

Title Page

A PHASE 2, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, MULTICENTER STUDY TO EVALUATE THE CLINICAL EFFECT, PHARMACODYNAMIC, PHARMACOKINETIC AND SAFETY PROFILE OF PF-06823859 IN ADULT PARTICIPANTS WITH ACTIVE CLE OR SLE WITH CUTANEOUS MANIFESTATIONS

Study Intervention Number:	PF-06823859
Study Intervention Name:	Not available
US IND Number:	166320
EudraCT/EU CT Number:	2023-503343-33-00
ClinicalTrials.gov ID:	NCT05879718
Pediatric Investigational Plan Number:	Not applicable
Protocol Number:	C0251013
Phase:	2
Sponsor Legal Address:	Pfizer Inc. 66 Hudson Boulevard East New York, NY 1001

Brief Title: A Phase 2 Multicenter Study to Evaluate PF-06823859 in Adult Participants With Active CLE or SLE With Cutaneous Manifestations

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Document History

Document	Version Date
Amendment 2	26 Oct 2023
Amendment 1	18 Sep 2023
Original protocol	29 Mar 2023

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs and any protocol administrative change letter(s).

Protocol Amendment Summary of Changes Table

Amendment 2 (26 Oct 2023)

Description of Change	Brief Rationale	Section # and Name
Clarified Inclusion Criterion #6: Added clarification that all systemic medications to control cutaneous lupus activity should be added at least 12 weeks prior to Day 1 except for corticosteroids. Topical or systemic corticosteroids must be initiated at least 8 weeks prior to Day 1.	Clarifying that to establish stable dose treatments of background medications, changes are made to specify the required treatment durations prior to Day 1 separately for systemic medications as well as topic or systemic corticosteroids.	Section 1.1. Synopsis and Section 5.1. Inclusion Criteria
Changed permitted systemic corticosteroid daily dose to 10 mg and treatment period to at least four weeks prior to Day 1. Added required 12 weeks treatment periods prior to Day 1 for newly initiated immunosuppressants and antimalarias.	Changes are made for consistency and clarifications as specified in the inclusion and exclusion criteria.	Appendix 9 Prohibited and Permitted Concomitant Medications
Added Exclusion Criterion #30: Participants with a history of hypersensitivity reactions to active	Requested by MHRA	Section 1.1. Synopsis and Section 5.2. Exclusion Criteria

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Description of Change	Brief Rationale	Section # and Name
drug or any of the excipients in the drug product or placebo.		
Added: 'Excipients included in either active study intervention or placebo include: L-Histidine, L-Histidine hydrochloride monohydrate, polysorbate 80, Sucrose (low endotoxin), EDTA disodium salt dihydrate, and water for injection.'	Requested by MHRA	Section 6.1 Study Intervention(s) Administered
• Removed [CCI] skin" from Early Termination visit. • Removed "[CCI] lesion skin" from Week 8, 32 and Early Termination visit. • Removed "[CCI] at Week 32 is optional." • Changed [CCI] procedure as a mandatory procedure if all [CCI] supplies are available at the site.	[CCI] supplies may not be available at some sites due to logistic reason. Skin [CCI] will be performed at time points that are more informative.	Section 1.3. Schedule of Activities and Section 8.7.4.1.2. Skin [CCI]
Updated the CLASI table	Administrative changes to improve readability	Appendix 15: Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI)
Updated the C-SSRS questionnaire.	Administrative changes to improve readability	Appendix 17 Columbia Suicide Severity Rating Scale (C-SSRS)
Other minor changes	To align with Pfizer's protocol template	Section 10.1.6. Dissemination of Clinical Study Data and Section 10.1.7. Data Quality Assurance

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The protocol amendment summary of changes table for past amendment can be found below:

Amendment 1 (18 Sep 2023)

Description of Change	Brief Rationale	Section # and Name
Exclusion criterion #6 a. The timeframe of exclusion in the first bullet point has been changed to 24 months to replace 6 to 12 months. b. Removed the fourth bullet point that requires participants who have a major CVD event within 6 to 12 months of the screening to be followed by a cardiologist.	Revised per request of EU CTR	Section 1.1. Synopsis, Section 5.2. Exclusion Criteria
Added text to allow participants that discontinue study intervention (PF-06823859 or placebo) early, to remain in the study to continue their protocol scheduled visits to minimize missing data. If the participant agrees to continue in the study, but not on study intervention, they may receive any medication required to control of their SLE/CLE after consultation with the sponsor medical monitor.	In efforts to minimize missing data, the EU CTR requested to add text that participants who discontinue study intervention for any reason (including lack of efficacy) and are willing to remain on study) are able to receive treatment to control their SLE/CLE.	Section 1.1. Synopsis, Section 4.1. Overall Design, Section 6.9.1. Permitted Background Medications, Section 7.1. Discontinuation of Study Intervention, and Appendix 11. Guidelines for Participant Safety Monitoring and Discontinuation
Inclusion criterion #5 added the following to this inclusion: erythema score of ≥2.	Clarifying that red erythema is needed to indicate moderate to severe inflammation required for eligibility.	Section 1.1. Synopsis, Section 5.1. Inclusion Criteria
Inclusion criterion #5 modified to indicate that CLASI activity score must be ≥8.	CLASI activity was only mentioned at the bottom of this inclusion criterion so	Section 1.1. Synopsis, Section 5.1. Inclusion Criteria

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Description of Change	Brief Rationale	Section # and Name
	was missed and now moved to top for clarity	
Exclusion criterion #3 clarified that participants with a diagnosis of SLE may be included with the equivalent of BILAG B, C, or D neurologic involvement (non-severe).	Because of the majority of SLE participants have at least mild neurologic manifestations, they generally participate as long as severe neurologic manifestations are absent.	Section 1.1. Synopsis, Section 5.2. Exclusion Criteria
Exclusion criterion #4 was amended to clarify that only participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin or carcinoma in situ of the uterine cervix that has been treated by excision at least 5 years prior to screening without recurrence may be eligible for inclusion. All other malignancies by history are excluded.	The EU CTR requested to exclude participants with history of malignancy in this Phase 2 study, however the 3 malignancies described are usually considered cured by excisional treatment if early and are usually allowed to participate if disease free after 5 years.	Section 1.1. Synopsis, Section 5.2. Exclusion Criteria
Exclusion criterion #20 now excludes participant individual with active or latent TB and requires clearance by local experts if the screening IGRA is positive or indeterminate.	Made in response to EU CTR request for participant safety in this Phase 2 study.	Section 1.1. Synopsis, Section 5.2. Exclusion Criteria; Section 8.3.6. Interferon Gamma Release Assay For TB Test
Exclusion criterion #23 added the text "It is recommended that a cardiologist review the screening ECG and provide an interpretation".	Recommendation of the cardiologist to read the ECG.	Section 1.1. Synopsis, Section 5.2. Exclusion Criteria
Exclusion criterion #25 "Other medical or psychiatric condition…" was moved from "Infection" to "Other Exclusion Criteria".	Updated to reflect the correct exclusion criteria.	Section 1.1. Synopsis, Section 5.2. Exclusion Criteria

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Description of Change	Brief Rationale	Section # and Name
Changed to require highly effective contraception; removed use of acceptable effective methods.	Changed per EU CTR request	Section 4.2.4. Choice of Contraception/Barrier Requirements, Section 5.3.1. Contraception, and Appendix 4. Contraceptive and Barrier Guidance
Added ferritin and LDH at all in-clinic visits in SoA and Appendix 2. Added additional labs in Appendix 2 for suspected HLH/MAS.	Added per request of EU CTR for additional monitoring for early detection of hemophagocytic lymphohistiocytosis.	Section 1.3. Schedule of Activities, Appendix 2. Clinical Laboratory Tests
Added C-SSRS at screening to exclude participants with suicidal risk.	Added per request of FDA.	Section 1.1. Synopsis, Section 1.3. Schedule of Activities, Section 5.2. Exclusion criteria, Section 8.3.11. Suicidal Ideation and Behavior Risk Screening, and Appendix 17. Columbia Suicide Severity Rating Scale (C-SSRS)
Added CLASI assessment at Week 60.	Added to obtain an assessment of durability of effect 20 weeks after last dose.	Section 1.3. Schedule of Activities
ET visit in SoA updated to add additional safety and efficacy assessments.	Added to ensure participant safety and ensure that all possible disease activity assessments are performed in the event the ET visit is the last assessment of participant.	Section 1.3. Schedule of Activities
Added a note to skin biopsies CCI [redacted] and skin biopsies-lesional in SoA to request that if a participant discontinues study participation at Week 8 and is willing to undergo skin punch biopsies that are normally scheduled	To avoid missing data, skin biopsy data at Week 8 may be used if Week 12 is missing.	Section 1.3. Schedule of Activities

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Description of Change	Brief Rationale	Section # and Name
at Week 12, that the skin punch biopsies be obtained at Week 8 and processed as for the Week 12 skin punch biopsies.		
Clarified that permanent discontinuation is a rationale for discontinuation for participants demonstrating severe or progressive SLE/CLE activity.	Response to EU CTR request to clarify the definition of a severe, progressive disease activity as a reason for discontinuation of study intervention.	Section 7.1. Discontinuation of Study Intervention
Added lack of efficacy as a reason for permanent discontinuation of study intervention.	Added at request of EU CTR	Section 7.1. Discontinuation of Study Intervention
Added lack of efficacy as a reason for discontinuation from the study.	Added at request of EU CTR	Section 7.2. Participant Discontinuation/Withdrawal From the Study
Added ferritin and LDH at all visits, added ad hoc local diagnostic testing done for confirmation of diagnosis or following hemophagocytic lymphohistiocytosis.	Added at request of EU CTR	Appendix 2. Clinical Laboratory Tests
Added that participants with an elevated ferritin must return for retest within a week, added that participants with confirmed diagnosis of hemophagocytic lymphohistiocytosis must permanently discontinue study intervention	Added at request of EU CTR for monitoring early diagnosis of hemophagocytic lymphohistiocytosis (macrophage activation syndrome) and adding as a reason for discontinuation.	Appendix 11. Guidelines for Participant Safety Monitoring and Discontinuation
Added adjudication committee to adjudicate suspected HLH/MAS.	Added an external HLH/MAS event adjudication committee to adjudicate suspected HLH/MAS events during the study.	Section 4.2.3. HLH/MAS Adjudication Committee, Appendix 10.1.5.2. External HLH/MAS Adjudication Committee

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Description of Change	Brief Rationale	Section # and Name
Changed "initial treatment" to "Q4W treatment", changed "long term extension treatment" to "Q8W treatment".	Changed per EU CTR request	Section 1.1. Synopsis, Section 1.2. Schema, Section 1.3. Schedule of Activities, and Section 4.1. Overall Design
Added NCT number to title page.	The NCT number is available now.	Title Page
Other minor changes (added spaces, mis-spellings, etc) throughout the document	Administrative changes to improve readability throughout the document.	Throughout the protocol

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:

A Phase 2, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study to Evaluate the Clinical Effect, Pharmacodynamic, Pharmacokinetic and Safety Profile of PF-06823859 in Adult Participants With Active CLE or SLE With Cutaneous Manifestations

Brief Title:

A Phase 2 Multicenter Study to Evaluate PF-06823859 in Adult Participants With Active CLE or SLE With Cutaneous Manifestations

Regulatory Agency Identification Number(s):

US IND Number:	166320
EudraCT/EU CT Number:	2023-503343-33-00
ClinicalTrials.gov ID:	NCT05879718
Pediatric Investigational Plan Number:	Not applicable
Protocol Number:	C0251013
Phase:	2

Rationale:

The purpose of this study is to provide an assessment of the PD, PK, efficacy and safety in participants with either SLE with cutaneous manifestations or CLE having skin lesions classified as chronic cutaneous and/or subacute cutaneous lupus.

Objectives, Endpoints, and Estimands:

Section 3 contains the complete list of objectives, endpoints and estimands. An abbreviated list of primary and secondary objectives, endpoints and estimands is shown below.

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Objective	Endpoint	Estimand
Primary	**Primary**	**Primary**
• To evaluate the effect of PF-06823859 on the type 1 IFN GS score at Week 12 in participants with CLE or SLE with cutaneous manifestations	• Change from baseline in type 1 IFN GS score in lesional skin at Week 12	E1 E1 evaluates the difference across the treatment arms in the mean values of change from baseline of continuous outcome of interest. The treatment effect is evaluated in the hypothetical population of participants who did not experience intercurrent events. The intercurrent events are: • Missing two consecutive doses of treatment • Exposure to a new or protocol prohibited dose of systemic medication for the treatment of cutaneous or systemic lupus manifestations
Key Secondary	**Key Secondary**	**Key Secondary**
• To evaluate the effect of PF-06823859 on the CLASI-A score at Week 12 in participants with CLE or SLE with cutaneous manifestations	• Change from baseline (%) in CLASI-A score at Week 12	E1 (same as above)
Other Secondary	**Other Secondary**	**Other Secondary**
• To evaluate the effect of PF-06823859 on the additional measures of CLASI-A score at Week 12 and over time in participants with CLE or SLE with cutaneous manifestations	• Percent change from baseline in CLASI-A (over time in addition to Week 12) • Change from baseline in CLASI-A (over time) • Achieving ≥50%, 4 or 7 points reduction in CLASI-A (over time)	• For continuous outcome E1 estimand will be used for the continuous outcomes at Week 0-12-time span and descriptive statistics will be used for later visits • E2 (for binary outcome) E2 evaluates the difference across the treatment arms in probabilities of response. The treatment effect is evaluated in the population of study participants who are randomized and treated irrespective of their

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Objective	Endpoint	Estimand
		compliance to the planned course of treatment. Observations for which an observed (CLASI-A) score may be confounded by the use of prohibited medications are assigned a non-responder status.
• To evaluate the effect of PF-06823859 on the PhGA in participants with CLE or SLE with cutaneous manifestations	• Change from baseline in PhGA (over time)	• For continuous outcome E1 estimand will be used for the continuous outcomes at Week 0-12-time span and descriptive statistics will be used for later visits.
• To evaluate the safety and tolerability of PF-06823859 in participants with CLE or SLE with cutaneous manifestations	• Incidence and severity of laboratory, vital signs, 12-lead ECG abnormalities, AEs, SAEs and withdrawals due to AEs over time	There is no defined estimand for these endpoints. They will be analyzed using Pfizer data standards as applicable.

Overall Design:

This is a Phase 2, double-blind, randomized, placebo-controlled, multicenter study to evaluate the clinical effect, PD, PK and safety profile of PF-06823859 in adult participants with active CLE or SLE with cutaneous manifestations.

Participants will participate in this study for approximately 65 weeks. This includes up to a 5-week screening period, a 12-week Q4W treatment period, a 36-week Q8W treatment period, and a 12-week follow-up period.

After up to a 5-week screening period, eligible participants will be randomized in a 2:1 ratio to receive either PF-06823859 CCI or placebo Q4W dosing on Day 1, Week 4 and Week 8 in addition to protocol permitted SOC treatment. Following assessments for the primary endpoint at Week 12, participants who are receiving active PF-06823859 or who are placebo non-responders (responder is defined by ≥4 point reduction from the baseline in CLASI-A score) will receive PF-06823859 CCI Q8W beginning at Week 16, while placebo responders will continue to be in the placebo group. The last dose of study intervention will be administered at Week 40 followed by last full study assessments at Week 48. The follow up visit will be conducted at Week 60.

Two IAs may be performed. The first IA may be performed at the time when about 50% of the participants complete the Week 12 visit. It may provide a non-binding recommendation of early stopping for futility but will not allow early stopping of the trial for efficacy and will

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not increase the type I error. The results of the IA may be used for internal decision making. The second IA may be performed after the last participant completes Week 12 to determine whether the mean decrease from baseline in the type 1 IFN GS score is greater in the PF-06823859 treatment arm than in the placebo treatment arm and if this difference is statistically significant. A similar comparison will be done for the key secondary outcome. It will be evaluated whether the mean value of percent decrease from baseline in the CLASI-A score is greater in the PF-06823859 treatment arm than in the placebo treatment arm and whether this difference is statistically significant.

Further details of analyses in safety and efficacy will be specified in the SAP. A separate SAP may be provided for the IA.

Number of Participants:

Approximately 48 participants will be enrolled in the study at approximately 30 investigator sites worldwide.

Note: "Enrolled" means a participant's, or their legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process and randomization to study intervention. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.

Study Population:

Inclusion and exclusion criteria are listed below:

Inclusion Criteria

Participants must meet the following inclusion criteria to be eligible for enrollment into the study:

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 ICD.

    - Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

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. Participants must be capable of giving signed informed consent as described in

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Appendix 1, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol. All participants should be willing to remain in the study to the end of the treatment period for safety, efficacy, PK and PD assessments, whether or not study intervention is discontinued.

Note:Participants should understand the study requirements and be committed to complete the study since excessive dropout will impair the ability to interpret results.

3. Participants must be willing to avoid application of topical medications to the index lesions (4 index lesions should be identified at screening and baseline) that are identified for potential biopsies in the study until after Week 32.

4. Participants must have adequate IV access for administration of study intervention and on-study blood sampling.

5. Have a diagnosis of histologically confirmed active CLE or SLE with cutaneous manifestations despite treatment with standard of care medications for at least 12 weeks defined as a score of ≥8 on the CLASI-A, an erythema score of ≥2 in the CLASI and historical biopsy (report to be available to disease activity adjudicators) within the past 10 years with either:

   a. Subacute cutaneous lupus erythematosus, or

   b. Discoid lupus erythematosus with at least one active discoid lesion (panniculitis, tumidus and chilblain lesions are excluded for the purposes of disease activity qualifying for eligibility and biopsy but are not exclusionary), or

   c. Both subacute and chronic cutaneous lupus erythematosus

   Note: If the lesion has not been previously biopsied, a biopsy will be required to confirm diagnosis during screening. CLASI-A score and biopsy results will be reviewed by independent central data reviewers and the centrally reviewed score will be the score used to base decisions on eligibility and post Week 12 dosing. The investigator should confirm that the CLASI-A has not decreased below eligibility (remains at least 8) at baseline.

6. All participants may be currently receiving EITHER a stable dose of an immunosuppressant (MTX, AZA, 6-MP, leflunomide, mizoribine, MMF), or dapsone or colchicine with or without antimalarials and/or corticosteroids, OR anti-malarials (hydroxychloroquine, chloroquine or quinacrine) in combination with corticosteroids (dose of oral corticosteroids must be between 5 and 10 mg/day prednisone equivalent) or permitted topical agents. Participants may not be receiving combinations of 2 or more immunosuppressants. Medications (whether topical and/or systemic) other than corticosteroids must have been started at least 12 weeks prior to Day 1. Topical or systemic corticosteroids must have been started at least 8 weeks prior to Day 1.

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Note: Stable dose is defined as no new therapy or as stable as possible with existing SOC therapies as above within 12 weeks of Day 1 for immunosuppressives or within 4 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 9 for allowable stable doses.

Weight:

7. Participants weighing greater than 40 kg and less than 130 kg and with a BMI of <40 kg/m^2.

Exclusion Criteria

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

Medical Conditions:

1. Have another skin disorder that would confound the results of the skin biopsy or clinical assessments in the study (eg, psoriasis, drug-induced eruptions or drug related lupus).

2. Active, severe lupus nephritis (World Health Organization Class III, IV) that requires or may require treatment with cytotoxic agents or high-dose CS. Participants with prior, controlled, renal disease treated with an ACE or ARB inhibitor and immunosuppressive therapy (cyclophosphamide or mycophenolate mofetil) and a serum creatinine ≤2 × ULN and either residual proteinuria up to ≤3 g/day or a 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 team 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 laboratory 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.

3. Severe active CNS lupus (eg, EULAR/ACR evidence of severe neurological disease and/or new or poorly controlled seizure disorder, acute confusional state, myelitis or aseptic meningitis, demyelinating syndrome, stroke or stroke syndrome, cerebellar ataxia or dementia related to SLE, active psychosis, organic brain syndrome, CVA, cerebritis or CNS vasculitis) requiring therapeutic intervention within 60 days of Day 1. Participants with a diagnosis of SLE and non-severe neurologic manifestations (equivalent to BILAG B, C or D such as isolated peripheral neuropathy, mild cognitive dysfunction, autonomic disorders that do not confound

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on-study assessments), are not excluded as long as they meet all other qualifying criteria for the study. Participants with ophthalmic neuropathy must have been evaluated by an ophthalmologist.

4. Cancer or any history of cancer within 5 years of screening (other than adequately resected basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ of the uterine cervix with no evidence of recurrence within the previous 5 years).

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

6. Have a history of:

   - A history of major cardiovascular or cerebrovascular event (stroke) or acute cardiac syndrome (MI, unstable angina pectoris, coronary stenting) within 24 months of screening
   - known pulmonary arterial hypertension
   - history of pulmonary embolism within 6 months of screening

   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.

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

8. Have any autoimmune or inflammatory disease that would interfere with interpretation of test results or clinical asseessments. This would include:

   a Mucocutaneous manifestations including but not limited to other skin disorders that would confound evaluation of the CLASI, such as psoriasis, dermatomyositis, Behcet's syndrome, systemic sclerosis, eczema, any other vasculitis such as ANCA vasculitis, dermatomyositis, polymyositis, mixed connective tissue disease, or other chronic skin conditions;

   b Musculoskeletal diseases including but not limited to rheumatoid arthritis, osteoarthritis that would confound assessment of lupus joint disease, 'rhupus', overlap syndromes, psoriasis/psoriatic arthritis, Behcet's syndrome, primary Sjogren's syndrome, mixed connective tissue disease or other chronic debilitating joint disorders;

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c Any other inflammatory autoimmune disease that would confound disease activity assessments such as inflammatory bowel disease, rheumatoid arthritis, primary Sjogren's syndrome, any other vasculitis such as ANCA vasculitis, dermatomyositis, polymyositis, mixed connective tissue disease.

Note: A decision about the suitability of the participant for enrollment will be made by the independent central reviewers and Pfizer clinical team**.**

9. History of any lymphoproliferative disorder such as 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).

Infection

10. 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 should be encouraged (per local guidelines) to do so prior to randomization. Participants should not receive the live herpes zoster vaccination (Zostavax®, Merck) within 4 weeks of planned randomization or on study; the recombinant adjuvant herpes zoster vaccine (Shingrix®, GSK) is permitted prior to and on study.

11. Required management of acute or chronic infections as follows:

    - Receiving any suppressive therapy for any chronic infection (such as pneumocystis, CMV, and atypical mycobacteria, herpes simplex) that, in the opinion of the investigator and sponsor, would place the participant at risk for reactivation. Participants who are receiving prophylactic therapy for herpes simplex virus may enroll and should continue this therapy for the duration of the study. Participants with no prior pneumocystis carinii infection may enroll if they are receiving prophylaxis for pneumocystis by permission of Pfizer clinical team.

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

    - Use of IV or IM antibacterials, antivirals, antifungals, or antiparasitic agents within 60 days of Day 1. Substitution of IM agents for oral agents because of 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.

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Prior/Concomitant Therapy:

12. A listing of permitted and prohibited topical and systemic corticosteroids is provided in Appendix 9.

13. Additional immunomodulatory drug exclusions see Appendix 9 for details.

14. Have received plasmapheresis within 12 weeks of screening or IVIg within 24 weeks of screening.

15. Treatment with any investigational drug(s) within 12 weeks of Day 1 for investigational biologics or within one month or 5 half-lives for investigational small molecules whichever is longer, and/or during study participation.

16. 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. Participants should not have received a Bacillus Calmette-Guérin (BCG) vaccination within 52 weeks of randomization.

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

Prior/Concurrent Clinical Study Experience:

18. 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**.**

Diagnostic Assessments:

19. Screening chest X-ray with changes suggestive of 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 screening may be used.

    Note: If a chest X-ray shows any abnormalities (nodules, infiltrates, scarring, stranding, etc), these findings must be documented to be stable compared to a prior chest X ray obtained at least 12 months previously. Findings due to SLE activity do not require the participant to be excluded.

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20. Infected with Mycobacterium TB: active TB or latent TB (see Section 8.3.6).

    a active TB infection is excluded.

    b If a participant has a positive or indeterminate IGRA at screening, the potential participant must be evaluated by a local expert (pulmonologist or infectious disease specialist) who may order additional testing as per local practice and will determine whether the potential participant has active or latent TB. If the local expert determines that the potential participant does not have active or latent TB, then the potential participant may be eligible for the study. A note from the specialist should be available in the source document and a summary of the specialists report must be provided to the Pfizer medical monitor to confirm that the participant does not have latent or active TB.

21. Known history of HIV based on documented history with positive test, or positive HIV test at screening.

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

22. Have evidence of active or latent infection of hepatitis B or hepatitis C based on screening tests (see Section 8.3.8).

23. Screening 12-lead 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. It is recommended that a cardiologist review the screening ECG and provide an interpretation.

24. Participants with ANY of the following abnormalities in clinical laboratory tests at Screening, as assessed by the study specific laboratory:

    - IgG levels below 500 mg/dL
    - Hemoglobin <9 g/dL (<90 g/L)
    - ANC $<1.0 \times 10^3/\mu L$
    - lymphocyte count $<0.4 \times 10^3/\mu L$, if the ALC is considered by the investigator to be a result of the underlying SLE disease or concomitant medications
    - Platelet count $<75 \times 10^3/\mu L$
    - Combined serum cystatin C and serum creatinine based eGFR <50 mL/min/1.73 m^2 based on CKD/EPI calculation

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- AST or ALT values ≥2 times the ULN
- Direct bilirubin greater than the ULN
- CK >3 times the ULN

Note: Screening laboratory tests with abnormal results may be repeated once to confirm abnormal results within the 5-week screening period. If results return to normal within the 5-week screening period, the participant may enter the study.

Other Exclusion Criteria:

25. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the judgment of the investigator make the participant inappropriate for the study. This would include the following answers on the CSSR-S questionnaire, which must be completed by the investigator at screening:
    - Suicidal ideation associated with actual intent and a method or plan in the past year: "Yes" answers on items 4 or 5 of C-SSRS (completed during screening).
    - Previous history of suicidal behaviors in the past 5 years: "Yes" answer (for events that occurred in the past 5 years) to any of the suicidal behavior items of the C-SSRS).
26. Investigator or site staff directly involved in the conduct of the study and their family members, site staff otherwise supervised by the investigator, and sponsor and sponsor delegate employees directly involved in the conduct of the study and their family members.
27. Significant trauma or major surgery or blood transfusion within 5 weeks of screening, or scheduled to occur during the study, excluding diagnostic surgery.
28. 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.
29. Participants who are currently vaping or using e-cigarettes.
30. Participants with a history of hypersensitivity reactions to active drug or any of the excipients in the drug product or placebo.

Study Arms and Duration:

The study intervention will be administered by IV infusion Q4W on Day 1, Week 4 and Week 8 in addition to protocol permitted SOC treatment. Following assessments for the primary endpoint at Week 12, participants will continue receiving study intervention Q8W beginning at Week 16, the last dose of study intervention will be administered at Week 40

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followed by last full study assessments at Week 48. The total duration of study participation excluding screening is 60 weeks.

Study Intervention(s)		
Intervention Name	**PF-06823859**	**Placebo for PF-06823859**
Arm Name	PF-06823859	Placebo for PF-06823859
Unit Dose Strength(s)	CCI	0 mg/mL
Dosage Level(s)	CCI	0 mg
Route of Administration	IV	IV
Use	Experimental	Placebo
IMP or NIMP	IMP	IMP

Study Arm(s)		
Arm Title	PF-06823859	Placebo for PF-06823859
Arm Type	Experimental	Placebo
Arm Description	Participants will receive CCI IV Q4W on Day 1, Week 4 and Week 8 and then CCI IV Q8W beginning at Week 16, the last dose of study intervention will be administered at Week 40.	Participants will receive placebo IV Q4W on Day 1, Week 4 and Week 8 and then placebo IV Q8W beginning at Week 16, the last dose of study intervention will be administered at Week 40.

Statistical Methods:

With the planned number of 48 randomized participants and 2:1 randomization rate, Week 12 outcomes are expected for about 24 participants in the active treatment group and about 12 participants in the placebo treatment group.

The primary endpoint is the CFB (GS) (ie, change from baseline in the type 1 IFN GS score) at Week 12. The expected standard deviation for the CFB (GS) based on the Pfizer study C0251002 for a similar indication is CCI. The difference in the true mean decreases of type 1 IFN GS scores at Week 12 across the treatment groups that will be detected with CCI power is CCI

The key secondary endpoint is %CFB (CLASI-A) (ie, percent change from baseline in the CLASI-A score). The expected standard deviation of %CFB (CLASI-A), based on the results of a recent study[1] with the similar population is CCI The difference in the mean decreases of %CFB (CLASI-A), across the treatment groups that will be detected with CCI power is CCI

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Primary Endpoint/Estimand Analysis:

The endpoint is the change from baseline of type 1 IFN GS score at Week 12. The ANCOVA method will be used for the comparison of the mean CFB (GS) values across the treatment groups. The observations of type 1 IFN GS scores within the cmITT dataset will be used. Observations for participants who do not have baseline or Week 12 observations will be excluded from the analysis. One-sided p-values will be used for a rejection of the null hypothesis that CFB in active PF-06823859 ≥ CFB in placebo, since an effective treatment is expected to decrease the GS more than placebo.

Secondary Endpoint/Estimand Analysis:

The continuous secondary endpoints are the percent change and change from baseline in CLASI-A score. The MMRM method will be used for the comparison of the means of changes from baseline across the treatment groups. The observations within the cmITT dataset will be used in the key secondary analysis to reduce the possibility of model non-convergence in this analysis. One-sided p-values will be used for a rejection of the null hypothesis that change (percent change) in active PF-06823859 ≥ change (percent change) in placebo, since an effective treatment is expected to decrease the CLASI-A score more than placebo.

The binary secondary outcomes include achieving ≥50%, 4 or 7 points reduction in CLASI-A. The BCS and CZ methods will be applied to the NRImITT dataset.

Ethical Considerations:

SLE is a chronic autoimmune disease and CLE is one form of SLE affecting just skin. These conditions significantly impair patients' quality of life. Available treatments do not provide relief for many patients and have well-characterized toxicities. Therefore, there is high unmet medical need for a novel, targeted, safe, and efficacious therapy for both SLE and CLE. Based on non-clinical and clinical study results with PF-06823859, along with evidence of type 1 interferons contributing to pathogenesis in SLE and CLE, Pfizer considers that there is reasonable probability that this drug will have a favorable benefit risk profile which supports conducting this Phase 2 study.

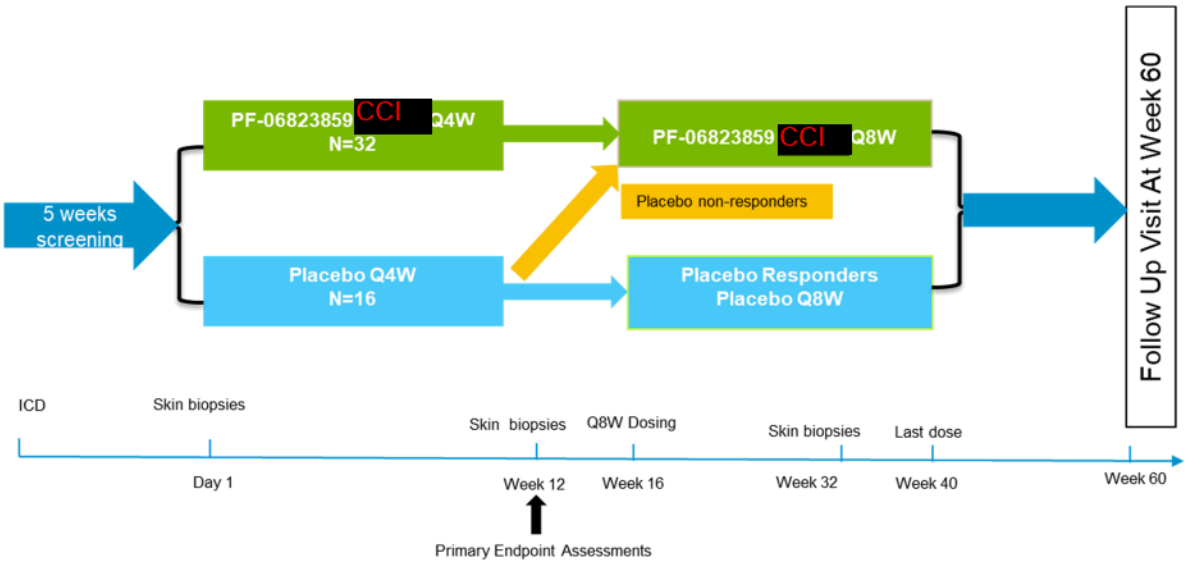
Risks of study participation include the use of a placebo arm, increased susceptibility to viral infections, complications of IV infusion administration, confounding conditions to other causes, and AEs associated with underlying disease. Mitigation strategies throughout screening and the study will be utilized to minimize these risks to participants.

Considering the measures to minimize risk to study participants, the potential risks identified in association with PF-06823859 are considered to be justified by the anticipated benefits that may be afforded to participants with SLE with skin lesion and CLE.

To minimize any missing data if a participant prematurely discontinues from study intervention, the sponsor is asking all participants to continue with their protocol scheduled visits. If study intervention is discontinued for any reason, the participant may receive any medication required to control of their SLE/CLE after consultation with the sponsor medical monitor.

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1.2. Schema



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1.3. Schedule of Activities

The SoA 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 SoA table, in order to conduct evaluations or assessments required to protect the well-being of the participant. In the event of a clinically significant laboratory abnormality obtained at a visit, participants should return for repeat laboratory assessments required for safety evaluation as per protocol.

Visit Identifier Abbreviations used in this table may be founded in Appendix 18	**Screening**	**Q4W Treatment Period**				**Q8W Treatment Period**									**Follow Up**		**Early Termination**	**Notes**
Visit Day/Week	**Days -35 to -1**	**BL Day 1**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**Wk 20**	**Wk 24**	**Wk 28**	**Wk 32**	**Wk 36**	**Wk 40**	**Wk 44**	**Wk 48**	**Wk 56**	**Wk 60**		• Day relative to start of study intervention (Day 1).
Visit Window	None	None	±3 Days based on Day 1 Visit			±7 Days based on Day 1 Visit												
Enrollment Procedures																		
Informed consent	X																	• See Section 8.1 for additional information.
Inclusion/ exclusion criteria	X	X																• See Section 5.1 and Section 5.2.
Demographics	X																	• See Section 5.3.
Medical History and Physical Examination																		
Medical history, SLE/CLE history	X																	
Prior SLE/CLE and non-SLE/CLE medications	X																	• See Section 6.9
Medical Procedures																		

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Visit Identifier Abbreviations used in this table may be founded in Appendix 18	**Screening**	**Q4W Treatment Period**				**Q8W Treatment Period**									**Follow Up**		**Early Termination**	**Notes**
Visit Day/Week	**Days -35 to -1**	**BL Day 1**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**Wk 20**	**Wk 24**	**Wk 28**	**Wk 32**	**Wk 36**	**Wk 40**	**Wk 44**	**Wk 48**	**Wk 56**	**Wk 60**		• Day relative to start of study intervention (Day 1).
Visit Window	None	None	±3 Days based on Day 1 Visit			±7 Days based on Day 1 Visit												
Vital signs	X	X	X	X	X	X	X	X		X		X		X		X	X	• See Section 8.3.2.
Weight	X	X				X								X			X	• See Section 8.3.1.
Height	X																	
Complete PE	X													X			X	• See Section 8.3.1.
Brief PE		X	X	X	X	X		X		X		X				X		
C-SSRS	X																	• The C-SSRS will be used to screen for suicidal ideation and behavior • See Section 8.3.11
ECG (12-lead)	X					X								X			X	• See Section 8.3.3. • See Appendix 8
Chest X-Ray, or CT within 12 weeks	X																	• See Section 8.3.7.
Contraception Check	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	• WOCBP should have their method of contraception recorded in their source documentation • See Section 5.3.1.
Telephone contacts									X		X		X		X			• See Section 8.1.1

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Visit Identifier Abbreviations used in this table may be founded in Appendix 18	**Screening**	**Q4W Treatment Period**				**Q8W Treatment Period**									**Follow Up**		**Early Termination**	**Notes**
Visit Day/Week	**Days -35 to -1**	**BL Day 1**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**Wk 20**	**Wk 24**	**Wk 28**	**Wk 32**	**Wk 36**	**Wk 40**	**Wk 44**	**Wk 48**	**Wk 56**	**Wk 60**		• Day relative to start of study intervention (Day 1).
Visit Window	None	None	±3 Days based on Day 1 Visit			±7 Days based on Day 1 Visit												
Laboratory Safety Assessments																		
Safety Laboratory	X	X	X	X	X	X	X	X		X		X		X		X	X	• See Section 8.3.4 for additional information. • See Appendix 2 for full list of assessments and some of those are being highlighted below for being administered at screening only.
HbsAg, HbcAb, HbsAb, and HCVAb (Hep B and Hep C reflex testing including HBV DNA, HCV RNA)	X																	• See Appendix 2.
HIV testing	X																	• Confirmation and documentation of negative HIV test result within 12 weeks prior to screening is acceptable • See Section 8.3.9
TB testing (IGRA)	X																	• See Section 8.3.6 and Appendix 2.
Serum FSH	X																	• To confirm WONCBP status only • See Appendix 2 and Section 10.4.3.

Visit Identifier Abbreviations used in this table may be founded in Appendix 18	**Screening**	**Q4W Treatment Period**				**Q8W Treatment Period**									**Follow Up**		**Early Termination**	**Notes**
Visit Day/Week	**Days -35 to -1**	**BL Day 1**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**Wk 20**	**Wk 24**	**Wk 28**	**Wk 32**	**Wk 36**	**Wk 40**	**Wk 44**	**Wk 48**	**Wk 56**	**Wk 60**		• Day relative to start of study intervention (Day 1).
Visit Window	None	None	±3 Days based on Day 1 Visit			±7 Days based on Day 1 Visit												
Serum β-Hcg	X																	• WOCBP only • See Appendix 2 and Section 10.4.3.
Lipid profile panel (fasting)	X					X								X			X	• 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. • See Section 5.3.3 and Appendix 2
Coagulation (PT, PTT, INR)	X	X				X								X			X	• See Appendix 2
Ferritin	X	X	X	X	X	X		X		X		X		X		X	X	• See Appendix 2
LDH	X	X	X	X	X	X		X		X		X		X		X	X	• See Appendix 2
Urine β-Hcg		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	• WOCBP only • Urine pregnancy test must be performed at Day 1 for all WOCBP prior to dosing with study intervention and at all subsequent visits. • Participants must have home pregnancy check monthly at the months where they do not have a clinic visit. • See Appendix 2 and Section 10.4.3.
UPCr	X	X	X	X	X	X		X		X		X		X		X	X	• UPCr at all clinic visits for participants with SLE • UPCr at screening only for participants with CLE • See Appendix 2

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Visit Identifier Abbreviations used in this table may be founded in Appendix 18	**Screening**	**Q4W Treatment Period**				**Q8W Treatment Period**									**Follow Up**		**Early Termination**	**Notes**
Visit Day/Week	**Days -35 to -1**	**BL Day 1**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**Wk 20**	**Wk 24**	**Wk 28**	**Wk 32**	**Wk 36**	**Wk 40**	**Wk 44**	**Wk 48**	**Wk 56**	**Wk 60**		• Day relative to start of study intervention (Day 1).
Visit Window	None	None	±3 Days based on Day 1 Visit			±7 Days based on Day 1 Visit												
Trial Treatment Procedures																		
IRT Registration	X																	• See Section 6.3
Randomization		X																• See Section 6.4
Study Intervention administration		X	X	X		X		X		X		X						• Week 8: Last dose for Q4W treatment; Week 16: First dose for Q8W treatment; Week 40: Last dose for Q8W treatment. • Study intervention must be administered after all study procedures and assessments have been completed. • See Section 6.1 for additional information
Infusion reaction monitoring		X	X	X		X		X		X		X						• This should be monitored during the infusion and until up to 60 minutes after the infusion, incl. vital signs and infusion reactions. • See Section 6.1.1
Clinical Assessments																		• Efficacy assessments must be performed prior to study intervention administration.
EULAR/ACR classification criteria for SLE	X																	• See Section 8.2.3 and Appendix 12.
Joint Assessment (28 swollen and tender/painful joint counts)	X	X	X	X	X	X		X		X		X		X		X	X	• See Section 8.2.4 and Appendix 13. • Only for participants with SLE
SLEDAI-2K	X	X	X	X	X	X		X		X		X		X		X	X	• See Section 8.2.5 and Appendix 14. • Only for participants with SLE
CLASI	X	X	X	X	X	X	X	X		X		X		X		X	X	• See Section 8.2.6 and Appendix 15.

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Visit Identifier Abbreviations used in this table may be founded in Appendix 18	**Screening**	**Q4W Treatment Period**				**Q8W Treatment Period**									**Follow Up**		**Early Termination**	**Notes**
Visit Day/Week	**Days -35 to -1**	**BL Day 1**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**Wk 20**	**Wk 24**	**Wk 28**	**Wk 32**	**Wk 36**	**Wk 40**	**Wk 44**	**Wk 48**	**Wk 56**	**Wk 60**		• Day relative to start of study intervention (Day 1).
Visit Window	None	None	±3 Days based on Day 1 Visit			±7 Days based on Day 1 Visit												
Photography	X	X	X	X	X	X	X	X		X		X		X			X	• Photography is required at all timepoints where there are CLASI assessments. • Photography is required at all timepoints where there are skin biopsies and CCI [redacted] • Refer to Section 8.2.2 for details.
Physician global assessment		X	X	X	X	X	X	X		X		X		X		X	X	• See Section 8.2.7 and Appendix 16.
Laboratory Biomarker Assessments																		
Skin biopsies-diagnostic	X																	• Only required if there is no documented histologic report to support the eligibility, skin biopsy must be performed during screening to confirm CLE or SLE diagnosis.
Skin biopsies-CCI [redacted]		X																• See Section 8.7.4.1.1; • If the participant discontinues study participation at Week 8, and is willing to undergo the skin punch biopsies, CCI [redacted] at Week 8, please obtain and process as for Week 12

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Visit Identifier Abbreviations used in this table may be founded in Appendix 18	**Screening**	**Q4W Treatment Period**				**Q8W Treatment Period**									**Follow Up**		**Early Termination**	**Notes**
Visit Day/Week	**Days -35 to -1**	**BL Day 1**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**Wk 20**	**Wk 24**	**Wk 28**	**Wk 32**	**Wk 36**	**Wk 40**	**Wk 44**	**Wk 48**	**Wk 56**	**Wk 60**		• Day relative to start of study intervention (Day 1).
Visit Window	None	None	±3 Days based on Day 1 Visit			±7 Days based on Day 1 Visit												
Skin biopsies-lesional		X			X					X*							X	• See Section 8.7.4.1.1 • If the participant discontinues study participation at Week 8, and is willing to undergo the skin punch biopsies, lesional at Week 8, please obtain and process as for Week 12 • Biopsy collection at Week 32 is optional
CCI skin		X																• See Section 8.7.4.1.2
CCI lesional skin		X	X		X													• See Section 8.7.4.1.2 • It is mandatory if all CCI supplies are available at the site.
CCI sample n		X	X	X	X					X							X	• See Section 8.7.4.3.3
CCI in blood		X	X	X	X					X							X	• See Section 8.7.4.2.4
Serum for CCI		X	X	X	X	X		X		X		X		X		X	X	• See Section 8.7.1
Blood for CCI		X	X	X	X	X		X		X		X		X		X	X	• See Section 8.7.2
Serum for total CCI		X	X	X	X	X		X		X		X		X			X	• See Section 8.7.3
Sample for flow cytometry	X	X	X		X					X						X		• See Section 8.7.4.3.4 • The screening sample is for research purposes only.
Serum for CCI		X	X	X	X	X		X		X		X		X		X	X	• See Section 8.7.4.3.5
Serum Immunoglobulins	X	X			X					X							X	• See Section 8.7.4.3.6
Complement, Standard	X	X	X	X	X	X		X		X		X		X		X	X	• See Section 8.7.4.3.7

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Visit Identifier Abbreviations used in this table may be founded in Appendix 18	**Screening**	**Q4W Treatment Period**				**Q8W Treatment Period**									**Follow Up**		**Early Termination**	**Notes**
Visit Day/Week	**Days -35 to -1**	**BL Day 1**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**Wk 20**	**Wk 24**	**Wk 28**	**Wk 32**	**Wk 36**	**Wk 40**	**Wk 44**	**Wk 48**	**Wk 56**	**Wk 60**		• Day relative to start of study intervention (Day 1).
Visit Window	None	None	±3 Days based on Day 1 Visit			±7 Days based on Day 1 Visit												
Anti-dsDNA	X	X	X	X	X	X		X		X		X		X		X	X	• At screening, baseline, Week 12 and Week 32 for participants with CLE. • All visits for participants with SLE. • See Section 8.7.4.3.8
APL antibodies	X																	• B2GPI IgG, IgM; anti-cardiolipin IgG, IgM at screening (repeat w/clotting events) • See Appendix 2
Serum ANA	X	X	X	X	X	X		X		X		X		X		X	X	• At screening, baseline, Week 12 and Week 32 for participants with CLE. • All visits for participants with SLE. • See Section 8.7.4.3.8
Serum ENA	X	X			X					X						X	X	• See Section 8.7.4.3.8
Pharmacokinetics																		
Serum PF-06823859 concentrations		X	X	X	X	X		X		X		X		X			X	• See Section 8.5 for sampling timepoints.
Immunogenicity Assessments																		
Serum ADA/NAb		X	X	X	X	X		X		X		X		X			X	• See Section 8.8

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Visit Identifier Abbreviations used in this table may be founded in Appendix 18	**Screening**	**Q4W Treatment Period**				**Q8W Treatment Period**									**Follow Up**		**Early Termination**	**Notes**
Visit Day/Week	**Days -35 to -1**	**BL Day 1**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**Wk 20**	**Wk 24**	**Wk 28**	**Wk 32**	**Wk 36**	**Wk 40**	**Wk 44**	**Wk 48**	**Wk 56**	**Wk 60**		• Day relative to start of study intervention (Day 1).
Visit Window	None	None	±3 Days based on Day 1 Visit			±7 Days based on Day 1 Visit												
Retained Research Samples																		
Genomic Retained Samples (Prep D1)		X																• If not collected on the designated collection day, collect at the next available time point when biospecimens are being collected in conjunction with a participant visit. • See Section 8.6.2 and Appendix 5.
Retained Samples (Prep R1)	X	X	X	X	X	X				X							X	• See Section 8.7.4.5 and Appendix 5 • Whole blood optimized for RNA
Retained Samples (Prep M2/Prep M3)		X	X	X	X	X				X							X	• See Section 8.7.4.5 and Appendix 5 • M2 for clarified urine • M3 for pellet
Retained Samples (Prep B1.5)		X	X	X	X	X				X							X	• See Section 8.7.4.5 and Appendix 5 • Plasma
Retained Samples (Prep B2.5)	X	X	X	X	X	X				X							X	• See Section 8.7.4.5 and Appendix 5 • Serum
Retained Samples Prep PBMC2		X			X					X							X	• See Section 8.7.4.5 and Appendix 5 • Peripheral blood mononuclear cells
Safety Assessments																		

Visit Identifier Abbreviations used in this table may be founded in Appendix 18	**Screening**	**Q4W Treatment Period**				**Q8W Treatment Period**									**Follow Up**		**Early Termination**	**Notes**
Visit Day/Week	**Days -35 to -1**	**BL Day 1**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**Wk 20**	**Wk 24**	**Wk 28**	**Wk 32**	**Wk 36**	**Wk 40**	**Wk 44**	**Wk 48**	**Wk 56**	**Wk 60**		• Day relative to start of study intervention (Day 1).
Visit Window	None	None	±3 Days based on Day 1 Visit			±7 Days based on Day 1 Visit												
Concomitant corticosteroids	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	• A detailed history of corticosteroid use will be collected. Participants may receive a prescribed oral daily dose of prednisone (or equivalent see Appendix 10). The investigator/site staff will review the participant's corticosteroid usage and record in the CRF at each study visit.
Other concomitant medications & non-drug treatments	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	• See Section 6.9 for additional information.
Serious and non-serious AE monitoring	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	• See Section 8.4 for additional information.
Monitoring for Infections (skin swab for herpetiform rash, if suspected)	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	• See Section 8.3.10 for additional information.

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2. INTRODUCTION

PF-06823859 is a potent, selective, humanized IgG1 neutralizing antibody directed against the human soluble cytokine IFNβ, a member of the type I IFN family that is currently being investigated in participants with cutaneous manifestations and active systemic lupus erythematosus. PF-06823859 contains 3 changes in the Fc region to eliminate effector function of the molecule, and it binds IFNβ to prevent signaling through the type I IFN AR.

2.1. Study Rationale

The purpose of this study is to provide an indication of the effects of PF-06823859 on suppression of a type 1 IFN GS in the affected target organ (skin) as well as clinical effects in patients with chronic cutaneous or subacute cutaneous lupus having either primary CLE or SLE.

2.2. Background

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, and the production of autoantibodies, are a prominent feature of the disease,[2] in addition to broad dysregulation of the immune system involving T cells, B cells, dendritic cells and macrophages. 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 patients 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 patients of African heritage.[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 NSAIDs are used in the treatment of arthralgias and cutaneous manifestations. Topical medications (calcineurin inhibitors, corticosteroids, retinoids and others) are also used for treating cutaneous manifestations. High dose corticosteroids, biologics and cytotoxic agents are used in more severe disease. Immunosuppressive agents such as cyclophosphamide, tacrolimus and rituximab may also be used depending on the severity and various organ systems involved.

Mucocutaneous disorders are the second most common organ manifestation in SLE, affecting most patients during their disease[8]. Cutaneous lupus in the absence of systemic lupus affects approximately the same number of people as SLE[9] alone. Taken together, the global population of patients with either SLE and skin disease or pure CLE is estimated to be approximately twice as large as the population affected by SLE. As with many cutaneous disorders, CLE and cutaneous manifestations of SLE have profound effects on patients' psychosocial health and patients often suffer from low self-esteem and depression[10]. Up to 20% of patients with cutaneous lupus may be resistant to commonly used topical therapies such as calcineurin cream or topical corticosteroids and will require systemic treatment. By

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contrast to recent drug approvals for SLE, there are currently no medications approved for the treatment of cutaneous lupus. Therefore, there is an unmet medical need for improved treatment of cutaneous manifestations of lupus. Prior to 2011, only 3 drugs were approved by the US FDA for the treatment of SLE: corticosteroids, hydroxychloroquine (Plaquenil) and low-dose aspirin, all of which have limitations due to either efficacy or toxicity. In March 2011, the US FDA approved belimumab (Benlysta) for treatment of SLE, and several months later in July 2011, the EC granted marketing authorization for Benlysta valid throughout the EU.[11,12]

In the late 1990s emerging evidence linked type 1 interferons, particularly IFNα produced by plasmacytoid dendritic cells, to disease activity in SLE. Although a number of IFNα blockers failed to show good clinical activity in controlled clinical trials, anifrolumab, a type 1 IFN receptor blocking antibody, was approved for treatment of SLE in 2021, based on therapeutic effect seen with type 1 interferon blockade for SLE.[13] Treatment with anifrolumab significantly reduced cutaneous disease activity compared to placebo, demonstrating that blockade of type 1 interferons was an effective approach for treating skin disease in lupus[14]. Despite anifrolumab's efficacy, the suppression of the type 1 IFN GS in blood correlates weakly with reduction in disease activity,[15] suggesting that there is more to understand about how type 1 interferons relate to disease activity.

PF-06823859 is a potent, selective, IgG1 monoclonal antibody directed against the human soluble cytokine IFNβ, a member of the type I IFN family of cytokines. PF-06823859 contains 3 mutations in the Fc region to eliminate effector function of the molecule, and it binds IFNβ and prevents signaling through the type I IFNAR. In comparison to the 13 isoforms of IFNα, there is a single IFNβ, gene product. IFNα isoforms are expressed by plasmacytoid dendritic cells, however IFNβ is produced by all nucleated cells. Whereas older research focused on the effects of IFNα isoforms produced by plasmacytoid dendritic cells as the prototypical type 1 interferons associated with disease activity in SLE, more recent data suggest that IFNβ, which is produced in all nucleated cells[16] and upregulated in SLE skin lesions and in B cells, contributes to the pathogenesis of SLE and that blockade of IFNβ, may be therapeutic in SLE.[17,18]

The clinical development program for PF-06823859 currently consists of one completed Phase 1 study in healthy adult participants (C0251001), one completed Phase 1 study in healthy adult Japanese participants (C0251005), and one ongoing Phase 2 study in adult participants with DM (C0251002).

Study C0251001 was a FIH, randomized, double-blind (ie, participant-blind, investigator-blind and sponsor-open), placebo-controlled dose escalation SAD and MAD study in healthy adult participants to evaluate safety, tolerability, pharmacokinetics, immunogenicity, and pharmacodynamics of PF-06823859. In the SAD and MAD periods of this study, 62 healthy participants were randomized; 48 of the 62 participants received PF-06823859 (IV or SC) and 14 participants received the corresponding placebo. Of the 48 participants, 26 received single escalating IV doses of 30, 100, 300, 900 or 2,000 mg of

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PF-06823859. Twenty-two (22) participants received doses of 100 (SC), 300 (SC), or 600 mg (IV, Q2W) × 3 doses or 600 mg (IV, Q4W) × 2 doses during the MAD period[19].

- PF-06823859 was generally safe and well tolerated when given up to 2,000 mg as a single IV dose and up to 1,800 mg when given in a multi-dose regimen (Q2W 600 mg/IV × 3). The most common reported AE for PF-06823859 was upper respiratory tract infection, likely due to viral infection. There was a low incidence of positive ADA and only one participant developed treatment-induced NAb following 3 SC injections. No AE was reported related to the development of ADA or NAb in healthy participants.

Study C0251002 is an ongoing multi-center, double-blind, randomized, placebo-controlled Phase 2 study to evaluate the efficacy, safety, and PK of PF-06823859. The preliminary results of the study are provided in the IB Section 6.2.2.

Available data from completed studies are presented in the IB.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of PF-06823859 may be found in the IB, which is the SRSD for this study.

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2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Eligibility		
Eligibility criteria require that participants have a diagnosis of SLE with cutaneous manifestations or CLE with either subacute or chronic cutaneous lupus erythematosus (excluding tumidus or chilblain manifestations).	Lupus skin eruptions can be difficult to discriminate from other skin disorders	Participants must have lupus skin involvement confirmed by biopsy either historically (report to be available for review by disease activity adjudicators) or be willing to have a diagnostic biopsy obtained for eligibility.
Study Intervention(s) PF-06823859 and Placebo for PF-06823859		
Use of a placebo arm.	Potential risk in a seriously ill participant being treated with ineffective background medications for 4 months.	Participants who experience worsening of disease may discontinue study intervention and receive alternative care. At Week 16, participants who are randomized to receive placebo treatment and who do not achieve a minimal response will have the opportunity to cross over to a regimen of active drug.
Increased susceptibility to viral infections.	There is a potential risk of increased susceptibility to viral infections with IFNβ blockade as with any antagonist of Type 1 interferon signaling (eg, anti-IFNAR1, anti-IFNα, JAK inhibitors).	AEs and SAEs related to infections will be assessed as AESI (see Section 8.4.8) and closely monitored as-needed. At-risk participants will be excluded during the screening process (see Section 5.2). Opportunistic and severe viral infections will be specifically reviewed by an IRC.
Increased susceptibility to malignancies	There is a potential risk for increased susceptibility to development of malignancies with many immunomodulators	Participants with recent histories of malignancies or malignancies with a high risk of recurrence will be excluded during screening. All malignancies will be reviewed by an IRC.
Interaction with other medicinal products and other forms of interaction.	New and potential drug-drug interaction with PF-06823859 currently unknown.	Potential drug-drug interactions are unlikely with this large molecule. Participants will abstain from prohibited concomitant treatments as described in Appendix 9.
Study Procedures		
4-mm skin punch biopsies will be obtained at 3 time points at baseline, Week 12 and Week 32 (optional)	There is a risk of bleeding, infection, scarring and discomfort from biopsies.	Only site personnel with experience in performing and handling skin biopsies and following skin biopsy sites will perform the on-study biopsies.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
CCI will be obtained at 5 time points at baseline, Week 4, Week 8, Week 12 and Week 32 (optional):	There is a risk of skin irritation, redness and discomfort from the CCI sites	Only site personnel with experience in performing and handling skin CCI will perform the on-study CCI collection.
Infusion reactions.	Infusion reactions are known risks associated with IV infusions of biologics.	Participants will be monitored for approximately 60 minutes after infusion for infusion reactions; specific guidance on acute prophylactic treatment of infusion related reactions and recommendations for future infusions of study intervention are provided in Section 6.1.1. Participants will be monitored for approximately 60 minutes after infusion for infusion reactions; specific guidance on acute prophylactic treatment of infusion reactions and recommendations for future infusions of study intervention are provided in Section 6.1.1.

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2.3.2. Benefit Assessment

Blockade of type 1 IFN receptors by anifrolumab was associated with suppression of a type 1 IFN GS, anti-dsDNA antibody reduction and clinical improvement in SLE disease activity, suggesting that blocking gene expression downstream of type 1 interferon could promote improvement in SLE disease activity. Based on the clinical effects observed in Study C0251002, PF-06823859 significantly suppressed a type 1 IFN GS in lesional skin, as well as reducing CDASI activity score in DM patients. These effects may provide benefit to study participants by reducing SLE or CLE disease activity. Furthermore, participants may also benefit from a better understanding of their health, based on study tests and assessments.

2.3.3. Overall Benefit/Risk Conclusion

PF-06823859 was safe and well tolerated in a DM phase 2 study. Taking into account the measures to minimize risk to study participants, the potential risks identified in association with PF-06823859 are justified by the anticipated benefits that may be afforded to participants with SLE or CLE.

3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Objective	Endpoint	Estimand*
Primary	**Primary**	**Primary**
• To evaluate the effect of PF-06823859 on the type 1IFN GS score at Week 12 in participants with CLE or SLE with cutaneous manifestations	• Change from baseline in type 1 IFN GS score in lesional skin at Week 12	E1 E1 evaluates the difference across the treatment arms in the mean values of change from baseline of continuous outcome of interest. The treatment effect is evaluated in the hypothetical population of participants who did not experience intercurrent events. The intercurrent events are: • Missing two consecutive doses of treatment • Exposure to a new or protocol prohibited dose of systemic medication for the treatment of cutaneous or systemic lupus manifestations.
Key Secondary	**Key Secondary**	**Key Secondary**
• To evaluate the effect of PF-06823859 on the CLASI-A score at Week 12 in participants with CLE or	• Change from baseline (%) in CLASI-A score at Week 12	E1 (same as above)

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Objective	Endpoint	Estimand*
SLE with cutaneous manifestations		
Other Secondary	**Other Secondary**	**Other Secondary**
• To evaluate the effect of PF-06823859 on the additional measures of CLASI-A score at Week 12 and over time in participants with CLE or SLE with cutaneous manifestations	• Percent change from baseline in CLASI-A (over time in addition to Week 12) • Change from baseline in CLASI-A (over time) • Achieving ≥50%, 4 or 7 points reduction in CLASI-A (over time)	• For continuous outcome E1 estimand will be used for the continuous outcomes at Week 0-12-time span and descriptive statistics will be used for later visits. • E2 (for binary outcome) E2 evaluates the difference across the treatment arms in probabilities of response. The treatment effect is evaluated in the population of study participants who are randomized and treated irrespective of their compliance to the planned course of treatment. Observations for which an observed (CLASI-A) score may be confounded by the use of prohibited medications are assigned a non-responder status.
• To evaluate the effect of PF-06823859 on the PhGA in participants with CLE or SLE with cutaneous manifestations	• Change from baseline in PhGA (over time)	• For continuous outcome E1 estimand will be used for the continuous outcomes at Week 0-12-time span and descriptive statistics will be used for later visits.
• To evaluate the safety and tolerability of PF-06823859 in participants with CLE or SLE with cutaneous manifestations	• Incidence and severity of laboratory, vital signs, 12-lead ECG abnormalities, AEs, SAEs and withdrawals due to AEs over time	There is no defined estimand for these endpoints. They will be analyzed using Pfizer data standards as applicable

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Objective	Endpoint	Estimand*
Exploratory	**Exploratory**	**Exploratory**
• To evaluate changes in molecular biomarkers from skin, blood and saliva in response to PF-06823859 and their ability to predict a response to treatment	• Data permitting, change over time in molecular biomarkers as described in Section 8.7	Endpoints will be analyzed descriptively.
• To characterize the PK of PF-06823859 in participants with CLE and SLE with cutaneous manifestations	• PK-06823859 concentrations	There is no defined estimand for these endpoints. They will be analyzed using Pfizer data standards as applicable.
• To characterize the immunogenicity of PF-06823859 in participants with CLE and SLE with cutaneous manifestation during the study	• Incidence of development of ADAs/NAb through the end of study visit	There is no defined estimand for these endpoints. They will be analyzed using Pfizer data standards as applicable.
• To evaluate the effect of PF-06823859 on SLE manifestations of disease (SLEDAI-2K score) in the participants with SLE	• Change from baseline in SLEDAI-2K score over time in the subpopulation of participants entering the study with a diagnosis of SLE over time	E1 (same as above)

* The additional supportive estimands and analyses will be described in the SAP.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 2, double-blind, randomized, placebo-controlled, multicenter study to evaluate the clinical effect, PD, PK and safety profile of PF-06823859 in adult participants with active CLE or SLE with cutaneous manifestations.

Participants will participate in this study for approximately 65 weeks. This includes up to a 5-week screening period, a 12-week Q4W treatment period, a 36-week Q8W treatment period, and a 12-week follow-up period.

After up to a 5-week screening period, eligible participants will be randomized in a 2:1 ratio to receive either PF-06823859 CCI or placebo Q4W dosing on Day 1, Week 4 and Week 8 in addition to protocol permitted SOC treatment. Following assessments for the primary endpoint at Week 12, participants who are receiving active PF-06823859 or who are placebo non-responders (responder is defined by ≥4 point reduction from the baseline in CLASI-A score) will receive PF-06823859 CCI Q8W beginning at Week 16, while

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placebo responders will continue to be in the placebo group. The last dose of study intervention will be administered at Week 40 followed by last full study assessments at Week 48. The follow up visit will be conducted at Week 60. To minimize any missing data if a participant prematurely discontinues from study intervention, the sponsor is asking all participants to continue with their protocol scheduled visits. If study intervention is discontinued for any reason, the participant may receive any medication required to control of their SLE/CLE after consultation with the sponsor medical monitor.

Two IAs may be performed. The first IA may be performed at the time when about 50% of the participants complete the Week 12 visit. It may provide a non-binding recommendation of early stopping for futility but will not allow early stopping of the trial for efficacy and will not increase the type I error. The results of the IA may be used for internal decision making. The second IA may be performed after the last participant completes Week 12 to determine whether the mean decrease from baseline in the type 1 IFN GS score is greater in the PF-06823859 treatment arm than in the placebo treatment arm and if this difference is statistically significant. A similar comparison will be done for the key secondary outcome. It will be evaluated whether the mean value of percent decrease from baseline in the CLASI-A score is greater in the PF-06823859 treatment arm than in the placebo treatment arm and whether this difference is statistically significant.

Further details of analyses in safety and efficacy will be specified in the SAP. A separate SAP may be provided for the IA.

Approximately 48 participants will be enrolled in the study at approximately 30 investigator sites worldwide.

4.2. Scientific Rationale for Study Design

This study is the first being conducted to provide data on efficacy, safety, tolerability, PK and PD of PF-06823859 in adult SLE or CLE participants with subacute or chronic skin lesion manifestations.

This Phase 2 study will assess differences in type 1 IFN GS in lesional skin and decrease in clinical activity as assessed by reduction in CLASI-A in participants treated with PF-06823859 CCI [redacted] Q4W compared to placebo in SLE or CLE with subacute and/or chronic lupus skin lesions at Week 12. In the subpopulation of participants with cutaneous manifestations of SLE, changes in SLE disease activity as assessed by SLEDAI will also be compared by treatment arm.

Up to a 48-week treatment period will provide long term safety, efficacy, tolerability, and durability data for PF-06823859 in this targeted patient population.

CCI [redacted]

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CCI

[redacted]

4.2.1. Patient Input Into Design

Patient input in the UK will be obtained from the NIHR. Information will include how lupus patients feel about the protocol assessment schedules, number and frequencies of biopsies, use of IV medication, and the frequency of medication administration (Q8W vs Q4W). This input will be used to drive patient facing study tools.

4.2.2. Diversity of Study Population

Reasonable attempts will be made to enroll participants representative of the patient population that will use PF-06823859 in clinical practice. The sponsor is considering sites in Latin America, Asia, US, and UK (where African heritage patients are expected to participate) in an effort to enroll participants with diverse racial and ethnic backgrounds The importance of enrolling diverse populations will be discussed during the site training.

4.2.3. HLH/MAS Adjudication Committee

Suspected HLH/MAS will be adjudicated by external independent safety event adjudication committees consisting of clinical experts to facilitate standardization of assessments within the program. The safety event adjudication committees will be blinded to treatment assignment in order to allow for unbiased categorization of AEs regardless of causality assessment.

Investigators will be responsible for obtaining and submitting the documentation to be reviewed by the safety event adjudication committee. Documentation includes, but is not limited to, the following: investigator and consultant notes, laboratory tests, imaging reports, autopsy report, and/or other investigational procedures within or in addition to the protocol requirements. These documents may be reviewed by Pfizer and/or its delegates.

Further information about this HLH/MAS event adjudication committee is provided in a charter, including a description of the scope of the committee's responsibilities, the process and definitions to be utilized by the committee for adjudication, and communication plan including timelines.

Additional safety event adjudication committees may be established during the study to standardize additional safety event assessments. As described above, individual committee charters will provide specific descriptions of the scope of responsibilities and the processes and definitions used to assess specific safety events.

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4.2.4. Choice of Contraception/Barrier Requirements

No developmental toxicity was identified in nonclinical studies conducted in still-growing monkeys (6-month chronic toxicity study) or infant animals exposed to PF-06823859 in utero, however the use of a highly effective method of contraception is required (see Appendix 4).

4.2.5. Collection of Retained Research Samples

Retained Research Samples will be collected and stored for further analyses which may, for example, provide greater understanding of the study intervention.

4.3. Justification for Dose

Modeling of PK, PD, and efficacy in DM participants in C0251002 (NCT03181893) supports selection of the CCI Q4W regimen. Data from the Phase 1 Study C0251001 (NCT02766621) and the Phase 2 Study C0251002 (NCT03181893) enabled development of a population PK/PD model to characterize the relationship between drug exposure, target engagement (total IFNβ, GS) and CCI is a biomarker downstream of IFNβ inhibition that is correlated with inflammation. In addition, an exposure-response model was developed to characterize the relationship between PF-06823859 exposure and clinical efficacy endpoints for CCI. The modeling results support the following key conclusions for DM participants in C0251002 (NCT03181893):

- PF-06823859 is highly bound (>99%) to IFNβ at the exposure corresponding to the CCI Q4W near complete target engagement was observed.
- Inhibition of CCI was significantly greater than placebo at CCI Q4W doses

In addition, the percent change from baseline levels in the type 1 IFN GS at Week 12 was markedly lower from lesional skin in DM participants treated with CCI PF-06823859 CCI compared to lesional skin from the placebo group CCI , demonstrating pharmacodynamic activity CCI .

SLE and CLE patients have inflammatory markers and type 1 IFN GS that are similar to those found in DM. Given the understanding of near complete target engagement provided by the PK/PD modeling for CCI Q4W, high specificity of PF-06823859 for IFNβ, significant suppression of type 1 IFN GS, an acceptable safety profile and the absence of observed off-target safety concerns from previous studies, the CCI Q4W regimen has been selected for evaluation in participants with SLE and CLE. Furthermore, many of the therapies used for the treatment of skin lesions in DM are also used for treatment in cutaneous lupus lesions, suggesting that PF-06823859 may also be effective for the treatment of cutaneous lupus.

A dose of CCI administered Q8W was chosen for treatment after Week 16 based on simulations from the population PK/PD which suggested high target occupancy (>99%) and potential ability to maintain clinical response at this less frequent and more convenient

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dosing regimen. It is expected that a dose of [redacted] Q4W or Q8W would achieve meaningful suppression of the type 1 IFN GS and ameliorate pathologic changes in affected skin of patients with both SLE and CLE.

4.4. End of Study Definition

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

A participant is considered to have completed the study if they have completed all periods of the study, including the last scheduled procedure shown in the SoA.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled, including participants across diverse and representative racial and ethnic backgrounds. If a prescreening tool is utilized for study recruitment purposes, it will include collection of information that reflects the enrollment of a diverse participant population including, where permitted under local regulations, age, sex, race, and ethnicity. 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.

Pfizer will review eligibility criteria verified by the investigator or qualified designee to confirm that participants meet study eligibility criteria before they are enrolled into the study. The enrollment approval process will be initiated for a participant after an informed consent document has been signed and the investigator or qualified designee has assessed the participant as eligible. The enrollment approval will be based on review of CRF/system data.

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 ICD.

    - Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

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. Participants must be capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed

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in the ICD and in this protocol. All participants should be willing to remain in the study to the end of the treatment- period for safety, efficacy, PK and PD assessments, whether or not study intervention is discontinued.

Note: Participants should understand the study requirements and be committed to complete the study since excessive dropout will impair the ability to interpret results.

3. Participants must be willing to avoid application of topical medications to the index lesions (4 index lesions should be identified at screening and baseline) that are identified for potential biopsies in the study until after Week 32.

4. Participants must have adequate IV access for administration of study intervention and on-study blood sampling.

5. Have a diagnosis of histologically confirmed active CLE or SLE with cutaneous manifectations despite treatment with standard of care medications for at least 12 weeks defined as a score of ≥8 on the CLASI-A, an erythema score of ≥2 in the CLASI and historical biopsy (report to be available to disease activity adjudicators) within the past 10 years with either:

   a. Subacute cutaneous lupus erythematosus, or

   b. Discoid lupus erythematosus with at least one active discoid lesion (panniculitis, tumidus and chilblain lesions are excluded for the purposes of disease activity qualifying for eligibility and biopsy but are not exclusionary), or

   c. Both subacute and chronic cutaneous lupus erythematosus

   Note: If the lesion has not been previously biopsied, a biopsy will be required to confirm diagnosis during screening. CLASI-A score and biopsy results will be reviewed by independent central data reviewers and the centrally reviewed score will be the score used to base decisions on eligibility and post Week 12 dosing. The investigator should confirm that the CLASI-A has not decreased below eligibility (remains at least 8) at baseline.

6. All participants may be currently receiving EITHER a stable dose of an immunosuppressant (MTX, AZA, 6-MP, leflunomide, mizoribine, MMF), or dapsone or colchicine with or without antimalarials and/or corticosteroids, OR anti-malarials (hydroxychloroquine, chloroquine or quinacrine) in combination with corticosteroids (dose of oral corticosteroids must be between 5 and 10 mg/day prednisone equivalent) or permitted topical agents. Participants may not be receiving combinations of 2 or more immunosuppressants. Medications (whether topical and/or systemic) other than corticosteroids must have been started at least 12 weeks prior to Day 1. Topical or systemic corticosteroids must have been started at least 8 weeks prior to Day 1.

   Note: Stable dose is defined as no new therapy or as stable as possible with existing SOC therapies as above within 12 weeks of Day 1 for immunosuppressives or within

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4 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 9 for allowable stable doses.

Weight:

7. Participants weighing greater than 40 kg and less than 130 kg and with a BMI of <40 kg/m^2.

5.2. Exclusion Criteria

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

Medical Conditions:

1. Have another skin disorder that would confound the results of the skin biopsy or clinical assessments in the study (eg, psoriasis, drug-induced eruptions or drug related lupus).

2. Active, severe lupus nephritis (World Health Organization Class III, IV) that requires or may require treatment with cytotoxic agents or high-dose CS. Participants with prior, controlled, renal disease treated with an ACE or ARB inhibitor and immunosuppressive therapy (cyclophosphamide or mycophenolate mofetil) and a serum creatinine ≤2 × ULN and either residual proteinuria up to ≤3 g/day or a 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 team 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 laboratory 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.

3. Severe active CNS lupus (eg, EULAR/ACR evidence of severe neurological disease and/or new or poorly controlled seizure disorder, acute confusional state, myelitis or aseptic meningitis, demyelinating syndrome, stroke or stroke syndrome, cerebellar ataxia or dementia related to SLE, active psychosis, organic brain syndrome, CVA, cerebritis or CNS vasculitis) requiring therapeutic intervention within 60 days of Day 1. Participants with a diagnosis of SLE and non-severe neurologic manifestations(equivalent to BILAG B, C or D such as isolated peripheral neuropathy, mild cognitive dysfunction, autonomic disorders that do not confound on-study assessments), are not excluded as long as they meet all other qualifying

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criteria for the study. Participants with ophthalmic neuropathy must have been evaluated by an ophthalmologist.

4. Cancer or any history of cancer within 5 years of screening other than adequately resected basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ of the uterine cervix with no evidence of recurrence within the previous 5 years).

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

6. Have a history of:

   - A history of major cardiovascular or cerebrovascular event (stroke) or acute cardiac syndrome (MI, unstable angina pectoris, coronary stenting) within 24 months of screening
   - known pulmonary arterial hypertension
   - history of pulmonary embolism within 6 months of screening

   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.

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

8. Have any autoimmune or inflammatory disease that would interfere with interpretation of test results or clinical assessments. This would include:

   a. Mucocutaneous manifestations including but not limited to other skin disorders that would confound evaluation of the CLASI, such as psoriasis, dermatomyositis, Behcet's syndrome, systemic sclerosis, eczema, any other vasculitis such as ANCA vasculitis, dermatomyositis, polymyositis, mixed connective tissue disease, or other chronic skin conditions

   b. Musculoskeletal diseases including but not limited to rheumatoid arthritis, osteoarthritis that would confound assessment of lupus joint disease, 'rhupus', overlap syndromes, psoriasis/psoriatic arthritis, Behcet's syndrome, primary Sjogren's syndrome, mixed connective tissue disease or other chronic debilitating joint disorders,

   c. Any other inflammatory autoimmune disease that would confound disease activity assessments such as inflammatory bowel disease, rheumatoid arthritis,

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primary Sjogren's syndrome, any other vasculitis such as ANCA vasculitis, dermatomyositis, polymyositis, mixed connective tissue disease.

Note: A decision about the suitability of the participant for enrollment will be made by the independent central reviewers and Pfizer clinical team.

9. History of any lymphoproliferative disorder such as 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).

Infection

10. 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 should be encouraged (per local guidelines) to do so prior to randomization. Participants should not receive the live herpes zoster vaccination (Zostavax®, Merck) within 4 weeks of planned randomization or on study; the recombinant adjuvant herpes zoster vaccine (Shingrix®, GSK) is permitted prior to and on study.

11. Required management of acute or chronic infections as follows:

    - Receiving any suppressive therapy for any chronic infection (such as pneumocystis, CMV, and atypical mycobacteria, herpes simplex) that, in the opinion of the investigator and sponsor, would place the participant at risk for reactivation. Participants who are receiving prophylactic therapy for herpes simplex virus may enroll and should continue this therapy for the duration of the study. Participants with no prior pneumocystis carinii infection may enroll if they are receiving prophylaxis for pneumocystis by permission of Pfizer clinical team.

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

    - Use of IV or IM antibacterials, antivirals, antifungals, or antiparasitic agents within 60 days of Day 1. Substitution of IM agents for oral agents because of 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.

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Prior/Concomitant Therapy:

12. A listing of permitted and prohibited topical and systemic corticosteroids is provided in Appendix 9.

13. Additional immunomodulatory drug exclusions see Appendix 9 for details.

14. Have received plasmapheresis within 12 weeks of screening or IVIg within 24 weeks of screening.

15. Treatment with any investigational drug(s) within 12 weeks of Day 1 for investigational biologics or within one month or 5 half-lives for investigational small molecules whichever is longer, and/or during study participation.

16. 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. Participants should not have received a BCG vaccination within 52 weeks of randomization.

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

Prior/Concurrent Clinical Study Experience:

18. 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.

Diagnostic Assessments:

19. Screening chest X-ray with changes suggestive of 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 screening may be used.

    Note: If a chest X-ray shows any abnormalities (nodules, infiltrates, scarring, stranding, etc), these findings must be documented to be stable compared to a prior chest X-ray obtained at least 12 months previously. Findings due to SLE activity do not require the participant to be excluded.

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20. Infected with Mycobacterium TB: active TB or latent TB (see Section 8.3.6).

    a active TB infection is excluded.

    b If a participant has a positive or indeterminate IGRA at screening, the potential participant must be evaluated by a local expert (pulmonologist or infectious disease specialist) who may order additional testing as per local practice and will determine whether the potential participant has active or latent TB. If the local expert determines that the potential participant does not have active or latent TB, then the potential participant may be eligible for the study. A note from the specialist should be available in the source document and a summary of the specialists report must be provided to the Pfizer medical monitor to confirm that the participant does not have latent or active TB.

21. Known history of HIV based on documented history with positive test, or positive HIV test at screening.

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

22. Have evidence of active or latent infection of hepatitis B or hepatitis C based on screening tests (see Section 8.3.8).

23. Screening 12-lead 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. It is recommended that a cardiologist review the screening ECG and provide an interpretation.

24. Participants with ANY of the following abnormalities in clinical laboratory tests at Screening, as assessed by the study specific laboratory:

    - IgG levels below 500 mg/dL
    - Hemoglobin <9 g/dL (<90 g/L)
    - ANC $<1.0 \times 10^3/\mu L$
    - lymphocyte count $<0.4 \times 10^3/\mu L$, if the ALC is considered by the investigator to be a result of the underlying SLE disease or concomitant medications
    - Platelet count $<75 \times 10^3/\mu L$
    - Combined serum cystatin C and serum creatinine based eGFR <50 mL/min/1.73 m^2 based on CKD/EPI calculation

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- AST or ALT values ≥2 times the ULN
- Direct bilirubin greater than the ULN
- CK >3 times the ULN

Note: Screening laboratory tests with abnormal results may be repeated once to confirm abnormal results within the 5-week screening period. If results return to normal within the 5-week screening period, the participant may enter the study.

Other Exclusion Criteria:

25. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the judgment of the investigator make the participant inappropriate for the study. This would include the following answers on the C-SSRS questionnaire, which must be completed by the investigator at screening:
    - Suicidal ideation associated with actual intent and a method or plan in the past year: "Yes" answers on items 4 or 5 of C-SSRS (completed during screening).
    - Previous history of suicidal behaviors in the past 5 years: "Yes" answer (for events that occurred in the past 5 years) to any of the suicidal behavior items of the C-SSRS).
26. Investigator or site staff directly involved in the conduct of the study and their family members, site staff otherwise supervised by the investigator, and sponsor and sponsor delegate employees directly involved in the conduct of the study and their family members.
27. Significant trauma or major surgery or blood transfusion within 5 weeks of screening, or scheduled to occur during the study, excluding diagnostic surgery.
28. 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.
29. Participants who are currently vaping or using e-cigarettes.
30. Participants with a history of hypersensitivity reactions to active drug or any of the excipients in the drug product or placebo.

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5.3. Lifestyle Considerations

In order to participate in this study, participants must be aware of the lifestyle guidelines and restrictions that apply during the study:

5.3.1. Contraception

The investigator or their designee, in consultation with the participant, will confirm that the participant is utilizing a highly effective method of contraception for the individual participant and their partner(s) from the permitted list of contraception methods (see Appendix 4, Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the SoA, 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, considering that their risk for pregnancy may have changed since the last visit.

In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued and document the requirement to use an alternate protocol-specified method, including if the participant will no longer use abstinence as the selected contraception method, or if pregnancy is known or suspected in the participant or partner.

5.3.2. Activity

Participants should avoid any strenuous new exercise program duting the study and should follow activity restrictions provided by the investigator following skin biopsies.

5.3.3. Other Restrictions

In order to participate in the study, participants must be aware of the following lifestyle guidelines and restrictions that apply during and after the study period.

- On study visit days that include fasting lipid panel, comply with fasting requirement or fast as able for at least 8 hours prior to the visit.
- On study visit days, do not smoke or ingest caffeine during the 30 minutes prior to blood pressure and heart rate measurements.
- During study, discontinue and avoid using certain medications and treatments including application of topical corticosteroids, tacrolimus ointment on skin lesion areas for biopsies.
- During the study, avoid exposure to the sun and agree to use the sunscreen.

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5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled in the study due to not meeting eligibility criteria. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, and any SAE.

5.4.1. Rescreening

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once as long as meeting the eligibility criteria is possible. Participants who are pregnant at their original screening visit may not rescreen.

Rescreening will include a subset of screening assessments as listed in the SoA.

5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Administration of Study Intervention

The following conditions may allow a participant to be randomized/started on study intervention once the conditions have resolved and the participant is otherwise eligible:

- Current febrile illness (temperature ≥38.0°C [≥100.4°F]) or any other acute illness within 48 hours before study intervention administration.
- Participant has received a live vaccine within 6 weeks.
- Participant is less than 5 days into a course of systemic antibiotic therapy.

If the delay is greater than 2 weeks, re-testing procedures should be discussed with the Medical Monitor.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study interventions are all prespecified investigational and non-investigational medicinal products/auxiliary medicinal products, medical devices, and other interventions (eg, surgical and behavioral) intended to be administered to the study participants during the study conduct.

For the purposes of this protocol, study intervention refers to PF-06823859 and placebo for PF-06823859.

6.1. Study Intervention(s) Administered

The study intervention will be administered by IV infusion Q4W on Day 1, Week 4 and Week 8 in addition to protocol permitted SOC treatment. Following assessments for the primary endpoint at Week 12, participants will continue receiving study intervention Q8W beginning at Week 16, the last dose of study intervention will be administered at Week 40

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followed by last full study assessments at Week 48. The follow up visit will be conducted at Week 60.

Study Intervention(s)		
Intervention Name	**PF-06823859**	**Placebo for PF-06823859**
Arm Name	PF-06823859	Placebo for PF-06823859
Type	Drug	Placebo
Dose Formulation	Solution for infusion	Solution for infusion
Unit Dose Strength(s)	CCI	0 mg/mL
Dosage Level(s)	CCI	0 mg
Route of Administration	IV	IV
Use	Experimental	Placebo
IMP or NIMP	IMP	IMP
Sourcing	Provided centrally by the sponsor. See IPM for more information.	Provided centrally by the sponsor. See IPM for more information.
Packaging and Labeling	CCI Each vial and carton will be labeled as required per country requirement. Study intervention will be blinded.	CCI Each vial and carton will be labeled as required per country requirement. Study intervention will be blinded.

Study Arm(s)		
Arm Title	PF-06823859	Placebo for PF-06823859
Arm Type	Experimental	Placebo
Arm Description	Participants will receive CCI IV Q4W on Day 1, Week 4 and Week 8 and then CCI IV Q8W beginning at Week 16, the last dose of study intervention will be administered at Week 40.	Participants will receive placebo IV Q4W on Day 1, Week 4 and Week 8 and then placebo IV Q8W beginning at Week 16, the last dose of study intervention will be administered at Week 40.

Excipients included in either active study intervention or placebo include: L-Histidine, L-Histidine hydrochloride monohydrate, polysorbate 80, Sucrose (low endotoxin), EDTA disodium salt dihydrate, and water for injection.

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6.1.1. Administration

The study intervention will be administered as an IV infusion over approximately 60 minutes using a calibrated infusion pump. After the infusion, the participants will be monitored for approximately 60 minutes for infusion reactions.

Section 6.1.1.1 provides details for infusion interruption and discontinuation.

6.1.1.1. Infusion Discontinuation

If a participant experiences symptoms typical of an anaphylactoid or hypersensitivity reaction (wheezing, stridor, oral or facial edema, hives, severe nausea and vomiting, evidence of circulatory collapse, the dosing administration should be discontinued immediately and permanently.

If a participant experiences symptoms typical of infusion reactions (eg, lightheadedness, nausea, chills, fever), the dosing administration should be stopped. At the discretion of the . investigator, the infusion can be restarted at a slower rate if symptoms resolve within 1 hour after the stop of infusion. If symptoms return, then the dosing administration should be discontinued immediately and permanently. Any signs or symptoms related to an infusion reaction should be treated according to the investigator's standard of care for treatment of hypersensitivity and reported as adverse events or serious adverse events if the event requires hospitalization or is life-threatening.

If there is an infusion interruption, the entire infusion duration should not exceed 3 hours.

If an infusion dose cannot be completed, the estimate of the dose portion should be documented in source record and CRF.

6.1.1.2. Infusion Reaction Assessment

Infusion reactions will be monitored according to the SoA. Infusion reactions may include but are not limited to erythema, induration, ecchymosis, pain, and pruritus.

Any signs or symptoms related to an infusion reaction should be treated according to the investigator's standard of care and reported as adverse events.

6.2. Preparation, Handling, Storage, and Accountability

1. The investigator or designee must confirm that appropriate conditions (eg, temperature) have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply, prepare, and/or administer study intervention.

3. 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

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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 temperatures since previously documented upon return to business.

4. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with actions taken. The site should actively pursue options for returning the study intervention to labeled storage conditions, 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. Specific details regarding the excursion definition and information to report for each excursion will be provided to the site in the IPM or other specified location.

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

6. Study interventions should be stored in their original containers.

7. The investigator, institution, head of the medical institution (where applicable), or authorized site staff is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the IPAL or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record.

8. Further guidance and information for the final disposition of unused study interventions are provided in the IPM, or other specified location. All destruction must be adequately documented. 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.

Upon identification of a product complaint, notify the sponsor within 1 business day of discovery as described in the IPM.

6.2.1. Preparation and Dispensing

The study intervention will be administered in a **blinded** fashion to the participants.

Study intervention should be prepared and dispensed by an unblinded appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance. A unblinded second staff member will verify the dispensing and preparation. After the preparation, the PF-06823859 and placebo will look and feel identical to ensure administration by infusion in blinded fashion by blinded site staff. See the IPM for instructions on how to prepare the study intervention for administration.

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6.3. Assignment to Study Intervention

Allocation of participants to treatment groups will proceed through the use of an IRT system. The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's ID and password, the protocol number, and the participant number. The site personnel will then be provided with a randomization number corresponding to the assigned treatment group, and DU or container number(s) 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 SoA.

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

6.4. Blinding

This is a double-blind study.

6.4.1. Blinding of Participants

Participants will be blinded to their assigned study intervention.

Circumstances where unblinding is permissible include:

- AE or SAE that in the best interest of the participant's wellbeing requires unblinding.

6.4.2. Blinding of Site Personnel

Investigators and other site staff will be blinded to participants' assigned study intervention.

Participants will be assigned to receive study intervention according to the assigned treatment group from the randomization scheme. Investigators will remain blinded to each participant's assigned study intervention throughout the course of the study. Only site personnel listed in **unblinded** roles (eg, pharmacist) shall **handle shipments, IP, and perform dose preparation and or verification activities.** Unblinded persons may not participant in the evaluation of any study participants. Unblinded site staff members are the only site personnel who can handle the IP packages and document treatment information.

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.

6.4.3. Blinding of the Sponsor

Sponsor staff will be blinded to participants' assigned study intervention, except for sponsor staff involved in the assignment or distribution of study intervention.

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Circumstances where unblinding is permissible while the study is ongoing include:

- Sponsor staff who are **not** directly involved with the conduct of this study will prepare analyses and documentation containing unblinded data to support interactions with the IRC, interim analysis, and regulatory submissions.

- Study monitors who perform IP accountability reviews at sites will be unblinded.

6.4.4. 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 study medical monitor 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 CRF.

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

6.5. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

The site will complete the required dosage Preparation Record located in the IPM. The use of the Preparation Record is preferred, but it does not preclude the use of an existing appropriate clinical site documentation system. The existing clinical site's documentation system should capture all pertinent/required information on the preparation and administration of the dose. This may be used in place of the Preparation Record after approval from the sponsor and/or designee.

6.6. Dose Modification

PF-06823859 dose modification is not allowed in this study.

If an infusion dose cannot be completed effort should be made to record the estimate of the completed portion, see Section 6.1.1.1.

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6.7. Continued Access to Study Intervention After the End of the Study

CCI [redacted] will be provided to participants at the end of their study participation. It is expected that participants will be treated as required with standard-of-care treatments, as advised by their usual care physician.

6.8. Treatment of Overdose

For this study, any dose of PF-06823859 greater than CCI [redacted] will be considered an reportable overdose if associated with an AE. Any overdose should be reported within 24 hours to Pfizer clinical team to discuss need for additional assessments which may include additional PK measurements.

There is no specific treatment for an overdose.

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

1. Contact the study medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities as medically appropriate and at least until the next scheduled follow-up.
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Pfizer Safety **only when associated with an SAE.**

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

6.9. Prior and Concomitant Therapy

Any prior history (any time prior to the signing of the ICD with no limitations of time) of immunosuppressives (eg AZA, 6-MP, leflunomide, mizoribine or mycophenolate and MTX), or biologics for SLE or CLE will be recorded on the CRF. Corticosteroids for SLE or CLE treatment over past year and any other prior medications taken during the 30 days prior to screening must be recorded on the CRF. Medications taken during screening period before the first dose of IP will be documented as prior medications.

6.9.1. Permitted Background Medications

It is expected that all participants in this study will be taking some background medication for their cutaneous lupus manifestations throughout the treatment period. Participants who are taking SOC at the time of enrollment should continue on their permitted background medications during the study. Potential participants taking permitted SOC background medication at the time of enrollment should keep background medication dosing as stable as possible for the duration of the study (see Appendix 9).

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No rescue medications are permitted on this study. If a participant requires medication that is not protocol permitted to control their lupus manifestations, the participant should discontinue study intervention and the investigator should contact Pfizer clinical team. Because of the long half-life of PF-06823859, investigators should consider carefully whether topical or systemic therapy may be best to treat disease activity within 3 half-lives of PF-06823859. To minimize any missing data if a participant prematurely discontinues from study intervention, the sponsor is asking all participants to continue with their protocol scheduled visits. If study intervention is discontinued for any reason, the participant may receive any medication required to control of their SLE/CLE after consultation with the sponsor medical monitor.

6.9.2. Prohibited Medications

See Appendix 9 for the full list of prohibited medications and appropriate washout periods. Please discuss medications not on this list with the medical monitor.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

It may be necessary for a participant to permanently discontinue study intervention. Reasons for permanent discontinuation of study intervention include the following:

- Anaphylactic or allergic reactions to study intervention;
- Pregnancy;
- AEs or SAEs that, in the best interest and wellbeing of the participant, may require permanent discontinuation of the study intervention in the opinion of either the sponsor or the investigator;
- Lost to follow-up;
- Lack of efficacy;
- Use of prohibited medications (see Appendix 9) for progressive/unstable SLE/ CLE that may impact on participant's safety and study results interpretation.

Full details for reasons regarding permanent discontinuation of study intervention (eg, liver injury, kidney injury, ECG changes) as well as monitoring criteria are included in Appendix 11.

Participants should be followed post-study intervention discontinuation for 20 weeks.

Note that discontinuation of study intervention does not represent withdrawal from the study. If study intervention is permanently discontinued, the participant should remain in the study to be evaluated for efficacy and safety. If the participant discontinues study intervention, they

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may receive any medication required to control of their SLE/CLE after consultation with the sponsor medical monitor. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed.

In the event of discontinuation of study intervention, it must be documented on the appropriate CRF/in the medical records whether the participant is discontinuing further receipt of study intervention or also from study procedures, posttreatment study follow-up, and/or future collection of additional information.

7.1.1. Temporary Discontinuation

Temporary discontinuation of study intervention may be medically necessary. On resumption of the study intervention, the participant will continue onto the next scheduled dosing (ie, no back dating) and BL monitoring will be repeated (see SoA).

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at their own request. Reasons for discontinuation from the study include the following:

- Refused further study procedures;
- Lost to follow-up;
- Lack of efficacy;
- Death;
- Study terminated by sponsor;
- Withdrawal of consent during any phase of the study.

Participants should be questioned regarding their primary reason for withdrawal for documentation in medical records and recording in the CRF. Please record withdrawal for both failure to improve or worsening of underlying disease as lack of efficacy.

The early discontinuation visit applies only to participants who are enrolled/randomized and then are prematurely withdrawn from the treatment. Participants should be questioned regarding their reason for withdrawal.

If a participant withdraws from the study, they may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

If the participant withdraws from the study and also withdraws consent (see Section 7.2.1) for disclosure of future information, no further evaluations will be performed and no additional data will be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

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7.2.1. Withdrawal of Consent

Participants who request to discontinue receipt of study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with them or persons previously authorized by the participant to provide this information. Participants should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. 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 the participant 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 attend a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible. Counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain whether 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, the participant will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Administrative 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 SoA. Protocol waivers or exemptions are not allowed.

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

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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 (chest X-ray, chest CT scan, HIV test, or interferon gamma release assay) conducted as part of the participant's routine clinical management 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 Section 8.3.7.

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 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 they have 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.

None of the safety laboratory analyses that are collected for this study are potentially unblinding.

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 in this study is approximately 570 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 700 mL.

8.1.1. Telehealth Visits

In this study telehealth visits are only permitted as indicated in the schedule of events. Telehealth visits may not substitute for any of the visits that require assessments performed at the study site.

Telehealth visits may be used to assess participant safety and collect data points. Telehealth includes the exchange of healthcare information and services via telecommunication technologies (eg, audio, video, videoconferencing software) remotely, allowing the participant and the investigator to communicate on aspects of clinical care, including medical advice, reminders, education, and safety monitoring. The following assessments must be performed during a telehealth visit (see the SoA):

- Review and record any AEs and SAEs since the last contact. Refer to Section 8.4.

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- Review and record any new concomitant medications or changes in concomitant medications since the last contact.

- Review and record contraceptive method and results of pregnancy testing. Confirm that the participant is adhering to the contraception method(s) required in the protocol. Refer to Appendix 4.

Study participants must be reminded to promptly notify site staff about any change in their health status.

8.2. Efficacy Assessments

8.2.1. Rater Qualifications

For specific rating assessments, only qualified raters will be allowed to evaluate and/or rate participants in this study. The efficacy assessments requiring rater qualification include:

- CLASI
- SLEDAI-2K
- EULAR/ACR classification criteria for SLE
- Joint Assessment

The minimum qualifications a rater must meet for each study rating assessment will be outlined in the training materials provided to each participating site. The level of experience with the target population (or equivalent), specific scale experience (or equivalent), and certification required (if applicable) will be provided on a rater qualification form and used to determine whether a rater is approved for a given assessment. It is expected that all raters performing CLASI, SLEDAI, and joint assessments will have had CCI experience performing these assessments in clinical trials. The rater must become certified to perform selected study assessments before they can participate in the conduct of the study. For specifically defined assessments, rater training and standardization exercises may be conducted, and written documentation will be provided by the site for each rater's certification. In return, each site will be provided written documentation outlining each rater's certification for specific study assessments. 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.

8.2.2. Photography

Photographs of all areas of skin involvement that are scored in the CLASI assessment will be taken at various time points as per SoA. CCI of skin involvement scored in the CLASI assessment is required. Photographs will be used for independent blinded adjudicators to verify entry criteria at Screening and adjudicate CLASI disease activity scores during the study.

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Additional photographs may be taken for confirmation of skin biopsy and CCI locations as per SoA. CCI for lesion CCI is required in order to track biopsy and CCI locations.

A copy of all photographs must be kept as part of site source documentation. Photography services will be provided through a central imaging vendor selected by the sponsor. Camera setup and detailed procedures to ensure consistency including photograph specifications (lighting, camera settings, etc) will be provided separately in a central imaging user manual and quick reference guide. Training will be provided to the sites by the imaging 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. Additional details of participant preparation for photography will be part of the central imaging user manual and quick reference guide.

8.2.2.1. Central Review Committee

This study will use a central review committee consisting of independent blinded external reviewers to ensure correct scoring of the CLASI using photographs of affected skin areas that are scored and other clinical data during the study as specified in SoA:

Re-training may occur as needed.

The results of the reviewed scores will be databased and may be used for the statistical analyses as described in the SAP.

Details on this process and additional information will be described in the Central Review Committee Charter.

8.2.3. EULAR/ACR Classification Criteria for SLE

The 2019 EULAR/ACR classification criteria for SLE include positive ANA at least once as an obligatory entry criterion; followed by additive weighted criteria grouped in 7 clinical (constitutional, hematologic, neuropsychiatric, mucocutaneous, serosal, musculoskeletal, renal) and 3 immunological (antiphospholipid antibodies, complement proteins, SLE-specific antibodies) domains, and weighted from 2 to 10 (See in Appendix 12). Participants accumulating ≥10 points are classified.

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8.2.4. Joint Assessment for SLE (28 Swollen and Tender/Painful Joint Counts)

Joint assessment will be performed at times specified in SoA. The joint assessment for this study will consist of the SJC (see Appendix 13) and the TJC and will be carried out on 28 joints: the shoulders, elbows, wrists (radiocarpal, carpal, and carpometacarpal bones were considered as a single unit), MCP joints (MCP 1, 2, 3, 4, and 5), thumb interphalangeal joint, 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, MTP joints (MTP 1, 2, 3, 4 and 5), interphalangeal joint 1 (foot) and 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 PRN NSAIDS/analgesics, or lower potency opioids 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 1. 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. To be counted in SLEDAI, a joint must be BOTH tender and swollen on the joint examination.

Table 1. 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 13.

8.2.5. SLEDAI-2K for SLE

The SRI-4 uses the SLEDAI-2K (see Appendix 14) as a rigorous assessment of the improvement in a participants disease activity[23].

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

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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.

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

CLASI will be assessed at times specified in the SoA. The CLASI (see Appendix 15) 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-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.

Clinical photographs of the area of active skin involvement will be obtained at Screening and study visits with CLASI assessment and used by adjudicators to verify the diagnosis of CLE prior to study entry as well as CLE disease activity during the study.

8.2.7. Physician Global Assessment

The PhGA is a measure of worsening in the participants general health status rather than the disease activity in a specific organ (see Appendix 16). 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 VAS by placing a mark on the scale between 0 (none), 1 (mild), 2 (moderate), and 3 (severe).

8.3. Safety Assessments

Planned time points for all safety assessments are provided in the SoA. Unscheduled safety measurements may be obtained at any time during the study to assess any perceived safety issues.

8.3.1. Physical Examinations

A complete physical examination will include, at a minimum, assessments of the head, ears, eyes, nose, mouth, skin, heart and lung examinations, lymph nodes, and gastrointestinal, musculoskeletal, and neurological systems. All abnormalities of the skin that will be scored in CLASI and joint abnormalities that will be scored in SLEDAI should be noted in the screening physical examination. Height and weight will also be measured by standardlized methods and recorded.

A brief physical examination will include, at a minimum, assessments of general appearance, the heart, lungs, skin, musculoskeletal, neurologic and participant reported symptoms in those systems. Findings on the physical exam should support disease activity manifestations scored in SLEDAI, CLASI and joint count.

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Investigators should pay special attention to clinical signs related to previous serious illnesses.

Physical examination findings collected during the study will be recorded on CRF. The exception is physical exam findings in heart, lungs, skin, musculoskeletal, neurologic systems that support scoring in CLASI, SLEDAI or joint count, which should be recorded in the eCRF to support correct scoring in the disease activity assessments. Any untoward physical examination findings that are identified during the active collection period and meet the definition of an AE or SAE (Appendix 3) must be reported according to the processes in Sections 8.4.1 to 8.4.3.

8.3.2. Vital Signs

Any untoward vital sign findings that are identified during the active collection period and meet the definition of an AE or SAE (Appendix 3) must be reported according to the processes in Sections 8.4.1 to 8.4.3.

8.3.2.1. Blood Pressure and Pulse Rate

BP and PR measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

BP and PR measurements should be preceded by at least 5 minutes of rest with the participant in a sitting position with the participant's arm supported at the level of the heart, in a quiet setting without distractions.

Vital signs will be taken before blood collection for laboratory tests and consist of a single measurement of PR and BP. The vital signs data will be recorded on the CRF.

8.3.2.2. Temperature and Respiratory Rate

Oral temperature (using a standardized oral thermometer will be obtained for all participants with SLE), and respiratory rate, will be assessed in all participants.

Respiratory rate collected during the study will be considered source data and will not be required to be reported, unless otherwise noted. Any untoward physical examination findings that are identified during the active collection period and meet the definition of an AE or SAE (Appendix 3) must be reported according to the processes in Sections 8.4.1 to 8.4.3.

8.3.3. Electrocardiograms

Standard 12-lead ECGs utilizing limb leads (with a 10-second rhythm strip) should be collected at times specified in the SoA section of this protocol using an ECG machine that automatically calculates the HR and measures PR interval, QT interval, QTcF, and QRS complex. Alternative lead placement methodology using torso leads (eg, Mason-Likar) should not be used given the potential risk of discrepancies with ECGs acquired using standard limb lead placement. All scheduled ECGs should be performed after the participant has rested quietly for at least 5 minutes in a supine position.

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If a) a postdose QTcF interval remains ≥60 ms from the baseline **and** is >450 ms; or b) an absolute QTcF value is ≥500 ms for any scheduled ECG for greater than 4 hours (or sooner, at the discretion of the investigator); or c) QTcF values get progressively longer, the participant should undergo continuous ECG monitoring. A cardiologist should be consulted if QTcF values do not return to less than the criteria listed above after 8 hours of monitoring (or sooner, at the discretion of the investigator).

ECGs will be collected locally. Any clinically significant changes from the screening ECG may potentially be AEs (Appendix 8) 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 QTcF values are in the acceptable range.

ECG values of potential clinical concern are listed in Appendix 8.

8.3.4. Clinical Safety Laboratory Assessments

See Appendix 2 for the list of clinical safety laboratory tests to be performed and the SoA for the timing and frequency. All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study in the AE section of the CRF. Clinically significant abnormal laboratory test findings are those that 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 significant and abnormal during participation in the study or within 20 weeks after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or study 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.

See Appendix 6 for suggested actions and follow-up assessments in the event of potential DILI.

See Appendix 7 for instructions for laboratory testing to monitor kidney function and reporting laboratory test abnormalities.

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8.3.5. Pregnancy Testing

A serum pregnancy test is required at screening. Following screening, pregnancy tests may be urine or serum tests, and must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the SoA. Following a negative pregnancy test result at screening, appropriate contraception must be commenced and a second negative pregnancy test result will be required at the baseline visit prior to the participant's receiving the study intervention. 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 IRBs/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.

8.3.5.1. At-Home Pregnancy Testing

If a participant requiring pregnancy testing cannot visit a local laboratory, a home urine pregnancy testing kit with a sensitivity of at least 25 mIU/mL may be used by the participant to perform the test at home, if compliant with local regulatory requirements. The pregnancy test outcome should be documented in the participant's source documents/medical records and relevant data recorded on the CRF. Confirm that the participant is adhering to the contraception method(s) required in the protocol.

8.3.6. Interferon Gamma Release Assay For TB Test

Participants will be screened for infection with TB using an IGRA test during screening or within 12 weeks prior to screening. The following are acceptable IGRA assays: QFT-G/QFT-G Plus test, QFT-GIT test and T-SPOT® TB test. Site personnel should follow the processing and analyses steps based on the assay chosen.

Documentation of IGRA product used and the test result must be in the participant's source documentation. If the results of the IGRA are indeterminateor positive the potential participant must be seen by a local expert (pulmonologist or an infectious disease specialist) who may order additional testing and will determine whether or not the participant has active or latent TB. If the local expert determines that the potential participant does not have active or latent TB, the potential participant may be eligible for the study. A note from the specialist should be available in the source document and a summary of the specialists report must be provided to the Pfizer medical monitor to confirm that the participant does not have latent or active TB.

8.3.7. Chest X-Ray (Screening only)

The study will accept a chest X-ray examination (or chest CT) performed up to 12 weeks prior to screening if available. Chest X-ray (posterior-anterior and lateral views are recommended). There should be no evidence of TB, general infections, heart failure, cavitary lesions or malignancy if taken at screening or within the 12 weeks prior to screening and must be read by a qualified radiologist or other locally qualified personnel. Documentation of the official reading must be available in the source documentation. Participants with changes

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suggestive of untreated latent or active TB infection may be enrolled after consultation with a pulmonary or infectious disease specialist who determines a low risk of infection.

8.3.8. Hepatitis Testing

All participants must undergo testing for HbsAg, HbcAb, and HbsAb.

- Participants who are negative for all 3 serology tests may be eligible.
- Participants who are HbsAg positive will be excluded.
- Participants who are HbsAg negative, HbcAb negative and HbsAb positive and provide a documentation of prior HBV vaccination, may be eligible for the study and will not require HBV DNA monitoring during the study.
- Participants who are HbsAg negative, HbcAb and HbsAb positive may be eligible if HBV DNA reflex test is negative during screening. Per local regulation:
    - HBV DNA testing may be performed locally or centrally.
    - Participants with HbsAg negative testing, but who test positive for HbcAb must have further testing for HbsAb. If HbsAb is negative, the subject will be excluded from the study.
    - Participants who are HbsAg negative, HbcAb negative and HbsAb positive without documentation of prior HBV vaccination AND/OR participants who are HbsAg negative, HbcAb positive, HbsAb positive, and HBV DNA negative assessed during screening, if enrolled, will continue to have HBV DNA assessed every 12 weeks throughout the study.
    - If detectable HBV DNA, participants will be excluded or discontinued from study participation.

For hepatitis C, all participants will undergo testing for HCVAb during Screening. Participants with positive HCVAb tests will be reflex tested for HCV RN. Only participants with negative HCVAb or HCV RNA will be allowed to enroll in the study. See Appendix 2. Hepatitis testing (HbsAg, HbcAb, HbsAb, HCVAb, and HCV RNA) will be performed by the central laboratory. HBV DNA testing will be performed locally as per country requirement.

8.3.9. HIV (Screening only)

All participants will be screened for HIV. HIV test should be performed at the central laboratory.Note: a documented negative HIV test within 3 months of screening is acceptable and does not need to be repeated. See Appendix 2.

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8.3.10. Herpetiform Rash

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

8.3.11. Suicidal Ideation and Behavior Risk Screening

The Columbia Suicide- Severity Rating Scale (CSSRS; Appendix 17) will be used to assess suicidal ideation and behavior. The CSSRS is a validated tool to evaluate suicidal ideation and behavior.[25]

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.

8.4. Adverse Events, Serious Adverse Events, and Other Safety Reporting

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

AEs may arise from symptoms or other complaints reported to the investigator by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative), or they may arise from clinical findings of the investigator or other healthcare providers (clinical signs, test results, etc).

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 the event meets the criteria for classification as an SAE or caused the participant to discontinue the study intervention (see Section 7.1).

During the active collection period as described in Section 8.4.1, each participant will be questioned about the occurrence of AEs in a nonleading manner.

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

8.4.1. 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 undergoing any study-related procedure and/or receiving study intervention, through and including a minimum of 20 weeks after the last administration of the study intervention.

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

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When a clinically important AE remains ongoing at the end of the active collection period, follow-up by the investigator continues until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator and Pfizer concurs with that assessment.

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 permanently 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.

Investigators are not obligated to actively seek information on AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and they consider the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the CT SAE Report Form.

8.4.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.4.1 are reported to Pfizer Safety on the CT SAE Report Form immediately upon awareness 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 its being available.

8.4.1.2. 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 8.4.1, 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.

As part of ongoing safety reviews conducted by the sponsor, any nonserious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

8.4.2. 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.

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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.

8.4.3. Follow-Up of AEs and SAEs

After the initial AE or 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 provided in Appendix 3.

8.4.4. 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 toward 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, IRBs/Ecs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

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

8.4.5. Environmental Exposure, Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Environmental exposure occurs when a person not enrolled in the study as a participant receives unplanned direct contact with or exposure to the study intervention. Such exposure may or may not lead to the occurrence of an AE or SAE. Persons at risk for environmental exposure include healthcare providers, family members, and others who may be exposed. An environmental exposure may include EDP, EDB, and occupational exposure.

Any such exposures to the study intervention under study are reportable to Pfizer Safety within 24 hours of investigator awareness.

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8.4.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A male participant who is receiving or has discontinued study intervention inseminates a female partner.
- A female nonparticipant is found to be pregnant while being exposed or having been exposed to study intervention because of environmental exposure. Below are examples of environmental EDP:
    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by ingestion, inhalation, or skin contact.
    - A male family member or healthcare provider who has been exposed to the study intervention by ingestion, inhalation, or skin contact then inseminates his female partner prior to or around the time of conception.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a participant/participant's partner, 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. Details of the pregnancy will be collected after the start of study intervention and until 20 weeks after the last dose of study intervention.
- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the CT SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the 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.

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

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preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. 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 including miscarriage and missed abortion should be reported as an SAE;
- 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.

8.4.5.2. Exposure During Breastfeeding

An EDB occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.
- A female nonparticipant is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental EDB is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study intervention by ingestion, inhalation, or skin contact.

The investigator must report EDB to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the CT SAE Report Form. When EDB occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study, so 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.

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An EDB report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accordance with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the EDB.

8.4.5.3. Occupational Exposure

The investigator must report any instance of occupational exposure 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 about the occupational exposure 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 must be maintained in the investigator site file.

8.4.6. Cardiovascular and Death Events

Not applicable.

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

Not applicable.

8.4.8. Adverse Events of Special Interest

AESI may include, but are not limited to, viral infections and opportunistic infections and infusion reactions.

AESIs are examined as part of routine safety data review procedures throughout the clinical trial and as part of signal detection processes. Should an aggregate analysis indicate that these prespecified events occur more frequently than expected, eg, based on epidemiological data, literature, or other data, then this will be submitted and reported in accordance with Pfizer's safety reporting requirements. Aggregate analyses of safety data will be performed on a regular basis per internal SOPs.

All AESIs must be reported as an AE or SAE following the procedures described in Sections 8.4.1 through 8.4.4. An AESI is to be recorded as an AE or SAE on the CRF. In addition, an AESI that is also an SAE must be reported using the CT SAE Report Form.

8.4.8.1. Lack of Efficacy

The investigator must report signs, symptoms, and/or clinical sequelae resulting from lack of efficacy. Lack of efficacy or failure of expected pharmacological action is reportable to Pfizer Safety **only if associated with an SAE**.

8.4.9. Medical Device Deficiencies

Not applicable.

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8.4.10. 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.

Medication errors are recorded and reported as follows:

Recorded on the Medication Error Page of the CRF	Recorded on the Adverse Event Page of the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
All (regardless of whether associated with an AE)	Any AE or SAE associated with the medication error	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.
- The administration of expired study intervention;
- The administration of an incorrect study intervention;
- The administration of an incorrect dosage;
- The administration of study intervention that has undergone temperature excursion from the specified storage range, unless it is determined by the sponsor that the study intervention under question is acceptable for use.

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.

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 the AE page of the CRF.

In the event of a medication dosing error, the sponsor should be notified within 24 hours.

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

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8.5. Pharmacokinetics

Blood samples of approximately 3 mL to provide a minimum of 1 mL serum, will be collected for measurement of serum concentrations of PF-06823859 as specified in the SoA.

PK samples will be collected at the following times:

- For all participants, blood samples will be collected preferably after vital signs data and within approximately 30 minutes prior to dosing and post-dose (±6 mins) (at the end of infusion in the opposite arm that the infusion was administered).

The actual date and time of each sample will be recorded. All efforts will be made to obtain the samples at the exact nominal time relative to dosing. If sample obtained >10% of the nominal time a protocol deviation should be recorded.

Any deviations from the PK sample handling procedure (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the sponsor.

Instructions for the collection and handling of PK samples will be provided in the Laboratory Manual by the sponsor.

A summary of PF-06823859 concentrations will include nominal time pre- and post-dose, where the set of statistics will include n, mean, median, variation, minimal, maximum, and the percentage of concentrations above the lower limit of quantification. Additionally, PK data collected in C0251013 will be used to inform the further development of the population PK/PD and exposure-response models.

8.6. Genetics

8.6.1. Specified Genetics

Specified genetic analyses are not evaluated in this study.

8.6.2. Retained Research Samples for Genetics

A 4-mL blood sample optimized for DNA isolation Prep D1 will be collected according to the SoA, as local regulations and IRBs/Ecs allow.

Retained Research Samples may be used for research related to the study intervention(s) and cutaneous lupus erythematosus, systemic lupus erythematosus, or related conditions. Genes and other analytes (eg, proteins, RNA, nondrug metabolites) may be studied using the retained samples.

See Appendix 5 for information regarding genetic research. Details on processes for collection and shipment of these samples can be found in the Laboratory Manual.

The results may be reported separately from CSR.

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8.7. Pharmacodynamics

In this section, all blood sample volumes are approximately expressed within ± 0.5 mL.

Biomarkers for PD analysis will be collected into appropriately labeled tubes at times specified in the SoA. The following samples for PD biomarkers will be collected pre-dose:

- Serum sample for CCI and blood sample for CCI levels to determine direct downstream of CCI
- Serum sample for CCI (total) levels to determine target engagement of PF-06823859.

PD results may be reported separately from CSR.

8.7.1. CCI

A 3-mL of blood (1.5-mL serum) for CCI protein analyses will be collected at the time points specified in the SoA. The sample(s) will be analyzed for changes in circulating CCI levels over time as a measure of pharmacodynamic activity.

Details on processes for collection and shipment of these sample(s) can be found in the laboratory manual.

8.7.2. CCI

A 3-mL of blood for CCI protein analyses will be collected at the time points specified in the SoA. The sample(s) will be analyzed for changes in circulating CCI levels over time as a measure of pharmacodynamic activity.

Details on processes for collection and shipment of these sample(s) can be found in the laboratory manual.

8.7.3. CCI

A 6-mL of blood (3-mL serum) for CCI protein analyses will be collected at the time points specified in the SoA. The sample(s) will be analyzed for changes in circulating total CCI levels over time as a measure of pharmacodynamic activity.

Details on processes for collection and shipment of these sample(s) can be found in the laboratory manual.

8.7.4. Biomarkers

Collection of samples for biomarker research is also part of this study.

Biomarker (blood, skin biopsy, skin CCI samples will be used for scientific research. Samples that remain after performing assays outlined in the protocol may be stored by Pfizer. Unless a time limitation is required by local regulations or ethical requirements, the samples will be retained indefinitely. If allowed by the ICD, stored samples

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may be used for additional testing to better understand the mechanism of action of the study intervention and its treatment effects on disease under study in this protocol.

The following samples for biomarker research are required and will be collected from all participants in this study as specified in the SoA:

- Skin biopsies (gene expression, histology, CCI ;
- CCI (exploratory gene expression and CCI ;
- CCI ;
- Blood for flow cytometry (T, B, and NK cell subsets and exploratory immunophenotyping);
- Blood for exploratory protein biomarkers (CCI immunoglobulins, autoantibodies, complement);

Optional samples for biomarker research that should be collected from participants in the study as appropriate are the following:

- Skin biopsy and CCI collections at Week 32

8.7.4.1. Skin Tissue Collections

8.7.4.1.1. Skin Biopsies

Skin biopsy collections are mandatory for the study. Skin biopsies will not be collected from the face and should be taken from skin lesions at least 5-cm in diameter and from CCI areas at least 1 cm away from the target lesion.

4-mm punch biopsies will be collected from lesional and CCI skin at the time points described in the SoA, processed, and shipped according to the instructions provided in the laboratory manual. Two parallel biopsies will be collected from each area. One biopsy will be bisected in half and preserved for gene expression analysis and histology. The other biopsy will be preserved to enable single cell multiomic analyses. Target lesions will be identified at baseline and all subsequent lesional biopsies should be collected from the same target lesion. Any biopsy material remaining after processing and analysis, may be sent to the Pfizer BioBank and may be used for additional exploratory analyses.

As skin biopsies may be associated with risk of bleeding or infection, participants will be instructed to contact the investigator or other designated site staff if they experience bleeding, warmth, swelling, tenderness, or erythema at the biopsy site. An unscheduled visit may be required for clinical assessment.

8.7.4.1.2. Skin CCI

Skin CCI collections are mandatory for the study if all CCI supplies are available at the site and need to be performed prior to skin biopsy procedure. CCI technique

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will be used to obtain skin samples for biomarker analysis in a simple and noninvasive manner. The CCI will be applied to lesional and CCI areas of the trunk or extremities. Samples will be collected by appropriately trained site staff at the time points specified in the SoA according to collection instructions provided in the laboratory manual. Target lesions will be identified at baseline and all subsequent CCI should be collected from the same target lesion. CCI will be performed in the same general location/area sampled by biopsies (approximately 1.0-1.5 cm from target biopsy lesion). CCI will be performed adjacent to biopsy sites (and not exactly at the same sites) in order to not perturb biopsied area, but to still maintain the same general characteristics that biopsied areas have.

8.7.4.2. Specified Gene Expression (RNA) Research

8.7.4.2.1. Gene Expression in Skin

One half of a 4-mm punch biopsy from CCI or lesional skin will be collected for RNA isolation, as described in Section 8.7.4.1.1. These samples will be analyzed for gene expression patterns in skin, including, but not limited to, expression of a type 1 IFN GS.

8.7.4.2.2. CCI in Skin

A 4-mm punch biopsy from CCI or lesional skin will be collected for CCI analysis, as described in Section 8.7.4.1.1. These samples may be analyzed for CCI expression patterns in isolated CCI Analyses performed will be for exploratory purposes only.

8.7.4.2.3. Gene Expression in CCI

A series CCI from CCI or lesional skin will be collected, as described in Section 8.7.4.1.2. Some of the CCI will be used for RNA isolation. The samples may be analyzed for gene expression in the CCI of the skin. Analyses performed will be for exploratory purposes only.

8.7.4.2.4. Gene Expression in Whole Blood

A 2.5-mL of blood for RNA isolation will be collected at the time points specified in the SoA. The samples may be analyzed for gene expression patterns in blood cells, including but not limited to expression of CCI Analyses performed will be for exploratory purposes only.

Details on processes for collection and shipment of these samples can be found in the laboratory manual.

8.7.4.3. Specified Protein Research

8.7.4.3.1. Histology of Skin

One half of a 4-mm punch biopsy from CCI or lesional skin maybe collected, as described in Section 8.7.4.1.1, fixed in formalin, and embedded in paraffin. The sample(s) will be analyzed for changes in overall skin morphology, mucin production, basement

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membrane structure, T cells, histiocytes, endothelial cells, B cells, and plasmacytoid dendritic cells using a variety of tissue stains and immunohistochemical techniques. Analyses performed will be for exploratory purposes only.

8.7.4.3.2. Protein Expression from CCI

A series CCI from CCI or lesional skin will be collected as described in Section 8.7.4.1.2. Some of the CCI will be used for protein isolation. The samples may be analyzed for changes in proteins in the upper epidermal regions of the skin. Analyses performed will be for exploratory purposes only.

8.7.4.3.3. Protein Expression in CCI

A 1.8-mL of CCI for protein analyses will be collected at the time points specified in the SoA. The sample(s) will be analyzed for changes in measurable proteins related to comorbid conditions. Analyses performed will be for exploratory purposes only.

Details on processes for collection and shipment of these samples can be found in the laboratory manual.

8.7.4.3.4. Flow Cytometry (TBNK & Immunophenotyping)

A 4-mL of blood for flow cytometry analysis will be collected at the time points specified in the SoA. The sample(s) may be analyzed for changes in T cells, B cells, and NK cells as well as broader immunophenotyping of subpopulations of lymphocytes. Analyses performed will be for exploratory purposes only.

Details on processes for collection and shipment of these samples can be found in the laboratory manual.

8.7.4.3.5. Total CCI

A 3-mL of blood for CCI protein analyses will be collected at the time points specified in the SoA. The sample(s) will be analyzed for changes in circulating CCI levels over time. Analyses performed will be for exploratory purposes only.

Details on processes for collection and shipment of these samples can be found in the laboratory manual.

8.7.4.3.6. Immunoglobulins

A 2.5-mL of blood for protein analyses will be collected at the time points specified in the SoA. The sample(s) will be analyzed for changes in immunoglobulins IgG, IgA, and IgM. Analyses performed will be for exploratory purposes only.

Details on processes for collection and shipment of these samples can be found in the laboratory manual.

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8.7.4.3.7. Complement

A 2.5-mL of blood for protein analyses will be collected at the time points specified in the SoA. The sample(s) will be analyzed for standard complement components such as, but not limited to, C3 and C4. Analyses performed will be for exploratory purposes only.

Details on processes for collection and shipment of these samples can be found in the laboratory manual.

8.7.4.3.8. Autoantibodies

Separate 2.5-mL of blood will be collected for the assessment of disease-associated auto-antibodies at the time points specified in the SoA. The sample(s) will be analyzed for ds-DNA, ANA, and ENA. Analyses performed will be for exploratory purposes only.

Details on processes for collection and shipment of these sample(s) can be found in the laboratory manual.

8.7.4.4. Specified Metabolomic Research

Specified metabolomic research is not included in this study.

8.7.4.5. Retained Research Samples for Biomarkers

These Retained Research Samples will be collected in this study:

- 2.5-mL blood for Prep R1 (whole blood optimized for RNA);
- 6-mL blood optimized for Prep B1.5 (plasma);
- 6-mL blood optimized for Prep B2.5 (serum);
- 2 × 4-mL blood optimized for Prep PBMC2 (peripheral blood mononuclear cells);
- 15-mL urine (Prep M2/Prep M3): 5-mL aliquotes from clarified urine for Prep M2 and the pellet for Prep M3

Retained Research Samples will be collected as local regulations and IRB/ECs allow according to the SoA.

Retained Research Samples may be used for research related to the study intervention(s) and cutaneous lupus erythematosus, systemic lupus erythematosus, or related conditions. Genes and other analytes (eg, proteins, RNA, nondrug metabolites) may be studied using the retained samples.

See Appendix 5 for information regarding genetic research. Details on processes for collection and shipment of these samples can be found in the laboratory manual.

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8.8. Immunogenicity Assessments

Blood samples of approximately 6 mL, to provide a minimum of 2 mL, will be collected within 30 mins prior to dosing for determination of ADA and NAb as specified in the SoA. Instructions for the collection and handling of biological samples will be provided in the laboratory manual or by the sponsor. The actual date and time of each sample will be recorded.

Samples collected for determination of ADA and NAb may also be used for additional characterization of the immune response and/or evaluation of the bioanalytical method, or for other internal exploratory purposes. These data will be used for internal exploratory purposes. The immunogenicity samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the immunogenicity sample handling procedure (eg, sample collection and processing steps, interim storage, or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised.

Immunogenicity results may be reported separately from CSR.

8.9. Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in the 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. Statistical Hypotheses

The primary (key secondary) null hypothesis is that the efficacy in the active (PF-06823859) treatment arm based on the primary (key secondary) endpoint is not superior to the efficacy of placebo treatment. The primary null hypothesis needs to be rejected at the one-sided significance level of 0.05 for the declaration of the superior efficacy of the active treatment arm.

9.1.1. Key Estimands

The characterization of the key estimands E1 and E2, that are used in the analyses are described in the Table 2 below. The study objectives, endpoints, and mapping between the analyses and estimands E1 and E2 are also described in Section 3.

The estimand E1 is used for the evaluation of the treatment effect on the continuous outcomes in the hypothetical (ideal) setting where participants do not experience poor

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compliance and are not exposed to the prohibited medications. This evaluation will be based on the analysis of the cmITT data set (see Section 9.2) where observations that are potentially affected by the poor compliance or exposure to the prohibited medication are removed from the analysis.

The estimand E2 is used for the evaluation of the treatment effect on the binary outcomes. In this evaluation a non-responder status is assigned to the outcome of interest if the outcome is expected to be affected by the prohibited medication or observation is missing. This assignment is often denoted as the non-responder imputation (NRI). We will use the name NRImITT (see Section 9.2) for the dataset where NRI is applied to the modified intent to treat (mITT) dataset.

The sensitivity of the results of the analyses based on the cmITT and NRImITT data sets will be explored by the application of the same statistical methods to the analysis of continuous and binary outcomes in the mITT dataset (see Section 9.2) with the following comparison of the results based on cmITT and mITT datasets. The details will be explained in the SAP.

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Table 2. Characterization of the Key Estimands

Notation for the estimand	Population targeted by the scientific question	Type of endpoint	Population-level summary for a given treatment	Metric for comparison between the treatment groups	Account for the intercurrent events
E1	Study participants in the hypothetical setting without poor compliance or prohibited medications	Continuous	Mean change from baseline	Difference of mean changes from baseline	Censoring (exclusion from the analysis) of observations potentially affected by the poor compliance or use of prohibited concomitant medications.
E2	All study participants	Binary	Probability of response	Difference of probabilities of response.	NRI (assignment to the non-responder status) to missing observations and observations potentially affected by the use of prohibited concomitant medications.

Other estimands may be used for assessing the robustness of results. If performed, they will be documented in the SAP.

9.1.2. Multiplicity Adjustment

There will be no adjustment for the multiplicity of comparisons across the different outcomes. The marginal (unadjusted for the multiplicity of comparisons) p-values will be reported for primary and key secondary outcomes only. The marginal (unadjusted for the multiplicity of comparisons) confidence intervals with 90% coverage will be reported for all of the comparisons across the groups.

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9.2. Analysis Sets

For purposes of analysis, the following analysis sets are defined:

Participant Analysis Set	Description
mITT	Observations for participants randomly assigned to study intervention who take at least 1 dose of study intervention. Participants will be analyzed according to the randomized intervention
Safety analysis set	Observations for participants randomly assigned to study intervention who take at least 1 dose of study intervention. Participants will be analyzed according to the product they actually received.
PK concentration set	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention and have at least 1 measurable concentration.
PD data set	Observations for participants randomly assigned to study intervention and who take at least 1 dose of study intervention and have at least 1 of PD parameters of interest. Participants will be analyzed according to the randomized intervention

Defined Analysis Set	Description
cmITT	Contains a subset of mITT dataset. Includes data collected up to and including Week 12 visits. Excludes observations of continuous efficacy outcomes that occur after the exposure to the prohibited medication or after missing of two consecutive doses of treatment.
NRImITT	Contains a subset of mITT dataset. Includes data collected up to and including Week 12 visits. Modifies observations of binary efficacy outcomes by assigning a non-responder status to the missing binary efficacy observations or observations that that occur after the exposure to the prohibited medication.

Prohibited medications include a protocol prohibited dose of corticosteroids, immunosuppressants, colchicine, retinoids, dapsone, or biologics. The additional details of the creation of the cmITT and NRImITT data sets will be described in the SAP.

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9.3. Statistical Analyses

The SAP will be developed and finalized before any analyses are performed and will describe the analyses and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned primary statistical analyses of the primary and secondary endpoints.

9.3.1. General Considerations

9.3.1.1. Analyses for Continuous Endpoints

The estimand E1 is described in the Section 9.1. The analysis for the estimand E1 is based on the cmITT data set. Missing values due to the defined intercurrent events are assumed to be missing at random. The sensitivity of results to this assumption will be explored, with details of any sensitivity analyses described in the SAP.

For the primary analysis of the type 1 IFN GS data, the only post-baseline visit will be the Week 12 visit and a comparison of mean change from baseline across treatment groups will use linear regression with ANCOVA.

For the analyses that have larger number (>2) of post-baseline repeated measures of continuous outcome the MMRM model will be used. The MMRM approach will use the change from baseline value of the continuous variable as an outcome and treatment, scheduled study (post-baseline) visit, baseline value of the variable of interest, treatment by visit interaction and baseline by visit interaction as fixed effects. The model will use the unstructured covariance matrix. The MMRM model is described in multiple textbooks including the books by Fitzmaurice, Laird and Ware (2011)[26] and by Mallinckrodt and Lipkovich (2017)[27]. For the primary and key secondary analysis, we will use the subset of cmITT data set that excludes observations collected after the Week 12 visit. This will reduce a potential for numerical problems caused by the missing values at later visits.

The p-values and 90% confidence intervals will be reported for the E1 analysis of primary and key secondary efficacy outcomes in the comparisons of the mean changes from baseline in active and placebo treatment arms. Only the confidence intervals with 90% coverage will be used for all other analyses of continuous outcomes.

9.3.1.2. Analyses for Binary Endpoints

The estimand E2, is described in the Section 9.1. This analysis is based on the NRImITT data set. We will use the BCS (Blyth and Still [1983][28] and Casella [1986][29]) method for the estimation of the probability of response at a given visit and a given treatment arm and CZ (Chan and Zhang, 1999)[30] method for comparison of the probability of response across the treatment arms. The confidence intervals with 90% coverage will be used in the summaries of analyses of binary outcomes.

9.3.1.3. Additional Analyses

Additional and supplementing analyses may be described in the SAP

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9.3.2. Primary Endpoint /Estimand Analysis

The endpoint is the change from baseline of type 1 IFN GS score at Week 12. The ANCOVA method will be used for the comparison of the mean CFB (GS) values across the treatment groups. The observations of type 1 IFN GS scores within the cmITT dataset will be used. Observations for participants who do not have baseline or Week 12 observations will be excluded from the analysis. One-sided p-values will be used for rejection of the null hypothesis that CFB in active PF-06823859 ≥ CFB in placebo, since an effective treatment is expected to decrease the GS more than placebo.

9.3.3. Secondary Efficacy Endpoints/Estimands Analysis

The continuous secondary endpoints are the percent change and change from baseline in CLASI-A score. The MMRM method will be used for the comparison of the means of changes from baseline across the treatment groups. The observations within the cmITT dataset will be used in the key secondary analysis to reduce the possibility of model non-convergence in this analysis. One-sided p-values will be used for rejection of the null hypothesis that change (percent change) in active PF-06823859 ≥ change (percent change) in placebo, since an effective treatment is expected to decrease the CLASI-A score more than placebo.

The binary secondary outcomes include achieving ≥50%, 4 or 7 points reduction in CLASI-A. The BCS and CZ methods will be applied to the NRImITT dataset.

9.3.4. Exploratory Efficacy Endpoint(s) Analysis

These analyses will be described in the SAP.

9.3.5. Safety Analyses

The safety data will be summarized in accordance with Pfizer Data Standards. All participants who receive at least 1 dose of study intervention (safety analysis set) will be included in the safety analyses. All safety data will be summarized descriptively through appropriate data tabulations, descriptive statistics, categorical summaries, and graphical presentations. Safety endpoints for the study include:

- Treatment-emergent AEs and SAEs.
- Withdrawals from active treatment due to AEs.
- Serious infections, defined as any infection (viral, bacterial, and fungal) requiring hospitalization or parenteral antimicrobials.
- Safety laboratory tests (eg, hematology [including coagulation panel], chemistry and lipid profiles).
- Vital signs.
- ECG.

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9.3.5.1. Electrocardiogram Analyses

CFB for the ECG parameters, HR, QTcF, and PR interval, and QRS complex will be summarized by treatment and time. The frequency of uncorrected QT values above 500 ms will be tabulated.

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

Safety QTcF Assessment

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

9.3.6. Pharmacokinetic analysis

The PK concentration population for PF-06823859 is defined as all enrolled participants who received at least one dose of PF-06823859 and in whom at least one concentration value is reported.

PK concentrations will be summarized and presented with summary statistics and, if appropriate, non-compartmental PK parameter estimates may be provided. A population PK model may be developed for the purpose of estimating PK parameters. Any population PK model developed to characterize the PK data will be reported separately.

Data permitting, the relationship between exposure and clinical responses (efficacy and safety) in study participants may be explored using either observed or modeled exposures. Any population analyses conducted will not be part of the clinical study report (CSR) and may be reported separately.

9.3.7. Other Analyses

Pharmacogenomic or biomarker data from Retained Research Samples may be collected during or after the trial and retained for future analyses; the results of such analyses are not planned to be included in the CSR.

9.4. Interim Analyses

Two IAs may be performed. The first IA may be performed at the time when about 50% of the participants complete the Week 12 visit. It may provide a non-binding recommendation of early stopping for futility but will not allow early stopping of the trial for efficacy and will not increase the type I error. The results of the IA may be used for internal decision making. The second IA may be performed after the last participant completes Week 12 to determine whether the mean decrease from baseline in the type 1 IFN GS score is greater in the PF-06823859 treatment arm than in the placebo treatment arm and if this difference is statistically significant. A similar comparison will be done for the key secondary outcome. It will be evaluated whether the mean value of percent decrease from baseline in the CLASI-A

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score is greater in the PF-06823859 treatment arm than in the placebo treatment arm and whether this difference across the treatment groups is statistically significant.

Further details of analyses in safety and efficacy will be specified in the SAP. A separate SAP may be provided for the IA.

Before any IA is performed, the details of the objectives, decision criteria, dissemination plan, and method of maintaining the study blind (if applicable) as per Pfizer's SOPs will be documented and approved. The analysis details will be documented and approved in the SAP. A separate SAP may be provided for the IA. The study team will remain blinded to all interim results.

9.5. Sample Size Determination

The effective treatment will cause a larger mean *decrease* in type 1 IFN GS score and a larger mean *decrease* in the CLASI-A score (%) from baseline in the active (PF-06823859) treatment group than in the placebo treatment group. Therefore, for each of the outcomes we would like to observe a negative and statistically significant difference (active - placebo) of mean changes from baseline values at week 12. The detection of the statistically significant treatment effect on the clinical outcome is desirable for the support of the subsequent clinical development of the compound. We therefore based sample size calculation on the key secondary endpoint: percent change from baseline in CLASI-A score at Week 12.

In the treatment efficacy analysis based on the primary (key secondary) endpoint the treatment is declared efficacious if at the end of the study the upper boundary of the two-sided 90% confidence interval of the estimated difference (active – placebo) in mean changes from baseline in type 1 IFN GS score (primary endpoint) or mean percent changes from baseline in CLASI-A score at Week 12 is below 0.

With the planned number of 48 randomized participants and 2:1 randomization rate, Week 12 outcomes are expected for about 24 participants in the active treatment group and about 12 participants in the placebo treatment group.

The primary endpoint is the CFB (GS) (ie, change from baseline in the type 1 IFN GS score) at Week 12. The expected standard deviation for the CFB (GS) based on the Pfizer study C0251002 for a similar indication is CCI The difference in the true mean decreases of type 1 IFN GS scores at Week 12 across the treatment groups that will be detected with CCI power is CCI.

The key secondary endpoint is %CFB (CLASI-A) (ie, percent change from baseline in the CLASI-A score). The expected standard deviation of %CFB (CLASI-A), based on the results of a recent study[1] with the similar population is CCI The difference in the mean decreases of %CFB (CLASI-A), across the treatment groups that will be detected with CCI power is CCI

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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 CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor, 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.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation 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 CFR, ICH GCP guidelines, the IRB/EC, European regulation 536/2014 for clinical studies, European Medical Device Regulation 2017/745 for clinical device research, 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.

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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 the ICH GCP guidelines 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 the investigator's representative will explain the nature of the study, including the risks and benefits, to the participant or their legally authorized representative and answer all questions regarding the study. The participant or their legally authorized representative should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representative (if allowed by local regulations) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each participant or their 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 or their legally authorized representative must be informed that their 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 or their legally authorized representative.

The participant or their legally authorized representative must be informed that their 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 their legally authorized representative is fully informed about their right to access and correct their personal data and to withdraw consent for the processing of their personal data.

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

Participants or their legally authorized representative must be reconsented to the most current version of the IRB/EC-approved ICD(s) during their participation in the study as required per local regulations.

A copy of the ICD(s) must be provided to the participant or their legally authorized representative (if allowed by local regulations).

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

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 will 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 participants 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 their actual identity and medical record ID. 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.

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

The sponsor maintains SOPs on how to respond in the event of unauthorized access, use, or disclosure of sponsor information or systems.

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10.1.5. Committees Structure

10.1.5.1. Internal Review Committee

This study will use an IRC. The IRC is independent of the study team and includes only internal members. The IRC charter describes the role of the IRC in more detail.

The IRC will be responsible for ongoing monitoring of the efficacy and safety of participants in the study according to the charter. The recommendations made by the IRC will be forwarded to the appropriate authorized Pfizer personnel for review and final decision. Pfizer will communicate such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data that are not endpoints, to regulatory authorities and investigators, as appropriate.

10.1.5.2. External HLH/MAS Adjudication Committee

This study will use an adjudication committee for adjudicating the suspected HLH/MAS events in the study according to the charter. This adjudication committee is independent of the study team and includes ONLY external members. The committee charter describes the role of the committee in more detail. Event documents may be requested from sites and may include (but not be limited to): hospital discharge summaries, operative reports, clinic notes, diagnostic tests, pathology reports, autopsy reports and death certificate information, as applicable. Obtaining and submitting this documentation will be the responsibility of the study site. In addition to the documentation provided by the site, the Pfizer Study Team or designee will provide available event related data from Pfizer systems as needed by the Committee.

10.1.6. 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 EudraCT/CTIS, and/or www.pfizer.com, and other public registries and websites in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its 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 results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

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EudraCT/CTIS

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

www.pfizer.com

Pfizer posts CSR synopses and plain-language study results summaries on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov. CSR synopses will have personally identifiable information anonymized.

Documents within marketing applications

Pfizer complies with applicable local laws/regulations to publish clinical documents included in marketing applications. Clinical documents include summary documents and CSRs including the protocol and protocol amendments, sample CRFs, and SAPs. Clinical documents will have personally identifiable information anonymized.

Data sharing

Pfizer provides researchers secure access to participant-level data or full CSRs for the purposes of "bona-fide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make data from these trials available 18 months after study completion. Participant-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information anonymized.

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.

10.1.7. 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.

Guidance on completion of CRFs will be provided in the CRF Completion Requirements document.

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.

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QTLs are predefined parameters that are monitored during the study. Important deviations from the QTLs and any remedial actions taken will be summarized in the CSR.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source records and 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, including definition of study-critical data items and processes (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, virtual, or on-site monitoring), are provided in the data management plan and monitoring plan maintained and utilized by the sponsor or designee.

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

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.

10.1.8. 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 eCRF that are from source documents must be consistent with the source documents or the discrepancies must be explained. The

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investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

In this study, the CRF will serve as the source document. A document must be available at the investigative site that identifies those data that will be recorded on the CRF and for which the CRF will be the source document.

Definition of what constitutes source data and its origin can be found in the Source Document Locator, which is maintained by the sponsor or sponsor's designee.

Description of the use of the computerized system is documented in the Data Management Plan, which is maintained by the sponsor.

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

The sponsor or designee will perform monitoring 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 guidelines, and all applicable regulatory requirements.

10.1.9. Study and Site Start and Closure

The study start date is the date of the first participant's first visit.

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, including (but not limited to) regulatory authority decision, change in opinion of the IRB/EC, or change in benefit-risk assessment. 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 sponsor or designee/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 the ICH GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

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If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

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.

10.1.10. Publication Policy

For multicenter trials, the primary publication will be a joint publication developed by the investigator(s) and Pfizer reporting the primary endpoint(s) of the study covering all study sites. The investigator(s) agree to refer to the primary publication in any subsequent publications. Pfizer will not provide any financial compensation for the investigators' participation in the preparation of the primary congress abstract, poster, presentation, or primary manuscript for the study.

Investigator(s) are free to publish individual center results that they deem to be clinically meaningful after publication of the overall results of the study or 12 months after primary completion date or study completion at all sites, whichever occurs first, subject to the other requirements described in this section.

The investigator(s) will provide Pfizer an opportunity to review any proposed publication or any other type of disclosure of the study results (collectively, "publication") before it is submitted or otherwise disclosed and will submit all publications to Pfizer 30 days before submission. If any patent action is required to protect intellectual property rights, the investigator(s) agree to delay the disclosure for a period not to exceed an additional 60 days upon request from Pfizer. This allows Pfizer to protect proprietary information and to provide comments, and the investigator(s) will, on request, remove any previously undisclosed confidential information before disclosure, except for any study-intervention or Pfizer-related information necessary for the appropriate scientific presentation or understanding of the study results. For joint publications, should there be disagreement regarding interpretation and/or presentation of specific analysis results, resolution of, and responsibility for, such disagreements will be the collective responsibility of all authors of the publication.

For all publications relating to the study, the investigator(s) and Pfizer will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors. The investigator will disclose any relationship with Pfizer and any relevant potential conflicts of interest, including any financial or personal relationship with Pfizer, in any publications. All authors will have access to the relevant statistical tables, figures, and reports (in their original format) required to develop the publication.

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10.1.11. Sponsor's Medically Qualified Individual

The contact information for the sponsor's MQI for the study is documented in the study contact list located in the supporting study documentation/study portal or other electronic system.

To facilitate access to their investigator and the sponsor's MQI for study-related medical questions or problems from non-study healthcare professionals, participants are provided with an ECC at the time of informed consent. The ECC contains, at a minimum, (a) protocol and study intervention identifiers, (b) participant's study identification number, (c) site emergency phone number active 24 hours/day, 7 days per week, and (d) Pfizer Call Center number.

The ECC is intended to augment, not replace, the established communication pathways between the participant and their investigator and site staff, and between the investigator and sponsor study team. The ECC is only to be used by healthcare professionals not involved in the research study, as a means of reaching the investigator or site staff related to the care of a participant. The Pfizer Call Center number is to be used when the investigator and site staff are unavailable. The Pfizer Call Center number is not for use by the participant directly; if a participant calls that number directly, they will be directed back to the investigator site.

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10.2. Appendix 2: Clinical Laboratory Tests

The following safety laboratory tests will be performed at times defined in the SoA 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 issues.

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Table 3. Protocol Required Safety Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count Platelet count WBC count with differential Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs) Coagulation (PT, PTT and INR)	CK Urea Creatinine/CystatinC eGFR Glucose (fasting) Calcium Sodium Potassium Chloride Total CO_2 (Bicarbonate) AST, ALT, LDH Total bilirubin Direct bilirubin[e] Alkaline phosphatase Albumin Total protein Ferritin Lipids[f] LDL HDL Triglycerides Total cholesterols	pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Urine Microscopic Culture[a] UPCr[d]	• Urine pregnancy test (β-Hcg)[c] **At screening:** • Serum FSH[b] • Serum pregnancy test (β-Hcg)[c] • HbsAg; HbcAb; HbsAb • HCVAb • IGRA • HIV testing • APL antibodies ○ B2GPI IgG, IgM; anti-cardiolipin IgG, IgM at screening (repeat w/clotting events) Reflex laboratory tests: • HBV DNA • HCV RNA *For suspected HLH/MAS:* Ferritin Platelets Fibrinogen serum levels Triglycerides IFNγ[g] CD163[g] CD25[g] CXCL9[g] IL-2[g] M-CSF[g]

Samples for central laboratory evaluations (ie, hematology, blood chemistry, urinalysis, dipstick, spot urine protein, and microscopic). 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. Laboratory tests may be repeated once during the 5-week screening period; the last value will be used to determine participant eligibility.

a. Only if UTI is suspected and urine microscopic is positive for greater than 10 WBC/HPF, urine culture must be performed locally and need to be reported to the source document.
b. For confirmation of postmenopausal status only.
c. Serum pregnancy testing is only required at screening. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/EC. Serum or urine β-Hcg for female participants of childbearing potential. If urine pregnancy testing is weak positive or indeterminate, a reflex of serum pregnancy test is required.
d. UPCr is only required at screening for participants with CLE. UPCr is required at all clinic visits specified in SoA for participants with SLE.
e. Only required if total bilirubin is elevated.
f. 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.
g. If locally available.

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.

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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 Meeting 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. Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:
  - Is associated with accompanying symptoms.
  - Requires additional diagnostic testing or medical/surgical intervention.
  - Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
- Exacerbation of a chronic or intermittent preexisting condition, including an increase in either frequency and/or intensity of the condition.
- New condition 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 or SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

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Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that 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 an SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed below:
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 admitted (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.

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d. Results in persistent or significant 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), that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Is a suspected transmission via a Pfizer product of an infectious agent, pathogenic or nonpathogenic

The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a participant exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

g. Other situations:

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations, such as significant medical events that 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 During the Active Collection Period

AE and SAE Recording/Reporting
The table below summarizes the requirements for recording AEs on the CRF and for reporting SAEs on the CT SAE Report Form to Pfizer Safety throughout the active collection period. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious AEs; and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

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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	All AEs or SAEs associated with EDP or EDB Note: Instances of EDP or EDB not associated with an AE or SAE are not captured in the CRF	All instances of EDP are reported (whether or not there is an associated SAE)* All instances of EDB are reported (whether or not there is an associated SAE)**
Environmental or occupational exposure to the product under study to a nonparticipant (not involving EDP or EDB)	None. Exposure to a study nonparticipant is not collected on the CRF	The exposure (whether or not there is an associated AE or SAE) must be reported***

* **EDP** (with or without an associated AE or SAE): any pregnancy information is reported to Pfizer Safety using the CT SAE Report Form and EDP Supplemental Form; if the EDP is associated with an SAE, then the SAE is reported to Pfizer Safety using the CT SAE Report Form.
** **EDB** is reported to Pfizer Safety using the CT SAE Report Form, which would also include details of any SAE that might be associated with the EDB.
*** **Environmental or occupational exposure:** AEs or SAEs associated with occupational exposure are reported to Pfizer Safety using the CT SAE Report Form.

- When an AE or 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 or 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 or SAE CRF page.

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- 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 or 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 listed below (as defined by the NCI-CTCAE). The latest available version of CTCAE will be used[31].

GRADE	Clinical Description of Intensity
1	MILD AE
2	MODERATE AE
3	SEVERE AE
4	LIFE-THREATENING; urgent intervention indicated
5	DEATH RELATED TO AE

CTCAE Definitions

A brief definition is provided to clarify the meaning of each AE term.

CTCAE Grades

The CTCAE displays Grades 1 through Grade 5 with unique clinical descriptions of severity for each AE based on this general guideline:

- **Grade 1:** Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- **Grade 2:** Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL
- **Grade 3:** Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting selfcare ADL
- **Grade 4:** Life-threatening consequences; urgent intervention indicated
- **Grade 5:** Death related to AE

A semi-colon indicates 'or' within the description of the grade.

A single dash (-) indicates a grade is not available.

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Not all grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than 5 options for Grade selection. Grade 5 (Death) is not appropriate for some AEs and is therefore not an opinion.

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 or SAE. The investigator will use clinical judgment to determine the relationship.
- 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.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- The investigator will also consult the IB and/or product information, for marketed products, in their assessment.
- For each AE or SAE, the investigator **must** document in the medical notes that they have reviewed the AE or SAE and have 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 their 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

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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 providers.
- 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 submitted documents.
- 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 DCT

- The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic DCT.
- If the electronic system is unavailable, then the site will use the paper SAE DCT (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic DCT (eg, eSAE or PSSA) or paper form (as applicable) as soon as the data become available.
- After the study is completed at a given site, the electronic DCT 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 DCT 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.

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SAE Reporting to Pfizer Safety via the 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, an alternative method should be used, eg, secured (Transport Layer Security) or password-protected email. If none of these methods can be used, 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.

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10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

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

The criteria below are part of Inclusion Criterion 1 (Age and Sex; Section 5.1) and specify the reproductive requirements for including female participants. Refer to Section 10.4.4 for a complete list of contraceptive methods permitted in the study.

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 definition below in Section 10.4.3).

OR

- Is a WOCBP and agrees to use a highly effective contraceptive method during the intervention period (for a minimum of 20 weeks after the last dose of study intervention). 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

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.

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For individuals with permanent infertility due to a medical cause other than the above (eg, müllerian 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 no menses for 12 months without an alternative medical cause. In addition:
  - A high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years of age and not using hormonal contraception or HRT.
  - A female on HRT and whose menopausal status is in doubt will be required to use one of the highly effective nonestrogen hormonal contraception methods if she wishes to continue her HRT during the study. Otherwise, she must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.4. Contraception Methods

Contraceptive use by men or women should be consistent with local availability/regulations regarding the use of contraceptive methods for those participating in clinical trials.

The following contraceptive methods are appropriate for this study:

<u>Highly Effective Methods That Have Low User Dependency</u>

1. Implantable progestogenonly hormone contraception associated with inhibition of ovulation.

2. Intrauterine device.

3. Intrauterine hormone-releasing system.

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.

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Highly Effective Methods That Are User Dependent

6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:

- Oral
- Intravaginal
- Transdermal

7. Progestogen-only hormone contraception associated with inhibition of ovulation:

- Oral
- Injectable

8. 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.

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10.5. Appendix 5: Genetics

Use/Analysis of DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Therefore, where local regulations and IRBs/ECs allow, a blood sample will be collected for DNA analysis.
- The scope of the genetic research may be narrow (eg, 1 or more candidate genes) or broad (eg, the entire genome), as appropriate to the scientific question under investigation.
- The samples may be analyzed as part of a multistudy assessment of genetic factors involved in the response to PF-06823859 or study interventions of this class to understand treatments for the disease(s) under study or the disease(s) themselves.
- The results of genetic analyses may be reported in the CSR or in a separate study summary, or may be used for internal decision making without being included in a study report.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained as indicated:
    - Retained samples will be stored indefinitely or for another period as per local requirements.
- Participants may withdraw their consent for the storage and/or use of their Retained Research Samples at any time by making a request to the investigator; in this case, any remaining material will be destroyed. Data already generated from the samples will be retained to protect the integrity of existing analyses.
- Samples for genetic research will be labeled with a code. The key between the code and the participant's personally identifying information (eg, name, address) will be held securely at the study site.

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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 DILI. Participants who experience a transaminase elevation above 3 × ULN should be monitored more frequently to determine if they are "adaptors" or are "susceptible."

In the majority of DILI cases, elevations in AST and/or ALT precede T bili elevations (>2 × ULN) by several days or weeks. The increase in T bili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and T bili values will be elevated within the same laboratory sample). In rare instances, by the time T bili 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 T bili 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 T bili baseline values within the normal range who subsequently present with AST OR ALT values ≥3 × ULN AND a T bili 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** T bili 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 T bili above the normal range: T bili level increased from baseline value by an amount of ≥1 × ULN **or** if the value reaches ≥3 × ULN (whichever is smaller).

Rises in AST/ALT and T bili 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.

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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 T bili for suspected Hy's law cases, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/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/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, or 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, liver imaging (eg, biliary tract), and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and T bili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the 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.

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10.7. Appendix 7: Kidney Safety Monitoring Guidelines

10.7.1. Laboratory Assessment of Change in Kidney Function and Detection of Kidney Injury

Standard kidney safety monitoring requires assessment of baseline and postbaseline serum creatinine (Scr measurement to eGFR [Scr-based eGFR] or [eCrCl]). Baseline and postbaseline Scys makes it feasible to distinguish AKI from other causes of Scr increase. If Scr increase is confirmed after baseline, then reflex measurement of Scys is indicated to estimate the combined Scr-Scys eGFR calculation (for adults only).

Regardless of whether kidney function monitoring tests are required as a routine safety monitoring procedure in the study, if the investigator or sponsor deems it necessary to further assess kidney safety and quantify kidney function, then these test results should be managed and followed per standard of care.

10.7.2. Age-Specific Kidney Function Calculation Recommendations

10.7.2.1. Adults (18 Years and Above)—2021 CKD-EPI Equations

2021 CKD-EPI Scr Only	**Scr** *(mg/Dl)*	**Scys** *(mg/L)*	**Recommended Egfr Equation**
Female	if ≤ 0.7	N/A	$eGFR = 143 \times (Scr/0.7)^{-0.241} \times (0.9938)^{Age}$
Female	if > 0.7	N/A	$eGFR = 143 \times (Scr/0.7)^{-1.200} \times (0.9938)^{Age}$
Male	if ≤ 0.9	N/A	$eGFR = 142 \times (Scr/0.9)^{-0.302} \times (0.9938)^{Age}$
Male	if > 0.9	N/A	$eGFR = 142 \times (Scr/0.9)^{-1.200} \times (0.9938)^{Age}$
2021 CKD-EPI Scr-Scys Combined	**Scr** *(mg/Dl)*	**Scys** *(mg/L)*	**Recommended Egfr Equation**
Female	if ≤ 0.7	if ≤ 0.8	$eGFR = 130 \times (Scr/0.7)^{-0.219} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Female	if ≤ 0.7	if > 0.8	$eGFR = 130 \times (Scr/0.7)^{-0.219} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Female	if > 0.7	if ≤ 0.8	$eGFR = 130 \times (Scr/0.7)^{-0.544} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Female	if > 0.7	if > 0.8	$eGFR = 130 \times (Scr/0.7)^{-0.544} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Male	if ≤ 0.9	if ≤ 0.8	$eGFR = 135 \times (Scr/0.9)^{-0.144} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Male	if ≤ 0.9	if > 0.8	$eGFR = 135 \times (Scr/0.9)^{-0.144} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Male	if > 0.9	if ≤ 0.8	$eGFR = 135 \times (Scr/0.9)^{-0.544} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Male	if > 0.9	if > 0.8	$eGFR = 135 \times (Scr/0.9)^{-0.544} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$

Inker LA et al. N Engl J Med. 2021 ;385 :1737-49.

10.7.3. Adverse Event Grading for Kidney Safety Laboratory Abnormalities

AE grading for decline in kidney function (ie, eGFR or eCrCl) will be according to KDIGO criteria.

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10.8. Appendix 8: ECG Findings of Potential Clinical Concern

ECG Findings That <u>May</u> Qualify as AEs
• Marked sinus bradycardia (rate <40 bpm) lasting minutes. • New PR interval prolongation >280 ms. • New prolongation of QTcF to >480 ms (absolute) or by ≥60 ms 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 PVCs, triplets, or short intervals (<30 seconds) of consecutive ventricular complexes.
ECG Findings That <u>May</u> Qualify as SAEs

• QTcF prolongation >500 ms.
• New ST-T changes suggestive of myocardial ischemia.
• New onset- LBBB (QRS complex >120 ms).
• New onset- right bundle branch block (QRS complex >120 ms).
• Symptomatic bradycardia.
• Asystole:
  ◦ In awake, symptom-free participants 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- participants 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).

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- Ventricular rhythms >30 seconds' duration, including idioventricular rhythm (HR <40 bpm), accelerated idioventricular rhythm (HR 40 bpm to <100 bpm), and monomorphic/polymorphic ventricular tachycardia (HR >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 SAEs

- 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.

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10.9. Appendix 9: Prohibited and Permitted Concomitant Medications

The prohibited concomitant medications listed below should not be taken in the C0251013 study.

The Pfizer study team is to be notified of any prohibited medications taken during the study. After consulting with the sponsor, the investigator will make a judgment on the ongoing study intervention administration for any participation with prohibited medication use during the study.

Medications		Treatment Period	Follow-up Period
Corticosteroids	Parenteral injections (eg, IA, IM, IV or epidural injection)	Prohibited • Oral or parenteral (IV or IM) corticosteroids at doses >10 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]) however patients experiencing these reactions should permanently discontinue study intervention. • Epidural corticosteroid injections are prohibited within 12 weeks of Day 1 and on study. • Rectal corticosteroids are prohibited for at least 12 weeks prior to Day 1 and on study • Intra-articular corticosteroids or hyaluronic acid within 4 weeks of Day 1 and on study.	Permitted
	Oral (prednisone or equivalent)	Permitted • Prednisone up to 10 mg/day (or equivalent) provided dose is stable for at least four weeks prior to Day 1 and corticosteroids were started at least 8 weeks prior to Day 1.	Permitted
	Topical	Permitted • Low potency topical steroids [class 6 (mild, such as desonide) or class 7 (least potent, such as hydrocortisone)]	

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Medications		Treatment Period	Follow-up Period
		are permitted on non-biopsied lesions. Prohibited for 4 weeks prior to Day 1 and throughout study on lesions identified for potential biopsies. • Medium or high potency topical corticosteroids must be discontinued ≥4 weeks prior to Day 1.	
Retinoids	Oral	Permitted if on a stable dose for ≥12 weeks prior to day 1 and throughout the study (eg, acitretin and isotretinoin) and in doses not to exceed 0.7 mg/kg/day on study	Permitted
	Topical	Permitted if on a stable dose for ≥12 weeks prior to day 1 and throughout the study (eg,- tretinoin, tazarotene) prohibited on lesions identified for biopsies, may be continued on non-biopsy lesions	Permitted
Immunosuppressive or immunomodulatory agents including MTX, AZA, 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. • These medications must be started 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 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.	Permitted
Sulfasalazine		Prohibited within 8 weeks of Day 1	Prohibited
Imiquimod		Prohibited within 12 weeks of Day 1	Prohibited
Thymopetidum		Prohibited	Prohibited

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Medications	Treatment Period	Follow-up Period
	Must be discontinued 4 weeks prior to baseline.	
Antimalarials (eg, hydroxychloroquine, chloroquine, quinacrine)	Permitted • Provided preexisting dose is stable for at least 12 weeks and treatment is not started/or stopped within 12 weeks of Day 1. • Must be started 12 weeks prior to 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, quinacrine 100 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
Lower potency opioids	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, adrenocorticotropic hormone (ACTH) by injection	Prohibited during treatment and within 28 days of Day 1	Prohibited

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Medications	Treatment Period	Follow-up Period
Investigational or marketed biologics (including but not limited to), etanercept, infliximab, certolizumab, adalimumab, golimumab, anakinra, belimumab, tocilizumab, sarilumab, abatacept, anifrolumab & ustekinumab.	Prohibited during treatment and prior to Day 1 • Anti-TNF therapies (etanercept, infliximab, certolizumab, adalimumab, golimumab), belimumab, anakinra, tocilizumab, sarilumab, anifrolumab, abatacept or ustekinumab within 8 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 8 weeks of Day 1 or 5 half-lives.	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, hydroxyurea or chlorambucil, or other alkylating agents	Prohibited during treatment and 24 weeks prior to Day 1.	Prohibited
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 to lesions that are identified for potential biopsies within 4 weeks of Day 1 and during the study. Permitted on non-biopsied lesions if ongoing for 8 weeks prior to Day 1.	Prohibited

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Medications	Treatment Period	Follow-up Period
Other investigational drugs or investigational combinations	Prohibited	Prohibited
B cell depleting therapy (eg, rituximab, ocrelizumab, 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 or dead vaccine and boosters	Permitted	Permitted
JAK Kinase inhibitors (eg, tofacitinib, ruxolitinib, abrocitinib, baricitnib)	Prohibited; all oral JAK inhibitors, must be discontinued at least 12 weeks prior to Day 1 ruxolitinib or other topical JAK inhibitor cream or ointment is prohibited for 8 weeks prior to Day 1 and on study	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.	
Dapsone	Permitted, oral dapsone is permitted on stable dose not exceeding 150 mg/day if started at least 8 weeks prior to Day 1.	Permitted
Herbal Medication	Only herbal medications with known pharmaceutical properties are allowed, otherwise these medications must be discontinued at least 4 weeks prior to randomization.	Permitted after a minimum of 20 weeks 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 and on study.	Permitted after a minimum of 20 weeks following last dose of study intervention.

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10.10. Appendix 10: 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.

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10.11. Appendix 11: Guidelines for Participant Safety Monitoring and Discontinuation

These guidelines for participant safety monitoring and discontinuation are to be applied to all participants in study C0251013. Additional individual participant monitoring is at the discretion of the investigator and dependent on any perceived safety concerns. Unscheduled clinical laboratories 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 laboratory 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 (eg, lymphopenia in SLE patients), repeat assessments between scheduled visits may be waived by the Pfizer clinical team following discussion with the principal investigator.

10.11.1. Safety Monitoring

The following laboratory abnormalities require re-testing within 1 week:

- Neutrophil counts <1000 neutrophils/mm^3;
- Lymphocyte counts <500 lymphocytes/mm^3 for the first event and then if associated with infection or at the investigators discretion;
- Platelet counts <50,000 platelets/mm^3;
- eGFR that is ≥ 40% reduction from baseline,
- Ferritin levels ≥ 1000 ng/mL
- 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 and/or 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 childbearing potential with any positive urine beta-human chorionic gonadotrophin (βhCG) test, the participant will have study drug interrupted and a serum sample submitted to the central laboratory for βhCG testing.

10.11.2. 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

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end of the double-blind period for safety and efficacy assessments, whether or not they continue to receive study intervention for the full 40-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 (IV) antimicrobial therapy, hospitalization for treatment, or meeting other criteria that require the infection to be classified as SAE;
- 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 unless due to surgery;.
- Participants who have serum ferritin ≥ 2000 ng/mL and/or any other laboratory or clinical findings diagnostic for hemophagocytic lymphohistiocytosis.
- All of the following laboratory abnormalities require discontinuation if they are confirmed (confirmation through retesting should occur within 1 week):
  - Two sequential absolute neutrophil counts <0.70 x 10^9/L (<700/mm^3);
  - Two sequential platelet counts <50 x 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 ULN[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 who become pregnant during the study;
  - Reduction of eGFR ≥40% from baseline value. If the eGFR decreases by greater than 40%, the test should be repeated to confirm the decrease, study intervention discontinued and the participant referred 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;

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- 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 protocol scheduled visits and assessments through Week 60. Any participant who withdraws consent must enter followup with their first followup 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 least 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. If the participant discontinues study intervention (PF-06823859 or placebo) prior to Week 40, they may receive any medication required to control of their SLE/CLE after consultation with the sponsor medical monitor.

Participants should be followed post study intervention discontinuation for 20 weeks due to the long half-life of study intervention. Additional followup visits may occur as needed until any clinically relevant abnormalities or AEs have resolved, returned to a baseline state, or are deemed clinically stable.

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10.12. Appendix 12: EULAR/ACR classification criteria for SLE

Criteria	Definition
ANA	ANA at a titer of ≥1:80 on Hep-2 cells or an equivalent positive test at least once. Testing by immunofluorescence on Hep-2 cells or a solid-phase ANA screening immunoassay with at least equivalent performance is highly recommended
Fever	Temperature >38.3°C
Leukopenia	White blood cell count <4,000/mm³
Thrombocytopenia	Platelet count <100,000/mm³
Autoimmune hemolysis	Evidence of hemolysis, such as reticulocytosis, low haptoglobin, elevated indirect bilirubin, elevated LDH, AND positive Coombs' (direct antiglobulin) test
Delirium	Characterized by 1) change in consciousness or level of arousal with reduced ability to focus, 2) symptom development over hours to <2 days, 3) symptom fluctuation throughout the day, 4) either 4a) acute/subacute change in cognition (eg, memory deficit or disorientation), or 4b) change in behavior, mood, or affect (eg, restlessness, reversal of sleep/wake cycle)
Psychosis	Characterized by 1) delusions and/or hallucinations without insight and 2) absence of delirium
Seizure	Primary generalized seizure or partial/focal seizure
Non-scarring alopecia	Non-scarring alopecia observed by a clinician[†]
Oral ulcers	Oral ulcers observed by a clinician[†]
Subacute cutaneous OR discoid lupus	Subacute cutaneous lupus erythematosus observed by a clinician: [†] Annular or papulosquamous (psoriasiform) cutaneous eruption, usually photodistributed If skin biopsy is performed, typical changes must be present (interface vacuolar dermatitis consisting of a perivascular lymphohistiocytic infiltrate, often with dermal mucin noted). OR Discoid lupus erythematosus observed by a clinician: [†] Erythematous-violaceous cutaneous lesions with secondary changes of atrophic scarring, dyspigmentation, often follicular hyperkeratosis/plugging (scalp), leading to scarring alopecia on the scalp If skin biopsy is performed, typical changes must be present (interface vacuolar dermatitis consisting of a perivascular and/or periappendageal lymphohistiocytic infiltrate. In the

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Criteria	Definition
	scalp, follicular keratin plugs may be seen. In longstanding lesions, mucin deposition may be noted)
Acute cutaneous lupus	Malar rash or generalized maculopapular rash observed by a clinician[†] If skin biopsy is performed, typical changes must be present (interface vacuolar dermatitis consisting of a perivascular lymphohistiocytic infiltrate, often with dermal mucin noted. Perivascular neutrophilic infiltrate may be present early in the course)
Pleural or pericardial effusion	Imaging evidence (such as ultrasound, X-ray, CT scan, MRI) of pleural or pericardial effusion, or both
Acute pericarditis	≥2 of 1) pericardial chest pain (typically sharp, worse with inspiration, improved by leaning forward), 2) pericardial rub, 3) ECG with new widespread ST elevation or PR depression, 4) new or worsened pericardial effusion on imaging (such as ultrasound, X-ray, CT scan, MRI)
Joint involvement	EITHER 1) synovitis involving 2 or more joints characterized by swelling or effusion OR 2) tenderness in 2 or more joints and at least 30 minutes of morning stiffness
Proteinuria >0.5 g/24 hours	Proteinuria >0.5 g/24 hours by 24-hour urine or equivalent spot urine protein-to-creatinine ratio
Class II or V lupus nephritis on renal biopsy according to ISN/RPS 2003 classification	Class II: Mesangial proliferative lupus nephritis: purely mesangial hypercellularity of any degree or mesangial matrix expansion by light microscopy, with mesangial immune deposit. A few isolated subepithelial or subendothelial deposits may be visible by immunofluorescence or electron microscopy, but not by light microscopy Class V: Membranous lupus nephritis: global or segmental subepithelial immune deposits or their morphologic sequelae by light microscopy and by immunofluorescence or electron microscopy, with or without mesangial alterations
Class III or IV lupus nephritis on renal biopsy according to ISN/RPS 2003 classification	Class III: Focal lupus nephritis: active or inactive focal, segmental, or global endocapillary or extracapillary glomerulonephritis involving <50% of all glomeruli, typically with focal subendothelial immune deposits, with or without mesangial alterations

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Criteria	Definition
	Class IV: Diffuse lupus nephritis: active or inactive diffuse, segmental, or global endocapillary or extracapillary glomerulonephritis involving ≥50% of all glomeruli, typically with diffuse subendothelial immune deposits, with or without mesangial alterations. This class includes cases with diffuse wire loop deposits but with little or no glomerular proliferation
Positive antiphospholipid antibodies	Anticardiolipin antibodies (IgA, IgG, or IgM) at medium or high titer (>40 APL, GPL, or MPL, or >the 99th percentile) or positive anti-β2GPI antibodies (IgA, IgG, or IgM) or positive lupus anticoagulant
Low C3 OR low C4	C3 OR C4 below the lower limit of normal
Low C3 AND low C4	Both C3 AND C4 below their lower limits of normal
Anti-dsDNA antibodies OR anti-Sm antibodies	Anti-dsDNA antibodies in an immunoassay with demonstrated ≥90% specificity for SLE against relevant disease controls OR anti-Sm antibodies

† This may include physical examination or review of a photograph.

Aringer M, Costenbader K, Daikh D, et al. 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus. Ann Rheum Dis. 2019;78(9):1151-59.

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10.13. Appendix 13: 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.



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.

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10.14. Appendix 14: 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.

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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.

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10.15. Appendix 15: 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 ... tick appropriate box)

☐ Dyspigmentation usually lasts less than 12 months (dyspigmentation score above remains)

☐ Dyspigmentation usually lasts at least 12 months (dyspigmentation score is doubled)

Alopecia



Recent Hair loss (within the last 30 days/as reported by patient)	
1-Yes 0-No	

NB: if scarring and non-scarring aspects seem to coexist in one lesion, please score both

Divide the scalp into four quadrants as shown. The dividing line between right and left is the midline. The dividing line between frontal and occipital is the line connecting the highest points of the ear lobe. A quadrant is considered affected if there is a lesion within the quadrant.

Alopecia (clinically not obviously scarred)		Scarring of the scalp (judged clinically)	
0-absent 1-diffuse; non-inflammatory 2-focal or patchy in one quadrant; 3-focal or patchy in more than one quadrant		0- absent 3- in one quadrant 4- two quadrants 5- three quadrants 6- affects the whole skull	

Total Activity Score (For the activity score please add up the scores of the left side i.e. for Erythema, Scale/Hypertrophy, Mucous membrane involvement and Alopecia)		Total Damage Score (For the damage score, please add up the scores of the right side, i.e. for Dyspigmentation, Scarring/Atrophy/Panniculitis and Scarring of the Scalp)	

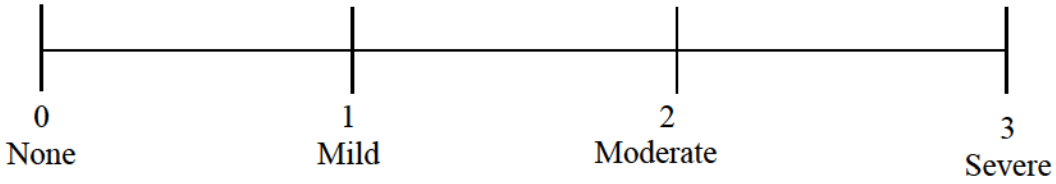
Albrecht J, Taylor L, Berlin JA, et al. The CLASI (Cutaneous LE Disease Area and Severity Index): an outcome instrument for cutaneous lupus erythematosus. J Invest Dermatol 2005;125(5): 889-894.

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10.16. Appendix 16: 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]

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10.17. Appendix 17: Columbia Suicide Severity Rating Scale (C-SSRS)

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 1 month**
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* Recent - ***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	___	___
© 2008 Research Foundation for Mental Hygiene, Inc. C-SSRS—Lifetime Recent - Clinical (Version 1/14/09) Page 1 of 2		

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SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**	**Past 3 months**
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 or Self-Interrupted 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 or self-interrupted ____	Yes ☐ No ☐ Total # of aborted or self-interrupted ____
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 ☐ Total # of preparatory acts ____	Yes ☐ No ☐ Total # of preparatory acts ____

	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* ____

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10.18. Appendix 18: Abbreviations

The following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
6-MP	6-mercaptopurine
Abs	Absolute
ACE	angiotensin-converting enzyme
ACR	American College of Rheumatology
ACTH	adrenocorticotropic hormone
ADA	anti-drug antibodies
ADL	activity/activities of daily living
AE	adverse event
AESI	adverse event of special interest
AKI	acute kidney injury
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
ANA	antinuclear antibody
ANC	absolute neutrophil count
ANCA	anti-neutrophil cytoplasmic autoantibody
ANCOVA	analysis of covariance
anti-dsDNA	anti–double-stranded DNA
anti-β2GPI	anti–β2-glycoprotein I
anti-TNF	anti-tumor necrosis factor
APL	antiphospholipid (antibodies)
ARB	angiotensin receptor blocker
AST	aspartate aminotransferase
AV	Atrioventricular
AZA	Azathioprine
B2GPI	Beta-2-glycoprotein I
BCG	Bacillus Calmette-Guérin
BL	Baseline
BILAG	British Isles Lupus Assessment Group
BID	twice daily
BMI	body mass index
BP	blood pressure
bpm	beats per minute
β-Hcg	β-human chorionic gonadotropin
Cav	conversion of AUC to average plasma concentration
CDASI	Cutaneous Dermatomyositis Disease Area and Severity Index
CFB	change from baseline
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase

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Abbreviation	Term
CKD-EPI	chronic kidney disease epidemiology
CLASI	Cutaneous Lupus Erythematosus Disease Area and Severity Index
CLASI-A	CLASI activity score
CLE	cutaneous lupus erythematosus
cmITT	censored modified intent to treat
CMV	Cytomegalovirus
CNI	calcineurin inhibitors
CNS	central nervous system
CO_2	carbon dioxide (bicarbonate)
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form
CRO	contract research organization
CS	Corticosteroid
C-SSRS	Columbia Suicide Severity Rating Scale
CSR	Clinical Study Report
CT	computed tomography/clinical trial
CTCAE	Common Terminology Criteria for Adverse Events
CTIS	Clinical Trial Information System
CTR	Clinical Trials Regulation
CVA	cerevrovascular accident
CVD	cardiovascular disease
DCT	data collection tool
DILI	drug-induced- liver injury
DM	Dermatomyositis
DU	dispensable unit
EBV	Epstein-Barr virus
EC	ethics committee
ECC	emergency contact card
ECG	electrocardiogram or electrocardiography
eCrCl	estimated creatinine clearance
eCRF	electronic case report form
EDB	exposure during breastfeeding
EDP	exposure during pregnancy
EDTA	ethylenediaminetetraacetic acid
eGFR	estimated glomerular filtration rate
ENA	extractable nuclear antigens
eSAE	electronic serious adverse event
ET	early termination
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials (European Clinical Trials Database)
EULAR	European League Against Rheumatism
FDA	Food and Drug Administration

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Abbreviation	Term
FIH	first in human
FSH	follicle-stimulating hormone
GI	Gastrointestinal
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GS	gene signature
HbcAb	hepatitis B core antibody
HbsAb	hepatitis B surface antibody
HbsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCQ	Hydroxychloroquine
HCV	hepatitis C virus
HCVAb	hepatitis C virus antibodies
HDL	high-density lipoprotein
Hep	Hepatitis
HIV	human immunodeficiency virus
HLH	haemophagocytic lymphohistiocytosis
HMG-CoA	3-hydroxy-3-methyl-glutaryl-coenzyme A
HR	heart rate
HRT	hormone replacement therapy
IA	interim analysis
IB	Investigator's Brochure
ICD	informed consent document
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	Identification
IFN	Interferon
IFNα	interferon-alpha
IFNβ	interferon-beta
IFNAR	IFN-α/β receptor
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IGRA	Interferon Gamma Release Assay
CCI [redacted]	
IM	Intramuscularly
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
IP	investigational product
IPAL	Investigational Product Accountability Log
IPM	investigational product manual

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Abbreviation	Term
IRB	Institutional Review Board
IRC	internal review committee
IRT	Interactive Response Technology
CCI [redacted]	
ISN/RPS	International Society of Nephrology/Renal Pathology Society
IV	Intravenous
IVIg	intravenous immunoglobulin
JAK	Janus Kinase
KDIGO	Kidney Disease: Improving Global Outcomes
LBBB	left bundle branch block
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LFT	liver function test
MAD	multiple ascending dose
MAS	macrophage activation syndrome
MCP	metacarpophalangeal
MHRA	Medicines and Healthcare products Regulatory Agency
MI	myocardial infarction
mITT	modified intent to treat
MMF	mycophenolate mofetil
MMRM	mixed modeling of repeated measures
MPA	mycophenolic acid
MQI	medically qualified individual
MRI	magnetic resonance imaging
MTP	metatarsophalangeal
MTX	methotrexate
CCI [redacted]	
NCI	National Cancer Institute
NAb	neutralizing antibodies
NIHR	National Institute for Health Research
NIMP	non-investigational medicinal product
NOAEL	no observed adverse effect level
NRI	non-responder imputation
NRImITT	NRI modified intent to treat
NSAIDs	non-steroidal anti-inflammatory drugs
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamic(s)
PE	physical examination
PhGA	Physician Global Assessment
PIP	proximal interphalangeal
PK	pharmacokinetic(s)
PR	pulse rate
PRN	as needed

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Abbreviation	Term
PSSA	Pfizer's Serious Adverse Event Submission Assistant
PT	prothrombin time
PTT	partial thromboplastin time
PVC	premature ventricular contraction
Q2W	every 2 weeks
Q4W	every 4 weeks
Q8W	every 8 weeks
QTc	corrected QT interval
QTcF	QTc corrected using Fridericia's formula
QTL	quality tolerance limit
QFT-G/QFT-G Plus	QuantiFERON®-TB Gold/QuantiFERON-TB Gold Plus test
QFT-GIT	QuantiFERON®-TB Gold In-Tube test
qual	qualitative
RBC	red blood cell
RNA	ribonucleic acid
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
Scr	serum creatinine
Scys	serum cystatin C
SJC	swollen joint count
SLE	systemic lupus erythematosus
SLEDAI	systemic lupus erythematosus disease activity index
SLEDAI-2K	systemic lupus erythematosus disease activity index 2000
SoA	schedule of activities
SOC	stand of care
SOP	standard operating procedure
SRI-4	SLE Responder Index 4
SRSD	Single Reference Safety Document
SUSAR	Suspected Unexpected Serious Adverse Reaction
T bili	total bilirubin
TB	tuberculosis
TBNK	T cells, B cells and NK cells
TJC	tender joint count
type 1 IFN GS	type 1 interferon gene signature
UK	United Kingdom
ULN	upper limit of normal
UPCR	urine protein creatinine ratio
US	United States
UTI	urinary tract infection
VAS	visual analog scale
WBC	white blood cell

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Abbreviation	Term
WHO	World Health Organization
Wk	week
WOCBP	woman/women of childbearing potential
WONCBP	woman/women of non-childbearing potential

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