent), Asians, and Hispanics.[4] The prevalence of lupus ranges from approximately 40 cases per 100,000 persons among Northern Europeans to more than 200 per 100,000 persons among blacks.[5] Although the

quality of care and survival of SLE patients have improved in the past two decades, further improvement depends on the availability of more effective and safer treatment modalities.

The treatment of SLE can be individualized and depends on symptom manifestations, organ involvement, and disease severity.[6,7] Antimalarials, low dose corticosteroids, and nonsteroidal anti-inflammatory drugs (NSAIDs) are used in the treatment of mild symptoms such as arthralgias and cutaneous manifestations. High dose corticosteroids and cytotoxic agents are used in more severe disease. Immunosuppressive agents such as cyclophosphamide, tacrolimus and rituximab are used depending on the severity and various organ systems involved. Development of novel therapies for SLE has been relatively slow partly because of the variability of the disease and partly because the disease is often responsive to corticosteroids and conventional immunosuppressive agents.

Prior to 2011, only 3 drugs were approved by the United States Food and Drug Administration (US FDA) for the treatment of SLE: corticosteroids, hydroxychloroquine (Plaquenil) and low-dose aspirin. These therapies are not ideal in terms of efficacy and toxicities. In March 2011, the US FDA approved belimumab (Benlysta) for treatment of SLE, and several months later in July 2011, the European Commission granted marketing authorisation for Benlysta valid throughout the European Union.[8,9] However, the magnitude of the clinical benefit of belimumab seems modest and the drug is indicated for treatment of patients with active SLE as a combination therapy with conventional modalities. Management of refractory lupus manifestations, minimization of treatment-related complications and prevention of disease flares and cumulative damage remain unsatisfactory. Therefore, there is an unmet need for the development of safer and more effective therapies that can induce a long-lasting remission in SLE.

SLE is characterized by broad dysregulation of the immune system that involves T and B cells, dendritic cells, and macrophages. The hallmark of the disease is the production of CCI [redacted] and the formation of immune complexes causing organ damage by deposition in the tissues. Pro-inflammatory cytokines play an important and diverse role in the pathogenesis of SLE, and their imbalance determines disease activity and severity.

Many key cytokines implicated in the pathogenesis of SLE are dependent on activation of Janus kinases (JAKs) for intracellular signaling.[10] The JAK family of cytoplasmic protein tyrosine kinases mediates the signalling of several pro-inflammatory cytokines, such as type I (JAK1/TYK2) and type II (JAK1/JAK2) interferons, IL-6 (JAK1/JAK2/TYK2), and IL-12 and IL-23 (JAK2/TYK2). PF-06700841 is an orally administered selective and reversible inhibitor of JAK1 and TYK2.[11]

2.2.1. Nonclinical overview

No adverse findings were observed in oral repeat-dose toxicity studies with PF-06700841 in rats and monkeys up to 6 and 9 months in duration, respectively. PF-06700841-related, non-adverse, target organs identified include the immune and hematolymphopoietic systems (thymus, spleen, lymph nodes, and bone marrow), cardiovascular system (blood pressure, heart rate, corrected QT wave interval [QTc]), gastrointestinal tract (body weight and weight gain effects), and adrenal gland (vacuolation). The findings in the thymus, spleen, lymph

nodes, and bone marrow are consistent with the pharmacological activity of PF-06700841. The no observed adverse effect level (NOAELs) in the 6-and 9-month toxicity studies were 45 mg/kg/day in rats (unbound maximum concentration (C_{max}) of 8280 ng/mL and area under the curve at 24 hours (AUC_{24}) of 69,700 ng•h/mL) and 20 mg/kg/day in monkeys (unbound C_{max} of 2260 ng/mL and AUC_{24} of 10,700 ng•h/mL). Adverse findings in the central nervous system (decreased activity, mortality, prostration, convulsions) were observed at high systemic exposures in pregnant, but not in non-pregnant rabbits.

In oral embryo-fetal development studies in rats and rabbits, adverse PF-06700841-related developmental effects occurred (lower embryo-fetal viability and mean fetal body weights, fetal skeletal malformations, external malformations). The developmental NOAEL in rabbits was 1 mg/kg/day (unbound C_{max} of 174 ng/mL and AUC_{24} of 608 ng•h/mL).

The developmental NOAEL in rats was not established and is <2 mg/kg/day (unbound C_{max} of 482 ng/mL and AUC_{24} of 2240 ng•h/mL), the lowest dose tested. No effects on female reproductive organs, as assessed by histopathologic examination, were noted in either the rat or monkey repeat-dose toxicity studies. PF-06700841 is not mutagenic in bacterial reverse mutation assays. Although PF-06700841 was positive for micronuclei formation in vitro (through an aneugenic mechanism), it did not induce micronuclei *in vivo* in rats at 55 mg/kg/day (unbound C_{max} = 7730 ng/mL and AUC_{24} = 88,300 ng•h/mL), the highest dose tested in the 1-month oral toxicity study.

Further details of the nonclinical safety program are provided in the current PF-06700841 Investigator's Brochure.

2.2.2. Clinical Overview

To date, the clinical development program for the oral tablet formulation of PF-06700841 comprises Phase 1 studies in adult healthy Western participants (B7931001; single ascending dose [SAD] and multiple ascending dose [MAD] study) and Japanese participants (B7931009; placebo controlled multidose study), an adsorption, distribution, metabolism and excretion study (B7931014), a formal QT study (B7931019) and Phase 1 and 2 studies in participants with chronic plaque psoriasis (B7931001, B7931004), alopecia areata (B7931005), ulcerative colitis (B7981005), Crohn's disease (B7981007), psoriatic arthritis (B7931030), and vitiligo (B7981019) and hidradenitis suppurative (C2501007). The studies conducted to date described in this section have all used oral administration of PF-06700841.

Table 1. Summary of Clinical Studies for Brepocitinib

Study Number	Study Design	Treatment Groups/Dose and Regimen	Number of Participants Enrolled/Completed	Treatment Duration	Status
Oral Administration					
Phase 1 Study					
B7931001[a]	This was a Phase 1, within cohort, randomized, double blind, third-party open, placebo-controlled, single- and multiple dose escalation, parallel group study to evaluate the safety, tolerability, PK and pharmacodynamics of brepocitinib in healthy participants and participants with plaque psoriasis and bioavailability of a tablet formulation relative to suspension formulation and the effect of food on a tablet formulation of brepocitinib.	SAD in HV: 1, 3, 10, 30, 100, and 200 mg single dose of brepocitinib or placebo MAD in HV: 10, 30, 100, or 175 mg QD, or 50 mg BID of brepocitinib or placebo Multiple doses in psoriasis participants: 30 mg QD or 100 mg QD of brepocitinib or placebo (QD) Bioavailability in HV: 100 mg Tablet (Fasted) or 100 mg Oral Solution/ Suspension (Fasted) or 100 mg Tablet (Fed)	SAD: 54 participants enrolled (41 active and 13 placebo)/51 completed (39 active and 12 placebo) MAD: 37 participants enrolled (26 active and 11 placebo)/33 completed (22 active and 11 placebo) Psoriasis: 30 participants enrolled (21 active and 9 placebo)/17 completed (10 active and 7 placebo) BA: 12 participants enrolled and completed (12 active)	SAD: single dose MAD: 10 days Psoriasis: 28 days BA: single dose	Completed Completed Completed Completed

Table 1. Summary of Clinical Studies for Brepocitinib

Study Number	Study Design	Treatment Groups/Dose and Regimen	Number of Participants Enrolled/Completed	Treatment Duration	Status
			Total 96 participants enrolled and 84 completed		
B7931009	This was a Phase 1, randomized, double-blind, third-party open, placebo-controlled study to evaluate the safety, tolerability, and PK after multiple oral doses of brepocitinib in healthy Japanese participants.	100 mg QD of brepocitinib or placebo	8 HVs (6 active and 2 placebo)	10 days	Completed
B7931010	This is an open-label, single dose, 2-period, 2-sequence crossover study in healthy volunteers to characterize brepocitinib PK profile and relative bioavailability following single oral dose formulation of IR tablets and MR tablets.	Sequence 1: a single oral dose of 30 mg brepocitinib IR tablets to a single oral dose of 30 mg brepocitinib MR tablets Sequence 2: a single oral dose of 30 mg brepocitinib MR tablets to a single oral dose of 30 mg brepocitinib IR tablets	8 participants enrolled and completed	Single doses	Completed
B7931014	This is a Phase 1, open label, non-randomized, 2 period, fixed sequence study to investigate the absorption, distribution, metabolism and excretion of [^{14}C PF 06700841] and to assess the absolute bioavailability and fraction of brepocitinib in healthy male participants using a ^{14}C microtracer approach.	Period A: an oral dose of 60 mg brepocitinib containing 300 nCi ^{14}C-brepocitinib; Period B: an oral dose of 60 mg unlabeled brepocitinib followed by an IV dose of 30 µg ^{14}C labeled brepocitinib (300 nCi)	6 enrolled and completed	Single doses	Completed

Table 1. Summary of Clinical Studies for Brepocitinib

Study Number	Study Design	Treatment Groups/Dose and Regimen	Number of Participants Enrolled/Completed	Treatment Duration	Status
B7931018	This was a Phase 1, randomized, 2 way crossover, multiple-dose, open label study of the effect of brepocitinib on single dose combination OC PKs in healthy female participants.	Treatment A: Single dose of combination OC in the form of 1 PORTIA (EE and LN) or equivalent oral tablet, containing EE 30 µg and LN 150 µg Treatment B: Single dose of combination OC in the form of 1 PORTIA (EE and LN) or equivalent oral tablet, containing of EE 30 µg and LN 150 µg on the morning of Day 10 following 9 days of brepocitinib dosed at 60 mg PO QD. Dosing with brepocitinib at 60 mg PO QD continued through until Day 13.	18 enrolled/17 completed	Multiple dose	Completed
B7931019	This is a Phase 1, 6-sequence, 3-period, participant- and investigator blinded and sponsor-open, crossover study in healthy volunteers to evaluate the brepocitinib effect on QTc interval. Each participant randomized will receive placebo, brepocitinib 200 mg and moxifloxacin (open label) in one of the 6 sequences. Moxifloxacin is positive control to demonstrate the study sensitivity and brepocitinib effect on QTc will be assessed by concentration-QT analysis.	Sequence 1: single dose of brepocitinib 200 mg to placebo to moxifloxacin 400 mg Sequence 2: single dose of brepocitinib 200 mg to moxifloxacin 400 mg to placebo Sequence 3: placebo to brepocitinib 200 mg to moxifloxacin 400 mg Sequence 4: placebo to moxifloxacin 400 mg to brepocitinib 200 mg Sequence 5: moxifloxacin 400 mg to brepocitinib 200 mg to placebo Sequence 6: moxifloxacin 400 mg to placebo to brepocitinib 200 mg	33 enrolled 32 completed	Single doses	Completed

Table 1. Summary of Clinical Studies for Brepocitinib

Study Number	Study Design	Treatment Groups/Dose and Regimen	Number of Participants Enrolled/Completed	Treatment Duration	Status
B7931033	This is a phase 1, open-label, fixed-sequence, 2-period study to investigate the effect of multiple oral doses of itraconazole on a single oral dose of brepocitinib PK in healthy volunteers.	Period 1: a single oral dose of 30 mg brepocitinib tablets Period 2: Itraconazole 200 mg once daily on Days 1-7 with a single oral dose of 30 mg brepocitinib tablets administered approximately 1 hour after itraconazole dosing on Day 4.	12 enrolled and completed	Single doses	Completed
B7931048	This is a phase 1, non-randomized, open label, single dose study to evaluate the pharmacokinetics, safety and tolerability of brepocitinib in participants with renal impairment and in healthy participants with normal renal function	A single oral dose of 30 mg brepocitinib tablets	Part 1: Severe renal impairment (8 enrolled /8 completed) Normal renal function (8 enrolled /8 completed) Part 2: Mild renal impairment (7 enrolled /8 planned) Moderate renal impairment (7 enrolled /8 planned) (as of 16 Feb 2022)	Single dose	Ongoing

Table 1. Summary of Clinical Studies for Brepocitinib

Study Number	Study Design	Treatment Groups/Dose and Regimen	Number of Participants Enrolled/Completed	Treatment Duration	Status
B7931058	This was a Phase 1, open-label study in healthy participants to investigate the PK of brepocitinib following single oral administration of modified release formulations under fed and fasted conditions in Part A and a randomized, double-blind, sponsor-open, placebo controlled study to evaluate safety, tolerability, and PK of brepocitinib following multiple oral administration of modified release formulation under fasted condition in Part B	*Part A: 60 mg IR tables or MR capsules* *Part B: 30 mg, 60 mg, 120 mg tablets*	*Part A: 12* healthy participants *Part B: 24* healthy participants	*Part A:* Single dose *Part B: Multiple dose*	Completed
Phase 2 Study					
B7931004	This was a Phase 2a, randomized, double-blind, placebo-controlled study to evaluate safety and efficacy of brepocitinib in participants with moderate to severe plaque psoriasis. The study consisted of 4 weeks of induction and 8 weeks of maintenance therapy periods.	brepocitinib: 60 mg QD to 30 mg QD 60 mg QD to 10 mg QD 60 mg QD to 100 mg QW 60 mg QD to placebo 30 mg QD; Or placebo	212 enrolled (189 active and 23 placebo)	12 weeks	Completed

Table 1. Summary of Clinical Studies for Brepocitinib

Study Number	Study Design	Treatment Groups/Dose and Regimen	Number of Participants Enrolled/Completed	Treatment Duration	Status
B7931005[b]	This is a Phase 2a randomized, double-blind, placebo-controlled, multicenter study with two extension periods to evaluate the efficacy and safety profile of ritlecitinib and brepocitinib in participants with moderate to severe AA. This includes a 24-week treatment period, a 4-week drug holiday (#1), an up to 12 month SBE period, a 4-week drug holiday (#2), and a 6-month CO Open Label Extension Period.	brepocitinib: 60 mg QD in 4-week induction and 30 mg QD in 20-week maintenance or placebo	142 enrolled (47 on active brepocitinib and 47 on placebo) /115 completed (36 on active brepocitinib and 34 on placebo) In extension 1, 96 participants entered SBE period, 32 received brepocitinib and 25 completed the study. In extension 2, 23 participants entered CO Extension Period and 5 participants received brepocitinib.	24 weeks in the original treatment period; 24 weeks in extension 1; 24 weeks in extension 2.	Completed
B7981005[b]	This is a Phase 2b, double-blind, randomized, placebo-controlled, parallel group, dose ranging study of oral ritlecitinib and brepocitinib as induction and chronic therapy in participants with moderate to severe ulcerative colitis. The study has 8-weeks of double-blind and placebo-controlled induction treatment period followed by a	Induction treatment period: brepocitinib 60 mg QD, 30 mg QD, and 10 mg QD or placebo Chronic treatment period: brepocitinib 30 mg QD	144 enrolled (142 treated)	32 weeks	Completed

Table 1. Summary of Clinical Studies for Brepocitinib

Study Number	Study Design	Treatment Groups/Dose and Regimen	Number of Participants Enrolled/Completed	Treatment Duration	Status
	24-week of chronic active treatment period.				
B7981007[b]	This is a Phase 2a, double-blind, randomized, placebo-controlled, parallel group study to evaluate the efficacy and safety of oral ritlecitinib and brepocitinib as induction and open label extension treatment in participants with moderate to severe Crohn's disease. The study has a 12-week of induction treatment period followed by a 52-week open label active treatment period.	Induction treatment period: brepocitinib 60 mg QD or placebo Extended open label treatment period: brepocitinib 30 mg QD	223 enrolled/ 255 planned/58 completed (as of 04 Feb 2022)	64 weeks	Ongoing
B7931028	This is a randomized, placebo-controlled, double-blinded study to evaluate the efficacy and safety of 3 doses of brepocitinib compared to placebo in patients with active systemic lupus erythematosus receiving concomitant standard of care therapy.	brepocitinib 15 mg/day oral brepocitinib 30 mg/day oral brepocitinib 45 mg/day oral Placebo	325 enrolled (350 planned) and 180 completed (as of 02 May 2022)	52 weeks	Ongoing
B7931030	This is a Phase 2b, randomized, double-blind, placebo-controlled, dose-range, parallel group study of brepocitinib to evaluate the efficacy of brepocitinib at 16 weeks and to evaluate the safety and efficacy	brepocitinib 60 mg QD, 30 mg QD, and 10 mg QD or placebo	219 enrolled 218 treated 203 completed Week 16 168 completed Week 52	60 mg and 30 mg QD 36 or 52 weeks, 10 mg QD 16 weeks	Completed

Table 1. Summary of Clinical Studies for Brepocitinib

Study Number	Study Design	Treatment Groups/Dose and Regimen	Number of Participants Enrolled/Completed	Treatment Duration	Status
	up to 1 year in participants with active psoriatic arthritis.				
B7981019[b]	This is a phase 2b randomized, double-blind, placebo-controlled, multicenter, dose-ranging study to evaluate the efficacy and safety profile of ritlecitinib with a partially blinded Extension Period to evaluate the efficacy and safety of ritlecitinib and brepocitinib in participants with active non-segmental vitiligo. The study has a 4-week induction, 20-week maintenance with ritlecitinib. After the 4-week of drug holiday, participants may receive brepocitinib during extended treatment period.	During Extension Period: brepocitinib 60 mg QD (4 weeks) to 30 mg QD (16 weeks)	Extension Group 1: 55 enrolled and 47 completed	20 weeks	Completed
C2501007	This is an ongoing Phase 2a, multicenter, randomized, double blind placebo-controlled, 16-week study evaluating the safety and efficacy of IRAK4 inhibitor PF-06650833, TYK2/JAK1 inhibitor brepocitinib, Tyk2 inhibitor PF-06826647 in adult with moderate to severe hidradenitis suppurativa.	PF-06650833 400 mg QD (16 weeks) brepocitinib 45 mg QD (16 weeks) PF-06826647 400 mg QD (16 weeks)	52 enrolled and 52 completed (as of 16 February 2022)	16 weeks	Ongoing

Table 1. Summary of Clinical Studies for Brepocitinib

Study Number	Study Design	Treatment Groups/Dose and Regimen	Number of Participants Enrolled/Completed	Treatment Duration	Status
Topical Administration					
Phase 1 Study					
B7931029	This is a Phase 1, single center, randomized, vehicle and white petrolatum-controlled, evaluator blinded study to assess the skin irritation potential with a range of concentrations of brepocitinib cream including vehicle and empty patch with white petrolatum under occlusive conditions in adult Japanese healthy participants.	brepocitinib cream 0% [vehicle], 0.1%, 0.3%, 1%, 3%, and empty patch with white petrolatum) were applied in all participants.	20 enrolled /20 completed	48 hrs (2 days)	Completed
Phase 2 Study					
B7931022	This is a Phase 2b, randomized, double blind, vehicle controlled, parallel group, dose ranging study to assess the efficacy, safety, tolerability and pharmacokinetics of brepocitinib cream applied once or twice daily for 6 weeks in participants with mild to moderate atopic dermatitis.	brepocitinib (topical) 0.1% QD 0.3% QD, BID 1% QD, BID 3% QD Vehicle QD, BID	292 enrolled and 240 completed	6 weeks	Completed
B7931023	This is a Phase 2b, randomized, double blind, vehicle controlled, parallel group, dose ranging study to assess efficacy, safety, tolerability and pharmacokinetics of brepocitinib	brepocitinib (topical) 0.1% QD 0.3% QD, BID 1% QD, BID 3% QD, BID Vehicle QD, BID	344 enrolled/treated 258 completed).	12 weeks	Completed

Table 1. Summary of Clinical Studies for Brepocitinib

Study Number	Study Design	Treatment Groups/Dose and Regimen	Number of Participants Enrolled/Completed	Treatment Duration	Status
	topical cream applied QD or BID for 12 weeks in participants with mild to moderate chronic plaque psoriasis				

AA = Alopecia areata; BID = Twice daily; CD = Crohn's disease; CO = Cross Over; HV = Healthy volunteers; IV = Intravenous; IR = Immediate release; MAD = multiple ascending dose; MR = Modified release; PK = Pharmacokinetic; PsO = Psoriasis; QD = Once daily; QTc = Interval corrected for heart rate; QW = Once weekly; SAD = Single ascending dose; SBE = Single blind extension; UC = Ulcerative colitis.

a. Participants who completed the 100 mg SAD and 100 mg MAD periods continued in the 50 mg BID period and received either placebo or brepocitinib twice daily according to original treatment assignment when randomized into the 100 mg SAD period.

b. Platform study that assessed efficacy and safety of ritlecitinib and a second investigational agent (brepocitinib) separately. Ritlecitinib is an orally bioavailable small molecule that irreversibly inhibits JAK3 and TEC family of kinases.

2.2.2.1. Safety Overview

Overall, PF-06700841 was generally safe and well tolerated in all clinical trials to date. There were no clinically meaningful findings in vital signs, electrocardiograms (ECG), suicidal behavior or ideation, or potential Hy's Law cases reported during these studies.

Refer to the current Investigator's Brochure (IB) for more details on the clinical safety information with PF-06700841.

2.2.2.1.1. Phase 1 Studies (B7931001 and B7931009)

The most commonly reported all causality treatment-emergent adverse events (TEAEs) across active healthy participants were serum creatinine increased (reported in 2 participants during the SAD period and 11 participants during the MAD period) without any changes in Cystatin C measured renal function. Neutropenia was reported in four participants during the MAD period, most of them were mild in severity except one with moderate, and none of them reached <500/mm^3 during the study. The most frequently observed laboratory abnormalities in healthy participants were elevated low density lipoprotein (LDL) and serum creatinine. There were no deaths or serious adverse events (SAEs) reported in the Phase 1 studies. One psoriasis participant receiving 100 mg QD of Study intervention (IP) in B7931001 experienced an adverse event of herpes zoster during the follow up period, after completing 28-day treatment.

2.2.2.1.2. Phase 2 Studies (B7931004 and B7931005)

A total of 189 psoriasis participants out of 212 enrolled in B7931004 were exposed to at least 1 dose of PF-06700841 during the study. The proportion of participants with all-causality TEAEs was comparable across all treatment arms but numerically higher in the active treatment arms (64.0% to 76.7%) than the placebo group (56.5%). The majority of participants in all treatment arms experienced mild or moderate all-causality TEAEs, and only 5.2% experienced severe all-causality TEAEs.

Overall, there were no dose dependent increases in the all-causality TEAEs. Most TEAEs in the Infection and Infestation class were mild to moderate except one participant who had two serious infections after taking a single dose of 60 mg PF-06700841 on Day 1. One participant in the 30 mg QD to 100 mg once a week (QW) group had squamous cell carcinoma of skin reported on Day 2 of treatment. One participant in the 30 to 10 mg group was confirmed to be pregnant after in the study 42 days and discontinued from the study with obstetrical ultrasound demonstrating fetal cleft lip.

Decreased reticulocytes, hemoglobin, and neutrophils were observed in the participants on active treatment during 4-week induction phase and returned toward baseline level during 8-week maintenance phase. Increases in serum creatinine from baseline were observed in all active treatment arms with no association of change in cystatin C based renal function measurement. Other commonly reported laboratory abnormalities were elevation of low density lipid (LDL) with no clinical meaningful changes in LDL/HDL ratio. There were no clinically meaningful changes from baseline observed in creatine kinase (CK) during the study. CK levels >10 × upper limit of normal (ULN) were observed in two participants

without adverse event. One moderate adverse event (AE) of CK-myoglobin increase was reported by one participant in the 30 to 10 mg QD group during the induction period, which was considered to be related to the IP by the investigator. No participant was discontinued from the study due to CK elevation.

In the study B7931005, 47 alopecia areata participants were exposed to at least one dose of PF-06700841. The most commonly reported TEAEs in the active treatment arm was in the Infections and Infestations system organ class (SOC) (51.1% in the IP vs 40.4% in the placebo). Other TEAEs were Gastrointestinal Disorders (23.4% in the IP vs 25.5% in the placebo). Most of those TEAEs were mild. There were two participants receiving PF-06700841 that experienced rhabdomyolysis after strenuously exercising during the study, which were not considered to be related to the IP by investigator assessment. Three participants experienced mild decreases in neutrophils, one participant had a mild reduction in platelets, and one participant a mild reduction in lymphocytes.

Please refer to the Investigator's Brochure for safety and efficacy findings in other brepocitinib Phase 1 and 2 studies.

2.2.2.2. Summary of PF-06700841 Pharmacokinetics in human

In Study B7931001, following single oral doses of 1 mg to 200 mg under fasted conditions, PF-06700841 was absorbed rapidly with median time to maximum (T_{max}) of 1 hour or less. Mean terminal half-life ($t_{½}$) ranged from 3.8 to 7.5 hours. In general, both the area under the plasma concentration time curve from time 0 extrapolated to infinity (AUC_{inf}) and maximum plasma concentration (C_{max}) appeared to increase proportionally with dose from 1 mg to 100 mg. Increases from 100 mg to 200 mg appear more than dose proportional, especially for AUC_{inf}.

On Day 10 of multiple dose administration, PF-06700841 was absorbed rapidly with median T_{max} of 1 to 1.5 hours or less across the entire range of doses, from a total daily dose of 10 mg up to 175 mg. Following attainment of C_{max}, the disposition of PF-06700841 was similar with that observed following single dose administration. Mean terminal half-life ($t_{½}$) ranged from 4.9 to 10.7 hours. Both area under the concentration time curve from time 0 to timeτ (AUC_t) and C_{max} generally appeared to increase proportionally with dose from 10 mg to 100 mg QD, with a trend towards greater than proportional increase from 100 mg to 175 mg QD. Accumulations, following once daily dosing, ranged from 1.1 to 1.4 for AUC_t and 0.8 to 1.1 for C_{max}. The urinary recovery of unchanged (Aeτ%) PF-06700841 on Day 10 across all doses ranged from 8.9% to 15.5%. Following multiple dose administration of PF-06700841 to participants with psoriasis for 28 days, the overall exposure observed was comparable to that in healthy participants at same dose level.

Refer to the current Investigators Brochure (IB) for more details on the PF-06700841 PK in humans.

2.2.2.3. Assessment of PF-06700841 Effect on QT

A formal QT study (B7931019) was recently completed. As the clinical study report (CSR) preparation is in progress, the results are considered draft and potentially subject to change.

Following a single dose of 200 mg PF-06700841, the maximum placebo-corrected QTcF change from baseline was observed at 3 hours post-dose with mean of 14.6 ms and 90% confidence interval (CI) of (12.4, 16.8 ms). Despite QTc increase seen, no clinically significant findings in ECG including QTc change from baseline >60 msec and QTc absolute value >500 msec were observed. As pre-defined in the protocol, concentration-QTcF (CQT) analysis was used to determine PF-06700841 effects on QT prolongation at relevant clinical exposures. The results from the CQT analysis suggested that the relationship between PF-06700841 concentration and QTcF change from baseline was most adequately described by an E_{max} model, in which the maximum QTcF change (E_{max}) was estimated to be 15.7 ms (90% CI: 13.2, 18.2 ms). The QTcF increase observed at a dose of 200 mg PF-06700841 appeared to reach maximum effect. Based on the model prediction, the mean change in QTcF at steady-state C_{max} of a 45 mg QD dose was 7.7 ms (90% CI: 6.5, 9.1 ms), which suggested that no positive QT effect is expected at PF-06700841 therapeutic doses up to 45 mg QD as the upper bound of two-sided 90% CI is <10 ms.[36] At PF-06700841 60 mg QD, the highest clinical dose being tested in Phase 2 studies, the mean QTcF increase at C_{max} was expected to be 8.8 ms (90%CI: 7.7, 10.2 ms) with the upper bound of 90% CI slightly exceeding 10 ms.

Refer to the current Investigator's Brochure (IB) for more details on the QT study design and results.

2.3. Benefit/Risk Assessment

PF-06700841, a TYK2/JAK1 inhibitor, is expected to offer therapeutic benefit in the treatment of SLE. Indeed, compared with other JAK inhibitors, inhibition of IL-12 and IL-23 signaling mediated by TYK2 inhibitory activity may provide a new and improved therapeutic benefit. Study participants could benefit from the potential achievement of disease control, improvement of signs and symptoms, as well as improvements in quality of life.

Based on the current clinical and nonclinical experience with brepocitinib and other information from other approved oral JAK inhibitors (eg, Xeljanz® (tofacitinib), Jakafi® (ruxolitinib), Olumiant® (baricitinib), and Rinvoq® (upadacitinib), the potential risks for brepocitinib include: (1) viral reactivation; (2) serious infection and opportunistic infections; (3) malignancy and lymphoproliferative disorders; (4) hematological abnormalities and other alterations in laboratory parameters: decreased neutrophil counts, change in lymphocyte counts, decreased hemoglobin level, decreased platelet counts, and elevation of hepatic transaminases; (5) alterations in the lipid profile; (6) increases in serum creatinine; (7) increases in creatine phosphokinase; (8) QT prolongation, (9) bone changes for oral route of administration in the administration in the <12 years of age group; (10) vaccinations: and (11) thromboembolism.

In the brepocitinib development program, there have been thromboembolic events reported in ongoing blinded clinical studies, where relationship to treatment is uncertain. Suspected thromboembolic events will be subject to review by an external blinded adjudication committee. In this study, B7931028, participants with any history of a pulmonary embolisms (unless these were caused by known antiphospholipid syndrome will be excluded from the protocol unless the participant has been adequately anticoagulated), exclusion criteria #5 and #6 have more detailed information.

Based on in vitro data, and the clinical DDI study of brepocitinib with itraconazole, moderate and strong cytochrome P450 3A (CYP3A) inducers, strong P-glycoprotein (P-gp) inhibitors, P-gp substrates and substrates of OCT2/MATE with a narrow therapeutic index, will be prohibited during oral PF-06700841 treatment periods in ongoing Phase 2 studies to minimize any potential significant drug interaction. Detailed information about in vitro assessments on drug metabolism, enzyme phenotype and drug-drug interaction can be found in the investigator's brochure.

In conclusion, the sponsor considers that the available information from the nonclinical and clinical studies completed to date with PF-06700841 provide a favorable benefit-risk profile and support its continued investigation as a potential treatment for SLE.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of PF-06700841 may be found in the current IB, which is the single reference safety document (SRSD) for this study.

3. OBJECTIVES, ESTIMANDS AND ENDPOINTS

Objectives:	**Endpoints:**	**Estimands:**
Primary:	**Primary:**	**Primary:**
• To evaluate the efficacy of 3 QD dose levels of PF-06700841 compared to placebo in participants with active SLE.	• Proportion of participants achieving the Systemic Lupus Erythematosus Responder Index (SRI) change of 4 (SRI-4) at Week 52.	E1: This composite estimand is defined as a population average treatment difference between PF-06700841 and placebo in the proportion of participants with active SLE who achieved the binary SRI-4 endpoint at Week 52 and did not discontinue treatment prior to Week 52. Treatment: PF-06700841, Placebo. Population: Participants with active SLE as defined by inclusion/exclusion criteria. Variable: SRI-4 at Week 52. A study participant will be considered as a non-responder for the visit of

Objectives:	Endpoints:	Estimands:
		interest after the occurrence of an intercurrent event. Intercurrent Events: Treatment discontinuation prior to Week 52 visit. Data post intercurrent events will be censored. Population level summary: treatment difference between PF-06700841 and placebo in proportions of responders using the composite endpoint.
Key Secondary:	**Key Secondary:**	**Key Secondary:**
• To evaluate the efficacy of 3 QD dose levels of PF-06700841 compared to placebo in participants with active SLE.	• Proportion of participants achieving the British Isles Lupus Assessment Group-Based Composite Lupus Assessment (BICLA) at Week 52.	E2: This composite estimand is defined as a population average treatment difference between PF-06700841 and placebo in the proportion of participants with active SLE who achieved the binary BICLA endpoint at Week 52 and did not discontinue treatment prior to Week 52. Treatment: PF-06700841, Placebo. Population: Participants with active SLE as defined by inclusion/exclusion criteria. Variable: BICLA at Week 52. A study participant will be considered as a non-responder for the visit of interest after the occurrence of an intercurrent event. Intercurrent Events: Treatment discontinuation prior to Week 52 visit. Data post intercurrent events will be censored. Population level summary: treatment difference between PF-06700841 and placebo in proportions of responders using the composite endpoint.

Objectives:	Endpoints:	Estimands:
Other Secondary:	**Other Secondary:**	Other Secondary:
• To assess attainment of low disease activity state of 3 QD dose levels of PF06700841 compared to placebo in participants with active SLE.	• Proportion of participants achieving the Lupus Low Disease Activity State (LLDAS) at Week 52.	E3: This composite estimand is defined as a population average treatment difference between PF-06700841 and placebo in the proportion of participants with active SLE achieving LLDAS at Week 52 and did not discontinue treatment prior to Week 52. Treatment: PF-06700841, Placebo. Population: Participants with active SLE as defined by inclusion/exclusion criteria. Variable: LLDAS at Week 52. A study participant will be considered as a non-responder for the visit of interest after the occurrence of an intercurrent event. Intercurrent Events: Treatment discontinuations prior to Week 52 visit. Data post intercurrent events will be censored. Population level summary: Treatment difference between PF06700841 and placebo in proportions of responders using the composite endpoint.
• To compare the corticosteroid use (prednisone or equivalent) in PF-06700841 treated participants relative to placebo.	• Proportion of participants achieving a reduction in prednisone (or equivalent) dose to ≤7.5 mg/day at Week 52 and sustained for 12 weeks prior to Week 52, in the subset of participants on prednisone >7.5 mg/day (or equivalent) at baseline.	There is no defined estimand for this endpoint.
• To evaluate the efficacy of PF-06700841 compared to placebo in participants with active SLE and with sustained reduction of oral corticosteroids.	• Proportion of participants achieving SRI-4 response with dose of prednisone (or equivalent) reduced to ≤7.5 mg/day and sustained for 12 weeks at Week 24 and Week 52, in the subset of participants	E4: This composite estimand is defined as a population average treatment difference between PF-06700841 and placebo in the proportion of participants who achieved the binary SRI-4 endpoint with sustained prednisone dose

Objectives:	Endpoints:	Estimands:
	with prednisone dose >7.5 mg/day (or equivalent) at baseline.	reduction to ⩽7.5 mg/day (or equivalent) for 12 weeks at Week 24 and Week 52, and did not discontinue treatment prior to Week 52, in the subset of participants with prednisone dose >7.5 mg/day (or equivalent) at baseline. Treatment: PF-06700841, Placebo. Population: Participants with active SLE as defined by inclusion/exclusion criteria and with prednisone dose >7.5 mg/day (or equivalent) at baseline. Variable: SRI-4 at Week 52 with sustained prednisone dose reduction ⩽7.5 mg/day (or equivalent) for 12 weeks at Week 24 and Week 52. Intercurrent Events: treatment discontinuations prior to Week 52 visit. Data post intercurrent events will be censored. Population level summary: treatment difference between PF-06700841 and placebo in proportions of responders using the composite endpoint.
• To evaluate the Cutaneous Lupus Erythematosus Disease Area and Severity Index activity (CLASI-A) score in the subset of participants with baseline CLASI-A score ≥10 in PF06700841 treated participants relative to placebo.	• Proportion of Participants with Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI-A) Total Activity Score ≥10 at Baseline with ≥50% Reduction in CLASI-A Total Activity Score	There is no defined estimand for this endpoint.

Objectives:	Endpoints:	Estimands:
• To evaluate the effect on fatigue of PF-06700841 treated participants relative to placebo.	• Change from baseline in the total scores of Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) at Week 52.	E5: This hypothetical estimand is defined as a population average treatment difference between PF-06700841 and placebo in the FACIT-F score at Week 52 as if none of the specified intercurrent events have occurred. Treatment: PF-06700841, Placebo. Population: Participants with active SLE as defined by inclusion/exclusion criteria. Variable: Change from baseline in total scores FACIT-F at Week 52. Intercurrent Events: Treatment discontinuations prior to Week 52 visit. Data post intercurrent events will be censored. Population level summary: The mean difference between each PF-06700841 group and placebo in the change from baseline in FACIT-F score at Week 52.
• To evaluate the effect on health-related quality of life of PF-06700841 treated participants relative to placebo.	• Change from baseline in the individual domain scores of the Lupus Quality of Life (LupusQoL) at Week 52.	E6: This hypothetical estimand is defined as a population average treatment difference versus placebo in the LupusQoL individual domain scores at Week 52 as if none of the specified intercurrent events have occurred. Treatment: PF-06700841, Placebo. Population: Participants with active SLE as defined by inclusion/exclusion criteria. Variable: change from baseline in the individual domain scores of LupusQoL at Week 52. Intercurrent Events: Treatment discontinuations prior to Week 52 visit. Data post intercurrent events will be censored.

Objectives:	Endpoints:	Estimands:
		Population level summary: The mean difference between each PF06700841 arm and placebo arm in the change from baseline in LupusQoL individual domain scores at Week 52.
• To assess time to first severe flare in PF-06700841 treated participants relative to placebo.	• Time to first severe flare as measured by the modified Safety of Estrogen in Lupus: National Assessment (SELENA)-Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) Flare Index (m-SSFI).	E7: This estimand is defined as a population average treatment hazard ratio between PF-06700841 and placebo, based on the Cox PH model, for the occurrence of the first severe flare event. However, the p-values will be derived using the log-rank test per protocol. Treatment: PF-06700841, Placebo. Population: Participants with active SLE as defined by inclusion/exclusion criteria. Variable: Time to first severe flare measured by modified SELENA-SLEDAI Flare Index. Intercurrent Events: Treatment discontinuations prior to Week 52 visit. Population level summary: Treatment differences between PF-06700841 doses and placebo in the hazard ratio of first severe flare occurrence.
• To evaluate the safety and tolerability of PF06700841 dose levels versus placebo.	• Incidence of treatment-emergent adverse events (AEs). • Incidence of serious AEs (SAEs) and AEs leading to discontinuation. • The incidence of clinically significant abnormalities in vital signs and ECGs. • The incidence of clinically significant abnormalities in clinical laboratory values.	There is no defined estimand for these endpoints and they will be analyzed using Pfizer data standards as applicable.

Objectives:	Endpoints:	Estimands:
CCI		

Objectives:	Endpoints:	Estimands:
CCI		

Objectives:	Endpoints:	Estimands:
[redacted]	[redacted]	
[redacted]	[redacted]	
[redacted]	[redacted]	

This study will use separate blinded adjudication committees consisting of independent external experts who will be responsible for the ongoing review and adjudication of the following efficacy and safety endpoints:

1. BILAG, SLEDAI and associated data.
2. Severe Flare.
3. Cardiovascular and thromboembolic events.
4. Malignancy.
5. Opportunistic infections.

In addition, a separate external data monitoring committee (E-DMC) will conduct unblinded reviews of all safety data on a regular basis throughout the duration of the trial (see the Data Monitoring Committee section). This E-DMC will make recommendations with regard to

continuing, stopping or altering the trial to a Sponsor Management Committee throughout the study.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 2b, double-blind, randomized, placebo controlled, parallel design, multicenter, dose-ranging study to assess the efficacy and safety of PF-06700841 in participants with active, moderate to severe generalized SLE. After a 7-week screening period, eligible participants will be randomly assigned to one of the four treatment groups (A-D in Table 2) in a 1:2:2:2 ratio such that participants will receive either 1 of three PF-06700841 QD dose levels (15 mg, 30 mg and 45 mg) or placebo every day for 52 weeks. All participants who are randomized should be encouraged to remain in the study to at least the end of the double-blind period to complete safety and efficacy assessments in order to reduce missing data as much as possible. It is expected that the only reasons for which a participant will withdraw from the study will be for withdrawal of consent or lost to follow-up.

Approximately 350 randomized participants (100 participants per treatment group except 50 participants for the PF-06700841 15 mg QD dose group) will participate in this study at approximately 185 investigative sites worldwide. Randomization will be stratified by screening disease severity (SLEDAI-2K total adjudicated score) and anti-dsDNA status. The purpose of the stratified randomization is to achieve balanced treatment groups in these stratification factors.

Table 2. Treatment Group

Treatment Group	Treatment Group Description	Participant Size
A	PF-06700841 15 mg QD	50
B	PF-06700841 30 mg QD	100
C	PF-06700841 45 mg QD	100
D	Placebo	100

For this study, the study intervention is PF-06700841. Blinded PF-06700841 and its matched placebo will be provided as tablets for oral administration. Participants will participate in this study for approximately up to 63 weeks. This includes up to a 7-week screening period, a 52-week treatment period, and a 4-week follow-up period.

4.2. Scientific Rationale for Study Design

The primary endpoint of the study is the proportion of participants achieving Systemic Lupus Erythematosus Responder Index (SRI)-4 at Week 52. The SRI is a disease activity index developed for use in systemic lupus erythematosus (SLE) clinical trials in collaboration with the FDA. It detects both improvement and worsening in the same and different organ systems, and it was validated in a long term clinical trial and is compatible with regulatory guidance from both the European Medicines Agency (EMA) and FDA. The SRI is a composite score utilizing the SLEDAI to assess improvement, the BILAG to assess

significant worsening or flares, and the physician global assessment (PhGA) to assess whether or not there has been any significant deterioration in the participant's overall condition. The 4-point improvement in the SRI has been shown to be a clinically meaningful change in large, randomized control studies.[12] Therefore, the SRI-4 was chosen for the primary efficacy assessment in this study. Based on published data 52 weeks of treatment is appropriate to establish efficacy of a new compound in SLE.

The key secondary endpoint of the study is the proportion of participants achieving BICLA response at Week 52. BICLA is a composite endpoint requiring that the following criteria are met: improvement in the BILAG-2004 score (improvement in all BILAG-2004 grade A scores at study entry to grades B, C, or D at follow-up; improvement in all BILAG-2004 grade B scores at study entry to grades C or D at follow-up); no worsening in the BILAG-2004 score (no new BILAG-2004 grade A scores; no more than 1 new BILAG-2004 grade B score); no increase compared to baseline in the SLEDAI-2K total score; no worsening compared to baseline (10-mm increase on a 100-mm visual analog scale) in the physician's global assessment of disease activity; and no disallowed prohibited changes in concomitant medications (corticosteroids, immunomodulators or antimalarials). BICLA was developed as an alternative method to the SRI-4 of detecting clinical activity in SLE and has been used to support the approval of anifrolumab as well as being used in other SLE investigational programs. [13] Compared to the SRI-4 which demonstrated improvement in disease activity as an absence of activity in an organ system, BICLA requires a decrease in disease activity in an affected organ system but also requires that all organ systems that are affected have demonstrated improvement. Additionally SRI considers disease activity to be reduced based on normalization of serological markers (CCI [redacted]) while BICLA (based on BILAG scoring) does not consider reduction in serologic markers as evidence of improvement.

In prior versions of this protocol, time to severe flare had been proposed as a major secondary endpoint, however Pfizer considers that it is scientifically justified to change the key secondary endpoint to BICLA in this study for 3 reasons. First, in prior versions of this protocol, the incidence of severe flare in a moderate to severe lupus population was considered to be 25% per year. This flare rate is an overestimation of what has been seen in multiple SLE studies conducted in patients with moderate to severe disease, where the severe flare rate generally approximates 5-10% annually. Based on this information, the major secondary endpoint of severe flare was estimated to be underpowered. Second, although there is fairly good concordance between SRI and BICLA, there is occasionally a difference in the reduction in disease activity assessed by these methods within the same study, as illustrated by the discrepancy observed in the 2 anifrolumab phase 2 studies. Elevating BICLA to a secondary endpoint recognizes the importance of looking for consistency between both outcome measures in the current trial. Finally, BICLA response, similar to SRI response, has been shown to correlated with general improvement in patient physical and mental health, demonstrating that BICLA response is clinically meaningful to both patients and health care providers. [14]

The presence of dsDNA antibodies is associated with a higher likelihood of developing renal involvement and is predictive of overall disease flare. Stratification by dsDNA (±) is to

ensure that participants who have a higher risk of developing renal disease or who are actively flaring at the time of study entry are evenly distributed cross treatment arms.

Adjudicated screening SLEDAI-2K scores differentiate participants by disease activity at the time of study entry. In some studies, participants with higher disease activity at study entry were more likely to demonstrate a benefit from a study intervention and more likely to have adverse events than participants with lower baseline disease activity. Stratification by adjudicated screening SLEDAI scores is to limit the possible confounding effects of disease activity on efficacy and safety outcomes.

It is desirable to have participants treated with corticosteroids (CS) on a dose as low as possible to minimize side effects/long term damage associated with administration of CS. A low dose of CS has been associated with a lower risk of sustaining long-term damage, hence the specification that participants should be tapered to a dose ≤7.5 mg/day of prednisone (or equivalent).

Approximately 350 participants will be enrolled in the study with 100 participants per treatment group with the exception of the PF-06700841 15 mg QD dose group, which will enroll approximately 50 participants. Based on evidence from other studies, the 15 mg dose does not inhibit inflammatory cytokine effects to the same extent as the proposed 30 mg and 45 mg doses and is likely to be a subtherapeutic dose. Because SLE is a severe debilitating disease and participants with unabated disease activity may accrue end-organ damage over time, it is decided to reduce the number of participants for the 15 mg QD dose arm.

It is estimated that 5 to 10% of study participants may be taking concomitant mycophenolate mofetil (MMF) at study entry. Target trough levels for therapeutic effect and levels at which risk of adverse effects of MMF are more likely to occur have been characterized and therapeutic drug monitoring to ascertain exposures within the defined target ranges can be obtained easily at central laboratories.[13] Glucuronidation is the primary metabolic pathway for MMF. Corticosteroids are potent inducers of the glucuronidation pathway. Therefore, as participants taper corticosteroids, the rate of MMF metabolism may decrease and MMF levels may rise by as much as 30-35%.[16] Since participants in this study are required to taper corticosteroids (when appropriate), measurement of the active metabolite of MMF, mycophenolic acid (MPA), prior to and following corticosteroid tapering will be evaluated in this study.

Trough levels of MMF will be measured at Day 1 and Week 40 at the central laboratory. The participant should refrain from taking their MMF dose immediately prior to these clinic visits and record the time of their last MMF dose. Should participants develop adverse events suggestive of high MMF levels (decreases in cellular blood counts, serious infections) additional safety monitoring of MPA levels may be requested.

CCI [redacted]

CCI

[redacted]

4.3. Justification for Doses

This Phase 2b, dose-ranging study will assess three PF-06700841 doses (15 mg, 30 mg and 45 mg) administered once a day (QD) for 52 weeks in comparison to placebo.

Doses selected for this Phase 2 study are based on the safety and efficacy observed to date with PF-06700841 in healthy participants (B7931001) and participants with active psoriasis (B7931001 and B7931004) and alopecia areata (B7931005). The overall safety profile to date with PF-06700841 has been acceptable with doses up to 60 mg QD for 4 weeks and 30 mg QD for up to 20 weeks in completed studies. Ongoing studies in inflammatory bowel disease (IBD) are assessing the 60 mg QD dose for up to 12 weeks, and an extended period at 30 mg QD for up to 52 weeks. The highest dose level selected for this study is 45 mg QD, lower than the top dose of 60 mg in the ongoing Phase 2 studies in IBD to reduce any potential safety risk, particularly associated with a population of SLE participants compared to the other populations currently being assessed in Phase 2. SLE participants are known to have a greater overall risk for severe infections due to underlying immune defects as well as to the common use of immunosuppressants, including corticosteroids.

Based on the preliminary population PK analysis with combined data from studies B7931001 in healthy participants and B7931004 in participants with moderate to severe psoriasis, the expected median steady state exposures (AUC_{24}) following 15, 30 and 45 mg QD are 677, 1360 and 2030 ng.h/mL, respectively in a patient population. As a result, the exposure of PF-06700841 (AUC_{24}) at 45 mg QD in this study are expected to be 56x and 8.6x below the AUC_{24} at the no observed adverse effect levels (NOAELs) observed in the 6-month rat (45 mg/kg/day) and 9-month monkey (20 mg/kg/day) studies, respectively. The pharmacological activity of PF-06700841 was assessed by reduction of high sensitivity C-reactive protein (hsCRP) in participants with moderate to severe psoriasis (B7931004). In study B7931004, the median reduction (percent change from baseline) of hsCRP observed at week 4 were approximately 61% and 76% with PF-06700841 30 and 60 mg QD treatment, respectively. Study B7931004 also showed that PF-06700841 reached maximal effect on hsCRP within approximately 2 weeks after start of treatment and remained constant throughout the 12-week treatment period. Previous studies suggested that the baseline levels of hsCRP in participants with moderate to severe psoriasis and active SLE were comparable (median of ~2.9 mg/dL in both participant populations). As a result, the median hsCRP reduction with PF-06700841 45 mg daily dose up to 52 weeks would expect to be between 61% to 76% in participants with active SLE in the current study.

Based on the preliminary exposure response analysis with Psoriasis Area and Severity Index (PASI) in participants with moderate to severe psoriasis in B7931004, PF-06700841 15 mg is estimated to provide a limited therapeutic effect in psoriasis compared to the 30 or 60 mg dose levels. A dose of 15 mg is included in this study to support characterization of the minimum effect of PF-06700841 treatment in participants with active SLE.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all periods of the study including the last visit.

The end of the study is defined as the date of the last visit of the last participant in the trial globally.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age and Sex:

1. Male or female participants between the ages of 18 (or the minimum country-specific age of consent if >18) and 75 years, inclusive, at the time of signing the informed consent document (ICD).

    - Refer to Appendix 4 for reproductive and contraceptive criteria for ~~male and~~ female participants.

Type of Participant and Disease Characteristics:

2. Participants who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures. All participants should be willing to remain in the study to the end of the double-blind period for safety and efficacy assessments, whether or not study intervention is discontinued.

3. Have a clinical diagnosis of SLE according to the 1997 update on the 1982 revised American College of Rheumatology (ACR) Criteria for the Classification of SLE see Appendix 8 OR meet at least 4 of the 2012 Systemic Lupus International

Collaborating Clinics (SLICC) classification criteria see Appendix 9, including at least 1 clinical criterion and 1 immunologic criterion, at least 6 months prior to dosing of study agent.

4. Have serologically positive SLE at the screening visit based on 1 of the following test results from the central laboratory during the screening period:

   - ANA titer ≥1:80, or
   - Positive anti-dsDNA.

   Note: The ANA and/or anti-double-stranded DNA (anti-dsDNA) measurement may be repeated once at the central laboratory within approximately 2 weeks of the initial value, and the value resulting from repeat testing may be accepted for enrollment eligibility if it meets the eligibility criterion.

5. All participants must be currently receiving EITHER a stable dose of an immunosuppressant [methotrexate (MTX), azathioprine (AZA)/6-mercaptopurine (6-MP), leflunomide, mizoribine, mycophenolate/mycophenolic acid (MMF)] with or without antimalarials and/or corticosteroids, OR anti-malarials (hydroxychloroquine or chloroquine) in combination with corticosteroids. Antimalarial or steroid monotherapy is not permitted. If receiving antimalarials in combination with corticosteroids, the minimum dose of corticosteroids permitted as part of this combination is 5 mg prednisone daily or an equivalent dose and steroids must have been started at least 8 weeks prior to Day 1. Participants may not be receiving combinations of 2 or more immunosuppressants.

   Note: Stable dose is defined as no new therapy or change in standard-of-care therapies as above within 12 weeks of Day 1 for immunosuppressives or within 2 weeks of Day 1 for corticosteroids, however brief fluctuations in therapy for toxicity are permitted (eg, holding a dose (≤7 days) or temporary reduction in corticosteroids of less than 3 mg/day. See Appendix 13 for allowable stable doses.

6. Have active disease defined as:

   - SLEDAI-2K score of ≥8 points at screening and at randomization, and “Clinical” SLEDAI-2K score of ≥6 points at both screening and at randomization.
   - NOTE: "Clinical" SLEDAI-2K score (See Appendix 11) is the SLEDAI-2K score without the inclusion of points attributable to any urine or laboratory results including immunologic measures.

a. For inclusion in the study, the Clinical SLEDAI-2K calculation for entry will exclude points for:

1. **Lupus Headache**,

2. **Skin disease** involving Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) Activity Erythema scores <2,

3. **Arthritis** scores must involve a minimum of 3 joints, both swollen and tender,

4. **Mucosal ulcers** which may have occurred within the previous 30 days but are not noted on exam and CLASI at the time of screening.

b. On the day of randomization, a minimum of 3 joints that are both swollen and tender is required if SLEDAI Arthritis is marked PRESENT. The site should check the joint exam prior to randomization to ensure there are ≥3 joints that are both tender and swollen to avoid a protocol deviation.

c. For SCREENING and ONSTUDY visits, SLEDAI arthritis SHOULD be scored per the glossary definitions if there are ≥2 joints with both swelling and tenderness noted on the joint assessment. However, the 4 points due to arthritis will not be counted towards the total and clinical SLEDAI-2K scores required for eligibility unless ≥3 joints are both swollen and tender are present. The adjudicators will review the joint exam to determine if there are enough swollen and tender joints present at screening to meet eligibility. Similarly, the SLEDAI rash, alopecia and mucosal ulcers SHOULD be scored if present as per usual SLEDAI glossary, at all visits (even if the CLASI score is not ≥2). The adjudicators will review the CLASI at screening to determine if the patient has enough mucocutaneous disease activity for eligibility.

- **AND**

BILAG Level A disease in ≥1 organ system (except renal or central nervous system [CNS]) or BILAG B disease in ≥2 organ systems if no level A disease is present at screening. At least one A or one B level body system grade must be in the Mucocutaneous or Musculoskeletal systems.

a. For eligibility at screening and at randomization, a Mucocutaneous B due to BILAG #6, mild skin eruption, must have a CLASI erythema activity score of >=2.

b. For eligibility at screening and at randomization, a Musculoskeletal B due to #42, moderate arthritis, must have ≥3 swollen, tender joints and a qualifying Musculoskeletal A score due to #41, severe arthritis, must show ≥6 tender, swollen joints on the screening joint count. (see Appendix 12).

c. For SCREENING and ONSTUDY visits, BILAG moderate arthritis SHOULD be scored per the usual BILAG convention if ≥1 joint with swelling and tenderness is present on the joint assessment, (BILAG is scored for arthritis but patient does not meet qualifying screening activity required for musculoskeletal BILAG B if <3 swollen tender joints are present). The adjudicators will review the joint exam to determine if there are enough swollen and tender joints present at screening to meet eligibility. Similarly, BILAG mucocutaneous scoring should be done as per usual BILAG convention at all visits, but the adjudicators with review CLASI scoring to ensure there is enough mucocutaneous activity at screening for eligibility.

   Note: Data from the SLICC, SLEDAI and BILAG evaluations will be reviewed by the Sponsor and/or the Sponsor-selected independent reviewer(s). For participants to receive their first administration of study agent, approval must be received by the Sponsor and/or Sponsor-selected independent reviewers.

Weight:

7. Participants weighing greater than 35 kg and less than 130 kg and with a BMI of <40.

Informed Consent:

8. Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Active, severe lupus nephritis (World Health Organization Class III, IV) that requires or may require treatment with cytotoxic agents or high-dose CS are excluded. Participants with prior, controlled, renal disease that has been treated with an ACE or ARB inhibitor and immunosuppressive therapy (cyclophosphamide or mycophenolate mofetil) with serum creatinine ≤2× upper limit of normal (ULN) and either residual proteinuria up to ≤3 g/day or a urine protein/creatinine ratio (UPCR) of ≤3 mg/mg or 339 mg/mmol are allowed if prior treatment has been demonstrated. Control of renal disease must be documented with at least 2 measurements of proteinuria or UPCR over the past 6 months. Participants with pure Type V membranous nephropathy must be biopsy confirmed if immunosuppressive therapy was not administered. Pfizer clinical and adjudicators will make the final decision regarding this exclusion criteria. If at all possible, biopsy results confirming the diagnosis should be available in the participant chart.

Note: The lab measurements related to lupus nephritis may be repeated once within approximately 2 weeks of the initial values, and the values resulting from repeat testing may be accepted for enrollment eligibility if they meet the eligibility criteria.

2. Have severe active central nervous system (CNS) lupus (eg, BILAG A neurological disease and/or active, poorly controlled seizure disorder, acute confusional state, myelitis, stroke or stroke syndrome, cerebellar ataxia or dementia related to SLE, active psychosis, organic brain syndrome, cerebrovascular accident [CVA], cerebritis or CNS vasculitis) requiring therapeutic intervention within 60 days of Day 1. Participants with BILAG B level neurologic disease are not excluded as long as they meet all other qualifying criteria for the study.

3. Have cancer or a history of cancer within 5 years of screening (other than adequately resected cutaneous basal cell, squamous cell carcinoma, or carcinoma in situ of the uterine cervix with no evidence of recurrence within the previous 3 years). If a participant is followed for a history of cancer that is considered to be treated and cured, a note from the oncologist or specialist following the participant for recurrence noting they are aware of and agree with potential participation should be available in the source document. Potential participants who have an unacceptably high risk of tumor recurrence may be rejected by the Sponsor or their delegate. Additionally, the participant is required to comply with recommended follow up testing with their specialist of record while participating in the study.

4. Have a history of a major organ transplant (eg, heart, lung, kidney, liver) or hematopoietic stem cell/marrow transplant or total lymphoid irradiation.

5. The following is exclusionary;

   - Any history of thrombosis (venous or arterial) or cerebrovascular ischemic event (stroke or transient ischemic attack [TIA]) within the last 6 months.

   - A history of an ischemic cerebrovascular event (stroke, TIA) within the past 12 months unless these were caused by known antiphospholipid syndrome and the participant has been adequately anticoagulated (and will continue on anticoagulation per guidelines) according to current guidelines for at least 6 months without a recurrence of any thrombotic event.

   - Any history of a pulmonary embolus, unless these were caused by known antiphospholipid syndrome and the participant has been adequately anticoagulated (and will continue on anticoagulation per guidelines) according to current guidelines for at least 6 months without a recurrence of any thrombotic event.

     Note: Any participant being treated for antiphospholipid syndrome or anticardiolipin antibodies must be adequately anticoagulated according to current local guidelines. Women with a history of antiphospholipid syndrome with prior obstetrical loss but with no prior thrombosis do not require anticoagulation for

eligibility. Sites should make every effort to obtain a medical history of at least 3 years duration to document that there have been no thrombotic events or an obstetrical history of repeat fetal losses. In the absence of this medical history information, a hematology consult may be required if antiphospholipid screening tests are positive.

6. Have acute coronary syndrome (eg, myocardial infarction, unstable angina pectoris), known pulmonary arterial hypertension or any history of significant cerebrovascular disease within 24 weeks of screening. If a previous MI (recorded on the ECG report as an 'old MI') of indeterminate age is present on the ECG and there is no known cardiac history, a cardiology consult may be requested.

7. Have preexisting demyelinating disorder such as multiple sclerosis, or other severe neurological deficits.

8. Have any autoimmune or inflammatory disease with mucocutaneous, musculoskeletal, renal, CNS, hematologic, or vascular manifestations that would interfere with interpretation of test results or clinical assessments. This would include but is not limited to rheumatoid arthritis, 'rhupus', overlap syndromes, psoriasis/psoriatic arthritis, eczema, inflammatory bowel disease, any other vasculitis such as ANCA vasculitis, mixed connective tissue disease. A decision about the suitability of the participant for enrollment will be made by the independent disease activity adjudicators.

9. A history of additional risk factors for torsade de pointes (TdP) (eg, heart failure [New York Heart Association status of class III or IV], hypokalemia, family history of Long QT Syndrome).

10. A participant with any condition possibly affecting oral drug absorption, eg, gastrectomy, clinically significant diabetic gastroenteropathy, or certain types of bariatric surgery such as gastric bypass. Procedures such as gastric banding or gastric sleeve procedure without a bypass surgery, that simply divide the stomach into separate chambers, are NOT exclusionary.

11. Have active fibromyalgia/myofascial/chronic pain that, in the investigator's opinion, would make it difficult to appropriately assess SLE activity for the purposes of this study.

12. Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation (defined in Section 8.2.10) or behavior or laboratory abnormality that may increase the risk associated with study participation or study intervention administration or may interfere with the interpretation of study results and, in the judgment of the investigator or sponsor, would make the participant inappropriate for entry into this study. Prior splenectomy is prohibited.

Prior/Concurrent Clinical Study Experience:

13. Participation in other interventional studies within 12 weeks or 5 half-lives, if known, whichever is longer, prior to study entry and/or during study participation. Participation in any observational studies during study participation which would require a participant to provide any study specific information including but not limited to the following: sponsor name of the study in which they are participating, the name of the study intervention, the indication being studied.

Note any investigational or experimental therapy or procedure for SLE must be discontinued for at least 12 weeks prior to Day 1.

Prior/Concomitant Therapy.

Please refer to Appendix 13: List of Prohibited and Permitted Concomitant Medications.

14. The following use of corticosteroids is exclusionary;

- Receiving >20 mg/ day of prednisone or equivalent (see Appendix 14) or have adjusted the dose of corticosteroids (with the exception of brief fluctuations; see Inclusion Criteria #5) within 2 weeks of Day 1.

- Have received oral or parenteral [intravenous (IV) or intramuscular (IM)] corticosteroids at doses >40-mg per day of prednisone (or equivalent see Appendix 14) within 8 weeks of Day 1, or are anticipated to require parenteral injection of corticosteroids during the study.

- Have had a joint injected with intra-articular corticosteroids or hyaluronic acid within 4 weeks of Day 1.

- Have received topical corticosteroids, (except for, corticosteroids that are inactivated by first- pass in the liver [for example mometasone, fluticasone, budesonide or beclomethasone]) other than stable doses of class 6 (mild, such as desonide) or class 7 (least potent, such as hydrocortisone), within 4 weeks of Day 1.

15. Have started or stopped treatment or adjusted the dose of antimalarials within 12 weeks of Day 1.

16. Have started or stopped treatment with an accepted standard of care immunosuppressant (azathioprine/6-mercaptopurine, methotrexate, leflunomide, mizoribine or mycophenolate) within 12 weeks of Day 1. The dose of immunosuppressants should be as stable as possible within 12 weeks of Day 1 and should only be changed for toxicity documented in the source document. No changes in the dose of immunosuppressants are acceptable within 4 weeks of Day 1. Please see Appendix 13 for acceptable doses.

17. Additional immunomodulatory drug exclusions see Appendix 13 for details:

    - No systemic calcineurin inhibitors within 12 weeks of Day 1. Topical creams and ointments must be discontinued within 4 weeks of Day 1. Optic calcineurin (eye drops) are permitted on study.
    - No cyclophosphamide or chlorambucil use within 24 weeks of Day 1.
    - No anti-tumor necrosis factor (anti-TNF) inhibitors (adalimumab, etanercept, infliximab, certolizumab, golimumab), anakinra or belimumab within 12 weeks of Day 1.
    - No tocilizumab, ustekinumab, or abatacept within 24 weeks of Day 1.
    - No rituximab, or investigational B cell targeted therapies within 24 weeks of Day 1.
    - No investigational or approved biologic therapies within 12 weeks of Day 1.
    - No history of hydroxyurea treatment.
    - No history of prior treatment with any lymphoid depleting therapy (Campath, anti-CD3, Lemtrada, alemtuzumab, total lymphoid irradiation).
    - No sulfasalazine within 12 weeks of Day 1.

18. Have received plasmapheresis within 12 weeks of screening or intravenous immunoglobulin (IVIg) within 24 weeks of screening.

19. Any prior treatment with an approved or investigational JAK inhibitor (ie, tofacitinib, baricitinib, filgotinib, upadacitinib)

20. Treatment with any non-biologic investigational drug(s) including non-JAK kinase inhibitors, within 12 weeks of Day 1 or within 5 half-lives, if known, whichever is longer, and/or during study participation.

21. Has been exposed to a live vaccine within 8 weeks of Day 1 or are expected to need/receive a live vaccine during the course of the study (with the exception of herpes zoster vaccination- refer to EC #27 below). Participants should not have received a Bacillus Calmette-Guérin (BCG) vaccination within 52 weeks of randomization.

22. Use of concomitant medications known to prolong the QT interval (see Appendix 13).

Please note that Appendix 13 does not provide an exhaustive list of such medications. If you have concerns that a concomitant medication may present a risk of QT prolongation please discuss this directly with the Pfizer Clinical Team.

23. Require concomitant treatment with prohibited concomitant medications (see Appendix 13).

24. Use of filgrastim, pegfilgrastim, erythropoietin or other bone marrow stimulants to improve cell counts within 12-weeks of screening.

Infection

25. Active bacterial, viral, fungal, mycobacterial or other infections (including but not limited to tuberculosis [TB] and atypical mycobacterial disease, allergic aspergillosis or cavitary lung lesions or granulomatous disease on chest x-ray). History of recurrent bacterial, viral, fungal, mycobacterial or other infections (including but not limited to TB and atypical mycobacterial disease, granulomatous disease on chest x-ray) that would substantially increase the risk to the participant if he or she participates in the study.

26. Have a history of any lymphoproliferative disorder such as Epstein-Barr virus (EBV) related lymphoproliferative disorder, history of lymphoma, leukemia, or signs and symptoms suggestive of lymphoproliferative disease, including lymphadenopathy or splenomegaly (other than primarily due to SLE).

27. Have a history (single episode) of disseminated herpes zoster or disseminated herpes simplex, or recurrent (more than 1 episode within last 5 years) localized, dermatomal herpes zoster.

    Note: All participants who have not received the herpes zoster vaccine at screening will be encouraged (per local guidelines) to do so prior to randomization; vaccination must occur >4 weeks prior to randomization and start of study intervention. Participants will be excluded if they were exposed to live herpes zoster vaccination (Zostavax®, Merck) within 4 weeks of planned randomization; the recombinant adjuvant herpes zoster vaccine (Shingrix®, GSK) is permitted prior to and on study.

28. Known history of human immunodeficiency virus (HIV) based on documented history with positive test, or positive HIV test at screening.

    Note: a documented negative HIV test within 12 weeks prior to screening is acceptable and does not need to be repeated.

29. Have evidence of clinically significant active or latent infection of hepatitis B or hepatitis C based on screening tests (see Section 8.2.5).

30. Have clinically relevant finding on a chest radiograph (or other diagnostic imaging study such as computed tomography [CT] or magnetic resonance imaging [MRI]with

pre-approval from Pfizer Clinical) such as the presence of TB, general infection, heart failure or malignancy. Findings due to SLE activity do not require the participant to be excluded.

31. Have required management of acute or chronic infections as follows:

    - Currently on any suppressive therapy for any chronic infection (such as pneumocystis, cytomegalovirus [CMV], and atypical mycobacteria, herpes simplex) that, in the opinion of the investigator and sponsor, would place the participant at risk for reactivation. Participants receiving prophylactic therapy for prior outbreaks of herpes simplex virus may be enrolled with the expectation that this treatment will continue for the duration of the study. Participants who have no prior pneumocystis carinii infections may be allowed to enroll if they are receiving prophylaxis for pneumocystis if they obtain permission from Pfizer Clinical.

    - Hospitalization for treatment of serious infections within 60 days of Day 1.

    - Use of IV or IM antibacterials, antivirals, antifungals, or anti-parasitic agents within 60 days of Day 1. Substitution of IM agents for oral agents because of gastrointestinal (GI) intolerance may be acceptable, as long as it does not otherwise meet the criteria for a serious infection (requires hospitalization or use of other IV antibiotics).

    - Use of oral antibiotics to treat an active infection within 14 days of Day 1.

32. Have evidence of untreated or inadequately treated latent *Mycobacterium tuberculosis* (TB) infection as evidenced by <u>any</u> of the following:

    a. Currently have active TB

    b. Have a past history of active TB.

    c. Have history of latent TB and completed latent TB treatment prior to screening.

    If a participant has been diagnosed with latent TB prior to screening and is currently receiving treatment for latent TB during the screening period, the participant may be eligible for the study ONLY if the participant is seen by a pulmonary or infectious disease consultant and confirmed to have no findings of active TB AND if the consultant agrees that the participant's latent TB can be adequately treated with INH and B6. The consultant will need to check the incidence of multidrug resistant TB locally to ensure that INH and B6 treatment is in the participant's best interest if the participant randomizes into the study. Documentation of when the participant's treatment began and how latent TB was diagnosed must be available in the source document. These participants should be discussed with Pfizer clinical prior to screening. The participant must agree to complete a course of INH and B6 during the study.

An interferon gamma release assay (IGRA) test performed at or within the 12 weeks prior to Day 1 is required; a negative test or immediate commencement of treatment for latent TB with INH/vitamin B6 is also required for eligibility. The following are acceptable IGRA assays:

- T-SPOT® TB test;
- QuantiFERON® - TB Gold In-Tube test (QFT-GIT);
- QuantiFERON® - TB Gold test (QFT-G);
- QuantiFERON® - TB Gold Plus test (QFT-G Plus).

NOTE: A Mantoux skin test is not an acceptable test in this study and an IGRA must be performed. An initial IGRA should be performed at the central laboratory so that at least one set of results will be available in the Pfizer database. If another test is required, it may be performed locally, and a T-SPOT® TB test (if available) would be preferred to another QuantiFERON® test.

If the results of the IGRA are:

- Negative, enrollment may proceed.
- Indeterminate, the test must be repeated; a different IGRA test should performed (eg, T-SPOT®, if available) for the repeat test. If the repeat IGRA test result is:
    - Indeterminant, participants may be enrolled after consultation with an infectious disease and/or pulmonary specialist indicating active TB is not present, the English translation of the specialist report must be provided to the Sponsor and the Sponsor must agree with enrollment.
- Positive: the participant must be seen by an infectious disease and/or pulmonary specialist who will review any radiographic and diagnostic studies (including chest CT scan, chest x-rays or chest MRIs), the interferon gamma release assay results, participant history, and any other pertinent information to determine whether the participant has latent or active TB, or any other active, chronic or latent disease in the chest including infection other than TB, malignancy or other clinically significant cardiovascular and/or pulmonary disease;

If the infectious disease and/or pulmonary specialist diagnoses:

- Active TB or other active or uncontrolled clinically significant pulmonary disease, the participant is not eligible.
- Latent TB, the infectious disease and/or pulmonary specialist will recommend a treatment for latent TB aligned with the participant's best interest and local

standard of care. The local incidence of multi-drug resistant TB should be considered in determining how the participant is treated.

- Once the infectious disease and/or pulmonary specialist report has been obtained, the sponsor must receive an English translation of the specialist report and the local incidence rate of multi-drug resistant TB for review. If the specialist recommends INH and vitamin B6 therapy as adequate treatment for latent TB for the prospective participant, the participant must agree to continue therapy during the study to completion of the course of treatment for latent TB per the local guidelines. If the participant agrees and is compliant, the participant may be eligible for the study if all other eligibility criteria are met.

- The only therapy acceptable for on-study treatment of latent TB is isoniazid (INH) plus vitamin B6.

Diagnostic Assessments:

33. Have a Chest radiograph (ie, chest x-ray or other appropriate diagnostic imaging such as computed tomography or MRI) taken at screening with changes suggestive of any active infection, prior untreated TB, heart failure, suspected malignancy, or any other clinically significant disease in the chest. A CT scan or chest x-ray performed within 12 weeks of expected randomization may be used.

    If a chest CT shows any abnormalities (nodules, infiltrates, scarring, stranding, etc), these must be documented to be stable compared to a prior chest radiograph obtained at least 12 months previously.

34. Screening 12 lead electrocardiogram (ECG) that demonstrates clinically significant abnormalities requiring treatment (eg, acute myocardial infarction, serious tachy or bradyarrhythmias) or that are indicative of serious underlying heart disease (eg, cardiomyopathy, major congenital heart disease, low voltage in all leads, Wolff Parkinson White syndrome) and other clinically relevant abnormalities which may affect participant safety or interpretation of study results. Specifically, participant with screening Fredericia corrected QT interval (QTcF) >450 milliseconds (msec) should be excluded. If QTcF exceeds 450 msec, the ECG should be repeated two more times and the average of the three QTcF should be used to determine the participant eligibility.

35. Participants with ANY of the following abnormalities in clinical laboratory tests at Screening, as assessed by the study specific laboratory and confirmed by a single repeat, if deemed necessary:

    - IgG levels below lower limits of normal;

    - Hemoglobin <9 g/dL (<90 g/L);

- Absolute neutrophil count (ANC) <1.2 x 10^9/L (<1200 mm^3);
- Absolute lymphocyte count (ALC) of <0.75 x 10^9/L (<750/mm^3); Note: Participants may be enrolled with an ALC <0.75 x 10^9/L but ≥0.5 x 10^9/L if the ALC is considered by the investigator to be a result of the underlying SLE disease or concomitant medications;
- Platelet count <75 x 10^9/L (<75,000/mm^3);
- Serum cystatin C-based estimated glomerular filtration rate (eGFR) <50 mL/min/1.73 m^2 based on the age appropriate calculation;
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) values ≥2 times the ULN;
- Total bilirubin ≥1.5 times the ULN; participants with a history of Gilbert's syndrome may have a direct bilirubin measured and would be eligible for this study provided the direct bilirubin is < ULN;
- Creatine kinase (CK) >3 times the ULN and positive urine myoglobin.

Note: Screening laboratory tests with abnormal results may be repeated once to confirm abnormal results within the 7-week screening period. If results return to normal within the 7-week screening period, the participant may enter the study.

Other Exclusionary Criteria:

36. Investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or Pfizer employees, including their family members, directly involved in the conduct of the study.
37. Have a history of severe allergic or anaphylactoid reaction to kinase inhibitors.
38. Have had significant trauma or major surgery or blood transfusion within 4 weeks of screening, or scheduled to occur during the study, excluding diagnostic surgery.
39. History of alcohol or drug abuse in investigator's opinion unless in full remission for greater than 12 months prior to first dose of study intervention.
40. Participants who are currently vaping or using e-cigarettes.

5.2.1. Randomization Criteria

Participants enrolled in the study will be randomly assigned to a treatment group provided they have satisfied all of the participant eligibility criteria. Participants in this study will be stratified based on two factors:

- Screening disease severity (Adjudicated total SLEDAI-2K score <10 versus ≥10).
- [redacted]

The use of stratification is to facilitate the investigation of the potential impact (if any) of the two stratification factors on efficacy including the participants screening disease severity (SLEDAI score <10 versus ≥10). A computer-generated randomization schedule will be used to assign participants to the treatment groups using an interactive response technology (IRT) system.

5.3. Lifestyle Considerations

5.3.1. Contraception

Participants must understand that they should avoid becoming pregnant during this study. The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected a protocol permitted method of contraception from the permitted list of contraception methods (see Appendix 4) and will confirm that the participant has been instructed in its consistent and correct use. The method of contraception used by the participant should be provided in the source document. At all visits, the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

5.3.2. Surgery

During the study, no elective surgery should occur without first consulting with the sponsor. Preferably, elective surgery should occur before the study or be delayed until participation in the study is completed.

The sponsor should be notified if a participant requires surgery (including dental surgery) during the study to determine whether the participant should discontinue from the study and/or discontinue the study intervention prior to the surgical procedure. In general, planned surgical procedures should not be performed unless the study intervention has been discontinued for at least 2 days (unless otherwise advised by the sponsor). In addition, the sponsor should be notified as soon as possible if a participant undergoes a surgical procedure without first informing the study staff.

5.3.3. Meals and Dietary Restrictions

Participants should refrain from all food and liquids (water and medications are permitted) for a minimum fast of 8 hours prior to the designated study visit days when a lipid profile panel is scheduled (see Schedule of Activities). Fasting is not required for safety laboratory tests or PK sampling when a lipid profile panel is not being performed.

Diabetics who are taking antidiabetic medications or participants who cannot reasonably tolerate an 8-12 hour fast should not eat immediately prior to the visit as far as possible.

In addition, it is recommended that participants not smoke (or use any tobacco products) or ingest caffeine on study visit days during the 30 minutes prior to blood pressure (BP) and heart rate (pulse) measurements.

5.3.4. Other Requirements

In order to participate in the study, participants must be made aware of the following lifestyle guidelines and restrictions that apply during and after the study period. Details of these lifestyle guidelines are provided in the sections as noted.

- Agree to avoid strenuous exercise on the day of a scheduled study visit and maintain adequate hydration, if possible.
- If enrolled with latent TB, must agree to remain compliant with INH and vitamin B6 therapy to completion of a course of latent TB treatment.
- On study visit days, take prescribed permitted concomitant medication, as needed, prior to the study visit, if it can be administered with water only.
- Must agree to avoid prolonged exposure to the sun and avoid use of tanning booths or other ultraviolet light sources during the study.
- Contact the study site investigator if there are any changes or additions to concomitant medications.
- All participants who are randomized should be encouraged to remain in the study through to the end of the double-blind period for safety and efficacy assessments, whether or not they continue to receive study intervention or are switched to non-protocol treatment; this is in order to reduce missing data as much as possible. It is expected that the only reasons for which a participant will withdraw from the study will be for withdrawal of consent or lost to follow-up. This was specifically requested by a regulatory authority to minimize missing data in participants who prematurely discontinue study intervention.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is

required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Participants who do not meet the eligibility criteria (screen failure was determined) may be re-screened once at a later date (must be at least ≥2 weeks after screening failure is determined to initiate any re-screening procedures). Any participant who is re-screened must be re-consented and receive a new participant number. All activities required for the screening visit must be repeated with the exception of CXR, IGRA and HIV test which do not need to be reobtained if they have been obtained within the protocol defined time period (12 weeks).

6. STUDY INTERVENTION

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

For the purposes of this protocol, the term study intervention may be used synonymously with study intervention.

6.1. Study Intervention(s) Administered

Blinded PF-06700841 tablets and matching placebo will be provided as tablets for oral administration. The PF-06700841, 5 mg and 25 mg tablets and their matching placebos will be supplied in blisters and labeled according to local regulatory requirements.

6.1.1. Administration

Study intervention will be self-administered by oral administration. Participants will swallow the study intervention whole, and will not manipulate or chew the study intervention prior to swallowing.

Participants will be encouraged to take the study intervention in the morning after breakfast whenever possible; however, the study intervention may be taken with or without food. On study visit days during the treatment period, participants should be instructed to refrain from dosing at home, and are instructed to take the study intervention at the investigator site. On study visit days requiring a scheduled lipid panel evaluation, participants should refrain from all food and liquids (water and medications are permitted) for a minimum fast of 8 hours prior to the study visit.

Participants interrupting study intervention for more than 14 days should be discussed with the sponsor for possible withdrawal from the study.

Any temporary hold on dosing of the study intervention during the study should be recorded in the case report form (CRF).

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention, as applicable for temperature-monitored shipments.

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperature since previously documented for all site storage locations upon return to business.

3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records). All study interventions will be accounted for using a study intervention accountability form/record.

4. Further guidance and information for the final disposition of unused study interventions are provided in the IP manual.

5. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the product label.

6. Study interventions should be stored in their original containers and in accordance with the labels.

7. Site staff will instruct participants on the proper storage requirements for take-home study intervention.

8. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with any actions taken. The site should actively pursue options for returning the study intervention to the storage conditions described in the labeling, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. It will not be considered a protocol deviation if Pfizer approves the use of the study intervention after the temperature excursion. Use of the study intervention prior to Pfizer approval will be considered a protocol deviation. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the IP manual.

9. The sponsor or designee will provide guidance on the destruction of unused study intervention (eg, at the site). If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer, and all destruction must be adequately documented.

Additional details about accountability, storage, destruction, and excursion reporting can be found in the IP manual.

6.2.1. Preparation and Dispensing

The study intervention will be dispensed using an IRT drug management system at each visit from Visit 2 to Visit 16. A qualified staff member will dispense the study intervention via unique container numbers in the blister cards provided, in quantities appropriate for the study visit schedule. The participant/caregiver should be instructed to maintain the product in the blister cards provided throughout the course of dosing and return the blister cards to the site at the next study visit.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Study Intervention

Allocation of participants to treatment groups will proceed through the use of an interactive response technology (IRT) system (interactive web-based response [IWR]). The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's identification (ID) and password, the protocol number, and the participant number. The site personnel will then be provided with a treatment assignment, randomization number, and dispensable unit (DU) or container number when study intervention is being supplied via the IRT system. The IRT system will provide a confirmation report containing the participant number, randomization number, and DU or container number assigned. The confirmation report must be stored in the site's files.

Study intervention will be dispensed at the study visits summarized in the Schedule of Activities.

Returned study intervention must not be redispensed to the participants.

The study-specific IRT reference manual and IP manual will provide the contact information and further details on the use of the IRT system.

Participants will be assigned to receive study intervention according to randomization scheme. Investigators will remain blinded to each participant's assigned study intervention throughout the course of the study.

6.3.2. Breaking the Blind

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's

treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's treatment assignment unless this could delay further management of the participant. If a participant's treatment assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and case report form (CRF)/data collection tool (DCT).

The study-specific IRT reference manual and IP manual will provide the contact information and further details on the use of the IRT system.

6.4. Study Intervention Compliance

Study intervention will be self-administered by oral administration. Participant compliance will be monitored by the appropriately designated study staff by the accounting of unused study intervention returned by the participant at study visits.

Participants will be directed to bring blister cards with any remaining study intervention to study visits for review. Compliance with expected consumption of dispensed study intervention will be assessed by comparing the expected number of doses to be taken to the number of doses returned (tablet count) during any given time period. Compliance will be documented on the CRF and in the source records.

If compliance is <80%, or >120%, the investigator or designee will counsel the participant and ensure steps are taken to improve compliance. If compliance is outside these limits, Pfizer clinical should be contacted as soon as possible to determine if the participant should discontinue study medication due to non-compliance and if any additional safety assessments are needed. Participants interrupting study intervention for more than 14 days, should be discussed with the sponsor for possible withdrawal from the study.

The investigator has the discretion to withdraw any participant from the study for reasons of non-compliance with the dosing regimen. Participants who are non-compliant with scheduled study visits or with study intervention should still be encouraged to return for all scheduled study visits. Inventory control of all study intervention must be rigorously maintained throughout the duration of the study until all study intervention has been accounted for and/or returned to the sponsor (or appointed agent). Any discrepancies noted between drug dispensing records and drug inventory must be reported to the sponsor.

6.5. Concomitant Therapy

Prohibited drugs must be discontinued according to protocol guidelines; a list of prohibited drugs with specific discontinuation recommendations is listed in Appendix 13.

Participants taking certain medications for SLE, and deriving inadequate benefit from them, may enter the study after a sufficient washout period for that medication. All biologic disease modifying anti-rheumatic drugs (DMARDs) are prohibited. Non-biologic DMARDs other than those listed in Appendix 13 are prohibited.

6.5.1. Corticosteroids

6.5.1.1. Use of Corticosteroids and Tapering Guidelines

Participants are allowed to receive a stable dose of oral corticosteroids at study entry as described in Section 4 and over the treatment period as described below. A detailed history of corticosteroid use will be collected at screening.

Participants may be given supplemental (ie, in addition to the stable dose) oral corticosteroids at baseline through Week 4 to control SLE disease activity. The maximum additional dose allowed is 10 mg per day above the Day 1 dose level, for a maximum of 14 days after which the previous dose must be resumed.

A single intramuscular IM dose of methylprednisolone (Depo-Medrol) 60 mg (or equivalent see Appendix 14) administered as 1 injection can be substituted for the oral corticosteroid allowed increase described above through Week 4 to control SLE disease activity. The baseline oral corticosteroid dose must not be modified in participants who receive IM corticosteroids.

To minimize potential long term side effects (including infection risk), PIs are required to decrease corticosteroids to the lowest safely tolerated dose when appropriate. The tapering goal for prednisone (or equivalent see Appendix 14) is 7.5 mg per day or less by the end of the two tapering windows (Week 12 and Week 40), however the corticosteroid tapering schedule is flexible and at the discretion of individual PIs based on participants' clinical signs and symptoms. Corticosteroid tapering is allowed only during Weeks 2-12 and Weeks 24-40.

The decision to initiate or intensify corticosteroid therapy should be carefully considered by the investigator, and depends on various factors, including the severity of the participants' symptoms and type of organ involvement. However, an important outcome in this study will be whether or not PF-06700841 permits tapering of corticosteroid use beyond tapering achieved with background therapy alone. In order to maximize the ability to detect a difference in corticosteroid use across arms in this study, beginning at Week 2 and continuing through Week 12, and again during Weeks 24-40, steroid tapering to an oral corticosteroid (OCS) dose of ≤7.5 mg/day is required in all participants when appropriate.

The following guidance must be adhered to for steroid tapering:

1. Do not need to taper steroids if the participant has new, worsening, still active SLE disease activity and meets any of the below criteria:

    - SLEDAI-2K activity which is worsened compared to baseline in major organ systems (renal, CNS, cardiopulmonary, vasculitis, fever, thrombocytopenia, or haemolytic anaemia, or gastrointestinal activity).

    - BILAG – any new BILAG A or B.

    - Moderate to severe skin disease as reflected by a CLASI activity score of ≥10.

2. Steroids MUST be tapered if the participating meets the following criteria:

    - The total SLEDAI score decreases by 4 points from baseline; AND

    - There is no new BILAG A or B.

3. Participants that do not meet the criteria in one or two of the scenarios above, must attempt to taper at the investigator's discretion.

For participants who have tapered during Weeks 2-12 and Weeks 24-40, the dose may be increased once during each of the 2 taper windows to a maximum dose of 20 mg/day (prednisone equivalent see Appendix 14) for a maximum of 14 days, after which the previous dose must be resumed.

Between Weeks 12-24, steroid doses should remain as stable as possible. No change in steroid dosing, either up or down, is allowed between Week 40-Week 52. In addition, any time prior to Week 28, if the dose of oral corticosteroids exceeds 30 mg/day, this should be discussed with the medical monitor and may result in discontinuation of study intervention.

6.5.1.2. Record of Corticosteroids

Participants will be required to follow the corticosteroid dosing guidelines during the treatment period of the study. The investigator/site staff will review the participants corticosteroid use at each study visit and record in the participant's CRF. It is recommended that corticosteroids be tapered as quickly as clinically feasible. No change in steroid dosing is allowed between Weeks 12-24 and Weeks 40-52. For concomitant use of corticosteroids for hypersensitivity reactions, insect bites or asthmatic exacerbations see Appendix 13.

In addition, the intake of oral corticosteroids taken by the participants during the study will be captured on a separate CRF. The CRF page will capture the name of the corticosteroid taken, indication for use, total daily dose, route of administration, and start date and stop dates of administration.

6.5.1.3. Management of Severe Flare and/or Worsening of Disease

During the treatment period, those participants who experience a severe flare requiring new or increased doses of immunosuppressants (including new or increased doses of corticosteroids beyond that outlined in Appendix 13: List of Prohibited and Permitted Concomitant Medications) or hospitalization, or worsening of disease requiring new or increased doses of immunosuppressants or hospitalization, will be discontinued from treatment, and will receive no further study intervention.

In addition, those participants who require oral corticosteroid doses greater than 15 mg/day prednisone (or equivalent see Appendix 14) at or after the Week 28 visit will be discontinued from treatment at that time point, other than those participants undergoing tapering and who receive the allowed single increase in corticosteroids (Section 6.5.1.1).

All participants who prematurely discontinue study intervention are encouraged to maintain consent and continue on with the study through Week 56 to minimize missing data. Participants who are not willing to remain on study should undergo early withdrawal procedures outlined in the Schedule of Activities.

6.6. Dose Modification

Not applicable.

6.7. Intervention After the End of the Study

No intervention will be provided to study participants at the end of the study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

For participant withdrawal/early withdrawal procedures (including post-withdrawal visit procedures) see Schedule of Activities and Section 8.

In order to minimize missing data, health authorities have requested that all participants that discontinue study intervention early, should continue with all scheduled study visits unless they withdraw consent.

For Guidelines for Monitoring and Discontinuations refer to Appendix 17.

Note that discontinuation of study intervention does not represent withdrawal from the study.

7.1.1. Temporary Discontinuation

Participants interrupting study intervention for more than 14 days, should be discussed with the sponsor for possible withdrawal from the study.

7.1.2. Rechallenge

Not applicable.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

At the time of discontinuing from the study, Schedule of Activities for assessments and for any further evaluations that need to be completed.

All participants who prematurely discontinue study intervention based on criteria outlined in the protocol are encouraged to maintain consent and continue on with the study through Week 56. Participants who are not willing to remain on study should undergo early withdrawal procedures outlined in the Schedule of Activities.

The early discontinuation visit applies only to participants who are randomized and then are prematurely withdrawn from the study. The participant will be permanently discontinued both from the study intervention and from the study at that time.

If a participant withdraws from the study, he/she may request destruction of any remaining samples, but data already generated from the samples will continue to be available, and may be used to protect the integrity of existing analyses. The investigator must document any such requests in the site study records.

If the participant withdraws from the study and also withdraws consent (see below) for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

When a participant withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported on the Clinical Trial (CT) SAE Report.

Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.

Withdrawal of Consent:

Participants who request to discontinue receipt of study intervention will remain in the study throughout Week 56 and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him or her or persons previously authorized by the participant to provide this information. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study;

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record;

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole is handled as part of Appendix 1.

8. STUDY ASSESSMENTS AND PROCEDURES

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study-specific procedures.

Study procedures and their timing are summarized in the Schedule of Activities. Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICD may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the Schedule of Activities.

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

The total blood sampling volume for individual participants during the treatment period is approximately 470 mL. The actual collection times of blood sampling may change. Additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 60 consecutive days.

Screening

For screening procedures, see Schedule of Activities.

Participants will be screened within 49 days prior to administration of the initial dose of study intervention in order to confirm that they meet the participant eligibility criteria for the study. The investigator (or appropriate delegate at the investigator site) will obtain informed consent from each participant in accordance with the procedures described in Appendix 1. Screening visits may occur over multiple visits to achieve all of the required testing.

Screening laboratory tests with abnormal results may be repeated once to confirm abnormal results. The last value will be used to determine eligibility. If results return to normal within the 7-week screening period, the participant may enter the study.

Participants who do not meet the eligibility criteria (screen failure was determined) may be re-screened once at a later date (which must be at least ≥2 weeks after screen failure was determined to initiate any re-screening procedures). Participants who are pregnant at the time of their initial screening visit may not be rescreened. Any participant who is re-screened must be re-consented and receive a new participant number. All activities required for the screening visit must be repeated. Participants are not permitted to rescreen if they have any of the following positive laboratory results: Hepatitis B surface antigen, Hepatitis B cDNA, Hepatitis C antibody, HIV screen or an IGRA.

Participant eligibility will be reviewed and confirmed by the sponsor and/or a consultant to the sponsor. Sites will be required to submit appropriate documentation of participants deemed to be eligible to review and approve. Participants cannot be randomized into the study until eligibility is confirmed.

Treatment Period

For treatment period procedures, see Schedule of Activities.

CCI [redacted]

CCI [redacted]

Follow-up Period/End of Study

For follow-up period and end of study procedures see Schedule of Activities section.

Follow-up contact will be completed at least 28 calendar days, and up to 34 calendar days after the last dose of the study intervention to capture any potential adverse events Appendix 3 and to confirm appropriate contraception usage see Appendix 4.

8.1. Efficacy Assessments

8.1.1. Rater Qualifications

For specific rating assessments, only qualified raters will be allowed to evaluate and/or rate participants in this study. The minimum qualifications a rater must meet for each study rating assessment will be outlined in the Rater Assessment Manual provided to each participating site. The level of experience with the target population (or equivalent), specific scale experience, and certification required (if applicable) will be listed and used to determine whether a rater is approved for a given assessment. Proposed raters who do not meet specific criteria but who may be qualified based on unique circumstances may be individually reviewed by the study clinical team to determine whether or not a waiver may be issued. The rater must become certified to perform selected study assessments before he or she can participate in the conduct of the study. For specifically defined assessments, rater training and standardization exercises may be conducted, and written and signed documentation will be provided by the site for each rater's certification. In return, each site will be provided written and signed documentation outlining each rater's certification for specific study assessments. Recertification may be required at periodic intervals during the study. The raters who administer specific study assessments will be documented in a centralized location and all site staff who administer ratings will be verified in the site study documentation during the conduct of the study.

8.1.2. American College of Rheumatology (ACR) Criteria for the Classification of SLE

Eligibility for the study will be evaluated according to the 1997 update on the 1982 revised American College of Rheumatology (ACR) Criteria for the Classification of SLE see Appendix 8 or by the Systemic Lupus International Collatoring Clinics (SLICC) see

Appendix 9. These criteria require that participants have met at least 4 of the 11 criteria either simultaneously or in succession to be classified as having SLE.[17]

8.1.3. Systemic Lupus International Collaborating Clinics (SLICC) criteria

The SLICC criteria for SLE classification requires: 1) Fulfillment of at least four criteria, with at least one clinical criterion AND one immunologic criterion OR 2) Lupus nephritis as the sole clinical criterion in the presence of ANA or anti-dsDNA antibodies.

8.1.4. Systemic Lupus Erythematosus Responder Index (SRI)-4

The primary objective of this study is to evaluate the efficacy of three PF-06700841 QD dose levels (15 mg, 30 mg and 45 mg) relative to placebo in participants with active SLE using the Systemic Lupus Erythematosus Responder Index (SRI) at 52 weeks. The primary endpoint of this study is the SRI-4 response rate at Week 52. The components of this composite endpoint are the Systemic Lupus Erythematosus Disease Activity Index-2000 (SLEDAI-2K),[18] the British Isles Lupus Assessment Group (BILAG) 2004,[19] and the Physician's Global Assessment (PhGA).

The endpoint is designed to assure that if improvements occur, they are not accompanied by clinically-relevant worsening. The SRI-4 requires demonstration of improvement in disease activity as measured by at least a 4-point reduction in SLEDAI-2K score as the first step in identifying a responder. Since the SLEDAI-2K 4-point improvement threshold is based on a published threshold for clinical meaningfulness, and because reduction in the score generally requires normalization of a manifestation, not just improvement, an SRI-4 response is also considered clinically meaningful. Once achieving at least, a 4-point reduction in the SLEDAI-2K, a participant must also show no worsening of disease as measured by BILAG and PhGA to be considered a responder. If either tool shows worsening, the participant is not considered a responder, despite an improvement in the SLEDAI-2K. All 3 of the components are needed to be scored as a responder for purposes of the analysis.

In order to be classified as a responder, participants meet all of the following criteria compared with baseline:

- ≥4 point reduction in the SLEDAI-2K score, and
- No new BILAG A organ domain score or 2 new BILAG B organ domain scores, and
- No worsening (<0.3 point increase) in PhGA score.

8.1.4.1. Systemic Lupus Erythematosus Disease Activity Index -2000 (SLEDAI-2K)

The SRI-4 uses the SLEDAI-2K (see Appendix 11) as a rigorous assessment of the improvement in a participants disease activity.[18]

The SLEDAI-2K contains 24 individual manifestations which will be scored by the investigator as either present or absent at the time of the visit or within the preceding 30 days of the visit. Each manifestation must be related to lupus; 16 are clinical items and 8 are

based on laboratory results. The manifestations can also be grouped into 9 organ systems for analysis (CNS, vascular, renal, musculoskeletal, cardiovascular and respiratory, mucocutaneous, immunologic, constitutional and hematologic). Scores are weighted from 1 to 8 points, based on the seriousness of the manifestation.

For the purposes of completing the SLEDAI at Weeks 2 and 6 [redacted] from the baseline and Week 4 visits should be used respectively.

8.1.4.2. British Isles Lupus Assessment Group (BILAG) 2004

The BILAG 2004 index see Appendix 12 is an assessment of the extent and severity of disease activity in individual organ systems.[19] It is an effective tool to detect worsening in a specific organ system because it is responsive to worsening severity of disease manifestations as well as the onset of new disease manifestations in specific organ domains. Only features attributable to SLE disease activity are recorded and not due to damage, infection, thrombosis (in absence of inflammatory process) or other conditions.

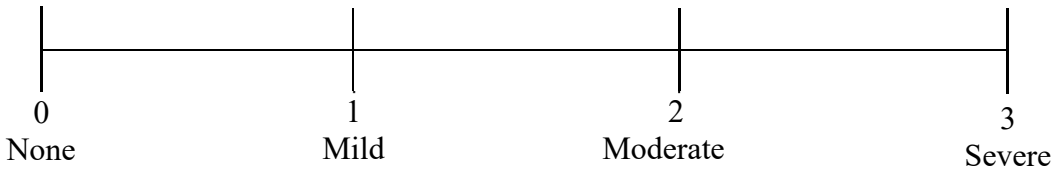
The BILAG 2004 contains 97 lupus related manifestations given a score of either new, worse, same, improving, or not present. The assessment refers to manifestations occurring in the last 4 weeks compared with the previous 4 weeks. Multiple manifestations and laboratory test (as applicable) are then combined into 9 organ domains (constitutional, mucocutaneous, neuropsychiatric, musculoskeletal, cardiorespiratory, GI, ophthalmic, renal and hematological). BILAG scoring is based on the "intention to treatment" paradigm. Each organ domain is given a score from A to E depending on the SLE clinical manifestations. An "A" score represents an increase in disease activity sufficient to normally require intensification of therapy with steroids or immunosuppressants. A "B" score represents moderate, reversible manifestations requiring antimalarials, NSAIDs, or low dose steroids. A "C" score reflects mild, stable disease. A "D" score indicates no current disease activity in a previously affected organ system. An "E" score indicates the organ system has never been involved.

8.1.4.3. Physician Global Assessment (PhGA)

The Physician Global Assessment (PhGA) is a measure of worsening in the participants general health status rather than the disease activity in a specific organ (see Appendix 18). The investigator will mark a visual analog scale answering the question "Evaluate the participants lupus activity since the last visit using the visual analog scale" indicating the participants overall disease activity at a particular visit. The investigator's response will be recorded using a visual analog scale (VAS) by placing a mark on the scale between 0 (none), 1 (mild), 2 (moderate), and 3 (severe).

Evaluate the participants lupus activity since the last visit using the VAS:

Place a vertical mark (|) across the line in the position that best describes your response.



[Note: Scale will be 100 mm in length]

8.1.5. *modified* SELENA-SLEDAI Flare Index (mSSFI)

The secondary objective is to assess the severe flare rate in PF-06700841 treated participants relative to placebo. The corresponding key secondary endpoint of this study is the time to first severe flare as measured by the *modified* SELENA-SLEDAI SLE Flare Index (SFI);[20] (see Appendix 19). This index categorizes SLE flares as either "mild or moderate" or "severe" based on 6 variables: change in SLEDAI-2K score from most recent assessment to current, change in signs or symptoms of disease activity, change in prednisone (or equivalent see Appendix 14) dose, use of new medication for disease activity or hospitalization, change in PhGA score, or hospitalization for SLE activity (severe flare only).

The *modified* SELENA-SLEDAI Flare Index (mSSFI) requires that a participant who has a SLEDAI score >12 is considered as having a severe flare only if they have one other component present. This modification was made because participants entering the trial with high disease activity (ie, ≥11) could too easily trigger a severe flare by minor increases in SLEDAI score.

Lupus flares will also be assessed using an experimental version of the modified SELENA-SLEDAI Flare Index (mSSFI), which eliminates medication criteria from the modified SELENA-SLEDAI SFI.[21] CCI [redacted] All severe SLE flares will be reviewed by a blinded central adjudication committee as discussed in Section 9.5.2.

8.1.6. British Isles Lupus Assessment Group Based Composite Lupus Assessment (BICLA)

An additional endpoint that will be evaluated in this study is the responder rate according to a composite endpoint, British Isles Lupus Assessment Group-Based Composite Lupus Assessment (BICLA) that includes the BILAG-2004, SLEDAI-2K, and PhGA of disease activity. The BILAG-2004 index was selected as the central score on the basis of its comprehensiveness, ability to capture partial improvement, and the clinical relevance of its scoring system.

In order to be classified as a responder, participants must meet all of the following criteria compared with baseline:

- BILAG-2004 improvement (all A scores at baseline improved to B/C/D and all B scores improved to C or D), and
- No worsening in disease activity (no new BILAG-2004 A scores or ≤1 new B score), and
- No worsening of total SLEDAI-2K score, and
- No significant deterioration (<10% worsening) in analogue PhGA.

8.1.7. Systemic Lupus International Collaborating Clinics (SLICC)/American College of Rheumatology (ACR) Damage Index for SLE

The Systemic Lupus International Collaborating Clinics (SLICC)/ACR Damage Index for SLE records damage occurring in participants with SLE regardless of the cause (see Appendix 10). The damage index does not include hematologic items such as cytopenias, since these can be a waxing and waning phenomena; other manifestations need to have been present for at least 6 months. It has been found to be well-defined and reliable for measuring organ damage. The SLICC/ACR damage index is useful both as a descriptor for participants included in studies, as well as an outcome measure for therapeutic trials and prognosis.[23]

8.1.8. Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI)

The Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI; see Appendix 20) was designed to convert subjective elements of disease severity into objective data by means of a scoring system.[24] This validated index has separate scores for activity and damage so that it is possible to monitor the course of the disease over time and in response to therapy. The CLASI activity (CLASI-A) score is based upon degree of erythema, scale, mucous membrane lesions, and non-scarring alopecia. Increased weight is assigned to the face and neck, relative to other less frequently involved parts of the body.

8.1.9. Photography

Photography will only be performed at sites in the United States and is an optional procedure.

For participants with a CLASI-A score ≥10 at baseline, clinical photographs of the area of active skin involvement should be obtained at baseline, Week 12, Week 24, Week 52, where possible (and, if applicable, at participant withdrawal or early withdrawal visit) as per Schedule of Activities. Areas photographed should be recorded in study documents so that the same areas will be photographed at the designated time points as per the Schedule of Activities. Additional photographs may also be taken at the investigator's discretion.

All photographs will be de-identified and will be used for purposes of this study only, they may also be used in external disclosures.

Photographic services will be provided through a central photography lab selected by the sponsor. Cameras and detailed procedures to assure consistency including photograph specifications (lighting, camera settings, etc) will be provided separately in a central photography lab instruction manual provided by vendor. Training will be provided to the sites by the vendor in order to standardize the photographs.

On the day of photography, participants are requested to avoid applying ointments onto their skin prior to the visit.

8.1.10. Joint Assessment (28 Swollen and Tender/Painful Joint Counts)

The joint assessment for this study will consist of the swollen joint count (SJC; see Appendix 21) and the tender/painful joint count (TJC) and will be carried out on 28 joints: the shoulders, elbows, wrists (radiocarpal, carpal, and carpometacarpal bones were considered as a single unit), metacarpophalangeal (MCP) joints (MCP 1, 2, 3, 4, and 5), thumb interphalangeal joint, proximal interphalangeal (PIP) joints (PIP 2, 3, 4, and 5), along with the following joints: temporomandibular joints, sternoclavicular joints, acromioclavicular joints, hip, ankle joints, transverse tarsal joints, metatarsophalangeal (MTP) joints (MTP 1, 2, 3, 4 and 5), interphalangeal joint 1 (foot) and proximal interphalangeal (PIP) joints of the foot (PIP 2, 3, 4 and 5) and the knees. Artificial and ankylosed joints will be excluded from the assessments.

Participants taking maintenance or as needed (PRN) NSAIDS/analgesics, or lower potency opioid should not take a dose of these medications within 12 hours prior to the joint assessment visits in order to allow a true assessment of the joint swelling and tenderness to be conducted.

Swelling and tenderness will be graded on a 2-point scale as described in Table 3. Joint count is recorded on the CRF as follows for this study: right tender joint, left tender joint and right swelling joint, left swelling joint.

Table 3. Joint Swelling and Tenderness Grades

Grade	Swelling Response	Tenderness Response
0	Not swollen	Not tender
1	Detectable synovial thickening with or without loss of bony contours, or bulging synovial proliferation with or without cystic characteristics	Positive response to questioning (tender), spontaneous response elicited (tender and winced), or withdrawal by participant on examination (tender, winced, and withdrew)

Every effort should be made to ensure each participant is evaluated by the same assessor during all study visits. In addition, every effort should be made to assess all 28 joints (in addition to the joints in the ankles and feet) at baseline since joints missing at baseline will not be included in the analysis throughout the study.

The joint assessment should be performed without the knowledge of Patient Reported Outcomes measures. A sample diagram and scoring sheet can be found in Appendix 21.

8.1.11. Lupus Low Disease Activity Score (LLDAS)

LLDAS is defined as (1) SLE disease activity index (SLEDAI-2K ≤4, with no activity in major organ systems (renal, central nervous system, cardiopulmonary, vasculitis, fever) and no haemolytic anaemia or gastrointestinal activity; (2) no new lupus disease activity compared with the previous assessment; (3) a Safety of Estogens in Lupus Erythematosus National Assessment (SELENA)-SLEDAI physician global assessment (scale 0-3) ≤1; (4) a current prednisolone (or equivalent) dose ≤7.5 mg/ daily; and (5) well tolerated standard maintenance doses of immunosuppressive drugs and approved biological agents.[22]

8.1.12. Patient Reported Outcome Measures (PROs)

Participants must complete all patient reported outcome (PRO) questionnaires before any other assessments per the schedule of assessments. All PROs should be completed in the following order, CCI [redacted] CCI [redacted] The amount of time required for a participant to complete the PRO questionnaires is approximately 20-30 minutes (depending on the visit and associated PROs). Upon completion of PROs by the participant, site staff must review forms for completeness.

8.1.12.1. Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) Version 4

The Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) version 4 scale is a patient completed questionnaire consisting of 13 items that assess fatigue each measured on a 4-point Likert scale over the past 7 days.[25,26,27] Instrument scoring yields a range from 0 to 52, with higher scores representing less fatigue. The FACIT-F has been validated for use SLE and has demonstrated good internal consistency, clinical sensitivity, and a high correlation with the SF 36 vitality domain. A copy of the FACIT-F version 4 questionnaire can be found in the PRO manual.

8.1.12.2. Lupus Quality of Life (LupusQoL) Questionnaire

The LupusQoL questionnaire is a validated questionnaire used to evaluate SLE-specific concepts of SLE as reported by patients .[31] It consists of 34 items in 8 different domains: physical health, emotional health, body image, pain, planning, fatigue, intimate relationship, and burden to others measured over a 5-point Likert response (0-4) over the past 4 weeks. To facilitate analysis and result interpretation, the individual domain scores are transformed from 0 to 100 scale wherein higher scores indicate better quality of life (QoL). A copy of the LupusQoL questionnaire can be found in the PRO manual.

8.1.12.3. Pain Intensity

Participants will assess their overall pain rating, joint pain at its worst and pain at its worst in the past 7 days on a 11-point NRS; '0' indicates no pain and '10' is pain as bad as it could be. Higher scores suggest worse pain intensity (see the PRO manual for details).

8.1.12.4. The Short Form (36) Health Survey (SF-36) Version 2, Standard

The 36-Item Short Form Health Survey version 2 standard version (SF36v2) is a validated generic health status measure which measures concepts of health related quality of life (HRQoL) over the past 4 weeks.[28,29,30] It measures 8 general health domains: physical function, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health. These domains can be summarized as physical component summary (PCS) and mental component summary (MCS). Higher scores on this questionnaire indicate a better QoL. A copy of the SF-36v2, standard questionnaire can be found in the PRO manual.

8.1.12.5. European Quality of Life-5 Dimensions-5 Level Version (EQ-5D-5L)

The EuroQoL 5 Dimensions (EQ-5D-5L) is a validated, standardized, generic instrument used to measure health states and utilities in various disease areas. The measure contains 5 items that cover mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, as well as a visual analogue scale.[32,33] Scores from the 5 domains maybe used to calculate a single index value, also known as a utility score.

There is also one visual analogue scale (VAS) item which records the respondent's self-rated health where the endpoints are labelled 'Best imaginable health state' and 'Worst imaginable health state'. A copy of the EQ-5D-5L questionnaire can be found in the PRO manual.

8.1.12.6. Patient's Global Assessment (PtGA)

The PtGA is an overall assessment of impact of SLE on a participant's health. Participants will rate their overall health as a result of SLE in the past 4 weeks on a 11-point Numeric Rating Scale with a score range of 0 (Very well) to 10 (very poorly). Lower scores on the scale suggest better health. A copy of the PtGA can be found in the PRO manual.

8.1.12.7. Patient Global Impression of Severity-Lupus (PGIS-L)

The PGIS-L is the participant's overall of assessment of severity of their SLE on a 5-point Likert scale ranging from 'None' to 'Very Severe' over the past 7 days. Higher scores on the scale suggest greater severity. This questionnaire is only collected for participants enrolled after protocol amendment 4 or 5 has been approved.

8.1.12.8. Patient Global Impression of Severity-Fatigue (PGIS-F)

The PGIS-F is the participant's overall of assessment of severity of their fatigue on a 5-point Likert scale ranging from 'None' to 'Very Severe' over the past 7 days. Higher scores on the scale suggest worse fatigue. This questionnaire is only collected for participants enrolled after protocol amendment 4 or 5 has been approved.

8.1.12.9. Patient Global Impression of Change (PGI-C)

The PGI-C is the participant's overall assessment of change in their SLE since the start of the study intervention. Participants will evaluate this change on a 5-point Likert scale ranging from 'Much better' to 'Much worse'. Higher scores on the scale suggest worsening of their SLE. This questionnaire is only collected for participants enrolled after protocol amendment 4 or 5 has been approved.

8.1.12.10. Health Care Resource Use (HCRU)

Participants utilization of the health care system outside of the clinical trial will be assessed using the Health Care Resource Use (HCRU) questionnaire. Questions will be asked to gauge any physician and specialist visits as hospitalization and emergency room visits stratified by those which are SLE related or not. The questionnaire is to be completed by the patient. A copy of the HCRU can be found in the PRO manual.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the Schedule of Activities. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety concerns.

8.2.1. Assessments at Screening Only

8.2.1.1. Medical History

Complete medical history, SLE disease history (including disease duration, extent of disease, and prior treatments), cardiovascular disease history, venous thromboembolic event history and smoking history will be collected at Screening.

8.2.1.2. Chest X-Ray

Chest radiograph (posterior-anterior and lateral views are recommended, however, local guidelines should be followed) or other approved diagnostic test (ie, CT scan with or without contrast or MRI) with no evidence of current, active TB or previous inactive TB, general infections, heart failure, malignancy, or other clinically significant findings in the chest taken at screening or within 12 weeks prior to Study Day 1 and read by a qualified radiologist. Documentation of the official reading must be located and available in the source documentation. A chest CT or MRI may be obtained in place of the chest x-ray, PA and lateral view, only with advance permission of Pfizer. If a chest CT or MRI shows any abnormalities (nodules, infiltrates, scarring, stranding, etc), these must be documented to be stable compared to a prior chest radiograph or MRI obtained at least 12 months previously.

Participants who entered the study with latent TB or who test positive for QFT-G during the study may have a chest x-ray (posterior-anterior and lateral views are recommended, however, local guidelines should be followed) or other approved diagnostic test (ie, CT scan with or without contrast or MRI) done at Weeks 24 and/or 56 of the study to monitor for active TB. If there is any evidence of active disease on the chest radiograph, study intervention must be stopped immediately (unless study intervention has already been stopped) and Pfizer Clinical should be notified.

8.2.2. Physical Examinations

A complete physical examination will include, at a minimum, head, ears, eyes, nose, mouth, skin, heart and lung examinations, lymph nodes, and gastrointestinal, musculoskeletal, and neurological systems.

A brief physical examination will include, at a minimum, assessments of general appearance, heart, lungs, skin, musculoskeletal and any other patient and participant-reported symptoms.

Physical examinations may be conducted by a physician, trained physician's assistant, or nurse practitioner as acceptable according to local regulation.

Height and weight will also be measured and recorded as per the Schedule of Activities. For measuring weight, a scale with appropriate range and resolution is used and must be placed on a stable, flat surface. Participants must remove shoes, bulky layers of clothing, and jackets so that only light clothing remains. They must also remove the contents of their pockets and remain still during measurement of weight.

8.2.3. Vital Signs

Vital signs (blood pressure, pulse rate, respirations and temperature) will be measured after 5 minutes of rest as indicated in the Schedule of Activities.

Blood pressure (BP) will be measured using a standard calibrated blood pressure measuring device. A BP device that uses multiple cuff sizes for the participant based on the arm circumference is required. The arm circumference at the midpoint of the length of the upper arm should be measured to determine the appropriate cuff size in accordance with the specifications of the BP measuring device. The properly sized and calibrated blood pressure cuff will be used to measure blood pressure each time. The use of an automated device for measuring BP and pulse rate is acceptable, although, when done manually, pulse rate will be measured in the brachial/radial artery for at least 30 seconds.

Participants should be seated in a chair, back supported, and arms bared (free of restrictions such as rolled-up sleeves, etc) and supported at the level of the heart. Measurements should be taken on the same arm (preferably the non-dominant arm) at each visit throughout the study after 5 minutes of rest and recorded to the nearest mm Hg. Participants should refrain from smoking (or use any tobacco products) or ingesting caffeine during the 30 minutes prior to the measurements.

When the timing of BP and pulse rate measurements coincides with a blood collection or other study procedure, BP and pulse rate should be obtained first.

Since all clinical assessments were validated using oral temperatures, it is important to ONLY take oral temperatures on study; oral thermometers will be supplied by the Sponsor if requested.

8.2.4. Electrocardiograms

Standard 12-Lead ECGs should be collected at times specified in the Schedule of Activities section of this protocol using the study specific ECG machine that automatically calculates the heart rate and measures PR, QT, and QTc intervals and QRS complex. All scheduled ECGs should be performed after the participant has rested quietly for at least 10 minutes in a supine position and prior to any blood collections.

A single ECG measurement will be collected at all scheduled visits except at baseline on Day 1 where ECG will be collected in triplicate approximately 2-4 minutes apart. At Week 2 visit, an ECG will be collected approximately 3 hours after dosing at the study site. The Day 1 ECG values (average of the triplicate measures) will serve as each participant's baseline values. If Day 1 ECG is missing, then screening ECG will serve as baseline value. To ensure safety of the participants, a qualified individual (investigator or sub-investigator) at the investigator site will make comparisons to baseline measurements. ECG data will be submitted to a central laboratory for measurement. The final ECG report from the central laboratory should be maintained in the participant's source documentation and be the final interpretation of the ECG recording. Any clinically significant changes from the baseline Day 1 ECG may potentially be AEs (Appendix 7) and should be evaluated further, as clinically warranted.

In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads be placed in the same positions each time in order to achieve precise ECG recordings. If a machine-read QTc value is prolonged, as defined above, repeat measurements may not be necessary if a qualified medical provider's interpretation determines that the QTc values are in the acceptable range.

ECG values of potential clinical concern are listed in Appendix 7.

8.2.5. Hepatitis Screening and Monitoring

During the study screening period, all participants will be screened for hepatitis B surface antigen (HBsAg), hepatitis surface antibody (HBsAb) and hepatitis B core antibody (HBcAb).

- Participants who are HBsAg positive will be excluded.
- Participants who have negative HBsAg, positive HBcAb, and negative HBsAb will be excluded.
- Participants who have negative HBsAg, negative HBcAb and positive HBsAb and provide a documentation of prior HBV vaccination are eligible for the study and will not require HBV DNA monitoring during the study.
- Participants who have negative HBsAg, positive HBcAb and positive HBsAb, whether or not they have received prior HBV vaccination, and participants who have

negative HBsAg, negative HBcAb and positive HBsAb without documentation of prior HBV vaccination are required to undergo HBV cDNA testing monthly.

- Participants will be excluded with detectable HBV DNA.

In addition, all participants will be screened for hepatitis C virus antibody (HCV Ab) during the study screening period. Participants who are positive for HCV Ab will be reflex-tested for hepatitis C virus ribonucleic acid (HCV RNA) and, if HCV RNA is positive, they will be screen-failed.

If hepatitis B reactivation has been confirmed during the study based upon the above evaluations, the participant should not receive further doses of the study intervention. Investigators should consider such as event as medically important and report the event as an SAE in accordance with the process described in Appendix 3.

8.2.6. Tuberculosis (TB) Screening and Monitoring

8.2.6.1. Interferon Gamma Release Assay (IGRA) Tuberculin Test

Participants should be screened for TB using an interferon gamma release assay (IGRA) and it is preferable that a QuantiFERON® gold test be obtained and sent to the central laboratory, although it is acceptable for a locally approved IGRA to be used per local guidelines. IGRA will be tested during screening or within 12 weeks prior to Day 1. The following are acceptable IGRA assays: T-SPOT® TB test, QuantiFERON®-TB Gold In-Tube test (QFT-GIT), QuantiFERON®-TB Gold test (QFT-G) or QuantiFERON®-TB Gold Plus test (QFT-G Plus). Site personnel should follow the processing and analyses steps based on the assay chosen. Ensure incubation steps are followed as appropriate. Documentation of IGRA product used and the test result must be in the participants source documentation.

A Mantoux skin test is not an acceptable test in this study and an IGRA test must be performed. An initial IGRA should be performed at the central laboratory so that at least one set of results will be available in the Pfizer database. If another test is required, it may be performed locally, and a T-SPOT® TB test (if available) would be preferred than another QuantiFERON® test.

Procedure for Indeterminate or Positive interferon gamma release assay tests at screening

- **Indeterminate interferon gammas release assay:** Participants with indeterminate IGRA results should have a different IGRA test obtained (eg, T-SPOT® instead of QuantiFERON®-TB Gold In-Tube test (QFT-GIT), QuantiFERON®-TB Gold test (QFT-G) or QuantiFERON®-TB Gold Plus test (QFT-G Plus) and must be seen by an infectious disease and/or pulmonary specialist who should recommend the appropriate repeat IGRA test, review all pertinent information and determine whether the risk of latent or active infection is low (ie, participant would be acceptable for immunosuppressant treatment without additional treatment). A copy of the specialist report stating that they do not think the participant has active or latent TB should be translated into English and provided to the Sponsor.

- **Positive interferon gamma release assay:** If the results of the initial and/or repeat test are positive, the participant must be seen by an infectious disease and/or pulmonary specialist. The infectious disease and/or pulmonary specialist will review the chest radiography (ie. chest x-rays, CT scan, etc.) along with all TB testing results and review any other pertinent information to determine whether the participant has latent or active TB, or any other active, chronic or latent pulmonary infection or malignancy or other clinically significant pulmonary disease. Participants with indeterminate IGRA results should have a different IGRA test obtained (eg, T-SPOT® instead of QuantiFERON®-TB Gold In-Tube test (QFT-GIT), QuantiFERON®-TB Gold test (QFT-G) or QuantiFERON®-TB Gold Plus test (QFT-G Plus); the consultant should recommend the appropriate repeat IGRA test.

Infectious disease and/or pulmonary specialist consultation

1. If the pulmonary specialist diagnoses latent TB during the screening period, the pulmonary specialist will recommend a treatment for latent TB aligned with the participant's best interest and local standard of care. The local incidence of multidrug resistant TB should be considered in determining how the participant is treated. Once the infectious disease and/or pulmonary specialist report has been obtained, the following must occur:

    - Report is translated into English and the local incidence rate of multi-drug resistant TB in the participant's home area must be provided to the sponsor for review.

        - If INH and vitamin B6 therapy are considered by the infectious disease and/or pulmonary specialist to be adequate treatment for latent TB for the prospective participant, the participant must agree to continue therapy during the study to complete the course of treatment for latent TB. If the participant agrees with this plan and the site monitors for compliance with this regimen on study, the participant may be eligible for randomization if they meet all other inclusion requirements and none of the exclusion criteria. The prospective participant agreement to take INH and B6 during the study and confirmation the site will track the subject's compliance appropriately should also be provided to the Sponsor.

    - Following review of specialist report, incidence of multidrug resistant TB and participants acceptance of required treatment for latent TB, the participant may be eligible for the study if all other eligibility criteria are met. The only therapy acceptable for on-study treatment of latent TB is a 9-month course of INH plus vitamin B6.

    - For participants who enter the study with latent TB on INH and vitamin B6, a follow up chest CT will be required at Week 56.

2. If a participant has been diagnosed with latent TB prior to screening, they must be seen by a pulmonary or infectious disease consultant who will review all radiographic studies and the participant's history to ensure that the patient does not have active TB. The consultant should also consider whether there is a high incidence of multi-drug resistant TB in the participant's region.

    - The consultant's report is translated into English and the local incidence rate of multi-drug resistant TB in the participant's home area must be provided to the sponsor for review.

    - If the participant has begun treatment for latent TB with therapy other than INH and B6, the consultant and participant must agree that changing to INH and B6 is in the participant's best interest. The only therapy acceptable for on-study treatment of latent TB is the equivalent of a 9-month course of INH plus vitamin B6. Adjustment of the treatment period or acceptance of treatments other than INH and B6 prior to screening should be discussed with Pfizer Clinical and may take into account the duration and type of therapy that has been documented prior to screening.

        - If the participant agrees with this treatment plan and the site monitors for compliance with this regimen on study, the participant may be eligible for randomization if they meet all other inclusion requirements and none of the exclusion criteria. The prospective participant agreement to take INH and B6 during the study and confirmation the site will track the participant's compliance appropriately should also be provided to the Sponsor.

        - For participants who enter the study with latent TB on INH and vitamin B6, a follow-up chest CT will be required at Week 56.

Refer to lab manual for any additional processing information and shipping instructions.

8.2.6.2. Additional Measures for Tuberculosis (TB) Monitoring

In addition to the tuberculosis (TB) screening already in place, additional testing for TB has been added at the Week 24 visit and at the Week 56 visit/end of study visit (and if applicable, at participant withdrawal/early withdrawal visit) to monitor for new cases of TB during the course of the study. The following measures have been included in this protocol to ensure the continued safety of participants and to further mitigate the risk of *Mycobacterium tuberculosis* infection:

- Participants should be carefully monitored throughout the study for signs and symptoms of TB, such as chest pain, difficulty breathing, wheezing, fever, cough, excessive sweating (especially at night), lymphadenopathy, hepatosplenomegaly, new fatigue, anorexia or new unplanned weight loss. Participants with these symptoms should be carefully evaluated to determine if these symptoms are due to SLE, TB, or other unrelated cause. Referrals to infectious disease and/or pulmonology specialists should be considered on an individual basis. The sponsor should be immediately

notified and may evaluate these cases in consultation with infectious disease and/or pulmonology specialists.

Procedure for Indeterminate or Positive interferon gamma release assay tests at Week 24 and/or Week 56:

- **Indeterminate interferon gamma release assay:** At both Week 24 and 56 the test should be repeated. The IGRA assay to be utilized for the repeat test should be a different assay than the first test (eg, T-SPOT®).

  - Participants who have an IGRA test result at Week 24 or Week 56 that is indeterminate should be seen by an infectious disease and/or pulmonary specialist who should determine whether the risk of TB infection is low (ie, it would be acceptable for the participant to remain in the study and continue immunosuppressant treatment without additional action). A report from the infectious disease and/or pulmonary specialist should be available in the source document. If the specialist determines that the risk of TB infection is low, the participant may remain in the study as per the Schedule of Activities. If the consultant determines that the risk of TB infection is not low, the recommendations of the consultant to determine whether active or latent TB infection is present should be followed and the final determination of the participants status and results of any other diagnostic testing reported to the Sponsor.

- **Positive interferon gamma release assay**: At both Week 24 and 56 the test should be repeated. The IGRA assay to be utilized for the repeat test should be a different assay than the first (eg, T-SPOT®). The participant should be thoroughly evaluated to exclude active TB. The sponsor should be notified as soon as possible. These participants should have study drug dosing interrupted immediately until details have been discussed with the sponsor and it has been determined whether the participant has active or latent TB. Evaluations should include, and may not be limited to:

  - Participant information to include at a minimum the following:

    - Close contact with someone with active TB (home, work, school, etc).

    - Work at a job that has an increased risk of acquiring TB (for example a healthcare or nursing home worker).

    - Physical examination.

    - Check for symptoms (fever, cough, weight loss).

    - Consultation with an infectious disease and/or pulmonary specialist should be obtained as soon as possible to determine whether the participant has active or latent TB. Radiographic studies required for diagnosis should be obtained as

per the recommendation of the consultant. The subject should stop study intervention immediately until the pulmonary specialist is able to confirm if the participant has latent or active TB.

- At Week 24, if the infectious disease and/or pulmonary specialist determines that the participant has active TB, the participant must discontinue study intervention permanently and should follow the infectious disease and/or pulmonary specialist recommendation for treatment. Sites should be aware that in many regions, new active or latent TB is a reportable disease and may require reporting to the local public health office. Investigators should consider such an event as medically important and report the event as an SAE in accordance with the process described in Appendix 3.

- At Week 24, if the infectious disease and/or pulmonary specialist determines that the participant has latent TB, the consultant should determine if INH and Vitamin B6 would be adequate therapy for latent TB. If the specialist agrees that INH and Vitamin B6 treatment is adequate treatment for latent TB, the participant agrees to start INH and B6 treatment and to comply with the treatment during the study, the participant should start INH and vitamin B6 treatment immediately, interrupt **study intervention** for 14 days and obtain blood chemistry assessments to include at a minimum ALT, AST, and bilirubin prior to re-starting study intervention.

  - The participant may restart study drug after these laboratory assessments have been determined to be in the normal range.

  - For any clinically significant laboratory results, Investigators should consider such an event as medically important and report the event as an SAE in accordance with the process described in Appendix 3.

  - The Sponsor strongly recommends that the participants who develop latent TB on study, should receive a 9-month course of INH and B6, INH and B6 therapy following the completion of study participation is at the discretion of the investigator.

  - The participant is required to have an additional chest X-ray or chest CT at Week 56.

- Participants that enter the study with latent TB or develop newly positive QFT-G results during the study may be required to have additional chest X-ray or chest CT at Weeks 24 and/or 56.

- At Week 56, if the consultant determines that the participant has active or latent TB, the participant should follow the infectious disease and/or pulmonary specialist recommendation for treatment. Sites should be aware that in many regions, new active or latent TB is a reportable disease and may require reporting to the local

public health office. Investigators should consider such an event as medically important and report the event as an SAE in accordance with the process described in Appendix 3.

- If treatment with high dose corticosteroids (oral doses ≥60 mg/day prednisone [or equivalent see Appendix 14] or pulse IV doses) is required to treat a documented severe lupus flare, or intercurrent medical condition, the participant should be evaluated for TB as soon as clinically feasible and preferably before starting the high dose corticosteroid treatment. In areas of high background TB prevalence, it is recommended that the evaluation be repeated following corticosteroid taper.

8.2.7. Monitoring for Infections

Participants will be monitored for development of any infection (viral, bacterial, and fungal). Infections will be classified as either treated or non-treated infections. All treated infections occurring during the study require identification of the causative organism, if feasible, whether by culture, antigen assay, serology, etc. (as appropriate) and the results (eg, any identified organisms or absence of growth) recorded in the CRF.

Treated infections are infections that:

- Require antimicrobial therapy by any route of administration or;
- Require any surgical intervention (eg, incision and drainage).

Treated infections will be further classified as serious or non-serious. Serious infections are treated infections that:

- Require intravenous antimicrobial therapy or;
- Required hospitalization for treatment or;
- Meet other criteria that require the infection to be classified as a SAE.

A participant who experiences a serious infection should be discontinued from treatment. A serious infection should be reported as a SAE and should be listed as the reason for discontinuation in the CRF. All serious infections occurring during the study should undergo appropriate laboratory investigations, including culture, and the results (eg, any identified organisms or absence of growth) be recorded in the CRF.

For participants who experience non-serious infections that require a temporary hold on dosing of the study intervention during the study see Section 6.1.1. Consultation with the sponsor is available.

8.2.7.1. Suspected Herpetiform Rash

For any occurrence of a suspected herpetiform rash (eg, herpes simplex and herpes zoster), specimens for viral deoxyribonucleic acid (DNA) analysis will be obtained: A swab of the

affected area should be collected for confirmation; a blood sample for viral surveillance will be collected for the analysis of viral load. Details for these collections will be provided in the laboratory manual.

8.2.8. Clinical Safety Laboratory Assessments

See Appendix 2 for the list of clinical safety laboratory tests to be performed and the Schedule of Activities for the timing and frequency. The direct Coombs test sent to a local laboratory should only be obtained if the investigator suspects that a clinically significant hemolytic anemia is present that will be reflected in a BILAG score for hemolytic anemia.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 days after the last dose of study intervention should be repeated at the central lab until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the Schedule of Activities.

If laboratory values from non-protocol-specified laboratory assessments performed at the institution’s local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the CRF.

8.2.9. Serum Creatinine, Serum Cystatin C and Estimated Glomerular Filtration Rate (eGFR)

Serum creatinine will be measured as part of serum chemistry at times specified in the Schedule of Activities section of the protocol. Creatinine elevations above the upper limit of normal (ULN) will be followed until resolution or return to baseline values. Serum creatinine based eGFR will be calculated. Serum cystatin C will be measured and cystatin C based eGFR will be calculated at corresponding times per Schedule of Activities.

The eGFR will be calculated using the 2 sets of equations developed by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), which utilize serum creatinine (SCr) and serum cystatin C (S Cystatin C) respectively (see Appendix 22).

8.2.10. Suicidal Ideation and Behavior Risk Monitoring

The Columbia-Suicide Severity Rating Scale (C-SSRS; Appendix 15) will be used to assess suicidal ideation and behavior. The C-SSRS is a validated tool to evaluate suicidal ideation and behavior.[34]

At the screening visit (baseline), if there are "yes" answers on items 4 and/or 5 in the past year, or on any question in the suicidal behavior section of the C-SSRS in the past 5 years, the participant will be excluded from the study.

At Week 24 visit the Since Last Visit version of the C-SSRS should be utilized. The Since Last Visit version refers to the participants experience since their last visit. If there are "yes" answers on items 4 and/or 5 or on any suicidal behavior question of the C-SSRS, the participant will be discontinued from treatment and referred to a mental health professional for appropriate evaluation and treatment. If the participant cannot be seen by a mental health professional within 24 hours, then the participant should be sent to a local emergency room for psychiatric assessment.

8.2.11. Pregnancy Testing

Pregnancy tests may be urine or serum tests, but must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in women of child bearing potential (WOCBP) at the times listed in the Schedule of Activities. Following a negative pregnancy test result at screening, appropriate contraception must be commenced and a negative pregnancy test result will be required at Day 1 prior to dosing and then prior to the participant's receiving the study treatment at all subsequent visits. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) and at the end of the study. Pregnancy tests may also be repeated if requested by institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded if the serum pregnancy result is positive.

8.3. Adverse Events and Serious Adverse Events

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

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

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE or that caused the participant to discontinue the study (see Section 7).

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

8.3.1. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Not applicable.

8.3.2. Time Period and Frequency for Collecting AE and SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including a minimum of 28 calendar days, except as indicated below, after the last administration of the study intervention.

For participants who are screen failures, the active collection period ends when screen failure status is determined.

If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

If a participant definitively discontinues or temporarily discontinues study intervention because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the CT SAE Report Form.

Follow-up by the investigator continues throughout and after the active collection period and until the event or its sequelae resolve or stabilize at a level acceptable to the investigator.

Investigators are not obligated to actively seek AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly report the SAE to Pfizer using the CT SAE Report Form.

8.3.2.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period are reported to Pfizer Safety on the CT SAE Report Form immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

SAEs occurring in a participant after the active collection period has ended are reported to Pfizer Safety if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to study intervention must be reported to Pfizer Safety.

8.3.2.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in Section 8.3.1, will be recorded on the AE section of the CRF.

The investigator is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the participant.

8.3.3. Method of Detecting AEs and SAEs

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

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.4. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

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

8.3.5. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, institutional review boards (IRBs)/ethics committees (ECs), and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the investigator's brochure and will notify the IRB/EC, if appropriate according to local requirements.

8.3.6. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the study intervention under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.3.6.1. Exposure During Pregnancy

Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study intervention and until 30 days after the last dose.

If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.6.2. Exposure During Breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated SAE, to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug's administration, the SAE is reported together with the exposure during breastfeeding.

8.3.6.3. Occupational Exposure

An occupational exposure occurs when, during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.

An occupational exposure is reported to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form, regardless of whether there is an associated SAE. Since the information does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

8.3.7. Cardiovascular and Death Events

Cardiovascular events will be reviewed as part of the regular safety review by the eDMC (see Section 9.5.1).

8.3.8. Adverse Events of Special Interest

Not Applicable.

8.3.8.1. Lack of Efficacy

"Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or SAE if they fulfill the definition of an AE or SAE.

8.3.9. Medication Errors

Medication errors may result from the administration or consumption of the study intervention by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Exposures to the study intervention under study may occur in clinical trial settings, such as medication errors.

Safety Event	**Recorded on the CRF**	**Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness**
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

Medication errors include:

- Medication errors involving participant exposure to the study intervention;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor should be notified immediately.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and nonserious, are recorded on an AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a CT SAE Report Form **only when associated with an SAE.**

8.4. Treatment of Overdose

For this study, any dose of study intervention greater than that prescribed for the participant within a 24-hour time period will be considered an overdose.

Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator/treating physician should:

1. Contact the medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities until study intervention can no longer be detected systemically (at least 10 days).
3. Obtain a blood sample for pharmacokinetic (PK) analysis within 2 days from the date of the last dose of study intervention if requested by the medical monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
5. Overdose is reportable to Safety **only when associated with an SAE.**

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

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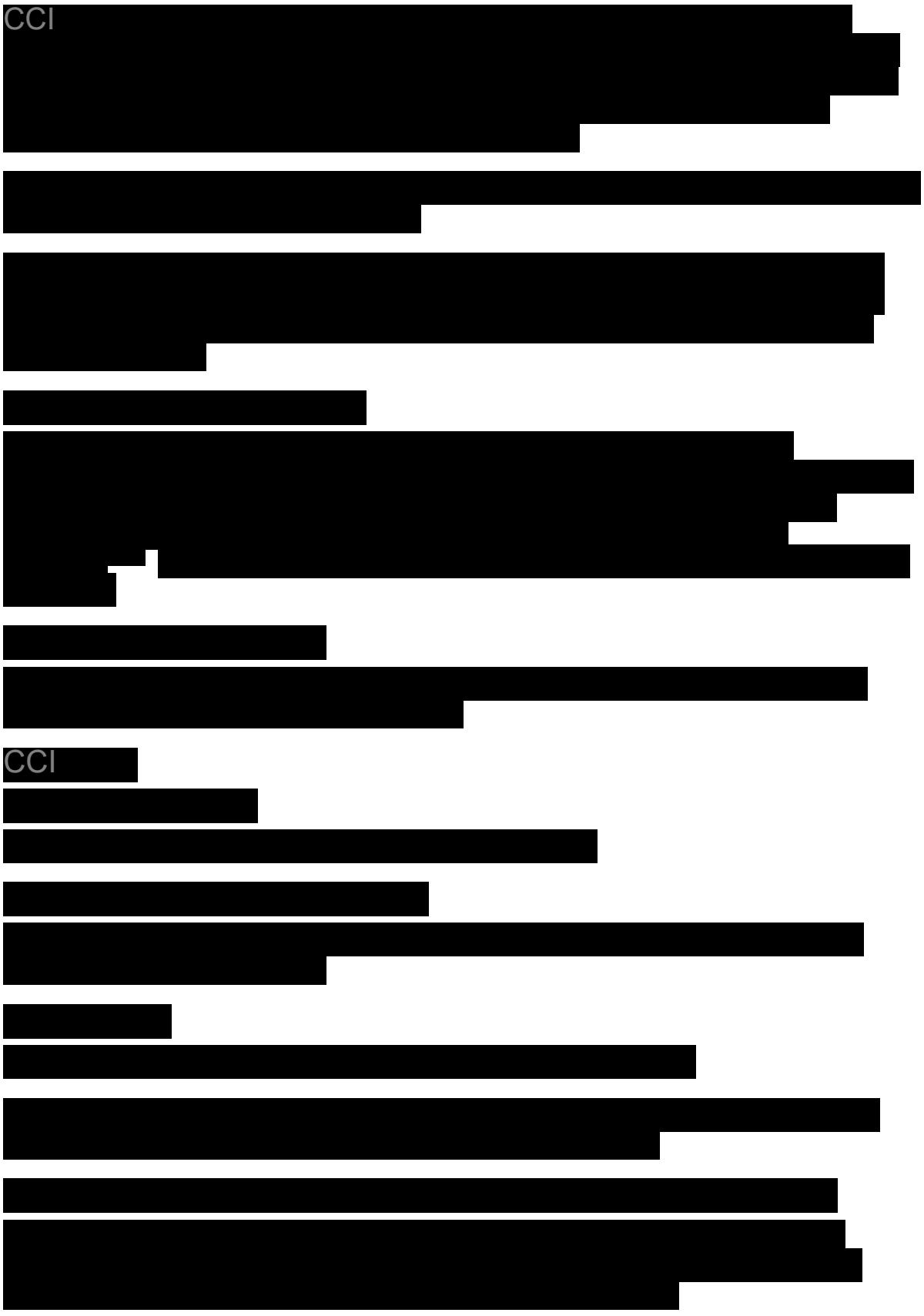

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9. STATISTICAL CONSIDERATIONS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in a statistical analysis plan (SAP), which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Estimands and Statistical Hypotheses

9.1.1. Estimands

The primary estimand for the primary endpoint of Systemic Lupus Erythematosus Responder Index (SRI-4) response at Week 52 will be the population average treatment difference between PF-06700841 and placebo in the proportion of participants with active SLE who achieved the SRI-4 endpoint at Week 52 and did not discontinue study intervention prior to

Week 52. SRI-4 response is a composite endpoint where a responder must meet criteria in the assessment of SLEDAI-2K, BILAG and PhGA. Data post intercurrent events will be censored and any participant who experienced these intercurrent events will be considered as a non-responder at Week 52. The population-level summary will be the differences in the proportions of SRI-4 responders at Week 52 between each treatment dose arm of PF-06700841 and the placebo arm. For the primary endpoint, a treatment policy estimand will also be included in the SAP as a secondary estimand to estimate the treatment difference in the SRI-4 response rate at Week 52 regardless of occurrence of any intercurrent events prior to Week 52. Additional sensitivity analyses involving the primary endpoint may be specified within the SAP.

Estimands are also defined corresponding to secondary objectives. In general, population will consist of participants with active SLE as defined by inclusion/exclusion criteria except those estimands for a subgroup of participants. Intercurrent events for secondary binary and continuous endpoints are defined similar to those events for the primary endpoint. For each binary endpoint, the main estimand is similarly defined as a composite estimand and any participant who experienced the specified intercurrent events will be considered as a non--responder; for each continuous endpoint the main estimand will be a hypothetical estimand and only data collected prior to the occurrence of intercurrent events will be included for analyses. Treatment policy estimand may be defined in the SAP for selected secondary endpoints.

Participants who had data missing due to COVID-19 or Russia-Ukraine conflict at Week 52 visit will be removed from analysis for that visit (eg, not included into numerator and denominator in the calculation of proportion of responders at the visit where the data are missing due to COVID-19 or Russia-Ukraine conflict).

9.1.2. Hypotheses and Decision Rules

Each of the 3 dose groups of the PF-06700841 will be compared with the placebo group for both the primary endpoint of SRI-4 response at Week 52 and the key secondary endpoint of the BICLA response at Week 52 in 6 hypotheses. Two families (FA and FB) of hypotheses are formed from these 6 hypotheses (Table 4). In order to control the overall family-wise type-I error rate, a sequentially rejective closed testing procedure is defined. The family FA serves as the gatekeeper before testing hypotheses in the family FB. The hypotheses in the family FB will not be formally tested unless all null hypotheses in the family FA are rejected. Additional details, including any future changes regarding the multiplicity control of the primary and key secondary endpoints at the overall family-wise type-I error rate of one-sided 0.025, will be handled within the SAP.

Table 4. Families of Hypotheses

Notation	Hypotheses	Family of Hypotheses
HvP1	H0: SRI-4 response rates at Week 52 are the same between the PF-06700841 45 mg dose group and the placebo group	FA

Table 4. Families of Hypotheses

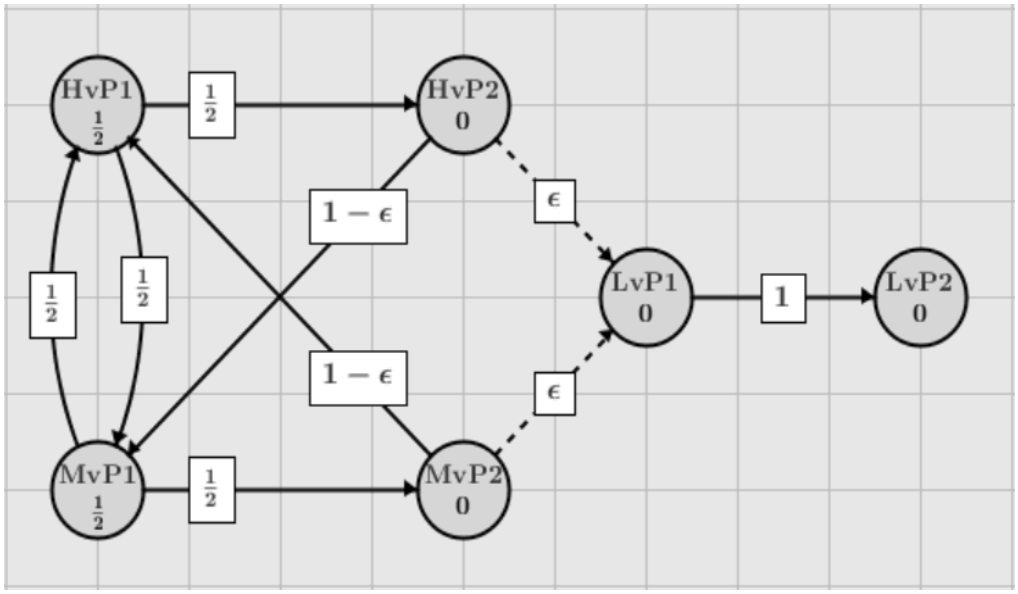
Notation	Hypotheses	Family of Hypotheses
	H1: The SRI-4 response rate at Week 52 for the PF-06700841 45 mg dose group is greater than the SRI-4 response rate for the placebo group	
HvP2	H0: BICLA response rates at Week 52 are the same between the PF-06700841 45 mg dose group and the placebo group	FA
	H1: The BICLA response rate at Week 52 for the PF-06700841 45 mg dose group is greater than the BICLA response rate for the placebo group	
MvP1	H0: SRI-4 response rates at Week 52 are the same between the PF-06700841 30 mg dose group and the placebo group	FA
	H1: The SRI-4 response rate at Week 52 for the PF-06700841 30 mg dose group is greater than the SRI-4 response rate for the placebo group	
MvP2	H0: BICLA response rates at Week 52 are the same between the PF-06700841 30 mg dose group and the placebo group	FA
	H1: The BICLA response rate at Week 52 for the PF-06700841 30 mg dose group is greater than the BICLA response rate for the placebo group	
LvP1	H0: SRI-4 response rates at Week 52 are the same between the PF-06700841 15 mg dose group and the placebo group	FB
	H1: The SRI-4 response rate at Week 52 for PF-06700841 15 mg dose group is greater than the SRI-4 response rate for the placebo group	
LvP2	H0: BICLA response rates at Week 52 are the same between the PF-06700841 15 mg dose group and the placebo group	FB
	H1: The BICLA response rate at Week 52 for the PF-06700841 15 mg dose group is greater than the BICLA response rate for the placebo group	

It follows from Bretz, et al. (2009)[38] that the multiple testing procedure is shown in a graphical presentation (Figure 1). The initial significance levels are equally assigned to two hypotheses (HvP1 and MvP1). The transition matrix is

$$G = \begin{pmatrix} 0 & 0.5 & 0.5 & 0 & 0 & 0 \\ 0 & 0 & 1-\varepsilon & 0 & \varepsilon & 0 \\ 0.5 & 0 & 0 & 0.5 & 0 & 0 \\ 1-\varepsilon & 0 & 0 & 0 & \varepsilon & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix},$$

where the order of the six hypotheses is (HvP1, HvP2, MvP1, MvP2, LvP1, LvP2). The ε is an infinitesimally small weight for the gatekeeping strategy. Since the regularity condition is met for the transition matrix, this testing procedure is a closed testing procedure and controls the family-wise type-I error rate for the multiple testing of both primary and the key secondary endpoints.

Figure 1. Testing Procedure



9.2. Sample Size Determination

The study randomized 350 participants in a 1:2:2:2 allocation ratio in the order of PF-06700841 15 mg, 30 mg, and 45 mg, and placebo arms. The primary endpoint of this study is the proportion of participants achieving SRI-4 response at Week 52. Using a Cochran-Maentel-Haenszel test, a placebo SRI-4 response rate of 40% at Week 52 and the true effect of treatment with PF-06700841 45 mg on SRI-4 response rate of 65% at Week 52, an overall type-I family-wise error α=0.025 (one-sided), and N=95 evaluable participants in both arms to account for potential loss of participants impacted by either the COVID-19 or Russia-Ukraine crises, we expect to have at least 88% power to reject the null hypothesis in HvP1. Using the same parameters and assuming a placebo BICLA response rate of 30% at Week 52 and the true effect of treatment with PF-06700841 45 mg on BICLA response rate of 47.5% at Week 52, we expect to have at least 58% power to reject the null hypothesis in HvP2. The calculation on sample size for key secondary endpoint assume primary endpoint hypotheses that were higher up in the testing hierarchy in Figure 1 were tested and rejected

9.3. Populations for Analysis

For purposes of analysis, the following populations are defined:

Population	Description
Safety Analysis Set	All participants randomly assigned to study intervention and who take at least one dose of study intervention. Participants will be analyzed according to the product they actually received.

Defined Population for Analysis	Description
Full Analysis Set	All participants randomly assigned to study intervention and received at least one dose of study intervention. Participants will be analyzed according to the product they were randomized.
CCI [redacted]	[redacted]
[redacted]	[redacted]

9.4. Statistical Analyses

The SAP will be developed and finalized before database lock and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.4.1. Efficacy Analyses

Continuous variables will be summarized by N, mean, median, standard deviation, minimum and maximum. Categorical variables will be summarized by count and percent of participants in each group. All summaries will be split by treatment group. Efficacy data will be listed, tabulated and summarized graphically, as appropriate. Model assumptions will be tested using appropriate statistical or graphical techniques. CCI [redacted]

If statistical hypothesis testing is performed, tests will be conducted at the α=0.025 (one-sided) level. Analysis results will include the estimated effect and 95% confidence intervals.

The primary population of interest for efficacy analysis is the Full Analysis Set (FAS) which will include all randomized participants who have received at least 1 dose of study intervention. Additional analysis populations may be defined in the SAP.

The final analyses will be performed when all participants complete Week 52.

Further details of analyses in efficacy will be specified in the statistical analysis plan.

9.4.2. Analysis of the Primary Endpoint

The primary endpoint is the proportion of SRI-4 responders at Week 52 and the primary analysis of this endpoint will be based on the Cochran-Mantel-Haenszel (CMH) approach

adjusting for stratification factors. The hypothesis testing of this endpoint will be based on the p-values for pairwise treatment between each dose group of PF-06700841 and the placebo group. Treatment difference in the proportion of responders for the active treatment groups compared to the placebo will be estimated based on the CMH approach. These estimates will be reported with 95% confidence intervals and one-sided p-values. A supplementary analysis using a generalized linear marginal model for repeated measures (GLMMRM) will be performed for the longitudinal SRI-4 endpoint data. This model will include treatment, visit, treatment by visit interaction as fixed effects. A common AR(1) variance-covariance matrix for all treatment groups will be used to model the variability among longitudinal observations within a participant. If there are any concerns with model convergence, covariance structures of compound symmetry will be attempted. Unlike the non-responder imputation for missing data in the primary analysis, missing at random is assumed for missing data in the GLMMRM analysis. Details will be provided in the SAP.

CCI [redacted]

9.4.3. Analysis of Secondary Endpoints

9.4.3.1. Analysis of Key Secondary Endpoint

The key secondary endpoint is the proportion of BICLA responders at Week 52 and the primary analysis of this endpoint will be conducted in the manner described above for the primary endpoint using the CMH approach adjusting for stratification factors. The hypothesis testing of this endpoint will be based on the p-values for pairwise treatment comparisons between each dose group of PF-06700841 and the placebo group. Treatment difference in the proportion of responders for the active treatment compared to the placebo will be estimated based on the CMH approach. These estimates will be reported with 95% confidence intervals and one-sided p-values.

9.4.3.2. Analysis of Other Secondary Endpoints

The proportion of participants achieving LLDAS, oral corticosteroid reductions, and SRI-4 response with sustained reduction of oral corticosteroids will be estimated using similar methods for the SRI-4 responder analysis.

A linear mixed model will be used to analyze the continuous longitudinal response of CLASI-A, FACIT-F and LupusQoL. This linear mixed model will include fixed effects for treatment, week, treatment by week interaction, and the stratification factors. Other covariates may be included in the analysis if deemed appropriate. Participant variable will be modeled as a random effect with an unstructured covariance. Further details regarding imputation methods for missing data and any sensitivity analyses will be provided in the SAP.

Occurrence of severe flares will be analyzed as a time to event endpoint. Time to first severe flare will be tested to compare treatment groups with placebo based on a log-rank test with estimates from the Kaplan-Meier product-limit method. The corresponding Kaplan-Meier plot will also be used to visualize differences in the incidence of flares over time. The hazard

ratio will be estimated using a Cox regression model. The stratification variables will be included as covariates when there is no convergence issue.

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9.4.6. Safety Analysis

The safety analysis will include all participants who have received at least one dose of study drug or placebo. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate. All safety endpoints will be listed and summarized in accordance with Pfizer Data Standards. Categorical outcomes (eg, AEs) will be summarized by participant counts and percentage. Continuous outcome (eg, BP, heart rate, ECG intervals, etc) will be summarized using N, mean, median, standard deviation, etc. Laboratory data, ECG intervals and vital signs crossing the thresholds of clinical concern will be tabulated according to sponsor Data Standards. Participant listings will be produced for these safety endpoints accordingly.

Data relevant to the assessment of suicidality will be mapped to the Columbia-Classification Algorithm of Suicide Assessment (C-CASA) codes. Baseline CCI C-SSRS data (mapped to C-CASA scores) will be summarized descriptively by treatment group at baseline CCI

Details of the safety analyses will be included in the SAP.

9.4.7. Adverse Events

The safety analyses will be carried out in the safety population and detailed analyses will be described in the SAP. CCI [redacted] There will be no adjustment for multiple comparisons or stratification factor in the analyses unless specified.

Nominal p-values (Tier 1 events only) and 95% confidence intervals (Tier 1 and Tier 2 events) will be provided for between treatment differences in the percentage of participants with events. Reporting p-values and confidence intervals will follow Pfizer standard practice in the 3-tier approach.

9.4.8. Electrocardiogram

Changes from baseline for the ECG parameters of heart rate, QT interval, QTc interval, PR interval, and QRS complex will be summarized by treatment and time.

The number (%) of participants with maximum postdose QTc values and maximum increases from baseline in the following categories will be tabulated by treatment:

Safety QTc Assessment

Degree of Prolongation	Mild (msec)	Moderate (msec)	Severe (msec)
Absolute value	>450-480	>480-500	>500
Increase from baseline		30-60	>60

In addition, the number of participants with uncorrected QT values >500 msec will be summarized.

9.5. Interim Analysis

An Interim analysis may be conducted when sufficient number of participants completes Week 52 visits and before the interim analysis is instigated, the details of the objectives, decision criteria, dissemination plan and method of maintaining the study blind per Pfizer's SOPs will be documented and approved in the E-DMC charter. In addition, the analysis details must be documented and approved in an interim analysis plan (IAP).

9.5.1. Data Monitoring Committee

This study will use an independent external data monitoring committee (E-DMC). The E-DMC will be responsible for ongoing monitoring of safety of participants in the study according to the charter.

This E-DMC will make recommendations with regard to continuing, stopping or altering the trial to a Sponsor Management Committee throughout the study. If an interim analysis is performed, the interim analysis results will also be provided to the E-DMC for review, stopping or altering the trial to a Sponsor Management Committee throughout the study.

Additional information can be obtained in the E-DMC charter.

9.5.2. Adjudication Committees

This study will also use separate blinded adjudication commitees consisting of independent external experts who will be responsible for the ongoing review of the following efficacy and safety endpoints:

1. BILAG, SLEDAI and associated data.
2. Severe Flare.
3. Cardiovascular and thromboembolic events.
4. Malignancy.
5. Opportunistic infections.

The results of the adjudication committees' decisions will be databased and be used for the statistical analyses of these endpoints. The details of these analyses will be described in the SAP.

Specific details on this process and additional information can be obtained in the adjudication committee charters.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines;
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, investigator's brochure (IB), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor and submitted to an IRB/EC by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the study intervention, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

10.1.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant [or his or her legally authorized representative] is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant or his or her legally authorized representative] is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants must be reconsented to the most current version of the ICD(s) during their participation in the study.

A copy of the ICD(s) must be provided to the participant or the participant's legally authorized representative.

Participants who are rescreened are required to sign a new ICD.

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10.1.4. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in [encrypted electronic and/or paper] form and will be [password protected or secured in a locked room] to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

10.1.5. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its standard operating procedures (SOPs).

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in participants) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. US Basic Results are generally submitted for posting within 1 year of the primary completion date (PCD) for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

EudraCT

Pfizer posts clinical trial results on EudraCT for Pfizer-sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

www.pfizer.com

Documents within marketing authorization packages/submissions

Pfizer complies with the European Union Policy 0070, the proactive publication of clinical data to the European Medicines Agency (EMA) website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the centralized procedure since 01 January 2015 and applications for line extensions and for new indications submitted via the centralized procedure since 01 July 2015.

Data Sharing

Pfizer provides researchers secure access to participant-level data or full CSRs for the purposes of "bona-fide scientific research" that contribute to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials 24 months after study completion. Participant-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.6. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must ensure that the CRFs are securely stored at the study site in [encrypted electronic and/or paper] form and are [password protected or secured in a locked room] to prevent access by unauthorized third parties.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided in the [monitoring plan] [contracts].

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will promptly provide copies of the inspection findings to the sponsor or its agent. Before response

submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

10.1.7. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator site.

Data reported on the CRF or entered in the electronic CRF (eCRF) that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in the study completion guidelines.

10.1.8. Study and Site Closure

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to the contract research organization (CRO) if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or GCP guidelines;
- Inadequate recruitment of participants by the investigator;

Discontinuation of further study intervention development. Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

10.1.9. Publication Policy

The results of this study may be published or presented at scientific meetings by the investigator after publication of the overall study results or 1 year after end of the study (or study termination), whichever comes first.

The investigator agrees to refer to the primary publication in any subsequent publications such as secondary manuscripts, and submits all manuscripts or abstracts to the sponsor 30 days before submission. This allows the sponsor to protect proprietary information and to provide comments and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study or Pfizer

intervention- related- information necessary for the appropriate scientific presentation or understanding of the study results.

For all publications relating to the study, the investigator will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors.

The sponsor will comply with the requirements for publication of the overall study results covering all investigator sites. In accordance with standard editorial and ethical practice, the sponsor will support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship of publications for the overall study results will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

If publication is addressed in the clinical study agreement, the publication policy set out in this section will not apply.

10.1.10. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the supporting study documentation/team SharePoint site/study portal/clinical trial management system (CTMS)/study team on demand (SToD) system.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card. The contact card contains, at a minimum, protocol and study intervention identifiers, participant numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the participant's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the participant directly, and if a participant calls that number, he or she will be directed back to the investigator site.

10.2. Appendix 2: Clinical Laboratory Tests

The following safety laboratory tests will be performed at times defined in the Schedule of Activities section of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory; or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety concerns.

Table 5. Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hemoglobin	BUN	pH	HBsAg
Hematocrit	Creatinine	Glucose	HBcAb
RBC count	Cystatin	(qual)	Hep B reflex, *if applicable*
Platelet count	eGFR Creatinine	Protein (qual)	HCVAb
WBC count with	eGFR Cystatin	Blood (qual)	Hep C reflex, *if applicable*
differential	Creatine	Ketones	HIV[d]
Total neutrophils (%, Abs)	Phosphokinase	Nitrites	β-hCG[e] FSH[f]
Eosinophils (%, Abs)	Glucose (fasting & non	Leukocyte	IGRA (T-SPOT® TB test, QFT-GIT, QFT-G
Basophils (%, Abs)	fasting)	esterase	or QFT-G Plus)
Lymphocytes (%, Abs)	Sodium	Myoglobin	CCI
Monocytes (%, Abs)	Potassium	Microscopy[b]	
Reticulocyte count (%,	Chloride	Spot Urine	
Abs)	Calcium	(Upr:Ucr)[c]	
PT/PTT/International	Total CO_2		
Normalized Ratio (INR)	(Bicarbonate)		
Complement (will include	AST, ALT		
but are not limited to	Total Indirect and		
C3 and C4)	Direct Bilirubin		
Direct Coombs test (local	Alkaline phosphatase		
laboratories)	Uric acid		
	Albumin		
	Total protein		
	Lipid Profile Panel:[a]		
	Total Cholesterol		
	LDL-Cholesterol (direct)		
	HDL-Cholesterol		
	Triglycerides		

a. Lipid profile panel requires a minimum fast of 8 hours as possible.
b. At all visits.
c. Preferably collected after the first morning void; will be analyzed at the central laboratory using an aliquot of spot urine collected from participants.
d. At screening only; confirmation and documentation of negative HIV test result within 12 weeks prior to screening is acceptable.
e. Serum/urine pregnancy tests for WOCBP; serum pregnancy test must be performed at screening for all WOCBP as defined in the eligibility criteria; urine pregnancy test must be performed at Day 1 for all WOCBP prior to dosing with study intervention and at all subsequent visits.
f. FSH at screening only to confirm post menopausal status.

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Investigators must document their review of each laboratory safety report.

Laboratory results that could unblind the study will not be reported to investigator sites or other blinded personnel until the study has been unblinded.

CCI [redacted]

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.
Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording adverse events on the CRF and for reporting serious adverse events on the Clinical Trial (CT) Serious Adverse Event (SAE) Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious adverse events (AEs); and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure	All AEs/SAEs associated with exposure during pregnancy or breastfeeding Occupational exposure is not recorded.	All (and exposure during pregnancy [EDP] supplemental form for EDP)

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the CT SAE Report Form/AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

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

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

- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.

- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

- The investigator will use clinical judgment to determine the relationship.

- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.

- The investigator will also consult the investigator's brochure (IB) and/or product information, for marketed products, in his/her assessment.

- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**

- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an

assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.
Follow-up of AEs and SAEs
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare professionals. • If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings including histopathology. • New or updated information will be recorded in the originally completed CRF. • The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as the data become available. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.

SAE Reporting to Pfizer Safety via CT SAE Report Form
• Facsimile transmission of the CT SAE Report Form is the preferred method to transmit this information to Pfizer Safety. • In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the CT SAE Report Form sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the CT SAE Report Form pages within the designated reporting time frames.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

10.4.1. Male Participants

No contraception methods are required for male participants in this study, as the calculated safety margin is ≥100-fold between the estimated maternal exposure due to seminal transfer and the NOAEL for serious manifestations of developmental toxicity in nonclinical studies.

10.4.2. Female Participant Reproductive Inclusion Criteria

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

- Is not a WOCBP (see definitions below in Section 10.4.3).

  OR

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), as described below during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate any study intervention(s). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

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

10.4.3. Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

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

For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

2. Postmenopausal female:

    - A postmenopausal state is defined as age 60 years or older or no menses for 12 months without an alternative medical cause.

    - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT).

    - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.4. Contraception Methods

Highly Effective Methods That Have Low User Dependency

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation*.

2. Intrauterine device (IUD).

3. Intrauterine hormone-releasing system (IUS).

4. Bilateral tubal occlusion.

5. Vasectomized partner.

Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

Highly Effective Methods That Are User Dependent

1. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
    - oral;
    - intravaginal*;
    - transdermal*.
2. Progestogen-only hormone contraception associated with inhibition of ovulation:
    - oral;
    - injectable.
3. Sexual abstinence:
    - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

***not approved in Japan.**

Collection of Pregnancy Information

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy (EDP) occurs if:

- A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the study intervention; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the study intervention;
    - An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).
- A male has been exposed (eg, because of treatment or environmental exposure) to the study intervention prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a participant or participant's partner becomes or is found to be pregnant during the participant's treatment with the study intervention, the investigator must report this

information to Pfizer Safety on the CT SAE Report Form and an EDP supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a participant reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) to Pfizer Safety using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the study intervention.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

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10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments

Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed “tolerators,” while those who show transient liver injury, but adapt are termed “adaptors.” In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as drug-induced liver injury (DILI). Participants who experience a transaminase elevation above 3 times the upper limit of normal (× ULN) should be monitored more frequently to determine if they are an “adaptor” or are “susceptible.”

In the majority of DILI cases, elevations in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) precede total bilirubin (TBili) elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same laboratory sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy’s law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant’s individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy’s law) cases to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

- For participants with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

    - Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The participant should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili for suspected cases of Hy's law, additional laboratory tests should include albumin, creatine kinase (CK), direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/international normalized ratio (INR), total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) and collection of serum sample for acetaminophen drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the liver function test (LFT) abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

10.7. Appendix 7: ECG Findings of Potential Clinical Concern

ECG Findings That <u>May</u> Qualify as Adverse Events (AEs)
• Marked sinus bradycardia (rate <40 bpm) lasting minutes. • New PR interval prolongation >280 msec. • New prolongation of QTcF to >480msec (absolute) or by ≥60 msec from baseline. • New-onset atrial flutter or fibrillation, with controlled ventricular response rate: ie, rate <120 bpm. • New-onset type I second-degree (Wenckebach) AV block of >30 seconds' duration. • Frequent premature ventricular complexes (PVCs), triplets, or short intervals (<30 seconds) of consecutive ventricular complexes.
ECG Findings That <u>May</u> Qualify as Serious Adverse Events (SAEs)

• QTcF prolongation >500 msec (will require discontinuation of study drug).
• New ST-T changes suggestive of myocardial ischemia.
• New-onset left bundle branch block (QRS >120 msec).
• New-onset right bundle branch block (QRS >120 msec).
• Symptomatic bradycardia.
• Asystole:
  • In awake, symptom-free patients in sinus rhythm, with documented periods of asystole ≥3.0 seconds or any escape rate <40 bpm, or with an escape rhythm that is below the AV node;
  • In awake, symptom-free patients with atrial fibrillation and bradycardia with 1 or more pauses of at least 5 seconds or longer;
  • Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120 bpm.
• Sustained supraventricular tachycardia (rate >120 bpm) ("sustained" = short duration with relevant symptoms or lasting >1 minute).
• Ventricular rhythms >30 seconds' duration, including idioventricular rhythm (rate <40 bpm), accelerated idioventricular rhythm (40< x <100), and

monomorphic/polymorphic ventricular tachycardia >100 bpm (such as torsades de pointes).

- Type II second-degree (Mobitz II) AV block.
- Complete (third-degree) heart block.

ECG Findings That Qualify as Serious Adverse Events

- Change in pattern suggestive of new myocardial infarction.
- Sustained ventricular tachyarrhythmias (>30 seconds' duration).
- Second- or third-degree AV block requiring pacemaker placement.
- Asystolic pauses requiring pacemaker placement.
- Atrial flutter or fibrillation with rapid ventricular response requiring cardioversion.
- Ventricular fibrillation/flutter.
- At the discretion of the investigator, any arrhythmia classified as an adverse experience.

The enumerated list of major events of potential clinical concern are recommended as "alerts" or notifications from the core ECG laboratory to the investigator and Pfizer study team, and not to be considered as all inclusive of what to be reported as AEs/SAEs.

10.8. Appendix 8: 1997 Update on the 1982 Revised American College of Rheumatology (ACR) Criteria for the Classification of SLE

The American College of Rheumatology (ACR) requires that any 4 or more of the 11 criteria are present, simultaneously or in succession to be classified as having SLE:

Criterion	Definition/Examples
1. Malar rash	Fixed erythema over the malar eminences, tending to spare nasolabial folds
2. Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging, atrophic scarring may occur in older lesions
3. Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
4. Oral ulcers	Usually painless oral or nasopharyngeal ulcers, observed by physician
5. Arthritis	Non-erosive, involving two or more peripheral joints, characterized by tenderness, swelling or effusion
6. Serositis	a. Pleuritis-- convincing history of pleuritic pain or rubbing heard by a physician or evidence of pleural effusion, OR b. Pericarditis--documented by electrocardiogram or rub or evidence of pericardial effusion
7. Renal disorders	a. Persistent proteinuria (>3+ or 500 mcg/day), OR b. Cellular casts in urine--may be red cell, hemoglobin, granular, tubular or mixed
8. Neurological disorder	a. Seizures--in the absence of offending drugs or known metabolic derangements, eg, uremia, ketoacidosis or electrolyte imbalance. OR b. Psychosis--in the absence of offending drugs or known metabolic derangements, eg, uremia, ketoacidosis or electrolyte imbalance.
9. Hematological disorder	a. Hemolytic anemia--with reticulocytosis, OR b. Leukopenia --<4000/cmm total on ≥2 occasions, OR c. Lymphopenia --<1500/cmm or two or more occasions, OR d. Thrombocytopenia --<100,000/cmm in the absence of offending drugs
10. Immunological disorder	a. Anti-DNA antibody to native DNA in abnormal titer, OR b. Anti-SM antibody to SM nuclear antigen, OR c. Anti-Phospholipid antibodies
11. Anti-nuclear antibody	Abnormal titer of ANA by immunofluorescence or an equivalent assay at any point in time and excluding drug causes

Tan EM, Cohen AS, Fries JF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982; 25:1271-7 and Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus [letter]. Arthritis Rheum 1997; 40:1725.

10.9. Appendix 9: Systemic Lupus International Collaborating Clinics (SLICC) criteria

The SLICC criteria for SLE classification requires: 1) Fulfillment of at least four criteria, with at least one clinical criterion AND one immunologic criterion OR 2) Lupus nephritis as the sole clinical criterion in the presence of ANA or anti-dsDNA antibodies.

Clinical Criteria:

1. Acute cutaneous lupus.
2. Chronic cutaneous lupus.
3. Oral ulcers: palate.
4. Nonscarring alopecia (diffuse thinning or hair fragility with visible broken hairs).
5. Synovitis involving two or more joints, characterized by swelling or effusion OR tenderness in two or more joints and thirty minutes or more of morning stiffness.
6. Serositis.
7. Renal.
8. Neurologic.
9. Hemolytic anemia.
10. Leukopenia (<4000/mm^3 at least once).
11. Thrombocytopenia (<100,000/mm^3) at least once.

Immunological Criteria

1. ANA above laboratory reference range.
2. Anti-dsDNA above laboratory reference range, except enzyme linked immunosorbent assay (ELISA): twice above laboratory.
3. Anti-Sm.
4. Antiphospholipid antibody: any of the following.
5. Low complement.
6. Direct Coombs test in the absence of hemolytic anemia.

Petri M, Orbai AM, Alarcón GS, et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum.2012; 64(8):2677-2686.

10.10. Appendix 10: Systemic Lupus International Collaborating Clinics (SLICC)/American College of Rheumatology (ACR) Damage Index for SLE

Score	Item
	Ocular (either eye, by clinical assessment)
0,1	Any cataract ever
0,1	Retinal change or optic atrophy
	Neuropsychiatric
0,1	Cognitive impairment (eg, memory deficit, difficulty with calculation, poor concentration, difficulty in spoken or written language, impaired performance level) OR major psychosis
0,1	Seizures requiring therapy for 6 months
0,1,2	Cerebrovascular accident ever (score 2 if >1)
0,1	Cranial or peripheral neuropathy (excluding optic)
0,1	Transverse myelitis
	Renal
0,1	Estimated or measured glomerular filtration rate <50%
0,1	Proteinuria ≥3.5g/24h
	OR
3	End-stage renal disease (regardless of dialysis or transplantation)
	Pulmonary
0,1	Pulmonary hypertension (right ventricular prominence, or loud P2)
0,1	Pulmonary fibrosis (physical and radiograph)
0,1	Shrinking lung (radiograph)
0,1	Pleural fibrosis (radiograph)
0,1	Pulmonary infarction (radiograph)
	Cardiovascular
0,1	Angina OR coronary artery bypass
0,1,2	Myocardial infarction ever (score 2 if >1)
0,1	Cardiomyopathy (ventricular dysfunction)
0,1	Valvular disease (diastolic murmur or systolic murmur >3/6)
0,1	Pericarditis for 6 months, OR pericardectomy
	Peripheral vascular
0,1	Claudication for 6 months
0,1	Minor tissue loss (pulp space)
0,1,2	Significant tissue loss ever (eg, loss of digit or limb)(score 2 if >1 site)
0,1	Venous thrombosis with swelling, ulceration, OR venous stasis
	Gastrointestinal
0,1,2	Infarction or resection of bowel below duodenum, spleen, liver or gallbladder ever, for any cause (score 2 if >1 site)
0,1	Mesenteric insufficiency
0,1	Chronic peritonitis
0,1	Stricture OR upper gastrointestinal tract surgery ever
0,1	Chronic pancreatitis
	Musculoskeletal
0,1	Muscle atrophy or weakness
0,1	Deforming or erosive arthritis (including reducible deformities, excluding avascular necrosis)
0,1	Osteoporosis with fracture or vertebral collapse (excluding avascular necrosis)
0,1,2	Avascular necrosis (score 2 if >1)
0,1	Osteomyelitis
0,1	Tendon rupture

	Skin
0,1	Scarring chronic alopecia
0,1	Extensive scarring of panniculum other than scalp and pulp space
0,1	Skin ulceration (excluding thrombosis for >6 months)
0,1	**Premature gonadal failure**
0,1	**Diabetes** (regardless of treatment)
0,1,2	**Malignancy** (exclude dysplasia) (score 2 if >1 site)

Damage (nonreversible change, and related to active inflammation) occurring since onset of lupus, ascertained by clinical assessment and present for at least **6 months** unless otherwise stated. Repeat episodes must occur at least 6 months apart to score 2. The same lesion cannot be scored twice.

Gladman D, Goldsmith C, Urowitz M, et al. The Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index for Systemic Lupus Erythematosus International Comparison. J Rheumatol. 2000; 27:373-6.

10.11. Appendix 11: Systemic Lupus Erythematosus Disease Activity Index-2000 (SLEDAI-2K)

Disease activity is assessed using a combination of the clinical history, physical exam (PE), organ specific functional tests, and serologic studies. Check box: If descriptor is present at the time of visit or in the preceding 30 days.

Score	Present	Descriptor	Definition
8		Seizure	Recent onset, exclude metabolic, infectious or drug causes.
8		Psychosis	Altered ability to function in normal activity due to severe disturbance in the perception of reality. Include hallucinations, incoherence, marked loose associations, impoverished thought content, marked illogical thinking, bizarre, disorganized, or catatonic behavior. Exclude uremia and drug causes.
8		Organic Brain Syndrome	Altered mental function with impaired orientation, memory, or other intelligent function, with rapid onset and fluctuating clinical features, inability to sustain attention to environment, plus at least 2 of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, or increased or decreased psychomotor activity. Exclude metabolic, infectious or drug causes.
8		Visual Disturbance	Retinal changes of SLE. Include cytoid bodies, retinal hemorrhages, serious exudate or hemorrhages in the choroid, or optic neuritis. Exclude hypertension, infection, or drug causes.
8		Cranial Nerve Disorder	New onset of sensory or motor neuropathy involving cranial nerves.
8		Lupus Headache	Severe, persistent headache; may be migrainous, but must be nonresponsive to narcotic analgesia.
8		CVA	New onset of cerebrovascular accident(s). Exclude arteriosclerosis.
8		Vasculitis	Ulceration, gangrene, tender finger nodules, periungual infarction, splinter hemorrhages, or biopsy or angiogram proof of vasculitis.
4		Arthritis	≥ 2 joints with pain and signs of inflammation (ie, tenderness, swelling, or effusion).
4		Myositis	Proximal muscle aching/weakness, associated with elevated creatine phosphokinase/adolase or electromyogram changes or a biopsy showing myositis.
4		Urinary Casts	Heme-granular or red blood cell casts.
4		Hematuria	>5 red blood cells/high power field. Exclude stone, infection or other cause.

Score	Present	Descriptor	Definition
4		Proteinuria	>0.5 gram/24 hrs.
4		Pyuria	>5 white blood cells/high power field. Exclude infection.
2		Rash	Inflammatory type rash.
2		Alopecia	Abnormal, patchy or diffuse loss of hair.
2		Mucosal Ulcers	Oral or nasal ulcerations.
2		Pleurisy	Pleuritic chest pain with pleural rub or effusion, or pleural thickening.
2		Pericarditis	Pericardial pain with at least 1 of the following: rub, effusion, or electrocardiogram or echocardiogram confirmation.
2		Low Complement	Decrease in C3 or C4 below the lower limit of normal for testing laboratory.
2		Increased DNA binding	Increased DNA binding by Farr assay above normal range for testing laboratory.
1		Fever	>38°C. Exclude infectious cause.
1		Thrombocytopenia	<100,000 platelets / x 10^9/ L, exclude drug causes.
1		Leukopenia	<3,000 white blood cell / x 10^9/ L, exclude drug causes.
		TOTAL SCORE	(Sum of weights next to descriptors marked present)

Gladman DD, Ibañez D, Urowitz MB. Systemic lupus erythematosus disease activity index 2000. J Rheumatol. 2002 Feb;29(2):288-91.

10.12. Appendix 12: British Isles Lupus Assessment Group Index (BILAG)-2004

- **Only record manifestations/items due to SLE Disease Activity**
- **Assessment refers to manifestations occurring in the last 4 weeks (compared with the previous 4 weeks)**
- **TO BE USED WITH THE GLOSSARY**

Record: **ND** **Not Done**
0 **Not present**
1 **Improving**
2 **Same**
3 **Worse**
4 **New**
Yes/No OR Value (where indicated)
***Y/N Confirm this is due to SLE activity (Yes/No)**

CONSTITUTIONAL
1. Pyrexia - documented > 37.5ºC ( )
2. Weight loss - unintentional > 5% ( )
3. Lymphadenopathy/splenomegaly ( )
4. Anorexia ( )

MUCOCUTANEOUS
5. Skin eruption - severe ( )
6. Skin eruption - mild ( )
7. Angio-oedema - severe ( )
8. Angio-oedema - mild ( )
9. Mucosal ulceration - severe ( )
10. Mucosal ulceration - mild ( )
11. Panniculitis/Bullous lupus - severe ( )
12. Panniculitis/Bullous lupus - mild ( )
13. Major cutaneous vasculitis/thrombosis ( )
14. Digital infarcts or nodular vasculitis ( )
15. Alopecia - severe ( )
16. Alopecia - mild ( )
17. Peri-ungual erythema/chilblains ( )
18. Splinter haemorrhages ( )

NEUROPSYCHIATRIC
19. Aseptic meningitis ( )
20. Cerebral vasculitis ( )
21. Demyelinating syndrome ( )
22. Myelopathy ( )
23. Acute confusional state ( )
24. Psychosis ( )
25. Acute inflammatory demyelinating polyradiculoncuropathy ( )
26. Mononeuropathy (single/multiplex) ( )
27. Cranial neuropathy ( )
28. Plexopathy ( )
29. Polyneuropathy ( )
30. Seizure disorder ( )
31. Status epilepticus ( )
32. Cerebrovascular disease (not due to vasculitis) ( )
33. Cognitive dysfunction ( )
34. Movement disorder ( )
35. Autonomic disorder ( )
36. Cerebellar ataxia (isolated) ( )
37. Lupus headache - severe unremitting ( )
38. Headache from IC hypertension ( )

MUSCULOSKELETAL
39. Myositis - severe ( )
40. Myositis - mild ( )
41. Arthritis (severe) ( )
42. Arthritis (moderate)/Tendonitis/Tenosynovitis ( )
43. Arthritis (mild)/Arthralgia/Myalgia ( )

CARDIORESPIRATORY
44. Myocarditis - mild ( )
45. Myocarditis/Endocarditis + Cardiac failure ( )
46. Arrhythmia ( )
47. New valvular dysfunction ( )
48. Pleurisy/Pericarditis ( )
49. Cardiac tamponade ( )
50. Pleural effusion with dyspnoea ( )
51. Pulmonary haemorrhage/vasculitis ( )
52. Interstitial alveolitis/pneumonitis ( )
53. Shrinking lung syndrome ( )
54. Aortitis ( )
55. Coronary vasculitis ( )

GASTROINTESTINAL
56. Lupus peritonitis ( )
57. Abdominal serositis or ascites ( )
58. Lupus enteritis/colitis ( )
59. Malabsorption ( )
60. Protein losing enteropathy ( )
61. Intestinal pseudo-obstruction ( )
62. Lupus hepatitis ( )
63. Acute lupus cholecystitis ( )
64. Acute lupus pancreatitis ( )

OPHTHALMIC
65. Orbital inflammation/myositis/proptosis ( )
66. Keratitis - severe ( )
67. Keratitis - mild ( )
68. Anterior uveitis ( )
69. Posterior uveitis/retinal vasculitis - severe ( )
70. Posterior uveitis/retinal vasculitis - mild ( )
71. Episcleritis ( )
72. Scleritis - severe ( )
73. Scleritis - mild ( )
74. Retinal/choroidal vaso-occlusive disease ( )
75. Isolated cotton-wool spots (cytoid bodies) ( )
76. Optic neuritis ( )
77. Anterior ischaemic optic neuropathy ( )

RENAL
78. Systolic blood pressure (mm Hg) value ( ) **Y/N***
79. Diastolic blood pressure (mm Hg) value ( ) **Y/N***
80. Accelerated hypertension Yes/No ( )
81. Urine dipstick protein (+=1, ++=2, +++=3) ( ) **Y/N***
82. Urine albumin-creatinine ratio mg/mmol ( ) **Y/N***
83. Urine protein-creatinine ratio mg/mmol ( ) **Y/N***
84. 24 hour urine protein (g) value ( ) **Y/N***
85. Nephrotic syndrome Yes/No ( )
86. Creatinine (plasma/serum) µmol/l ( ) **Y/N***
87. GFR (calculated) ml/min/1.73 m^2 ( ) **Y/N***
88. Active urinary sediment Yes/No ( )
89. Active nephritis Yes/No ( )

HAEMATOLOGICAL
90. Haemoglobin (g/dl) value ( ) **Y/N***
91. Total white cell count (x 10^9/l) value ( ) **Y/N***
92. Neutrophils (x 10^9/l) value ( ) **Y/N***
93. Lymphocytes (x 10^9/l) value ( ) **Y/N***
94. Platelets (x 10^9/l) value ( ) **Y/N***
95. TTP ( )
96. Evidence of active haemolysis Yes/No ( )
97. Coombs' test positive (isolated) Yes/No ( )

Isenberg DA, Rahman A, Allen E, et al. BILAG 2004. Development and initial validation of an updated version of the British Isles lupus assessment group's disease activity index for participants with systemic lupus erythematosus. Rheumatology 2005;44:9026.

Note: Direct Coombs test to confirm hemolytic anemia may be performed at any visit but should only be performed if the investigator suspects a clinically significant hmolytic anemia that will be scored on the BILAG.

10.13. Appendix 13: List of Prohibited and Permitted Concomitant Medications

Stable dose is defined as no new therapy or change in standard-of-care therapies as above within 12 weeks of Day 1 for immunosuppressives or within 2 weeks of Day 1 for corticosteroids.

Medications		**Treatment Period**	**Follow-up Period**
Corticosteroids	Parenteral injections (eg, IA, IM, IV or epidural injection)	Prohibited • An IM dose of methylprednisolone (DepoMedrol) 60 mg (or equivalent) administered as 1 injection can be substituted for the oral corticosteroid allowed increase described in the protocol. • Oral or parenteral (IV or IM) corticosteroids at doses >40 mg per day of prednisone (or equivalent) within 8 weeks of Day 1 and on study. • Corticosteroids are permitted as clinically indicated for hypersensitivity reactions, insect bites or asthmatic exacerbations (up to 125 mg IV hydrocortisone or oral methylprednisolone dose pack with top dose of oral methylprednisolone 24 mg [or prednisone 30 mg or oral equivalent]) up to Week 12 and between Weeks 24 and 40. • Epidural corticosteroid injections are prohibited within 12 weeks of Day 1 and on study. • Intra-articular corticosteroids or hyaluronic acid >4 weeks of Day 1 and on study.	Permitted
	Oral (prednisone or equivalent)	Permitted • Prednisone up to 20 mg/day (or equivalent) provided dose is stable for at least two weeks prior to Day 1 and corticosteroids were started at least 8 weeks prior to Day 1. If a participant is receiving antimalarials in combination with corticosteroids as background medication without an immunosuppressant, the minimum dose of corticosteroids allowed at baseline is 5 mg/day prednisone or equivalent. • Participants with active disease at baseline can receive the increased dose of corticosteroids as early as Day 1, up to	Permitted

Medications		Treatment Period	Follow-up Period
		the Week 4 visit and then the dose should be tapered back to the preceding dose. The maximum additional dose allowed is 10 mg/day prednisone equivalence above the Day 1 dose level, for a maximum of 14 days after which the previous dose must be resumed. • A single intramuscular dose of methylprednisolone (Depo-Medrol; maximum dose 60 mg) is allowed up to Week 4 as an alternative to increasing the oral dose. • Steroid tapering is required (if appropriate) between Weeks 2-12 and Weeks 24-40; reductions of steroids should not take place outside of these windows. • For participants who have had corticosteroids tapered during the allowed windows, the corticosteroid dose may be increased once during each of the 2 tapering windows to the dose preceding the last taper step. • Rectal administration of corticosteroids, if necessary, should be short-term and using topical preparations.	
	Topical	Permitted • Low potency topical steroids [class 6 (mild, such as desonide) or class 7 (least potent, such as hydrocortisone)] are allowed except on day of study visit. • Medium or high potency topical corticosteroids must be discontinued ≥4 weeks prior to Day 1.	
Immunosuppressive or immunomodulatory agents including methotrexate (MTX), azathioprine (AZA) 6-mercaptopurine (6-MP), leflunomide, mizoribine or mycophenolate (including mycophenolate mofetil, mycophenolate mofetil hydrochloride, and mycophenolate sodium).		Permitted • Provided preexisting dose is as stable as possible for 12 weeks prior to Day 1. • No new immunosuppressives or increase in dose is allowed during the treatment period. • Participants can be on 1 of the following cytotoxic agents: MTX (maximum 25 mg/week), AZA (maximum 200 mg/day), 6-MP, (maximum 100 mg/day) mizoribine (maximum 150 mg/day), leflunomide (maximum	Permitted

Medications	Treatment Period	Follow-up Period
	dose 20 mg/day), mycophenolate (2 g/day of MMF or 1.44 g/d of MPA), but not on any combination of these cytotoxic agents. • Substitution of one immunosuppressive medication or antimalarial drug for another may be permitted for safety related issues after discussion with the sponsor.	
Sulfasalazine	Prohibited	Prohibited
Thymopetidum	Prohibited Must be discontinued 4 weeks prior to baseline.	Prohibited
Antimalarials (eg, hydroxychloroquine, chloroquine,)	Permitted • Provided preexisting dose is stable for at least 12 weeks and treatment is not started/or stopped within 12 weeks of Day 1. • No new antimalarial drugs or increase in dose is allowed during the treatment period. • Maximal doses: HCQ 400 mg/day; chloroquine 250 mg/day. • Antimalarials produced by a licensed compounding pharmacy (eg, quinacrine) in the country of administration and using pharmaceutical grade components are allowed. • Substitution of one antimalarial medication for another may be permitted for safety related issues after discussion with the sponsor.	Permitted
High potency opioid (eg, fentanyl, morphine, buprenorphine, hydromorphone, methadone, oxycodone)	Prohibited for at home use by the participant.	Prohibited

Medications	Treatment Period	Follow-up Period
Lower potency	Permitted except for within 12 hours of scheduled clinical visits: • Tramadol (Ultram, Zydol; Zamadol, Ultracet, Tramal) ≤300 mg/day. • Hydrocodone (Vicodin, Lortab) ≤30 mg/day. • Codeine (Paveral, Tylenol #2 and #3) ≤200 mg/day. • Propoxyphene HCl (Darvon, Darvocet, Doloxene), Propoxyphene napsylate (DarvonN, DarvocetN 100) ≤300 mg/day	
Thalidomide, lenalidomide, dapsone, adrenocorticotropic hormone (ACTH) by injection	Prohibited during treatment and within 28 days of Day 1	Prohibited
Investigational or marketed biologics (including but not limited to), etanercept, infliximab, certolizumab, adalimumab, golimumab, anakinra, belimumab, tocilizumab, abatacept, anifrolumab & ustekinumab.	Prohibited during treatment and prior to Day 1 • Anti TNF therapies (etanercept, infliximab, certolizumab, adalimumab, golimumab), belimumab or anakinra within 12 weeks of Day 1. • Tocilizumab, abatacept or ustekinumab within 24 weeks of Day 1. • Rituximab or any other lymphocyte depleting biologic therapy within 24 weeks of Day 1. • Any other biologic therapy (including investigational and approved agents) within 12 weeks of Day 1.	Prohibited
HMG CoA reductase inhibitors ("statins" such as simvastatin, rosuvastatin, atorvastatin, lovastatin, pravastatin, fluvastatin)	Permitted	Permitted
Angiotensin pathway antihypertensives (eg, ACE inhibitors, angiotensin receptor blockers (ARBs)	Permitted	Permitted
Parental (IV or IM) antibiotics (antibacterials, antivirals, antifungals, or anti-parasitic agents)	Prohibited 60 days prior to Day 1. Permitted during treatment period.	Permitted
Cyclophosphamide or chlorambucil or other alkylating agents	Prohibited during treatment and 24 weeks prior to Day 1	Prohibited

Medications	Treatment Period	Follow-up Period
CNIs (cyclosporine, tacrolimus, picrolimus, or voclosporin)	Prohibited during treatment and within 12 weeks of Day 1: • No systemic calcineurin inhibitors within 12 weeks of Day 1. • Optic topical preparations (eye drops) are permitted on study. • Topical creams and ointments must be discontinued within 4 weeks of Day 1.	Prohibited
Other investigational drugs or investigational combinations	Prohibited	Prohibited
B-cell depleting therapy (eg, rituximab, epratuzumab, atacicept)	Prohibited during treatment and 24 weeks or 5 half-lives (if known), whichever is longer prior to Day 1.	Prohibited
Non B cell depleting therapies eg, alemtuzumab [Lemtrada®, CamPath®] or total lymphoid irradiation, etc	Prohibited	Prohibited
Any live (live attenuated) vaccines	Prohibited	Prohibited
ANY bone marrow stimulating agents (eg, filgrastim, pegfilgrastim, erythropoietin	Prohibited during treatment and for 12 weeks prior to screening.	Prohibited
Inactivated vaccine and boosters	Permitted	Permitted
JAK Kinase inhibitors (eg, tofacitinib, ruxolitinib)	Prohibited	Prohibited
NSAIDS	Permitted, participants should endeavor to maintain a stable dose during the study duration PRN NSAID are permitted for treatment of non-SLE events eg. fever, headache, they should not be taken within 12 hrs of joint assessment.	
Moderate and strong CYP3A inducers: Efavirenz nevirapine barbiturates carbamazepine modafinil phenobarbital phenytoin rifampin troglitazone pioglitazone rifabutin St. John's Wort	Prohibited	Permitted after a minimum of 48 hours (approximately 5 half-lives) following last dose of study intervention.

Medications	Treatment Period	Follow-up Period
Strong P-gp inhibitors: Quinidine P-gp substrates with narrow TI: Digoxin Substrates of OCT2/MATE: dofetilide		
Herbal Medication	Herbal medications with known pharmaceutical properties are allowed, only if there is documented evidence of no moderate to strong CYP3A induction, otherwise these medications must be discontinued at least 4 weeks prior to randomization.	Permitted after a minimum of 48 hours (approximately 5 half-lives) following last dose of study intervention.
Colchicine	Permitted: Dose must not exceed 0.6 mg BID for at least 8 weeks prior to Day 1.	Permitted after a minimum of 48 hours (approximately 5 half-lives) following last dose of study intervention.
Medications know to prolong QT interval with potential risk of Torsades de Pointes. Antiarrhythmics (eg, disopyramide, procainamide, quinidine, sotalol) Macrolides (eg, azithromycin, clarithromycin, erythromycin) Fluoroquinolones (eg, ciprofloxacin, levofloxacin, moxifloxacin) Antifungals (eg. fluconazole, ketoconazole, pentamidine, voriconazole) Antipsychotics (eg, haloperidol, thioridazine, ziprasidone) Antidepressants (eg, citolopram, escitalopram) Opioids (eg, methadone) Others (eg, cocaine, cilostazol, donepezil)	Prohibited; This is general guidance and specific medications should be checked. Please contact Pfizer clinical with any questions.	Permitted after a minimum of 48 hours (approximately 5 half-lives) following last dose of study intervention.

10.14. Appendix 14: Oral Corticosteroids, Systemic Equivalencies

Glucocorticoid	**Equivalent Dose (mg)**
Short Acting	
Cortisone	25
Hydrocortisone	20
Intermediate Acting	
Methylprednisolone	4
Prednisolone	5
Prednisone	5
Triamcinolone	4
Long Acting	
Betamethasone	0.6
Dexamethasone	0.75

Lacy CF, Armstrong LL, Goldman MP, et al. *Drug Information Handbook*, Ninth Edition. Cleveland, OH: LexiComp Inc;2001-2002:1354.

10.15. Appendix 15: Columbia Suicide Severity Rating Scale (CSSRS)

C-SSRS for Screening (Baseline) Visit:

At the screening visit (baseline), if there are "yes" answers on items 4 and/or 5 in the past year, or on any question in the suicidal behavior section of the C-SSRS in the past 5 years, the participant will be excluded from the study.

SUICIDAL IDEATION		
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime: Time He/She Felt Most Suicidal**	**Past __ Months**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
INTENSITY OF IDEATION		
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. Lifetime - ***Most Severe Ideation:*** _____ (*Type # (1-5)*) _____ (*Description of Ideation*) Past X Months - ***Most Severe Ideation:*** _____ (*Type # (1-5)*) _____ (*Description of Ideation*)	Most Severe	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	___	___

Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____	____

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**	**Past __ Years**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	**Yes No** ☐ ☐ Total # of Attempts _____	**Yes No** ☐ ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	**Yes No** ☐ ☐	**Yes No** ☐ ☐

Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted ____	Yes ☐ No ☐ Total # of interrupted ____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted ____	Yes ☐ No ☐ Total # of aborted ____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐

Suicidal Behavior: Suicidal behavior was present during the assessment period?		Yes ☐ No ☐	Yes ☐ No ☐
Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* ____	*Enter Code* ____	*Enter Code* ____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* ____	*Enter Code* ____	*Enter Code* ____

C-SSRS for Post-Baseline Visits:

At Week 24 visit the Since Last Visit version of the C-SSRS should be utilized. The Since Last Visit version refers to the participants experience since their last visit. If there are "yes" answers on items 4 and/or 5 or on any suicidal behavior question of the C-SSRS, the participant will be discontinued from treatment and referred to a mental health professional for appropriate evaluation and treatment. If the participant cannot be seen by a mental health professional within 24 hours, then the participant should be sent to a local emergency room for psychiatric assessment.

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Since Last Visit**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐
INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). ***Most Severe Ideation:*** ____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____
Duration ***When you have the thoughts, how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Since Last Visit**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes No** ☐ ☐ Total # of Attempts _____ **Yes No** ☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes No** ☐ ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes No** ☐ ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes No** ☐ ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes No** ☐ ☐
Suicide:	**Yes No** ☐ ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

Posner K, Oquendo MA, Gould M, et al. Columbia classification algorithm of suicide assessment (C-CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. Am J Psychiatry 2007;164(7):1035-43.

10.16. Appendix 16: Select Laboratory Values from the Common Terminology Criteria for Adverse Events (CTCAE) v4.03

CTCAE v4.03 Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**CTCAE v4.03** Adverse Event Term Definition
Alanine aminotransferase (ALT) increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	A finding based on laboratory test results that indicate an increase in the level of alanine aminotransferase (ALT or SGPT) in the blood specimen.
Alkaline phosphatase increased	>ULN 2.5 x ULN	>2.5 5.0 x ULN	>5.0 20.0 x ULN	>20.0 x ULN	A finding based on laboratory test results that indicate an increase in the level of alkaline phosphatase in a blood specimen.
Anemia	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated	A disorder characterized by a reduction in the amount of hemoglobin in 100 ml of blood. Signs and symptoms of anemia may include pallor of the skin and mucous membranes, shortness of breath, palpitations of the heart, soft systolic murmurs, lethargy, and fatigability.
APTT Prolonged	>ULN - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN; hemorrhage	-	An abnormal laboratory test result in which the partial thromboplastin time is found to be greater than the control value. As a possible indicator of coagulopathy, a prolonged partial thromboplastin time (PTT) may occur in a variety of diseases and disorders, both primary and related to treatment.
Aspartate aminotransferase (AST) increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	A finding based on laboratory test results that indicate an increase in the level of aspartate aminotransferase (AST or SGOT) in a blood specimen.

CTCAE v4.03 Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**CTCAE v4.03** Adverse Event Term Definition
Blood bilirubin increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 10.0 x ULN	>10.0 x ULN	A finding based on laboratory test results that indicate an abnormally high level of bilirubin in the blood. Excess bilirubin is associated with jaundice.
Cholesterol high	>ULN - 300 mg/dL; >ULN - 7.75 mmol/L	>300 - 400 mg/dL; >7.75 - 10.34 mmol/L	>400 - 500 mg/dL; >10.34 - 12.92 mmol/L	>500 mg/dL; >12.92 mmol/L	A finding based on laboratory test results that indicate higher than normal levels of cholesterol in a blood specimen.
CPK increased	>ULN - 2.5 x ULN	>2.5 x ULN - 5 x ULN	>5 x ULN - 10 x ULN	>10 x ULN	A finding based on laboratory test results that indicate an increase in levels of creatine phosphokinase in a blood specimen.
Hemoglobin increased	Increase in >0 - 2 gm/dL above ULN or above baseline if baseline is above ULN	Increase in >2 - 4 gm/dL above ULN or above baseline if baseline is above ULN	Increase in >4 gm/dL above ULN or above baseline if baseline is above ULN	-	A finding based on laboratory test results that indicate increased levels of hemoglobin in a biological specimen.
Hypercalcemia	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; Ionized calcium >ULN - 1.5 mmol/L	Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L; Ionized calcium >1.5 - 1.6 mmol/L; symptomatic	Corrected serum calcium of >12.5 - 13.5 mg/dL; >3.1 - 3.4 mmol/L; Ionized calcium >1.6 - 1.8 mmol/L; hospitalization indicated	Corrected serum calcium of >13.5 mg/dL; >3.4 mmol/L; Ionized calcium >1.8 mmol/L; life-threatening consequences	A disorder characterized by laboratory test results that indicate an elevation in the concentration of calcium (corrected for albumin) in blood.
Hyperglycemia	Fasting glucose value >ULN - 160 mg/dL; Fasting glucose value >ULN - 8.9 mmol/L	Fasting glucose value >160 - 250 mg/dL; Fasting glucose value >8.9 - 13.9 mmol/L	>250 - 500 mg/dL; >13.9 - 27.8 mmol/L; hospitalization indicated	>500 mg/dL; >27.8 mmol/L; life-threatening consequences	A disorder characterized by laboratory test results that indicate an elevation in the concentration of blood sugar. It is usually an indication of diabetes mellitus or glucose intolerance.
Hyperkalemia	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0 - 7.0 mmol/L; hospitalization indicated	>7.0 mmol/L; life-threatening consequences	A disorder characterized by laboratory test results that indicate an elevation in the concentration of potassium in the blood; associated with kidney

CTCAE v4.03 Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**CTCAE v4.03** Adverse Event Term Definition
					failure or sometimes with the use of diuretic drugs.
Hypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L; hospitalization indicated	>160 mmol/L; life-threatening consequences	A disorder characterized by laboratory test results that indicate an elevation in the concentration of sodium in the blood.
Hypertriglyceridemia	150 mg/dL - 300 mg/dL; 1.71 mmol/L - 3.42 mmol/L	>300 mg/dL - 500 mg/dL; >3.42 mmol/L - 5.7 mmol/L	>500 mg/dL - 1000 mg/dL; >5.7 mmol/L - 11.4 mmol/L	>1000 mg/dL; >11.4 mmol/L; life-threatening consequences	A disorder characterized by laboratory test results that indicate an elevation in the concentration of triglyceride concentration in the blood.
Hyperuricemia	>ULN - 10 mg/dL (0.59 mmol/L) without physiologic consequences	-	>ULN - 10 mg/dL (0.59 mmol/L) with physiologic consequences	>10 mg/dL; >0.59 mmol/L; life-threatening consequences	A disorder characterized by laboratory test results that indicate an elevation in the concentration of uric acid.
Hypoalbuminemia	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	≥2 g/dL; <20 g/L	Life-threatening consequences; urgent intervention indicated	A disorder characterized by laboratory test results that indicate a low concentration of albumin in the blood.
Hypocalcemia	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L; symptomatic	Corrected serum calcium of <7.0 - 6.0 mg/dL; <1.75 - 1.5 mmol/L; Ionized calcium <0.9 - 0.8 mmol/L; hospitalization indicated	Corrected serum calcium of <6.0 mg/dL; <1.5 mmol/L; Ionized calcium <0.8 mmol/L; life-threatening consequences	A disorder characterized by laboratory test results that indicate a low concentration of calcium (corrected for albumin) in the blood.
Hypoglycemia	<LLN - 55 mg/dL; <LLN - 3.0 mmol/L	<55 - 40 mg/dL; <3.0 - 2.2 mmol/L	<40 - 30 mg/dL; <2.2 - 1.7 mmol/L	<30 mg/dL; <1.7 mmol/L; life-threatening consequences; seizures	A disorder characterized by laboratory test results that indicate a low concentration of glucose in the blood.
Hypokalemia	<LLN - 3.0 mmol/L	<LLN - 3.0 mmol/L; symptomatic; intervention indicated	<3.0 - 2.5 mmol/L; hospitalization indicated	<2.5 mmol/L; life-threatening consequences	A disorder characterized by laboratory test results that indicate a low concentration of potassium in the blood.

CTCAE v4.03 Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**CTCAE v4.03** Adverse Event Term Definition
Hyponatremia	<LLN - 130 mmol/L	-	<130 - 120 mmol/L	<120 mmol/L; life-threatening consequences	A disorder characterized by laboratory test results that indicate a low concentration of sodium in the blood.
Hypophosphatemia	<LLN - 2.5 mg/dL; <LLN - 0.8 mmol/L	<2.5 - 2.0 mg/dL; <0.8 - 0.6 mmol/L	<2.0 - 1.0 mg/dL; <0.6 - 0.3 mmol/L	<1.0 mg/dL; <0.3 mmol/L; life-threatening consequences	A disorder characterized by laboratory test results that indicate a low concentration of phosphates in the blood.
Lipase increased	>ULN 1.5 x ULN	>1.5 2.0 x ULN	>2.0 5.0 x ULN	>5.0 x ULN	A finding based on laboratory test results that indicate an increase in the level of lipase in a biological specimen.
Lymphocyte count increased	-	>4000/mm^3 20,000/mm^3	>20,000/mm^3	-	A finding based on laboratory test results that indicate an abnormal increase in the number of lymphocytes in the blood, effusions or bone marrow.
Neutrophil count decreased	<LLN - 1500/mm^3; <LLN - 1.5 x 10e9 /L	<1500 - 1000/mm^3; <1.5 - 1.0 x 10e9 /L	<1000 - 500/mm^3; <1.0 - 0.5 x 10e9 /L	<500/mm^3; <0.5 x 10e9 /L	A finding based on laboratory test results that indicate a decrease in number of neutrophils in a blood specimen.
Platelet count decreased	<LLN - 75,000/mm^3; <LLN - 75.0 x 10e9 /L	<75,000 - 50,000/mm^3; <75.0 - 50.0 x 10e9 /L	<50,000 - 25,000/mm^3; <50.0 - 25.0 x 10e9 /L	<25,000/mm^3; <25.0 x 10e9 /L	A finding based on laboratory test results that indicate a decrease in number of platelets in a blood specimen.
Proteinuria	1+ proteinuria; urinary protein <1.0 g/24 hrs	Adults: 2+ proteinuria; urinary protein 1.0 - 3.4 g/24 hrs;	Adults: urinary protein >=3.5 g/24 hrs;	-	A disorder characterized by laboratory test results that indicate the presence of excessive protein in the urine. It is predominantly albumin, but also globulin.
Serum amylase increased	>ULN 1.5 x ULN	>1.5 2.0 x ULN	>2.0 5.0 x ULN	>5.0 x ULN	A finding based on laboratory test results that indicate an increase in the levels of amylase in a serum specimen.

Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 published May 28, 2009 (V 4.03: June 14, 1010). U.S. Department of Health and Human Services/National Institute of Health/ National Cancer Institute.

10.17. Appendix 17: Guidelines for Participant Safety Monitoring and Discontinuation

These guidelines for participant safety monitoring and discontinuation are to be applied to all participants in study B7931028. Additional individual participant monitoring is at the discretion of the investigator and dependent on any perceived safety concerns. Unscheduled clinical labs may be obtained at any time during the study to assess such concerns, and a participant may be withdrawn at any time at the discretion of the investigator. If it is not possible for a participant to return to a site for a repeat labs prior to the next scheduled visit, the investigator should note this in the source document. For participants who have a history of known intermittent out of range laboratory assessments, repeat assessments between scheduled visits may be waived by the Pfizer Clinical team following discussion with the principal investigator.

10.17.1. Safety Monitoring

- The following laboratory abnormalities require re-testing within 1 week:
  - Neutrophil counts <1000 neutrophils/mm^3;
  - Lymphocyte counts <500 lymphocytes/mm^3;
  - Platelet counts <50,000 platelets/mm^3;
  - eGFR that is 40% or greater reduction from baseline,
  - UPCR >3 mg/mg
  - Any single AST and/or ALT elevation ≥3 times the upper limit of normal (repeat laboratory testing should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, GGT, PT [prothrombin time] with INR [international normalized ratio], and alkaline phosphatase), regardless of the total bilirubin. (Please note that 3 times the upper limit of normal increases in ALT, AST need confirmation on separate blood draw before undertaking thorough evaluation for liver injury);
  - Any single hemoglobin value <8.0 g/dL or one that drops 2 gm/dL below baseline;
  - For women of child-bearing potential with any positive urine beta-human chorionic gonadotrophin (β-hCG) test, the participant will have study drug interrupted and a serum sample submitted to the central laboratory for β-hCG testing.

10.17.2. Permanent Discontinuation of Study Intervention

The sponsor's Clinical team should be consulted as soon as possible and participants may be discontinued from study intervention if any of the following occur during the study. All participants who are randomized should be encouraged to remain in the study through to the end of the double-blind period for safety and efficacy assessments, whether or not they continue to receive study intervention for the full 52 week treatment period, to reduce

missing data as much as possible. Participants may be discontinued from study intervention if any of the following occur during the study:

- Serious infections defined as any infection (viral, bacterial, and fungal) requiring parenteral antimicrobial therapy, hospitalization for treatment, or meeting other criteria that require the infection to be classified as serious adverse event;
- Other serious or severe AEs, at the discretion of the investigator or sponsor;
- Participants who require high potency opioids for pain control for more than 10 consecutive days or within the last 7 days before the last dose;
- All of the following laboratory abnormalities require discontinuation if they are confirmed (confirmation through re-testing should occur within 1 week):
  - Two sequential absolute neutrophil counts $<0.75 \times 10^9$/L ($<750/mm^3$);
  - Two sequential platelet counts $<50 \times 10^9$/L ($<50,000/mm^3$);
  - Two sequential AST or ALT elevation ≥3 times the upper limit of normal with at least one total bilirubin value ≥2 times the upper limit of normal[a];
  - Two sequential AST or ALT elevation ≥3 times the upper limit of normal accompanied by signs or symptoms consistent with hepatic injury[a];
  - Two sequential AST or ALT elevation ≥5 times the upper limit of normal, regardless of total bilirubin or accompanying signs or symptoms[a];
  - Female participants found to be pregnant during the study;
  - Marked prolongation of the QTcF interval to >500 msec or >60 msec change from baseline (Day 1) ECG. If QTcF exceeds these limits, the ECG should be repeated 2 more times and the average of the 3 QTcFs should be used to determine the discontinuation;
  - Reduction of eGFR cystatin of greater than 40% from baseline value. If the eGFR cystatin decreases by greater than 40%, the test should be repeated to confirm the decrease, study intervention discontinued and the participant refered to a nephrologist;
  - Increase of UPCr to >3 mg/mg for any participant who entered the study with a UPCR ≤2 mg/mg Or a 50% increase in UPCR for participants who entered the study with a UPCR >2 mg/mg;

- Participants who are definitively diagnosed with any thromboembolic event such as a pulmonary embolism or deep venous thrombosis, arterial thrombosis or cerebrovascular events (thromboembolic stroke, transient ischemic attack [TIA], etc.) for which the participant is hospitalized and/or requires intravenous or invasive (surgical or interventional radiological) treatment. Participants should have appropriate diagnostic testing performed to document the thrombotic event (ultrasound, CT angiography, lung scintigraphy, pulmonary angiography, CT venography) and the Pfizer medical monitor should be notified;

- Other serious or severe AEs, after consultation with the Pfizer medical monitor or designee.

a. In each case, there is a need for additional investigations, such as review of ethanol, recreational drug and dietary supplement consumption; testing for acute hepatitis A, B or C infection and biliary tract imaging should be promptly discussed with the Pfizer medical monitor or designee.

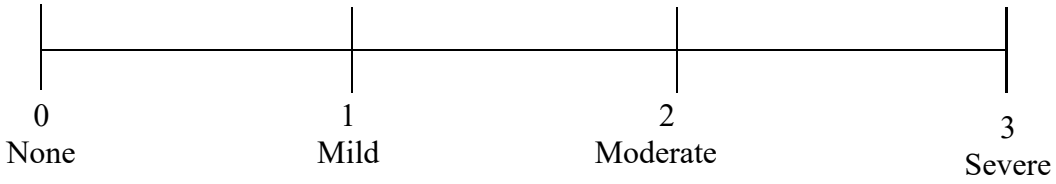
Any participant who elects to discontinue study intervention but does not withdraw consent should return for all scheduled visits and safety and efficacy assessments, and complete all study-specified assessments through Week 56. Any participant who withdraws consent must enter follow-up with their first follow-up visit occurring 1 week after their last dose whenever possible, until the event has returned to normal or baseline levels or is deemed clinically stable. If a participant is lost to follow up, the site should document attempts to contact the participant to continue in the study by registered mail (at last 2 attempts); phone calls and offers to provide transportation to the clinic should be extended. The procedures scheduled for the early withdrawal visit will be performed on the last day the participant takes study intervention or as soon as possible thereafter. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by the participant to provide this information.

Participants will be followed post drug discontinuation for 28 days. Additional follow-up visits may occur as needed until any clinically relevant abnormalities or adverse events have resolved, returned to a baseline state, or are deemed clinically stable.

10.18. Appendix 18: Physician Global Assessment (PhGA)

Evaluate the participants lupus activity since the last visit using the visual analog scale (VAS):

Place a vertical mark (|) across the line in the position that best describes your response.



[Note: Scale will be 100 mm in length]

10.19. Appendix 19*: modified* SELENA-SLEDAI Flare Index (mSSFI)

Mild or Moderate Flare

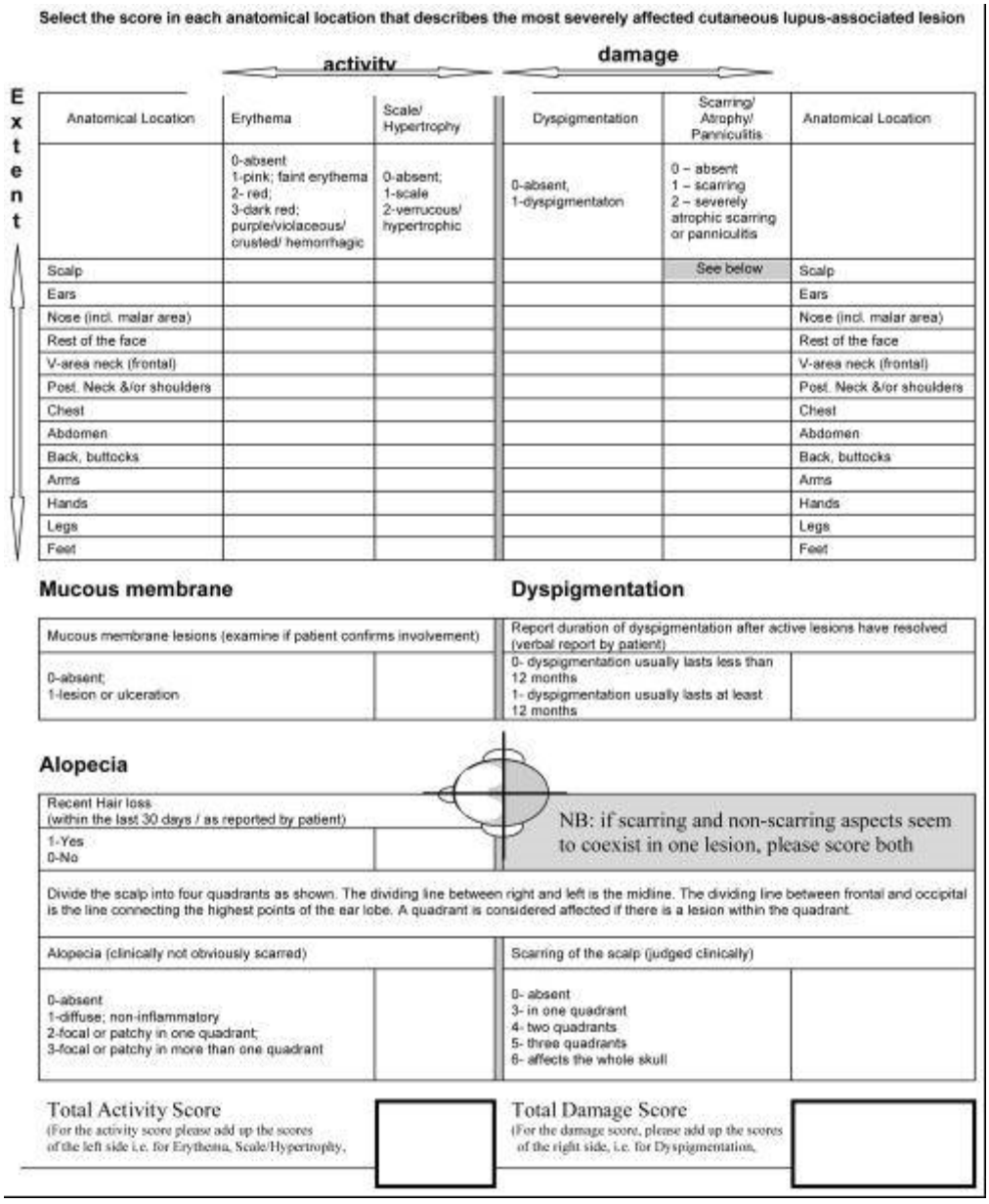
Increase in SLEDAI instrument score of 3 points or more (but not to more than 12)
New/worse: Discoid, photosensitive, profundus, bullous lupus,
Nasopharyngeal ulcers
Pleuritis
Pericarditis
Arthritis
Fever (SLE)
Increase in prednisone, but not to >0.5 mg/kg/day
Added NSAID or hydroxychloroquine for SLE activity
≥1.0 increase in PGA score, but not to more than 2.5

Severe Flare

Increase in SLEDAI instrument score to greater than 12
New/worse: CNS-SLE
Cutaneous vasculitis,
Vasculitis
Nephritis
Myositis
Plt <60,000
Hemolytic anemia: Hb <70 g/L or decrease in Hb >30 g/L
Requiring: double prednisone, or prednisone increase to >0.5 mg/kg/day, or = hospitalization
Increase in prednisone to >0.5 mg/kg/day
New cyclophosphamide, azathioprine, methotrexate for SLE activity
Hospitalization for SLE activity
Increase in Physician's Global Assessment score to >2.5

Petri M, Buyon J, Kim M. Classification and definition of major flares in SLE clinical trials. Lupus. 1999; 8: 685-91.

10.20. Appendix 20: Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI)



Select the score in each anatomical location that describes the most severely affected cutaneous lupus-associated lesion

	activity		damage		
Extent	Anatomical Location	Erythema	Scale/ Hypertrophy	Dyspigmentation	Scarring/ Atrophy/ Panniculitis	Anatomical Location
		0-absent 1-pink; faint erythema 2- red; 3-dark red; purple/violaceous/ crusted/ hemorrhagic	0-absent; 1-scale 2-verrucous/ hypertrophic	0-absent, 1-dyspigmentaton	0 – absent 1 – scarring 2 – severely atrophic scarring or panniculitis	
	Scalp				See below	Scalp
	Ears					Ears
	Nose (incl. malar area)					Nose (incl. malar area)
	Rest of the face					Rest of the face
	V-area neck (frontal)					V-area neck (frontal)
	Post. Neck &/or shoulders					Post. Neck &/or shoulders
	Chest					Chest
	Abdomen					Abdomen
	Back, buttocks					Back, buttocks
	Arms					Arms
	Hands					Hands
	Legs					Legs
	Feet					Feet

Mucous membrane

Mucous membrane lesions (examine if patient confirms involvement)	
0-absent; 1-lesion or ulceration	

Dyspigmentation

Report duration of dyspigmentation after active lesions have resolved (verbal report by patient)	
0- dyspigmentation usually lasts less than 12 months 1- dyspigmentation usually lasts at least 12 months	

Alopecia

Recent Hair loss (within the last 30 days / as reported by patient)	
1-Yes 0-No	

NB: if scarring and non-scarring aspects seem to coexist in one lesion, please score both

Divide the scalp into four quadrants as shown. The dividing line between right and left is the midline. The dividing line between frontal and occipital is the line connecting the highest points of the ear lobe. A quadrant is considered affected if there is a lesion within the quadrant.

Alopecia (clinically not obviously scarred)		Scarring of the scalp (judged clinically)	
0-absent 1-diffuse; non-inflammatory 2-focal or patchy in one quadrant; 3-focal or patchy in more than one quadrant		0- absent 3- in one quadrant 4- two quadrants 5- three quadrants 6- affects the whole skull	

Total Activity Score (For the activity score please add up the scores of the left side i.e. for Erythema, Scale/Hypertrophy,		Total Damage Score (For the damage score, please add up the scores of the right side, i.e. for Dyspigmentation,	

Albrecht J, Taylor L, Berlin JA, et al. The CLASI (Cutaneous LE Disease Area and Severity Index): an outcome instrument for cutaneous lupus erythematosus. J Invest Dermatol 2005;125(5): 889-894.

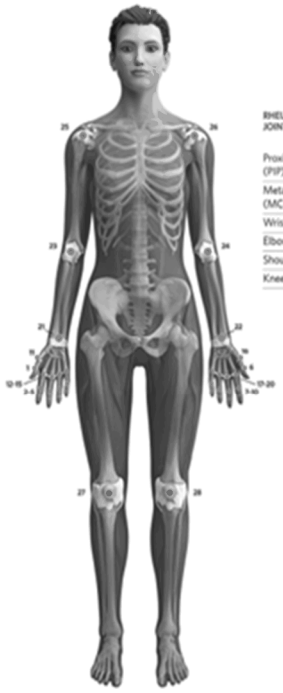
10.21. Appendix 21: Joint Assessment (28-Count)

Rheumatoid Arthritis Scoring Sheet

Read the instructions to the patient.

"I am going to examine various joints for swelling and tenderness. Please say yes or no if there is tenderness when I press a specific joint."

Examine each joint listed in order. Record a check if swelling or tenderness upon palpation is present. Total the number of swollen and tender joints.



RHEUMATOID ARTHRITIS JOINT COUNT

Proximal interphalangeal (PIP) joints	1-10
Metacarpophalangeal (MCP) joints	11-20
Wrists	21-22
Elbows	23-24
Shoulders	25-26
Knees	27-28

RIGHT	SWOLLEN	TENDER	LEFT	SWOLLEN	TENDER
1. 1st PIP	☐	☐	**6.** 1st PIP	☐	☐
2. 2nd PIP	☐	☐	**7.** 2nd PIP	☐	☐
3. 3rd PIP	☐	☐	**8.** 3rd PIP	☐	☐
4. 4th PIP	☐	☐	**9.** 4th PIP	☐	☐
5. 5th PIP	☐	☐	**10.** 5th PIP	☐	☐
11. 1st MCP	☐	☐	**16.** 1st MCP	☐	☐
12. 2nd MCP	☐	☐	**17.** 2nd MCP	☐	☐
13. 3rd MCP	☐	☐	**18.** 3rd MCP	☐	☐
14. 4th MCP	☐	☐	**19.** 4th MCP	☐	☐
15. 5th MCP	☐	☐	**20.** 5th MCP	☐	☐
21. Wrist	☐	☐	**22.** Wrist	☐	☐
23. Elbow	☐	☐	**24.** Elbow	☐	☐
25. Shoulder	☐	☐	**26.** Shoulder	☐	☐
27. Knee	☐	☐	**28.** Knee	☐	☐
SUBTOTALS					

TOTAL **SWOLLEN**	
TOTAL **TENDER**	
TOTAL RA JOINT COUNT	

Starz TW, Moreland LW, Levesque MC. Quantitative joint assessment to improve RA outcomes. J Musculoskel Med 2011;28:79-84.

10.22. Appendix 22: eGFR Calculations

The estimated GFR (eGFR) will be calculated using the 2 sets of equations developed by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), which utilize serum creatinine (SCr) and serum Cystatin C respectively.

$CKD\text{-}EPI_{2009Scr}$

If female and SCr is ≤0.7 mg/dL:

- GFR (mL/min/1.73 m^2) = 144 x $(Scr/0.7)^{-0.329}$ x 0.993^{age} (x 1.159, if black).

If female and SCr is >0.7 mg/dL:

- GFR (mL/min/1.73 m^2) = 144 x $(Scr/0.7)^{-1.209}$ x 0.993^{age} (x 1.159, if black).

If male and SCr is ≤0.9 mg/dL:

- GFR (mL/min/1.73 m^2) = 141 x $(Scr/0.9)^{-0.411}$ x 0.993^{age} (x 1.159, if black).

If male and SCr is >0.9 mg/dL:

- GFR (mL/min/1.73 m^2) = 141 x $(Scr/0.9)^{-1.209}$ x 0.993^{age} (x 1.159, if black).

$CKD\text{-}EPI_{2012cys}$

If female and Scys is ≤0.8 mg/L:

- GFR (mL/min/1.73 m^2) = 133 x $(Scys/0.8)^{-0.499}$ x 0.996^{age} x 0.932.

If female and Scys is >0.8 mg/L:

- GFR (mL/min/1.73 m^2) = 133 x $(Scys/0.8)^{-1.328}$ x 0.996^{age} x 0.932.

If male and Scys is ≤0.8 mg/L:

- GFR (mL/min/1.73 m^2) = 133 x $(Scys/0.8)^{-0.499}$ x 0.996^{age}.

If male and Scys is >0.8 mg/L:

- GFR (mL/min/1.73 m^2) = 133 x $(Scys/0.8)^{-1.328}$ x 0.996^{age}.

10.23. Appendix 23: Abbreviations

Abbreviation	Term
6-MP	6-mercaptopurine
ACR	American College of Rheumatology
AE	adverse event
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
CCI	[redacted]
ANC	absolute neutrophil count
CCI	[redacted]
AZA	Azathioprine
β-hCG	beta-human chorionic gonadotropin
CCI	[redacted]
BCG	Bacillus Calmette-Guérin
BICLA	British Isles Lupus Assessment Group-Based Composite Lupus Assessment
BID	twice a day
BILAG	British Isles Lupus Assessment Group
CCI	[redacted]
BP	blood pressure
C-CASA	Columbia-Classification Algorithm of Suicide Assessment
C_{max}	maximum (or peak) serum concentration
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CLASI	Cutaneous Lupus Erythematosus Disease Area and Severity Index
CLASI-A	Cutaneous Lupus Erythematosus Disease Area and Severity Index activity score
CMV	Cytomegalovirus
CNS	central nervous system
CMH	Cochran-Mantel-Haenszel
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CS	Corticosteroids

Abbreviation	Term
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Rating Scale
CT	clinical trial; computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTMS	clinical trial management system
CVA	cerebrovascular accident
CYP3A	cytochrome P450 3A
DCT	data capture tool
DILI	drug-induced liver injury
DMARDs	Disease modifying anti-rheumatic drugs
DMC	Data management committee
DNA	deoxyribonucleic acid
DU	dispensable unit
EBV	Epstein-Barr virus
EC	ethics committee
ECG	Electrocardiogram
E-DMC	external data monitoring committee
EDP	exposure during pregnancy
ED_{50}	Median effective dose
eGFR	estimated glomerular filtration rate
ELISA	Enzyme linked immunosorbent assay
EMA	European Medicines Agency
CCI	[redacted]
EOS	end of study
CCI	[redacted]
EU	European Union
EudraCT	European Clinical Trials Database
EW	early withdrawal
FACIT-F	Functional Assessment of Chronic Illness Therapy-Fatigue
FAS	Full analysis set
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GI	Gastrointestinal
GLMMRM	generalized linear marginal model for repeated measures
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV DNA	hepatitis B virus deoxyribonucleic acid
CCI	[redacted]

Abbreviation	Term
HCVAb	hepatitis C virus antibody
HCV RNA	hepatitis C virus ribonucleic acid
HDL	High density lipoprotein
HEENT	head, eyes, ears, nose and throat
Hep B	hepatitis B
Hep C	hepatitis C
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HR	heart rate
HRT	Hormone replacement therapy
CCI [redacted]	[redacted]
IAP	Interim Analysis Plan
IB	Investigator's Brochure
IBD	Inflammatory bowel disease
ICD	informed consent document
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	Identification
CCI [redacted]	[redacted]
IGRA	interferon gamma release assay
IM	Intramuscular
IND	investigational new drug
INF	Interferon
INH	Isoniazid
INR	international normalized ratio
IRB	institutional review board
IRT	interactive response technology
IUD	intrauterine device
IUS	Intrauterine hormone-releasing system
IV	Intravenous
IVIg	intravenous immunoglobulin
IWR	interactive web-based response
JAK	Janus kinase
K_2EDTA	potassium edetic acid (ethylenediaminetetraacetic acid)
LDL	Low density lipoprotein
LFT	liver function test
LLDAS	Lupus Low disease activity score
LLN	lower limit of normal
Lupus QoL	Lupus Quality of Life
MAD	multiple ascending dose
MCP	Metacarpophalangeal

Abbreviation	Term
MCS	mental component summary
mSSFI	modified SELENA-SLEDAI Flare Index
MMF	mycophenolate mofetil
MPA	mycophenolic acid
MTX	Methotrexate
N/A	not applicable
CCI	[redacted]
NOAEL	no-observed-adverse-effect-level
NSAIDs	nonsteroidal anti-inflammatory drugs
OCT2/MATE	organic cation transporter
OCS	oral corticosteroids
PASI	Psoriasis Area and Severity Index
PBMC	peripheral blood mononuclear cells
PCD	primary completion date
PCS	physical component summary
CCI	[redacted]s
PE	physical examination
P-gp	p-glycoprotein
PhGA	physician global assessment
PI	Principal Investigator
PIP	proximal interphalangeal
CCI	[redacted]
PR interval	period of time on the ECG, in milliseconds, that extends from beginning of P wave until beginning of QRS complex
PRN	pro re nata or as needed
PRO	participant reported outcome
PT	prothrombin time
PVC	Premature ventricular complexes
CCI	[redacted]
PTT	partial thromboplastin time
QD	once a day
QFT-G	QuantiFERON® - TB Gold
QFT-GIT	QuantiFERON® - TB Gold In-Tube test
QFT-G plus	QuantiFERON® - TB Gold Plus test
QoL	quality of life
QRS complex	combination of the Q wave, R wave and S wave on the ECG
QTc	Correct QT interval
QTcF	Frederica's corrected QT interval
QT interval	ECG measure between Q wave and T wave
QW	Once weekly
RNA	ribonucleic acid
SAD	single ascending dose

Abbreviation	Term
SAE	serious adverse event
SAP	statistical analysis plan
SCr	Serum creatinine
SELENA	Safety of Estrogen in Lupus Erythematosus: National Assessment
SELENA-SLEDAI SLE Flare Index	Safety of Estrogen in Lupus: National Assessment-Systemic Lupus Erythematosus Disease Activity Index Systemic Lupus Erythematosus Flare Index
CCI	[redacted]
SFI	Systemic Lupus Erythematosus Flare Index
SJC	swollen joint count
SLE	systemic lupus erythematosus
SLEDAI	Systemic Lupus Erythematosus Disease Activity Index
SLEDAI-2K	Systemic Lupus Erythematosus Disease Activity Index-2000
SLICC	Systemic Lupus International Collaborating Clinics
SOC	System Organ Class
SOP	standard operating procedure
SPC	summary of product characteristics
SRI	systemic lupus erythematosus responder index
SRI-4	systemic lupus erythematosus responder index change of 4
SRSD	single reference safety document
SToD	Study team on demand
SUSAR	suspected unexpected serious adverse reactions
TB	Tuberculosis
TEAE	treatment-emergent adverse event
CCI	[redacted]
T_{max}	time drug is present at maximum concentration in serum
TIA	Transient ischemic attack
TYK2	tyrosine kinase 2
ULN	upper limit of normal
Upr:Ucr	urine protein to urine creatinine ratio
US	United States
VAS	visual analog scale
VHP	Voluntary Harmonization Procedure
VTE	venous thromboembolic events
VZV	varicella zoster virus
WBC	white blood cell
WOCBP	women of childbearing potential
WONCBP	women of non-childbearing potential

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