A PHASE 1, RANDOMIZED, MULTI-CENTER, DOUBLE-BLIND, SPONSOR OPEN, PLACEBO-CONTROLLED, SINGLE AND MULTIPLE DOSE-ESCALATION STUDY TO EVALUATE THE SAFETY, TOLERABILITY, PHARMACOKINETICS AND PHARMACODYNAMICS OF PF-06835375 IN SUBJECTS WITH SEROPOSITIVE SYSTEMIC LUPUS ERYTHEMATOSUS OR RHEUMATOID ARTHRITIS

Investigational Product Number:	PF-06835375
Investigational Product Name:	Not applicable (N/A)
United States (US) Investigational New Drug (IND) Number:	CCI [redacted]
European Clinical Trials Database (EudraCT) Number:	2017-003077-34
Protocol Number:	C1131001
Phase:	1

Document History

Document	Version Date	Summary of Changes and Rationale
Amendment 2	09 November 2018	1. Removed multiple clinical and laboratory assessments beyond Week 16 (Schedule of Activities). *Rationale: To remove unnecessary assessments beyond Week 16, based on emerging safety, PD and PK data, and which will not provide information crucial for defining the overall safety signal for PF-06835375.* 2. Decreased frequency of visits and visit assessments for subjects who remain in the study beyond 52 weeks (Schedule of Activities). *Rationale: To remove unnecessary study assessments (including samples) which will not be informative due to a lack of disease activity requirements for entry and emerging data Reduction of study visits beyond Week 52 will maintain an appropriate level of follow up for safety at given the emerging safety profile of PF-06835375 and the established safety signal from B-cell depleting agents.* 3. Added complement lab for SLE subjects at Screening (Schedule of Activities). *Rationale: To align with SLICC and* CCI *lab requirements.* 4. Removed follow up due to immunogenicity related AE (Schedule of Activities, Sections 3.1, 3.5, 6.2). *Rationale: To align with frequency of immunogenicity testing while retaining the option for additional visits if needed for safety.* 5. Added a requirement of sentinel dosing in

		Part B in specific circumstances. *Rationale: To align Part A and B for safety monitoring at a given dose.* 6. Allowed independent dose escalation in Part A and Part B, provided SC is used in Part B (Section 3.3). *Rationale: To dose escalate SC cohorts based on safety, tolerability, PK and PD (B cell counts) from previous SC cohorts due to potential differences in bioavailability between IV and SC administration.* 7. Changed dose escalation criterion to require detectable B cells for a minimum of 2 consecutive visits at least 2 weeks apart, starting at Week 12 (Section 3.4). *Rationale: To align dose escalation criterion with the end-of-study discharge criteria. This rationale is based on emerging safety, PK and PD profile of PF-06835375 and clinical experience with approved B cell depleting agents, including that for rituximab (redosing occurs with undetectable B-cell counts).* 8. Clarified lymphopenia criterion in individual stopping rules with respect to pre-dose abnormalities (Section 3.4.3). *Rationale: To appropriately consider pre-dose lymphopenia (common in SLE), subjects with Grade 1 or 2 pre-dose lymphophenia (CTCAE v4.0) and 2 grade shift or less will not be considered to have this met individual stopping criterion.* 9. Removed requirement for "stable or increasing" B-cell counts for end of study/subject discharge for subjects who have B cell counts above lower limit of normal (LLN; 80 cells/μl) at Week 16 visit (Section 3.5).

		Rationale: Remove unnecessary and additional study visits after B-cell LLN has been reached. The natural fluctuations of B-cell counts obviate the need for additional visits once the LLN threshold has been met. 10. Revised timing for end of study/subject discharge after Week 16 by requiring B cells to reach new stable or increasing detectable level for minimum of two consecutive visits starting at Week 20 (Section 3.5). *Rationale: To harmonize end-of-study discharge criteria with follow up commitment based on revised dose-escalation criteria.* 11. Removed text applicable only for studies using a Medical Device (Sections 8.2.3). *Rationale: To remove text not applicable for this study since medical device is not used.* 12. Administrative clarifications (Sections 3.1, 3.4.1, 4.4.1, 7.1.1). *Rationale: To provide minor clarifications.*
Amendment 1	16 February 2018	1. Changed screening window from 30 days to 45 days (Schedule of Activities). *Rationale: To increase screening window given sizable number and complex nature of screening labs and required turnaround time.* CCI [redacted] 3. Changed scheduled limited physical exam to 6 hours post-dose, provided no new ongoing AEs or safety concerns (Schedule of Activities).

		Rationale: To improve study feasibility at sites. 4. Clarified window for assessments post-dose (Schedule of Activities). *Rationale: To incorporate protocol administrative letter.* 5. Clarified criteria used to determine SLE and RA diagnosis and sample collection in case of combined diagnoses (Schedule of Activities, Sections 7.6.2 and 7.6.3). *Rationale: To clarify criteria used for RA and SLE diagnosis used for assessments in Schedule of Activities and blood sample collection regimen.* 6. Changed JC virus sample collection to one sample (Schedule of Activities, Sections 7.1.1 and 7.1.14). *Rationale: To update based on availability of JC virus test.* 7. Removed bioavailability from PD endpoints (Sections 2 and 9.3.2). *Rationale: To remove an endpoint which may not be calculated accurately given the uncertainty in doses and high number of cohorts.* 8. Modified PK endpoints (Section 2) to align with Tables 5 and 6 (Section 9.3.2); CCI [redacted] *Rationale: To harmonize protocol sections and to include only key PK endpoints as secondary.* 9. Clarified time point for secondary endpoint of depletion of B and cTfh cells (Section 2).

		Rationale: To clarify specific time for evaluating B and cTfh cell depletion. 10. Removed a requirement for two RA or SLE subjects per each cohort in Part B (Sections 3.1 and 4.3). *Rationale: To allow for faster enrollment, given that this is primarily safety and tolerability study.* 11. Clarified that sponsor may elect to add more subjects into cohorts for any reason, including but not limited to a greater than expected PD effect (Section 3.1). *Rationale: To clarify sponsor may elect a higher number of subjects per cohort for any reason but the total number of subjects enrolled in study will be up to a total of approximately 112 subjects.* 12. Clarified that in cohorts A1-A4, sentinel dosing will apply only to the first four subjects (Section 3.2). *Rationale: To clarify sentinel dosing.* 13. Clarified that sentinel dosing is required only when a given dose level is administered for the first time in Part A and not required in Part B (Sections 3.1 and 3.2). *Rationale: To clarify sentinel dosing requirements.* 14. Clarified a minimum number of subjects per cohort, required to proceed with dose escalation (Section 3.4.1). *Rationale: To have sufficient data to determine whether dose escalation is appropriate.* 15. Clarified dose escalation stopping rules for repeat cohorts (Section 3.4.2).

		Rationale: To clarify that if any dose cohort is repeated, this additional cohort will be considered a separate cohort for the purpose of dose escalation stopping rules. 16. Clarified criteria for end of study (Section 3.5). *Rationale: To clarify that only one criterion is needed to be met for end of study.* 17. Clarified restrictions on investigational biologics, which are biosimilars (Exclusion criterion #2, Section 4.2). *Rationale: To allow an appropriate time frame since dosing with biosimilars.* CCI [redacted] *Rationale: To harmonize entry criteria during the entire study.* 19. Clarified exclusion criterion 7 (Section 4.2). *Rationale: To incorporate protocol administrative letter.* 20. Clarified TB exclusion criteria (Criterion #12, Section 4.2). *Rationale: To clarify that subjects with current or past history of active TB or inadequately treated latent TB (or where documentation of treatment is not available) are not eligible.* 21. Clarified when re-screening and repeating screening assessments is permitted (Section 6.1 and Schedule of Activities). *Rationale: To clarify procedures for repeating screening assessments and*

		re-screening. 22. Added a requirement for sites to obtain approval from sponsor clinician for screening and dosing of each subject (Section 6.1 and Schedule of Activities). *Rationale: To ensure implementation of sentinel dosing and to ensure screening of an appropriate number of subjects in each cohort.* 23. Allowed extension of screening window by 5 days contingent on sponsor approval for scheduling or logistics reasons (Section 6.1). *Rationale: To avoid unnecessary re-screening procedures.* 24. Increased blood volume in Part A and clarified blood volumes are approximate (Section 7.7). *Rationale: To update blood volume due to added Day 57 blood samples to clarify that blood volumes are approximate given additional blood samples may be taken eg, for safety assessments or to repeat screening procedures (if appropriate).* 25. Changed assessments during early termination visit to harmonize with the rest of the protocol (Section 6.3). *Rationale: To harmonize data across the study.* 26. Removed band neutrophils from laboratory tests and clarified safety labs (Section 7.1.1). *Rationale: To remove laboratory test that is not required for safety and to clarify definition of safety labs.* 27. Added neck & throat assessment as a part of the physical examination (Section 7.1.3).

		Rationale: To incorporate protocol administrative letter. 28. Clarified that temperature can be also measured at forehead (Section 7.1.4). *Rationale: To incorporate protocol administrative letter.* 29. Clarified recommended and mandatory timeframe for contraception (Inclusion criterion 4 in Section 4.1, Section 4.4.1). *Rationale: To incorporate protocol administrative letter.* 30. Clarified criterion for IGRA repeat without sponsor approval (Sections 6.1 and 7.1.10). *Rationale: To clarify criterion for repeating IGRA TB test without sponsor approval.* 31. Clarified how adverse events associated with vaccinations may be managed and included a requirement for appropriate equipment and personnel to manage anaphylaxis or serious vaccine reactions (Section 7.6.1.3). *Rationale: To incorporate protocol administrative letter and to clarify requirements for sites.* CCI [redacted] [redacted] 33. Minor administrative changes and typographical corrections: Schedule of Activities, Section 7.6.1.1, Appendix 5, exclusion criteria 22 (Section 4.2), Sections 1.2.5, 3.1, 3.4.1 and 6.2. *Rationale: To incorporate protocol administrative letters, to correct*

		typographical errors and to provide additional minor clarifications.
Original protocol	23 August 2017	Not applicable (N/A)

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

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APPENDICES

SCHEDULE OF ACTIVITIES

The schedule of activities table provides an overview of the protocol visits and procedures. Refer to the STUDY PROCEDURES and ASSESSMENTS sections 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 on the schedule of activities table, in order to conduct evaluations or assessments required to protect the well-being of the subject.

Part A (Single Ascending Dose)

Protocol activity	Outpatient	Inpatient			Outpatient										
Visit Identifier[a]	**Screening**[ff]	**Day 1**[hh]		**Day 2**	**Day 4**	**Day 8**	**Day 15**	**Day 29**	**Week 6/ Day 43**	**Week 8/ Day 57**	**Week 12/Day 85**	**Week 16 /Day 113**	**Post-week 16 (every 4 weeks until 52 weeks)**[b]	**Post-week 52 (every 12 weeks)**	**End of study visit**[c]
Visit window	-45 to -1	None			±1 day		±3 days				±7 days			±14 days	
Visit window (days)	-45 to -1	1		2	3-5	7-9	12-18	26-32	40-46	54-60	78-92	106-120	N/A	N/A	N/A
		Pre-dose	Post-dose[d]												
Enrollment Procedures															
Informed consent	X														
Inclusion/exclusion criteria	X	X													
Medical history	X														
Medication history	X														
Demography	X														
CRU confinement[e]		X	X	X											
Medical Procedures															
For all subjects															
Physical examination[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital signs[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECG[h]	X	X	X	X	X	X	X	X	X	X	X	X			
Weight and height[i]	X	X										X	X[j]		
Chest X-ray[k]	X														
C-SSRS[l]	X	X										X			
[redacted] CCI	[redacted]	[redacted]								[redacted]		[redacted]		[redacted]	

Protocol activity	Outpatient	Inpatient		Outpatient										
Visit Identifier[a]	**Screening**[ff]	**Day 1**[hh]	**Day 2**	**Day 4**	**Day 8**	**Day 15**	**Day 29**	**Week 6/ Day 43**	**Week 8/ Day 57**	**Week 12/Day 85**	**Week 16 /Day 113**	**Post-week 16 (every 4 weeks until 52 weeks)**[b]	**Post-week 52 (every 12 weeks)**	**End of study visit**[c]
Visit window	-45 to -1	None		±1 day		±3 days				±7 days			±14 days	
Visit window (days)	-45 to -1	1	2	3-5	7-9	12-18	26-32	40-46	54-60	78-92	106-120	N/A	N/A	N/A
		Pre-dose	Post-dose[d]											
For subjects with RA[gg]														
ACR/EULAR Criteria	X													
Patient's Global Assessment of Arthritis	X	X							X		X		X	
For subjects with SLE[gg]														
SLICC Criteria	X													
CCI	[redacted]	[redacted]							[redacted]		[redacted]		[redacted]	
Laboratory Assessments														
Safety laboratory[n]	X	X	X	X	X	X	X	X	X	X	X	X	X	
FSH[o]	X													
Serum pregnancy[p]	X	X				X					X			
Urine pregnancy[p]		X			X		X	X	X	X		X	X	
IGRA TB	X										X			
HIV and Hepatitis B & C[q]	X													
Viral Surveillance[r]		X							X		X	X[l]		
JCV		X									X	X[l]		
Serum Ig[s]	X	X					X		X	X	X	X[l]	X	
[redacted] CCI		[redacted]	[redacted]											
Pharmacokinetics														
PK serum[u]		X	X	X	X	X	X	X	X	X	X			
Immunogenicity serum[v]		X				X	X	X	X	X	X	X		
Laboratory Biomarker Assessments														
For all subjects														
[redacted] CCI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]		[redacted]					[redacted]		[redacted]	[redacted]				
[redacted]		[redacted]					[redacted]			[redacted]				
[redacted]	[redacted]	[redacted]				[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]		

Protocol activity	Outpatient	Inpatient		Outpatient										
Visit Identifier[a]	**Screening**[ff]	**Day 1**[hh]	**Day 2**	**Day 4**	**Day 8**	**Day 15**	**Day 29**	**Week 6/ Day 43**	**Week 8/ Day 57**	**Week 12/Day 85**	**Week 16 /Day 113**	**Post-week 16 (every 4 weeks until 52 weeks)**[b]	**Post-week 52 (every 12 weeks)**	**End of study visit**[c]
Visit window	-45 to -1	None		±1 day		±3 days				±7 days			±14 days	
Visit window (days)	-45 to -1	1	2	3-5	7-9	12-18	26-32	40-46	54-60	78-92	106-120	N/A	N/A	N/A
		Pre-dose	Post-dose[d]											
ESR		X				X	X		X	X	X	X		
BAFF		X				X	X		X	X	X	X[ll]		
[redacted]												CCI		
[redacted]														
[redacted]														
[redacted]														
[redacted]														
[redacted]														
For subjects with SLE[gg]														
Anti-nuclear antibodies	X	X									X			
[redacted]														
[redacted]														
[redacted]														
[redacted]														
CCI [redacted]														
[redacted]														
[redacted]														
[redacted]														
[redacted]														
[redacted]														
Investigational and Non-Investigational Product administration														
Pre-treatment[z]		X												
Administration of PF-06835375 or placebo[aa]		X												
[redacted] CCI														
[redacted]														

Protocol activity	Outpatient	Inpatient		Outpatient										
Visit Identifier[a]	**Screening**[ff]	**Day 1**[hh]	**Day 2**	**Day 4**	**Day 8**	**Day 15**	**Day 29**	**Week 6/ Day 43**	**Week 8/ Day 57**	**Week 12/Day 85**	**Week 16 /Day 113**	**Post-week 16 (every 4 weeks until 52 weeks)**[b]	**Post-week 52 (every 12 weeks)**	**End of study visit**[c]
Visit window	-45 to -1	None		±1 day		±3 days				±7 days			±14 days	
Visit window (days)	-45 to -1	1	2	3-5	7-9	12-18	26-32	40-46	54-60	78-92	106-120	N/A	N/A	N/A
		Pre-dose	Post-dose[d]											
Monitoring														
Contraception check	X	→	X	→	→	→	→	→	→	→	→	→	→	X
Serious and non-serious adverse event monitoring	X	→	→	→	→	→	→	→	→	→	→	→	→	X
Concomitant treatment(s)		X	→	→	→	→	→	→	→	→	→	→	→	X
TB monitoring[cc]		X	X	→	→	→	→	→	→	→	→	→	→	X
Infections monitoring[dd]	X	X	→	→	→	→	→	→	→	→	→	→	→	X
Infusion Site Reactions[ee]		X	→	→	X									

Abbreviations: →= ongoing/continuous event; ACR/EULAR = American College of Rheumatology/European League Against Rheumatism; CCI [redacted] BAFF = B-cell activating factor; CCI [redacted] C-SSRS = Columbia-Suicide Severity Rating Scale; CRU = clinical research unit; ECG = electrocardiogram; ESR = erythrocyte sedimentation rate; FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; CCI [redacted] Ig = Immunoglobulin; IGRA = Interferon gamma release assay; JCV = JC virus; PK = Pharmacokinetic; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus; CCI [redacted] SLICC= Systemic Lupus International Collaborating Clinics; TB = tuberculosis.

a. Day relative to start of study treatment (Day 1).
b. Subjects, who do not meet the criteria to leave the study at Week 16, will continue with clinic visits every four weeks until Week 52 and then every 12 weeks until they meet these criteria.
c. B cell counts data will be available only after subject completes the clinic visit due to the required shipment of samples to central lab and their processing time. Once subject meets the criterion, a phone visit will take place within approximately 1-2 weeks. This phone visit will be considered the end of study visit/last visit. Subjects may be requested to return for additional follow up visits, and additional safety assessments may be performed beyond the end of study visit for safety reasons as determined by the Investigator in consultation with the sponsor medical monitor.
d. Specific times for post-dose assessments are noted in the Post-dose Day 1 & Post-dose Day 29 Schedule of Activities below.
e. Prior to admission, review changes in the subject's medical history, concomitant medications and medical procedures since the Screening visit, perform contraception check and confirm that there are no changes to subject's eligibility. If a subject has any clinically significant, study related abnormalities at the conclusion of a scheduled inpatient portion of the study, it is at the investigator's discretion to ask the subject to remain in the clinical unit until it is safe for outpatient follow up. The investigator must promptly notify the sponsor clinician or medical monitor. If the subject is unable or unwilling to remain in the clinical unit, the investigator should make every effort to arrange follow up evaluations at appropriate intervals. All Day 2 assessments should be completed prior to discharge from the research unit.
f. A full physical exam will be performed at Screening, Day 1 pre-dose and Week 16, and as needed at the discretion of the investigator. A limited physical exam will be conducted at all other times.
g. Includes pulse rate, sitting blood pressure and temperature.

h. ECGs will be collected in triplicate on Day 1 and Day 2. Single ECGs will be collected at all other times.
i. Height will be measured only at Screening. Height and Weight will be measured without shoes.
j. Assessment to be performed starting at Week 28 and every 12 weeks thereafter until Week 52.
k. Subjects who had chest X-ray performed within 3 months prior to the Screening visit do not require chest X-ray, provided documentation is available.
l. C-SSRS Lifetime will be performed at Screening. All subsequent assessments will be Since Last Visit.
CCI [redacted]
n. Includes hematology, chemistry and urinalysis. Fasting is not required.
o. Serum FSH will be performed to confirm postmenopausal status for females who have been amenorrheic for at least 12 consecutive months. If post-menopausal for ≥5 years, it is at the investigator's discretion whether to confirm post-menopausal status by FSH.
p. Serum pregnancy test will be conducted at a central lab. Urine pregnancy test will be conducted locally. For female subjects of childbearing potential, 2 negative pregnancy tests are required prior to receiving IP on Day 1 (1 negative serum pregnancy test at Screening and 1 negative urine pregnancy test on Day 1). Results of serum pregnancy test on Day 1 are not required prior to dosing.
q. Includes hepatitis B surface antigen (HepBsAg), hepatitis B core antibody (HepBcAb) and hepatitis C antibody (HCVAb). Only subjects who are positive for HCV Ab will be reflex-tested for hepatitis C virus ribonucleic acid (HCV RNA).
r. Includes testing for cytomegalovirus (CMV), Epstein Barr virus (EBV), herpes simplex virus type 1 (HSV-1), herpes simplex virus type 2 (HSV-2) and varicella zoster virus (VZV). Additional samples for viral surveillance sample may be taken at the time of an adverse event, as clinically appropriate.
s. Includes total Ig, IgA, IgG, IgE and IgM.
C [redacted]
C
u. At dosing visits, PK samples will be collected preferably after vital signs and ECG, and within approximately 1 hour prior to dosing and at the end of infusion. If end of infusion is within 10 minutes of a scheduled PK sample, then only the scheduled sample will be collected.
v. Includes anti-drug antibodies (ADA) and neutralizing antibodies (NAb). During dosing visits, samples to assess ADA and NAb will be collected prior to investigational drug administration.
C [redacted]
C
I
C
C
z. Approximately 1 hour prior to the administration of IP, each subject will be pre-treated with 1000 mg of oral acetaminophen, and an oral antihistamine (eg, 25 mg of oral diphenhydramine).
aa. The total infusion time will be 120 minutes ±10 minutes, unless a different time is needed to manage symptoms typical of infusion reactions. In such a case, the entire duration of study drug infusion should not exceed approximately 4 hours unless a different time is communicated to the site by the sponsor.
CCI [redacted]
cc. Please see Section 7.1.10 for details.
dd. Please see Section 7.1.11 for details.
ee. Subjects will be continuously monitored for infusion site reactions from the start of drug administration until the end of infusion and then at time points indicated in the Schedule of Activities. Infusion site reactions may be monitored beyond the time points indicated in the Schedule of Activities based on investigator's assessment.
ff. Screening assessments may be repeated, provided this was approved by the sponsor clinician or medical monitor. Please see Section 6.1 for exceptions and details on potential re-screening. Sites must obtain an approval from sponsor study clinician to proceed with screening of each subject.
gg. SLE subjects must meet SLICC criteria described in Appendix 5, RA subjects must meet 2010 ACR/EULAR criteria described in Appendix 6. If subject meets criteria for both RA and SLE (note: this is relatively rare), then both SLE and RA assessments should be performed.
hh. In order to ensure sentinel dosing is implemented, sites need to obtain written approval from the sponsor clinician to proceed with dosing of each subject in this study.

Part B (Multiple Ascending Dose)

Protocol activity	Outpatient	Inpatient					Outpatient											
Visit Identifier[a]	**Screening**[gg]	**Day 1**[ii]		**Day 2**	**Day 4**	**Day 8**	**Day 15**	**Day 29**[b]		**Day 30**[c]	**Day 36**	**Week 6/ Day 43**	**Week 8/ Day 57**	**Week 12/ Day 85**	**Week 16/ Day 113**	**Post-Week 16 (every 4 weeks)**[d]	**Post-Week 52 (every 12 weeks)**	**End of study visit**[e]
Visit window	-45 to -1	None			±1 day		±3 days							±7 days			±14 days	
Visit window (days)	-45 to -1	1		2	3-5	7-9	12-18	26-32		27-33	33-39	40-46	54-60	78-92	106-120	N/A	N/A	N/A
		Pre-dose	Post-dose[f]					Pre-dose	Post-dose[f]									
Enrollment Procedures																		
Informed consent	X																	
Inclusion/exclusion criteria	X	X																
Medical history	X																	
Medication history	X																	
Demography	X																	
CRU confinement[b]		X	X	X														
Medical Procedures																		
For all subjects																		
Physical examination[g]	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	
Vital signs[h]	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	
ECG[i]	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	
Weight and height[j]	X	X													X	X[k]		
Chest X-ray[l]	X																	
C-SSRS[m]	X	X						X							X			
[redacted] CCI [redacted]	[redacted]	[redacted]											[redacted]		[redacted]		[redacted]	
For subjects with RA[hh]																		
ACR/EULAR Criteria	X																	
Patient's Global Assessment of Arthritis	X	X											X		X		X	
For subjects with SLE[hh]																		
SLICC Criteria	X																	
CCI [redacted]	[redacted]	[redacted]											[redacted]		[redacted]		[redacted]	
Laboratory Assessments																		
Safety laboratory[o]	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	
FSH[p]	X																	

Protocol activity	Outpatient	Inpatient					Outpatient											
Visit Identifier[a]	**Screening**[gg]	**Day 1**[ii]		**Day 2**	**Day 4**	**Day 8**	**Day 15**	**Day 29**[b]		**Day 30**[c]	**Day 36**	**Week 6/ Day 43**	**Week 8/ Day 57**	**Week 12/ Day 85**	**Week 16/ Day 113**	**Post-Week 16 (every 4 weeks)**[d]	**Post-Week 52 (every 12 weeks)**	**End of study visit**[e]
Visit window	-45 to -1	None			±1 day		±3 days							±7 days			±14 days	
Visit window (days)	-45 to -1	1		2	3-5	7-9	12-18	26-32		27-33	33-39	40-46	54-60	78-92	106-120	N/A	N/A	N/A
		Pre-dose	Post-dose[f]					Pre-dose	Post-dose[f]									
Serum pregnancy[q]	X	X					X								X			
Urine pregnancy[q]		X				X		X			X	X	X	X		X	X	
IGRA TB test	X														X			
HIV and Hepatitis B & C[r]	X																	
Viral Surveillance[s]		X											X		X	X[k]		
JCV		X													X	X[k]		
Serum Ig[t]	X	X						X					X	X	X	X[k]	X	
[redacted] CCI																		
Pharmacokinetics																		
PK serum[v]		X	X	X	X	X	X	X	X		X	X	X	X	X			
Immunogenicity serum[w]		X					X	X				X	X	X	X	X		
Laboratory Biomarker Assessments																		
For all subjects																		
[redacted] CCI																		
ESR		X					X	X					X	X	X	X		
BAFF		X					X	X					X	X	X	X[k]		
[redacted] CCI																		
For subjects with SLE[hh]																		
Anti-nuclear antibodies	X	X													X			

Protocol activity	Outpatient	Inpatient					Outpatient											
Visit Identifier[a]	**Screening**[gg]	**Day 1**[ii]		**Day 2**	**Day 4**	**Day 8**	**Day 15**	**Day 29**[b]		**Day 30**[c]	**Day 36**	**Week 6/ Day 43**	**Week 8/ Day 57**	**Week 12/ Day 85**	**Week 16/ Day 113**	**Post-Week 16 (every 4 weeks)**[d]	**Post-Week 52 (every 12 weeks)**	**End of study visit**[e]
Visit window	-45 to -1	None			±1 day		±3 days							±7 days			±14 days	
Visit window (days)	-45 to -1	1		2	3-5	7-9	12-18	26-32		27-33	33-39	40-46	54-60	78-92	106-120	N/A	N/A	N/A
		Pre-dose	Post-dose[f]					Pre-dose	Post-dose[f]									
[redacted] CCI																		
Anti-phospholipid antibodies		X													X			
Banked Biospecimens																		
[redacted] CCI																		
Investigational and Non-Investigational Product administration																		
Pre-treatment[aa]		X						X										
Administration of PF-06835375 or placebo[bb]		X						X										
[redacted] CCI																		
Monitoring																		
Contraception check	X	X		X	→	→	→	X		X	→	→	→	→	→	→	→	X
Serious and non-serious adverse event monitoring	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X
Concomitant treatment(s)		X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X
TB monitoring[dd]		X		X	→	→	→	X		X	→	→	→	→	→	→	→	X
Infections monitoring[ee]	X	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X
Infusion/Injection Site Reactions[ff]			X	→	→	X			X	→	X							

Abbreviations: →= ongoing/continuous event; ACR/EULAR = American College of Rheumatology/European League Against Rheumatism; CCI [redacted] BAFF = B-cell activating factor; CCI [redacted] C-SSRS = Columbia-Suicide Severity Rating Scale; CRU = clinical research unit; ECG = electrocardiogram; ESR = erythrocyte sedimentation rate; FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; CCI [redacted] Ig = Immunoglobulin; IGRA = Interferon gamma release assay; JCV = JC virus; PK = Pharmacokinetic; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus; CCI [redacted] SLICC= Systemic Lupus International Collaborating Clinics; TB = tuberculosis.

a. Day relative to start of study treatment (Day 1).
b. Prior to admission to the research unit, review changes in the subject's medical history, concomitant medications and medical procedures since the Screening visit, perform contraception check and confirm that there are no changes to subject's eligibility. If a subject has any clinically significant, study related abnormalities at the conclusion of a scheduled inpatient portion of the study on Day 2 or at the end of the outpatient visit on Day 29, it is at the investigator's discretion to ask the subject to remain in the clinical unit until it is safe for outpatient follow up. The investigator must promptly notify the sponsor clinician or medical monitor. If the subject is unable or unwilling to remain in the clinical unit, the investigator should make every effort to arrange follow up evaluations at appropriate intervals. All Day 2 assessments should be completed prior to discharge from the research unit.
c. Day 30 phone visit to occur one day after administration of IP on Day 29. It is at investigator's discretion to conduct an in clinic visit instead of a phone visit.
d. Subjects, who do not meet the criteria to leave the study at Week 16, will continue with clinic visits every four weeks until Week 52 and then every 12 weeks until they meet these criteria. Post-week 16, some assessments will be conducted only every 12 weeks indicated with a footnote below.
e. B cell counts data will be available only after subject completes the clinic visit due to the required shipment of samples to central lab and their processing time. Once subject meets the criterion above, a phone visit will take place within approximately 1-2 weeks. This phone visit will be considered the end of study visit/last visit. Subjects may be asked to return for additional follow up visits beyond the anticipated end of study visit for safety reasons as determined by the Investigator in consultation with the sponsor medical monitor.
f. Specific times for post-dose assessments are noted in the Post-dose Day 1 & Post-dose Day 29 Schedule of Activities below.
g. A full physical exam will be performed at Screening, Day 1 pre-dose and Week 16, and as needed at the discretion of the investigator. A limited physical exam will be conducted at all other times.
h. Includes pulse rate, sitting blood pressure and temperature.
i. ECGs will be collected in triplicate on Day 1, Day 2 and Day 29. Single ECGs will be collected at all other times.
j. Height will only be measured at Screening. Height and Weight will be measured without shoes.
k. Assessment to be performed starting at Week 28 and every 12 weeks thereafter until Week 52.
l. Subjects who had chest X-ray performed within 3 months prior to the Screening visit do not require chest X-ray, provided documentation is available.
m. C-SSRS Lifetime will be performed at Screening. All subsequent assessments will be Since Last Visit.
C [redacted]
o. Includes hematology, chemistry and urinalysis. Fasting is not required.
p. Serum FSH will be performed to confirm postmenopausal status for females who have been amenorrheic for at least 12 consecutive months. If post-menopausal for ≥5 years, it is at the investigator's discretion whether to confirm post-menopausal status by FSH.
q. Serum pregnancy test will be conducted at a central lab. Urine pregnancy test will be conducted locally. For female subjects of childbearing potential, 2 negative pregnancy tests are required prior to receiving investigational product on Day 1 (1 negative serum pregnancy test at Screening and 1 negative urine pregnancy test on Day 1). Results of serum pregnancy test on Day 1 are not required prior to dosing.
r. Includes hepatitis B surface antigen (HepBsAg), hepatitis B core antibody (HepBcAb) and hepatitis C antibody (HCVAb). Only subjects who are positive for HCV Ab will be reflex-tested for hepatitis C virus ribonucleic acid (HCV RNA).
s. Includes testing for cytomegalovirus (CMV), Epstein Barr virus (EBV), herpes simplex virus type 1(HSV-1), herpes simplex virus type 2 (HSV-2) and varicella zoster virus (VZV). Additional samples for viral surveillance sample may be taken at the time of an adverse event, as clinically appropriate.
t. Includes total Ig, IgA, IgG, IgE and IgM.

CC [redacted]

v. At dosing visits, PK samples will be collected preferably after vital signs and ECG, and within approximately 1 hour prior to dosing and at the end of infusion. The sample at the end of infusion pertains only to IV cohorts and does not pertain to subcutaneous (SC) cohorts. If end of infusion is within 10 minutes of scheduled PK sample, then only the scheduled sample will be collected.

w. Includes anti-drug antibodies (ADA) and neutralizing antibodies (NAb). During dosing visits, samples to assess ADA and NAb will be collected prior to investigational drug administration.

CC [redacted]

aa. Approximately 1 hour prior to the administration of IV or SC doses of IP, each subject will be pre-treated with 1000 mg of oral acetaminophen, and an oral antihistamine (eg, 25 mg of oral diphenhydramine).

bb. The total infusion time will be 120 minutes ±10 minutes, unless a different time is needed to manage symptoms typical of infusion reactions. In such a case, the entire duration of study drug infusion should not exceed approximately 4 hours unless a different time is communicated to the site by the sponsor.

CCI [redacted]

dd. Please see Section 7.1.10 for details.

ee. Please see Section 7.1.11 for details.

ff. For SC administration, subjects will be monitored continuously for injection site reactions for 30 minutes following study drug administration and then at time points indicated in the Schedule of Activities. For IV administration, subjects will be continuously monitored for infusion site reactions from start of drug administration until the end of infusion and then at time points indicated in Schedule of Activities. Infusion/injection site reactions may be monitored beyond the time points indicated in the Schedule of Activities based on investigator's assessment.

gg. Screening assessments may be repeated provided this was approved by the sponsor clinician or medical monitor. Please see Section 6.1 for exceptions and details on potential re-screening. Sites must obtain an approval from sponsor study clinician to proceed with screening of each subject.

hh. SLE subjects must meet SLICC criteria described in Appendix 5, RA subjects must meet 2010 ACR/EULAR criteria described in Appendix 6. If subject meets criteria for both RA and SLE (note: this is relatively rare), then both SLE and RA assessments should be performed.

ii. In order to ensure sentinel dosing is implemented, sites need to obtain written approval from the sponsor clinician to proceed with dosing of each subject in this study.

Post-dose Day 1 (Parts A & B) & Post-dose Day 29 (Part B)[a]

Visit Identifier	Day 1/Day 29[k]																	
Study Hour	-2 to 0	0	0.25	0.5	0.75	1	1.5	2	2.5	3	3.5	4	4.5	5	5.5	6	8	12[b]
Medical procedures																		
Physical examination	X[c]															X[d]		
Vital signs	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG[e]	X							X				X				X	X	X
Laboratory assessments																		
Safety laboratory[f]	X																X	
Pharmacokinetics																		
PK serum[g]	X							X				X				X	X	X
CCI																		
[redacted]	[redacted]											[redacted]					[redacted]	
[redacted]	[redacted]											[redacted]					[redacted]	
[redacted]	[redacted]			[redacted]				[redacted]								[redacted]		
Investigational product administration																		
Beginning of infusion or injection of PF-06835375 or placebo		X																
Monitoring																		
Serious and non-serious adverse event monitoring	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X
Concomitant treatment(s)	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X
Infusion and Injection Site Reactions[l]		X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X

Abbreviations: →= ongoing/continuous event; ECG = electrocardiogram; PK = Pharmacokinetic.

a. Only assessments with post-dose time points are included in this table. For these assessments, pre-dose time points are also included, as applicable. For a complete list of pre-dose assessments, please refer to the Schedule of Activities for Parts A and B above.

b. Applies only to Day 1. Scheduled assessments on Day 29 will finish 8 hours post-dose.

c. Full physical exam will be conducted on Day 1 pre-dose. A limited physical exam will be conducted on Day 29 pre-dose.

d. A limited physical exam will be conducted 6 hours post-dose on both dosing days: Day 1 and Day 29. If any new adverse reactions are observed after injection/infusion on these dosing days and these AEs have not resolved by 6 hours post-dose or if any safety concerns, a limited physical exam will be conducted at 12-hours post-dose on Day 1 and at 8 hours post-dose on Day 29 instead.

e. ECGs will be collected in triplicate in Part A on Days 1, in Part B on Days 1 and 29.

f. Includes hematology, chemistry and urinalysis. Fasting is not required.

g. PK samples will be collected preferably after vital signs and ECG. A pre-dose PK sample will collected within approximately 1 hour prior to dosing. A PK sample will be collected at the end of infusion (this sample at the end of infusion pertains only to IV cohorts and does not pertain to SC cohorts). If the end of infusion is within 10 minutes of scheduled PK sample, then only the scheduled sample will be collected. If infusion duration is greater than 2 h and 10 min, then the scheduled 2 hour post-dose PK sample will not be collected.

[redacted]

j. For SC administration, subjects will be monitored continuously for injection site reactions for 30 minutes following study drug administration and then at least at 0.5, 1, 2, 3, 4, 6, 8 hours post-dose. For IV administration, subjects will be continuously monitored for infusion site reactions from start of drug administration until the end of infusion and then at least every 30 min post-dose until end of Day 1/Day 29. Infusion/injection site reactions may be monitored beyond the time points indicated in the Schedule of Activities based on investigator's assessment.

k. All efforts should be made to perform the assessments (including blood sample collection) at the exact nominal time relative to dosing. However, assessments (including obtained blood samples) performed within 10% of the nominal time (eg, within 6 minutes of a 60 minute sample) from dosing will not be captured as a protocol deviation. The exact time of the sample collection must be noted on the source document and data collection tool (CRF).

PROTOCOL SUMMARY

Background and Rationale

PF-06835375 is a humanized, afucosyl immunoglobulin (Ig) G1 antibody against C-X-C chemokine receptor type 5 (CXCR5), a surface receptor that is expressed on B cells, bona *fide* follicular T helper (Tfh) cells, and circulating follicular T helper-like (cTfh) cells.[a]

PF-06835375 is currently in development for the treatment of systemic lupus erythematosus (SLE). However, there is potential utility for targeting CXCR5 for the treatment of systemic autoimmune diseases more broadly. Therefore, other diseases, such as rheumatoid arthritis (RA), remain under consideration given their shared underlying pathophysiology of aberrant humoral immune responses involving B cells and Tfh cells.

CXCR5 is expressed by B cells, bona fide Tfh cells, and cTfh cells and, mediates their trafficking to and participation in germinal center (GC) immune responses.[1] GCs, a critical component of the humoral immune response, are sites where antigen-activated B cells undergo somatic hypermutation and immunoglobulin (Ig) class switching of the antibodies they produce. Bona fide Tfh cells provide instructive signals to aid this process, which culminates in the production of affinity-matured antibodies. Humoral "memory" of the GC immune response is maintained by long-lived plasma cells, which sustain antibody levels, and by memory B cells, which, upon re-challenge with antigen, trigger secondary GC immune responses with cognate help from memory Tfh cells that lead to the production of more high-affinity plasma cells.[2] cTfh cells are thought to differentiate into bona fide Tfh cells upon re-encountering antigen to support these memory responses, as well.[3]

PF-06835375 is a selective antibody directed against the CXCR5 receptor that has two distinct mechanisms of action: (1) depletion of CXCR5-positive cells through antibody-dependent cellular cytotoxicity (ADCC), and (2) antagonism of C-X-C Motif Chemokine Ligand 13 (CXCL13)-dependent signaling. By utilizing an antibody that is also antagonistic, cells that escape killing may still be inhibited from trafficking to and participating in GC immune responses. As such, the working hypothesis is that by targeting CXCR5 through a combination of depletion and antagonism, PF-06835375 will effectively impair autoreactive GC reactions, including humoral memory responses, thereby suppressing autoantibody maturation and production known to, in part, underlie autoimmune disease pathology.

The goal of this first in human (FIH) study is to evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of PF-06835375. In particular, PD characterization will include assessment of magnitude and duration of CXCR5-positive cell

[a] Bona fide Tfh cells are located within lymphoid organs (ie, spleen, lymph nodes, tonsils, Peyer's patches, and mucosa-associated lymphoid tissue). cTfh cells are located in the peripheral blood.

depletion and recovery. Inhibition of the humoral immune responses via PF-06835375-mediated depletion of CXCR5-positive cells offers the potential for clinical evaluation in a population of seropositive autoimmune subjects. Consequently, a mixed population of seropositive SLE or RA subjects will be enrolled into this study.

Objectives and Endpoints

Primary Objective:	**Primary Endpoints:**
• To evaluate the safety and tolerability of single and multiple ascending intravenous (IV) and subcutaneous (SC) doses of PF-06835375 in subjects with SLE and RA.	• Incidence of dose limiting or treatment related adverse events (AEs). • Incidence, severity and causal relationship of treatment emergent AEs (TEAEs) and withdrawals due to TEAE. • Incidence of abnormal chemistry, hematology, and urinalysis laboratory findings through the end of study. • Abnormal and clinically relevant changes in vital signs and electrocardiogram (ECG) parameters. • Incidence of infections.
Secondary Objectives:	**Secondary Endpoints:**
• To evaluate the effect of PF-06835375 on depletion of circulating CXCR5 positive B cells and cTfh cells over time in subjects with SLE and RA.	• Change from baseline in the number of circulating CXCR5 positive B cells and cTfh cells on Day 29 single dose of PF-06835375 and at Week 8 following multiple doses of PF-06835375.

• To characterize pharmacokinetics (PK) profile of PF-06835375 in subjects with SLE and RA.	• Serum PF-06835375 PK parameters after single and multiple doses:
	  • Single Ascending Dose Phase: C_{max}, T_{max}, AUC_{inf}, AUC_{last}.
	  • Multiple Ascending Dose Phase:
	  • First Dose: C_{max}, T_{max}, AUC_{tau}.
	  • Multiple Dose: C_{max}, T_{max}, AUC_{last}, AUC_{tau}, C_{min} and observed accumulation ratio (R_{ac}), peak-to-trough ratio (PTR).

• To evaluate immunogenicity of PF-06835375 in subjects with SLE and RA.	• Incidence of development of anti-drug antibodies (ADAs)/neutralizing antibodies (NAbs).
CCI [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Study Design

This is a Phase 1, randomized, multi-center, double-blind, sponsor open, placebo-controlled, single and multiple dose-escalation study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of PF-06835375 in subjects with seropositive SLE or RA. Both intravenous (IV) and subcutaneous (SC) routes of administration will be tested.

This study will include two parts: Part A, consisting of approximately eight single ascending dose (SAD) cohorts, and Part B, consisting of approximately 6 multiple ascending dose (MAD) cohorts. Cohorts in Part A will be initiated sequentially. Subjects in Part B will receive two doses of investigational product, first dose on Day 1 and second dose on Day 29, and will be enrolled concurrently with Part A following the completion of the initial cohorts in Part A (See Section 3.3). Subjects who are randomized in Part A will not be eligible to participate in Part B of this study.

This study will enroll up to a total of approximately 112 subjects at approximately 10 sites. Individual subjects are expected to stay in the study approximately 6-12 months (including screening), contingent on meeting criteria described for the end of study (See Section 3.5). Subjects who withdraw from the study may be replaced at the discretion of the sponsor. A replacement subject will receive the same treatment as the withdrawn subject.

Both SLE and RA subjects will be enrolled into this study. Minimum disease activity (ie, Systemic Lupus Erythematosus Disease Activity Index 2000, CCI , or Disease Activity Score 28, DAS28) cutoffs is not required for entry as inclusion criteria. All subjects

in both Part A and B will be followed for a minimum of 16 weeks prior to being able to qualify for study completion based on the cellular recovery (See Section 3.5).

It is at the sponsor's discretion to dose escalate (See Section 3.4.1), to repeat the same dose, or to test a lower dose based on emerging data.

Throughout the study, B cell counts obtained from CLIA (Clinical Laboratory Improvement Amendments) certified central lab will be used for clinical decision making (inclusion/exclusion criteria, dose escalation, initiation of Part B and for the end of study criteria).

Study Treatments

For this study, the investigational product is PF-06835375 or placebo.

PF-06835375 50 mg/mL injection is presented as a sterile solution for subcutaneous (SC) and intravenous (IV) administration.

Placebo for PF-06835375 injection is presented as a sterile solution for SC and IV administration.

In addition, Pfizer Global Clinical Supply (GCS), Worldwide Research and Development (WRD) will provide CCI vaccine. CCI will be purchased from commercial sources and will be packaged and presented with appropriate labels.

CCI

All study treatments will be administered at the investigational site as detailed in the investigational product (IP) Manual.

Statistical Methods

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

The final analysis will be conducted when all subjects have completed all study visits. In addition, unblinded data will be analyzed when all subjects have completed Week 16 visit or discontinued. This analysis may take place prior to the enrollment of the optional cohort.

Adverse events, Electrocardiograms (ECGs), blood pressure, pulse rate, oral temperature, continuous cardiac monitoring, and safety laboratory data will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of subjects. Any clinical laboratory, ECG, vital sign abnormalities of potential clinical concern will be described. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

The PK concentration population is defined as enrolled subjects who received at least one dose of PF-06835375 and have at least 1 concentration. The PK parameter analysis population is defined as all enrolled subjects who received at least one dose of PF-06835375 and that have at least 1 of the PK parameters of interest. Samples from subjects who received the placebo will not be analyzed routinely.

The pharmacodynamic (PD) analysis population is defined as all randomized subjects treated who have at least one PD assessment in at least one cohort. PD assessments will include but not limited to CCI data, soluble protein analytes, whole-blood ribonucleic acid (RNA) (inflammation and disease-related) and responses to vaccines. The data will be summarized and plotted by treatment group and sampling time.

CCI

1. INTRODUCTION

1.1. Mechanism of Action/Indication

PF-06835375 is a humanized, afucosyl immunoglobulin (Ig) G1 antibody against C-X-C chemokine receptor type 5 (CXCR5), a surface receptor that is expressed on B cells, *bona fide* follicular T helper (Tfh) cells, and circulating follicular T helper-like (cTfh) cells.[a]

1.1.1. Indication

PF-06835375 is currently in development for the treatment of systemic lupus erythematosus (SLE). However, there is potential utility for targeting CXCR5 for the treatment of systemic autoimmune diseases more broadly. Therefore, other diseases, such as rheumatoid arthritis (RA), remain under consideration given their shared underlying pathophysiology of aberrant humoral immune responses involving B cells and Tfh cells.

1.2. Background

1.2.1. Drug Development Rationale

CXCR5 is expressed by B cells, bona fide Tfh cells, and cTfh cells and, mediates their trafficking to and participation in germinal center (GC) immune responses.[1] GCs, a critical component of the humoral immune response, are sites where antigen-activated B cells undergo somatic hypermutation and immunoglobulin (Ig) class switching of the antibodies they produce. Bona fide Tfh cells provide instructive signals to aid this process, which culminates in the production of affinity-matured antibodies. Humoral "memory" of the GC immune response is maintained by long-lived plasma cells, which sustain antibody levels, and by memory B cells, which, upon re-challenge with antigen, trigger secondary GC immune responses with cognate help from memory Tfh cells that lead to the production of more high-affinity plasma cells.[2] cTfh cells are thought to differentiate into bona fide Tfh cells upon re-encountering antigen to support these memory responses, as well.[3]

Importantly, the generation of autoreactive B cells responding to self-antigen can arise from GC reactions, with undesired consequences. Indeed, numerous chronic, systemic autoimmune diseases, such as SLE, RA, myositis, Sjögren's syndrome, anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis and scleroderma, show evidence of autoreactive humoral responses. In addition, increased frequencies of cTfh cells have been detected in the peripheral blood of patients with many of these autoimmune diseases compared to healthy controls, including both SLE and RA, the levels of which often correlate with autoantibody titers and/or disease severity.[4,5] Taken together, these data highlight CXCR5-positive cells (ie, B cells, Tfh cells, and cTfh cells) as potential therapeutic targets for multiple systemic autoimmune diseases.

[a] Bona fide Tfh cells are located within lymphoid organs (ie, spleen, lymph nodes, tonsils, Peyer's patches, and mucosa-associated lymphoid tissue). cTfh cells are located in the peripheral blood.

PF-06835375 is a selective antibody directed against the CXCR5 receptor that has two distinct mechanisms of action: (1) depletion of CXCR5-positive cells through antibody-dependent cellular cytotoxicity (ADCC), and (2) antagonism of CXCL13-dependent signaling. By utilizing an antibody that is also antagonistic, cells that escape killing may still be inhibited from trafficking to and participating in GC immune responses. As such, the working hypothesis is that by targeting CXCR5 through a combination of depletion and antagonism, PF-06835375 will effectively impair autoreactive GC reactions, including humoral memory responses, thereby suppressing autoantibody maturation and production known to, in part, underlie autoimmune disease pathology.

The goal of this first in human (FIH) study is to evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of PF-06835375. In particular, PD characterization will include assessment of magnitude and duration of CXCR5-positive cell depletion and recovery. Inhibition of the humoral immune responses via PF-06835375-mediated depletion of CXCR5-positive cells offers the potential for clinical evaluation in a population of seropositive autoimmune subjects. Consequently, a mixed population of seropositive SLE or RA subjects will be enrolled into this study.

1.2.2. Systemic Lupus Erythematosus

Systemic Lupus Erythematosus (SLE) is a chronic systemic autoimmune disease that can affect virtually any organ, including the skin, joints, kidneys, lungs and central or peripheral nervous system. Immunologic abnormalities, especially the loss of tolerance and production of anti-nuclear antibodies (ANA), are a prominent feature of SLE.[6] 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. SLE is more prevalent in certain racial and ethnic groups, such as African-Americans, Asians, and Hispanics. The prevalence of SLE ranges from approximately 40 cases per 100,000 persons among Northern Europeans to more than 200 per 100,000 persons among African-Americans.[7]

Available therapies for SLE offer limited clinical benefit, rarely induce lasting remissions, and are associated with significant side effects (eg, cytopenias, increased infection and malignancy risk, hemorrhagic cystitis, and bone marrow suppression). Furthermore, although a central role for B and/or T cells in SLE pathogenesis has long been recognized, existing biologics targeting either B cells (eg, rituximab [Rituxan®], belimumab [Benlysta®]) or T cells alone (eg, abatacept [Orencia®]) have demonstrated modest or minimal clinical benefit. Belimumab is approved for the treatment of autoantibody-positive active SLE.[8] These targeted modalities have not been shown to be effective at reducing autoreactive memory, possibly due to limited effects on GC reactions, and, consequently have limited effect on SLE disease flares. There remains a major unmet need for safer and/or more effective therapies that can induce a long-lasting remission in SLE.

1.2.3. Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a progressive, systemic autoimmune disease characterized by synovitis that damages diarthroidal joints and is accompanied by fatigue, anemia, and bone loss. Rheumatoid arthritis has a prevalence of 0.5% to 1.0% and a peak incidence between 40 and 60 years of age and affects primarily women.[9,10] Most RA patients show seropositivity for RA-associated autoantibodies, such as anti-citrullinated peptide antibodies (ACPA) or rheumatoid factor (RF), which may contribute to the chronic inflammation of the synovium and subsequent joint damage that are hallmarks of RA disease pathology.[11] In addition, approximately 30% of RA patients show formation of ectopic lymphoid organs in inflamed synovia, which appears to correlate with enhanced autoantibody production and disease severity.[12]

There are multiple approved therapeutic options for managing the pain and slowing the progression of RA, but none are curative. Disease-modifying antirheumatic drugs (DMARDs) are the standard treatments for RA; conventional synthetic DMARDs (csDMARDs), such as methotrexate, are used either alone or in combination with newer biologic DMARDs. Use of biologic DMARDs, most commonly tumor necrosis factor-α (TNFα) inhibitors, is indicated when symptoms are not adequately controlled with csDMARDs. Despite the numerous treatments for RA, there remain significant numbers of patients who do not achieve remission or indeed adequate reduction in disease activity.

1.2.4. Nonclinical Pharmacology

In vitro, PF-06835375 selectively binds human and cynomolgus monkey CXCR5-positive cells with high affinity. PF-06835375 does not bind mouse, rat, or rabbit CXCR5 orthologs and therefore, the cynomolgus monkey is the only pharmacologically relevant species for toxicity testing.

In vitro functional assays have shown that PF-06835375 possess both potent depleting and antagonistic activity. Indeed, PF-06835375 triggers ADCC of CXCR5-positive cells in human donor and cynomolgus monkey leukocytes. PF-06835375 does not have agonist or antagonist activity on any of the nineteen chemokine receptor family members related to CXCR5. Additional details are available in the Investigator Brochure.

In vivo studies in cynomolgus monkeys have confirmed that PF-06835375 elicits a dose-dependent depletion of CXCR5-positive cells that subsequently recover over time. To evaluate the functional impact of PF-06835375 on humoral memory responses, a vaccine recall response study was conducted in cynomolgus monkeys previously immunized against tetanus. PF-06835375 partially inhibited anti-tetanus toxoid Immunoglobulin G (IgG) titers elicited by a CCI [redacted] challenge, thereby demonstrating that PF-06835375 can affect in vivo humoral memory responses. Additional details are available in the Investigator Brochure.

1.2.5. Nonclinical Pharmacokinetics

Single-dose pharmacokinetics (PK) and repeat-dose toxicokinetics (TK) were evaluated in cynomolgus monkeys following intravenous (IV) or subcutaneous (SC) dosing of PF-06835375. The bioavailability of PF-06835375 after subcutaneous administration was estimated to be greater than 50%. After single IV dosing in cynomolgus monkeys, the PK of PF-06835375 were characterized by a low clearance (CL), and a low volume of distribution (V_{ss}), consistent with the PK profile for a typical human IgG1 monoclonal antibody (mAb). There were no apparent sex-related differences in systemic exposure (as assessed by the maximum observed concentration [C_{max}] and area under the concentration-time curve from zero to 168 hours [AUC_{168}]) following dosing once every 2 weeks at 5 (IV), 20 (SC) or 200 (IV) mg/kg. Systemic exposure was higher after repeat dosing and increased in a dose-proportional manner. The overall incidence of anti-drug antibody (ADA) induction was 14% (4 of 28 animals) across dose groups, and serum concentrations on Study Day 43 were generally lower in ADA-positive animals compared to ADA-negative animals.

1.2.6. Nonclinical Safety

Administration of PF-06835375 once every two weeks by IV bolus or SC injection for up to 2 months in cynomolgus monkeys resulted in dose-independent depletion (maximum pharmacology reached at the lowest dose) of total B cells and cTfh/Tfh cells in the peripheral blood and spleen, and was associated with decreases in total lymphocyte and white blood cell counts and decreased lymphoid follicular cellularity in the spleen, lymph nodes and gut-associated lymphoid tissue for the dose range tested (5-200 mg/kg/dose). These changes were nonadverse, partially to fully reversible, and consistent with the expected pharmacology of PF-06835375. PF-06835375 did elicit cytokine release in the in vitro soluble and solid phase cytokine release assay using human whole blood or peripheral blood mononuclear cells (PBMCs), however, cytokine release was not detected in the repeat-dose toxicity studies in cynomolgus monkeys. At a SC dose of 20 mg/kg/dose, there were no local injection site reactions. Reproductive and developmental toxicity studies have not been conducted, but there were no findings in male and female reproductive tissues evaluated in the repeat-dose toxicity studies. The no observed adverse effect level (NOAEL) was 200 mg/kg/dose IV, the highest dose tested, which was associated with systemic exposure of 5220 μg/mL (C_{max}) and 438,000 μg•h/mL (AUC_{168}).

Additional information for PF-06835375 may be found in the single reference safety document (SRSD), which for this study is the current Investigator's Brochure.

1.3. Dose Rationale

The doses being proposed for this study are based on data from in vivo nonclinical pharmacology and toxicology studies. A model-based approach was adopted to characterize the relationship between dose, PF-06835375 concentrations, and modulation of B cell and cTfh cells in the serum of cynomolgus monkeys. Based on the PK profiles of PF-06835375 in cynomolgus monkeys, the exposure in humans is expected to be similar to that of a typical IgG1 antibody.[13] Therefore, a two-compartment PK model was used to simulate PF-06835375 serum concentrations following different doses in humans.

Published monkey and human PK/PD data for SBI-087,[a] a B cell depleting therapeutic, was used to translate B cell depletion parameters for PF-06835375 from monkey to human.[14,15] Specifically, SBI-087 B cell depletion parameters in monkey and human were obtained by characterizing the available SBI-087 PK/PD data using the same model that was developed for PF-06835375.[14,15] A comparison of the B cell depletion parameters for SBI-087 between monkey and human provided a cross-species scaling factor that was applied to the monkey B cell depletion parameters with PF-06835375 to predict corresponding B cell depletion parameters in human. Unlike B cells, no human data were available for cTfh cell depletion; therefore translation of cTfh cell depletion was assumed to be similar to that for B cells. Using baseline B and cTfh cell counts in SLE patients and predicted human cell depletion parameters, B cell and cTfh cell depletion kinetics following PF-06835375 administration in humans were simulated.[15]

Using a human equivalent dose (HED) approach, the maximum recommended starting dose is 6.5 mg/kg (assuming a safety factor of 10). The proposed starting dose for this study is 0.03 mg IV (~0.4 μg/kg), which is predicted to result in ~50% depletion of B cells relative to baseline. Relative to 1/10th of exposures at monkey NOAEL, the proposed starting dose provides a safety margin of 42,800 fold for C_{max} and 60,100 fold for average observed concentration (C_{av}). Based on HED approach the safety margin for proposed starting dose for a 70 kg individual is 150,500 fold (HED = 64.5 mg/kg). For the highest planned dose of 100 mg IV, the safety margins are 13 fold for C_{max} and 18.1 fold for C_{av} relative to 1/10th of exposures at monkey NOAEL.

The predicted efficacious dose of PF-06835375 is 10-30 mg IV multiple-dose regimen (dose on Day 1 and Day 29), and is based on the assumption that B cells in blood need to be depleted to ≤1 cells/μL for ~8 weeks for clinical efficacy. The PK/PD model may under predict the efficacious dose as it relies on data from another B cell depleting agent (ie, SBI-087) and the efficacious dose criterion only focuses on B cell depletion; the effects of PF-06835375 on cTfh and bona fide Tfh cells may lead to a lower efficacious dose range. PF-06835375 serum concentrations following the final (second) dose of 10-30 mg IV multi-dose regimen (dose on Day 1 and Day 29) were estimated as noted above and the predicted C_{max} was 4.78-15.08 μg/mL and the predicted C_{av} (calculated as $AUC_{tau/28}$) was 1.36-4.06 μg/mL. Relative to 1/10th of exposures at monkey NOAEL, the predicted efficacious dose provides a safety margin of 34.6-109 fold for C_{max} and 64.3-192 fold for C_{av}.

In the multiple ascending dose (MAD) phase, the second dose will be given 4 weeks after the first dose. This dosing interval was selected based on PK/PD modeling and with consideration for repeat dosing in future multiple dose studies. Considering the dosing interval for the multiple dose phase of this study (4 weeks) will be different from the Good

[a] SBI-087 is a humanized small modular immunopharmaceutical (SMIP™) biological agent directed against the CD20 antigen located on B lymphocytes.

Laboratory Practice (GLP) monkey toxicity study (every 2 weeks), C_{av} is chosen to set the PK exposure limit. Moreover, since the NOAEL in the GLP monkey toxicity study was the maximum dose (200 mg/kg IV) evaluated, the exposure stopping limit will be set to a C_{av} of 261 µg/mL, determined as $1/10^{th}$ of the NOAEL mean C_{av} exposure of 2610 µg/mL (calculated as $AUC_{168}/168$ reported in Section 1.2.6). Projected human exposures and safety margins relative to exposure stopping limit are listed in Table 1 for the planned dose levels, including single (Cohorts A1-A8) and multiple (Cohorts B1-B5) dose administration. Doses may be modified or repeated and MAD cohorts may be dosed SC or IV based on emerging data, but dose escalation will be restricted such that predicted exposures will not increase more than in semi-logarithmic increments. For any dose administered, the predicted exposure will not exceed the exposure stopping limit.

Table 1. Predicted Median Human Exposures and Safety Multiples for Expected Doses

Cohort	Proposed Human Dose	Predicted human exposure			Safety Multiples[c]
		C_{max} (µg/mL)	AUC[a] (µg*day/mL)	C_{av} (µg/mL)[b]	C_{av}
Single-Dose Cohorts:					
A1	0.03 mg IV	0.0122	0.1210	0.00434	60100
A2	0.1 mg IV	0.0433	0.4220	0.0151	17300
A3	0.3 mg IV	0.1240	1.23	0.044	5930
A4	1 mg IV	0.42	4.18	0.149	1750
A5	3 mg IV	1.24	11.9	0.424	616
A6	10 mg IV	4.2	40.8	1.46	179
A7	30 mg IV	12.7	123	4.38	59.6
A8	100 mg IV	40.3	402	14.4	18.1
Repeat-Dose Cohorts:					
B1	0.3 mg SC[d]	0.0314	0.591	0.0211	12400
B2	1 mg SC[d]	0.107	1.96	0.0699	3730
B3	3 mg SC[d]	0.32	5.85	0.209	1250
B4	10 mg SC[d]	1.08	19.5	0.698	374
B5	30 mg SC[d]	3.3	59.3	2.12	123

a. Single dose: AUC_{inf}; Multiple dose: AUC_{tau} after 2nd dose where tau = 28 days.
b. C_{av} is calculated as AUC divided by 28 days.
c. Based on exposure stopping limit of C_{av} = 261 ug/mL, determined as $1/10^{th}$ of the NOAEL mean C_{av} exposure of 2610 ug/mL.
d. SC bioavailability assumed to be 60%.

AUC = Area under the curve; C_{av} = Average observed concentration; C_{max} = Maximum observed concentration; IV = Intravenous; NOAEL = No observed adverse effect level; SC = Subcutaneous.

1.4. Rationale for Assessment of Immune Function with Vaccine Challenges

The functional effects of PF-06835375 on humoral immunity will be evaluated CCI [redacted] vaccine challenge. As described in Section 1.6, both of these vaccines have been approved for use in humans, and contain inactivated immunogenic components of the specific pathogen. The purpose of the vaccine challenges is to develop an understanding of the PD properties, particularly related to

the degree of B cell and cTfh cell depletion. Assessment of the effect of PF-06835375 on neoantigen responses is precedented given prior observation of B cell depletion on neoantigen response.[16] The reduced response to CCI in toxicity studies with non-human primates exposed to PF-06835375 supports further assessment of the recall response in humans to best assess the exposure/response properties.

CCI

CCI

1.6. Summary of Benefits and Risks

Based on the available nonclinical data, the risks and potential benefits for PF-06835375 are considered to be favorable and support clinical development in subjects with SLE and RA.

SLE and RA both have higher prevalence in females and hence the trial objectives cannot be met without inclusion of women of childbearing potential (WoCBP). Nonclinical data to date (Section 1.2.6) have not identified any risk to reproductive organs in sexually mature cynomolgus monkeys, the pharmacologically relevant species. Given that an enhanced pre- and postnatal development study (ePPND) will be conducted later in development, this protocol that allows enrollment of WoCBP has stringent requirements to mitigate unintended exposures (pregnancy testing and use of contraceptives; see Section 4.4.1). Subjects will be followed for a minimum of 16 weeks after Day 1 during the study, which extends beyond predicted drug exposure of five half-lives based on expected PK.

Based on studies with other B cell and T cell depleting agents, there is a dose-dependent risk for infusion and injection reactions with PF-06835375, potentially severe. Subjects will be closely monitored for 8-12 hours post-infusion as per Schedule of Activities. As described in Section 5, subjects will be pre-medicated to mitigate this risk, and peri- and post-infusion medications to manage infusion and/or injection reactions will be available for subjects receiving IP.

Studies with other B cell depleting agents indicate the potential for viral and non-viral infections with PF-06835375, including severe cases resulting in death. Multiple agents that deplete B cells have been approved in both oncology and non-oncology indications (including rituximab, ocrelizumab, obinatuzumab and ofatumumab) and all carry label warnings for infections. Progressive multifocal leukoencephalopathy (PML) resulting in death has occurred with B cell depleting agents (most notably rituximab given the extensive use in multiple diseases), and has also been observed in SLE and RA subjects receiving immunosuppressive agents. Investigators should consider PML in any patient with new onset of or changes in pre-existing neurological signs or symptoms (See Section 7.1.14). The role of the Tfh subset of T cells in human immunity has yet to be established, and may contribute to the effective control of acute and chronic pathogens. Although no serious or opportunistic infections were observed in pre-clinical toxicity studies in non-human primates, subjects will be closely monitored throughout the study for signs/symptoms of infections. While appropriate risk mitigation has been incorporated into the study, possible risks will be communicated to study participants in the informed consent document.

Cytopenias have been observed with other depleting antibodies, including neutropenia, thrombocytopenia and anemia. Subject blood counts will be closely monitored throughout the study, including both CXCR5-positive cells and other cell lineages.

The PD of PF-06835375 will be evaluated [redacted]. When adverse reactions to the [redacted] occur, they are generally mild in nature and last for one or two days only. Symptoms include erythema and swelling around the injection site, feelings of general malaise, headache, myalgia and fever, and can be managed with paracetamol. Severe reactions are extremely rare; subjects with concomitant illnesses and a personal history of an allergic reaction to the [redacted] vaccine will be excluded.

[redacted]

Trumenba is approved for active immunization to prevent invasive disease caused by *Neisseria meningitidis* serogroup B, and is approved for use in individuals 10 through 25 years of age. The Centers for Disease Control and Prevention (CDC) has recommended use of Trumenba routinely for people 10 years or older who are at an increased risk for serogroup B meningococcal infections. The immunogenicity of Trumenba has been assessed in two-dose and three-dose regimens in multiple clinical trials to establish the safety profile.[17] As of 23 March 2017, Trumenba has been approved in the European Union (EU) for active immunization of individuals 10 years and older to prevent invasive meningococcal disease caused by Neisseria meningitidis serogroup B.

In total, in controlled clinical studies in which over 15,000 active subjects (mostly 10 through 25 years of age) received at least one dose of Trumenba, serious adverse events (SAEs) were reported at similar rates by active and control (both under 2.0%). Overall non-serious adverse events (AEs) in controlled studies were similar between active and control; AEs that occurred at a frequency of at least 2% and were more frequently observed in subjects who received Trumenba than subjects in the control group were local injection site pain, fever, and headache. Severe allergic reactions have been observed (rarely) with Trumenba, and Epinephrine and other appropriate agents used to manage immediate allergic reactions must be immediately available should an acute anaphylactic reaction occur following administration of Trumenba.[18]

2. STUDY OBJECTIVES AND ENDPOINTS

Primary Objective:	**Primary Endpoints:**
• To evaluate the safety and tolerability of single and multiple ascending intravenous (IV) and subcutaneous (SC) doses of PF-06835375 in subjects with SLE and RA.	• Incidence of dose limiting or treatment related adverse events (AEs). • Incidence, severity and causal relationship of treatment emergent AEs (TEAEs) and withdrawals due to treatment emergent adverse events. • Incidence of abnormal chemistry, hematology, and urinalysis laboratory findings through the end of study. • Abnormal and clinically relevant changes in vital signs and electrocardiogram (ECG) parameters. • Incidence of infections.
Secondary Objectives:	**Secondary Endpoints:**
• To evaluate the effect of PF-06835375 on depletion of circulating CXCR5 positive B cells and cTfh cells in subjects with SLE and RA.	• Change from baseline in the number of circulating CXCR5 positive B cells and cTfh cells on Day 29 single dose of PF-06835375 and at Week 8 following multiple doses of PF-06835375.

• To characterize pharmacokinetics (PK) profile of PF-06835375 in subjects with SLE and RA.	• Serum PF-06835375 PK parameters after single and multiple doses:
	  • Single Ascending Dose Phase: C_{max}, T_{max}, AUC_{inf}, AUC_{last}.
	  • Multiple Ascending Dose Phase:
	  • First Dose: C_{max}, T_{max}, AUC_{tau}.
	  • Multiple Dose: C_{max}, , T_{max}, AUC_{last}, AUC_{tau}, C_{min} and observed accumulation ratio (R_{ac}), peak-to-trough ratio (PTR).

• To evaluate immunogenicity of PF-06835375 in subjects with SLE and RA.	• Incidence of development of anti-drug antibodies (ADAs)/neutralizing antibodies (NAbs).
CCI [redacted]	[redacted]
[redacted]	[redacted]

3. STUDY DESIGN

3.1. Study Overview

This is a Phase 1, randomized, multi-center, double-blind, sponsor open, placebo-controlled, single and multiple dose-escalation study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of PF-06835375 in subjects with seropositive SLE or RA. Both IV and SC routes of administration will be tested.

This study will include two parts: Part A, consisting of approximately eight single ascending dose (SAD) cohorts, and Part B, consisting of approximately 6 multiple ascending dose (MAD) cohorts. Fewer cohorts may be included in each part at Sponsor's discretion. Cohorts in Part A will be initiated sequentially. Subjects in Part B will receive two doses of investigational product (first dose on Day 1 and second dose on Day 29), and will be enrolled concurrently with Part A following the completion of the initial cohorts in Part A (See Section 3.3). Subjects who are randomized in Part A will not be eligible to participate in Part B of this study.

This study will enroll up to a total of approximately 112 subjects at approximately 10 sites.

The study includes a Screening visit to assess eligibility and subsequent visits for a minimum of 16 weeks. Subjects who meet the end of study criteria (See Section 3.5) will have one follow-up phone call visit which will represent the end of study visit. Subjects, who do not meet the criteria to leave the study at Week 16, will continue with clinic visits every four weeks until Week 52 and then every 12 weeks until they meet these criteria. Overall, subjects are expected to stay in the study approximately 6-12 months (including screening). Subjects who withdraw from the study may be replaced at the discretion of the sponsor. A replacement subject will receive the same treatment as the withdrawn subject.

Both SLE and RA subjects will be enrolled into this study. Minimum disease activity (ie, CCI or DAS28 cutoffs) is not required for entry as inclusion criteria. All subjects in both Part A and B will be followed for a minimum of 16 weeks prior to being able to qualify for study completion based on the cellular recovery (See Section 3.5).

It is at the sponsor's discretion to dose escalate (See Section 3.4.1), to repeat the same dose, or to test a lower dose based on emerging data.

Throughout the study, B cell counts obtained from a CLIA (Clinical Laboratory Improvement Amendments) certified central lab will be used for clinical decision making (inclusion/exclusion criteria, dose escalation, initiation of Part B and for the end of study criteria).

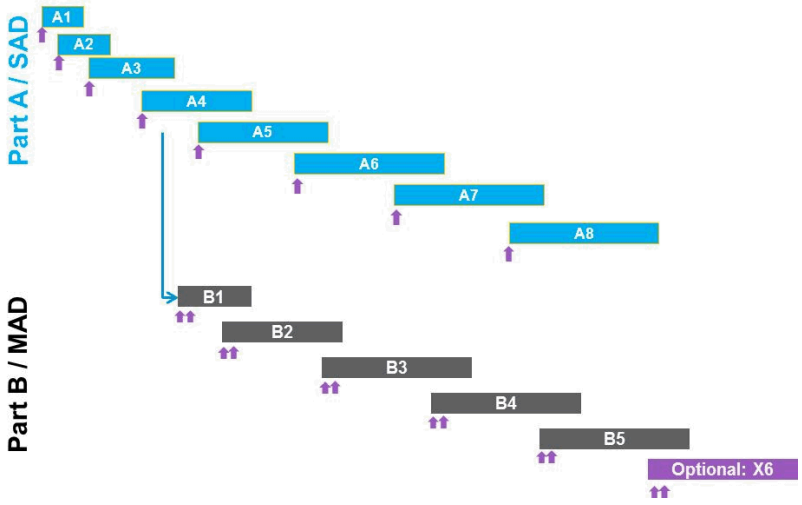
Table 2. Planned Cohorts

Cohort Name	Administration Route	Proposed Human Dose[a] (mg)	Expected Number of Subjects Per Cohort[c]
Part A (SAD)			
A1	IV	0.03	3a, 1p
A2	IV	0.1	3a, 1p
A3	IV	0.3	3a, 1p
A4	IV	1	3a, 1p
A5	IV	3	6a, 2p
A6	IV	10	6a, 2p
A7	IV	30	6a, 2p
A8	IV	100	6a, 2p
Part B (MAD)			
B1	SC	0.3	6a, 2p
B2	SC[b]	1	6a, 2p
B3	SC[b]	3	6a, 2p
B4	SC[b]	10	6a, 2p
B5	SC[b]	30	6a, 2p
X6[d]	SC[b]	up to 30	Up to 24 total (16a, 8p)

Abbreviations: a = active, p = placebo; IV = Intravenous; SC = subcutaneous

a. Doses may be changed based on available emerging safety, tolerability, PK and PD.
b. Route of administration may be changed based on available emerging safety, tolerability, PK and PD.
c. Sponsor may elect to add more subjects into the planned cohorts for any reason, including but not limited to eg, subject withdrawal, higher than expected PD effect, etc. The study will enroll up to a total of approximately 112 subjects.
d. Optional cohort called "X".

Figure 1. Study Schematic



3.2. Sentinel Dosing

In view of the mechanism of action (B cell and cTfh cell depletion), the interval between sentinel subjects and the remainder of the cohort is proposed to mitigate any unanticipated acute safety risks (ie, infusion/injection site reactions). Sentinel dosing will be employed as follows:

- In Part A, for Cohorts A1-A4 (with 4 subjects planned), subjects will be dosed IV at least 24 hours apart. In order to avoid investigator unblinding, the one subject on placebo in these cohorts may be enrolled in any sequence. The sponsor medical monitor will communicate with investigator(s) from each site after dosing of each subject (and prior to dosing of the next subject) in order to determine whether it is safe to proceed with continued dosing within a cohort.

  If the sponsor decides to increase the number of subjects in these A1-A4 cohorts, the sentinel dosing will apply only to the first four subjects as described in the paragraph above. After the sponsor medical monitor determines it is safe to proceed, the remaining subjects can be enrolled and dosed simultaneously.

- In Part A, for cohorts A5-A8 (with more than 4 subjects planned), the first two subjects dosed IV will include one PF-06835375 and one placebo subject. If safety and tolerability profile is acceptable in these two subjects, dosing of additional subjects can occur 24 hours after dosing of the first two subjects. These additional subjects within a cohort may be enrolled and dosed simultaneously. The determination to proceed with dosing of additional subjects will be made by the sponsor following communication between sponsor medical monitor and investigator(s) from sites which enrolled sentinel subjects.

- In Part B, for all SC cohorts, sentinel dosing for the first two subjects (as described for Cohort A5-A8 above) will only be employed if a given SC dose level (or higher) was not previously tested in Part A using the IV route of administration. For example, if Cohort A4 (single 1 mg IV dose) has not been tested, sentinel dosing will be used in Cohort B2 (two SC doses of 1 mg). If safety and tolerability profile is acceptable in two subjects after the first of two doses, dosing of additional subjects can occur 24 hours after dosing of the first two subjects.

  If in Part B the SC bioavailability is low and the decision is made to change the route of administration to IV, then sentinel dosing in Part B will not be repeated for dose levels already administered in Part A.

Sentinel dosing in either Part A or Part B will not be used if the sponsor elects to test a dose equal to or lower than the highest dose already studied.

3.3. Initiation of Part B

Part B of the study is expected to be initiated after B cell counts in Part A have been depleted to approximately 10 cells/µl. B cell counts obtained from CLIA (Clinical Laboratory Improvement Amendments) certified central lab will be used for this determination.

The decision to progress to Part B will be made at a dose escalation meeting following the review of the available data on safety/tolerability, PK and PD from Part A (See Section 3.4). The first dose in Part B will be administered via SC route. When progressing to Part B, this dose escalation meeting will also include a review of available safety data at the same IV dose level in Part A. In addition, the next IV dose cohort in Part A will be dosed prior to dosing the first dose level in Part B.

3.4. Dose Escalation and Stopping Rules

3.4.1. Dose Escalation

The decision to progress to the next higher dose in Parts A and B will be made following the review of available safety/tolerability, PK and PD data for the preceding dose levels (in a respective Part) and after the sponsor (Medical Monitor, Clinical Pharmacologist and Study Statistician at a minimum) and investigators (with active subjects or subjects enrolled in the dose level under review) determine that it is safe to proceed to the next dose level.

Once Part B has been initiated, dosing in subsequent cohorts in Part B may occur either via SC or IV routes. Specific criteria for dose escalation in Part B are provided below:

- SC route of administration in Part B: dose escalation in SC cohorts in Part B may occur independent of IV cohorts in Part A.

- IV route of administration in Part B: dose escalation in Part B will only occur after subjects have been dosed wih a three-fold higher IV dose in Part A. For example, dosing in B2 (two 1 mg IV doses) may commence after dosing in Cohort A5 (single 3 mg IV dose) occurred.

If the decision has been made to dose escalate, it is at sponsor's discretion whether to proceed with dose escalation. It is also at sponsor's discretion whether to repeat the same dose or to test a lower dose based on emerging data. The dose escalation meeting will review infusion and injection site reactions, and the sponsor will provide guidance to Investigators on management of injection/infusion reactions in the subsequent cohort, including the need for pre-medication with corticosteroids.

Review of ongoing safety data will continue after dose escalation has either been completed or stopped and subjects remain active in the study. These meetings will include a similar group as the dose escalation meetings, and will be scheduled every three months at a minimum.

Dose escalation can proceed after the following criteria are met:

- For cohorts with 4 planned subjects, all 4 subjects have been dosed. For cohorts with 8 planned subjects, at least 6 subjects have been dosed, including at least one placebo subject.

- Sponsor medical monitor and investigators who enrolled subjects in a given cohort have reviewed all available safety data for dosed subjects, including:

    - minimum of 2 weeks of safety and tolerability data after the last study drug dose, AND

    - minimum 1 week of PK data after the last study drug dose.

- In Part A, for cohorts A1-A4 (with 4 subjects planned), 4 subjects have completed two weeks post-dose in the study. In Part A, for Cohorts A5-A8 and B1-B5 (with 8 subjects planned), 6 subjects must complete two weeks post-dose in the study.

- The majority of subjects dosed with PF-06835375 in a given cohort have a detectable B cell count (obtained from the CLIA certified central lab; LLOQ = 1 B cell per μL of blood) for a minimum of 2 consecutive visits at least 2 weeks apart, starting at Week 12. Subjects, who reach detectable B cell counts and withdraw from the study earlier, will be considered as having met this criterion. Subjects who withdraw from the study prior to reaching a detectable B cell count will not be counted in the cohort size (this will be limited to 1 subject per cohort of 4 or 2 subjects per cohort of 8). Investigators will have access only to de-identified B-cell count data to remain blinded.

- The sponsor and majority of investigators with active subjects and/or subjects enrolled in the dose level under review (includes only subjects who received IP) agree to proceed to the next dose level based on the overall safety profile. For the purpose of defining the majority of investigators, only one investigator from each site will be counted.

3.4.2. Dose Escalation Stopping Rules

Dose escalation stopping rules will be used to determine whether the maximal tolerated dose has been attained. Dose escalation will be stopped if it is determined that the limits of safety and/or tolerability have been reached based on the criteria described in this section. This decision will be made after a discussion takes place between the sponsor study team and the investigator. The sponsor study team may not overrule the investigator's decision to stop dose escalation. If dose escalation is stopped because of any of these criteria, additional cohorts may receive the same or lower doses of the investigational product.

The dose escalation will be terminated based on the following criteria:

- If ≥2 subjects within a dose cohort develop *Common Terminology Criteria for Adverse Events* (CTCAE) v4.0 Grade 3 adverse event considered to be serious (ie, SAE) in the same organ system, or if 1 subject develops a CTCAE v4.0 Grade 4 or higher SAE, considered related to study drug, and not clearly related to the underlying disease (ie SLE or RA) process, concomitant medications or supplements.
    - Laboratory abnormalities known to be associated with B-cell depleting therapies (neutropenia, thrombocytopenia and anemia) will not be considered for this criterion, instead these laboratory abnormalities will be considered for Individual Stopping Rules (Section 3.4.3).
- If 50% or more subjects within a dose cohort experience a CTCAE v4.0 Grade 3 or higher infusion reaction as defined by the criteria in Appendix 7.
- If a confirmed or probable case of Progressive Multifocal Leukoencephalopathy is observed, the sponsor will hold dosing for all subjects until the benefit risk assessment of PF-06835375 is re-evaluated by the sponsor (See Section 7.1.14). If the sponsor concludes the benefit risk assessment is favorable, investigators will be consulted on whether to proceed as described in this section.
- If, at any dose level, the mean exposure for the treatment group reaches or exceeds the exposure stopping limit of C_{av} of 261 μg/mL, OR, based on the observed data, the group mean C_{av} of the next planned dose is projected to exceed the exposure stopping limit (See Section 1.3). Modified doses may be explored if they are not expected to exceed PK stopping criteria.

If any dose cohort is repeated, this additional cohort will be considered a separate cohort for the purpose of this dose escalation stopping rules.

To determine whether any of the above criteria for stopping dose escalation have been met, the sponsor will convene a dose review team meeting between the sponsor (including at minimum Medical Monitor or Clinical Lead, Clinical Pharmacologist and Statistician) and Investigators who have active subjects or who enrolled in the dose cohort under review, to review adverse event(s) and all relevant safety data. This meeting may take place as part of standard dose escalation meeting or ad-hoc based on emerging safety data. Unblinding to determine relatedness to investigational product may be considered.

If any of the above criteria is considered to have been met as determined by unanimous decision of the dose review team members OR if a unanimous decision cannot be reached:

- No further doses should be administered at this dose and no dose escalation will proceed.

- Enrollment of the study may continue at a lower dose or a lower dose cohort may be added to the study.

Otherwise, upon unanimous decision of the dose review team members that it is safe to proceed, one of the following decisions may be made by the sponsor:

- Enrollment of the cohort may resume as planned.
- The cohort may be expanded at the same dose.
- Enrollment of the study may continue at a lower dose or a lower dose cohort may be added to the study.

Unanimous decision is defined as all Investigators who have active subjects or enrolled in the dose cohort under review (one Investigator per site) and sponsor medical representative (medical monitor or clinical lead) agree.

3.4.3. Individual Stopping Rules

If an individual subject develops any of the following, the subject will not receive a second dose of IP in Part B. Subjects in Part B (MAD cohort) who meet these criteria and who have received the first dose of IP will remain in the study and continue to be followed per the Schedule of Activities:

- Laboratory values meeting criteria for potential drug induced liver injury (see Section 8.4.2).
- Illness or clinical adverse event that prevents daily activity and requires medical intervention (ie CTCAE v4.0 Grade 3).
- Any serious adverse event (irrespective of relatedness to study drug).
- Any infection requiring the use of oral or parenteral antibiotics between first and second dosing of IP requires approval by sponsor clinician or medical monitor prior to subject receiving a second dose of IP.
- Increase in SLE or RA disease activity requiring use of prohibited medications (See Appendix 2), OR doses or formulations of medications inconsistent with those allowed (See Appendix 3).
- Prior CTCAE v4.0 Grade 4 infusion reaction during first infusion.

The following criteria will not be considered as Individual Stopping Rules (due to the anticipated effects of PF-06835375 on blood counts):

- Lymphopenia: CTCAE v4.0 Grade 2 lasting 14 days or less OR Grade 3 lymphopenia lasting 7 days or less. For subjects with abnormalities present on Day 1 prior to dose (ie, CTCAE v4.0 Grade 1 or 2), a two-grade shift lasting 14 days or less.

- Neutropenia: CTCAE v4.0 Grade 2 lasting 7 days or less OR Grade 3 lasting 3 days or less.

- Thrombocytopenia: CTCAE v4.0 Grade 2 lasting 7 days or less OR Grade 3 lasting 3 days or less.

3.5. Criteria for End of Study

All subjects will be followed through the Week 16 visit. In order for the Week 16 visit to be the subject's last clinic study visit, B cell counts meet at least one of these criteria:

- B cell count is ≥50% of baseline value AND is stable or increasing between Week 12 and Week 16 measurements, OR

- B cell count is ≥ lower limits of normal (defined as 80 cells/μl[19]) at Week 16.

If at least one of the above criteria are not met at Week 16, subjects will continue in the study and will be followed until B cell count meets at least one of these criteria:

- B cell count is ≥50% of baseline value AND is stable or increasing between the two measurements at least two weeks apart, OR

- B cell count is ≥ lower limits of normal (defined as 80 cells/μl[19]), OR

- B cell count reaches a new stable (or increasing) detectable level AND subject is clinically stable for minimum of two consecutive visits, each at least two weeks apart, based on the assessment by both the sponsor AND the investigator. The earliest B cell count that can be considered for this criterion is from the Week 20 visit. As a result, subjects will not be discharged prior to availability of Week 24 lab results for B cells under this criterion.

B-cell counts obtained from CLIA certified central lab will be used for this determination.

Baseline value is defined as the average of Screening and Day 1 pre-dose values. In cases where only one value (ie, screening or Day 1 pre-dose) is available, this one value will be used as the baseline. Stable is defined as ±5 cell/μl. Values obtained by the central lab will be used.

B cell counts data will be available only after subject completes the clinic visit due to the required shipment of samples to central lab and their processing time. Once subject meets the criteria for the end of study described above, a phone visit will take place within approximately 1-2 weeks, prior to the next scheduled in clinic visit. This phone visit will be considered the end of study visit/last visit.

Subjects may be asked to return for additional follow up visits beyond the anticipated end of study visit for safety reasons as determined by the Investigator in consultation with the sponsor medical monitor.

4. SUBJECT ELIGIBILITY CRITERIA

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects 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 subject is suitable for this protocol.

Subject eligibility should be reviewed and documented by an appropriate member of the investigator's study team before subjects are included in the study.

4.1. Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Evidence of a personally signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study.

2. Willing and able to comply with scheduled visits, treatment plan, laboratory tests and other study procedures.

3. Male or female subjects between the ages of 18 and 70 years (inclusive) at the time of Screening visit.

4. Subjects who are, in the opinion of the investigator, sexually active and at risk for pregnancy with their partner(s) must agree to use one highly effective form of contraception as outlined in this protocol for the duration of the study and for at least three months after the last dose of investigational product. In addition, based on contraception use recommendations from other similar agents that deplete B-cells, the sponsor strongly recommends that all subjects use highly effective contraception for a minimum of 6 months following the last dose of IP. This time frame of 6 months after the last dose of IP is strongly recommended but not required. Male subjects who are sexually active must agree to use a condom to prevent potential transmission of investigational product in seminal fluid starting for the same duration.

Female subjects of non-childbearing potential must meet at least 1 of the following criteria:

a. Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause and have a serum follicle-stimulating hormone (FSH) level confirming the postmenopausal state; If post-menopausal for ≥5 years, it is at the investigator's discretion whether to confirm post-menopausal status by FSH.

b. Have undergone a documented hysterectomy and/or bilateral oophorectomy.

c. Have medically confirmed ovarian failure.

All other female subjects (including female subjects with tubal ligations) are considered to be of childbearing potential.

5. For females of childbearing potential, two negative pregnancy tests (one negative serum pregnancy test at Screening and one negative urine pregnancy test on Day 1) are required before receiving the investigational product.

6. Body Mass Index (BMI) of 17.5 to 40 kg/m^2 AND total body weight >45 kg.

7. Subjects must meet diagnostic criteria either for Rheumatoid Arthritis or Systemic Lupus Erythematosus below:

   a. ***Rheumatoid Arthritis criteria***:

      - Confirmed diagnosis of Rheumatoid Arthritis according to the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) criteria (See Appendix 6) at Screening, with symptom duration at least 6 months prior to Screening visit.

      - Positive with Rheumatoid Factor and/or anti-citrullinated peptide antibody (ACPA) at Screening.

   b. ***Systemic Lupus Erythematosus (SLE) criteria***:

      - Confirmed diagnosis of SLE according to the Systemic Lupus International Collaborating Clinics (SLICC) Classification Criteria (See Appendix 5) at Screening, with symptom duration at least 6 months prior to Screening visit.

      - Positive antinuclear antibody (ANA) titer ≥1:80 AND/OR positive anti-double-stranded deoxyribonucleic acid (anti-dsDNA) AND/OR anti-Smith antibodies at Screening.

4.2. Exclusion Criteria

Subjects with any of the following characteristics/conditions will not be included in the study:

1. Investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or subjects who are Pfizer employees, including their family members, directly involved in the conduct of the study.

2. Participation in other studies involving investigational drug(s) within 30 days or 5 half-lives (whichever is longer) prior to study entry and/or during study participation. For investigational biologics, 5 half-lives or 180 days preceding the first dose of the investigational product (whichever is longer). If subjects participated in studies involving investigational biologics, which are biosimilars, the timeframe from previous use described in Appendix 2 will apply instead.

3. Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.

4. Subjects with DAS28 score >5.1 can be enrolled only after consultation with the sponsor medical monitor.

5. Subjects with Clinical SLEDAI-2K score >8 can be enrolled only after consultation with the sponsor medical monitor.

6. Active central nervous system (CNS) manifestations, systemic vasculitis or pleuro/pericarditis which, in the opinion of the investigator or sponsor, is uncontrolled within 2 months of the Screening visit or leading to the incapacity of the subject to comply with consent and protocol requirements.

7. Active lupus nephritis, as defined by any of the following:

    - Proteinuria >1.5 g/24 hr or urinary protein to urinary creatinine ratio [Upr/Ucr] >2.0 at Screening; only one of these two tests is required at Screening.

    - Presence of red blood cell (RBC) casts or ≥10 RBC/hpf (in the absence of infection or menstrual hematuria at Screening);

    - Estimated Glomerular Filtration Rate (eGFR) <60ml/min/1.73 m^2 at Screening. The following formula will be used: 175 x (Serum creatinine)$^{-1.154}$ × (Age)$^{-0.203}$ × (0.742 if female) × (1.212 if African-American);

- Requiring high-dose prednisone (greater than or equal to 40 mg/day) within 3 months prior to Screening;

- Requiring hemodialysis or cyclophosphamide (Cytoxan) within the 6 months prior to Screening.

8. Secondary antiphospholipid antibody syndrome (APS) associated with a thromboembolic event in 12 months prior to Screening and/or associated with any prior history of cerebro- or cardiovascular event due to APS.

9. Subject is taking or has taken prohibited medications (See Appendix 2), OR taking doses or formulations of medications not consistent with those allowed (See Appendix 3).

10. Presence of any other systemic rheumatic disease other than and not related to SLE/RA (Secondary Sjogren's syndrome is permitted).

11. Baseline chronic co-morbidities (other than SLE/RA) requiring systemic corticosteroid therapy (such as asthma or inflammatory bowel disease) starting 6 months prior to the Screening. Systemic is defined as oral, rectal, or any injectable route of administration (thus other routes are allowed, including inhaled, topical, ophthalmic, otic, and intranasal).

12. Subjects with any of the following infections or infections history:

    a. Active clinically significant viral, bacterial, or fungal infection, or any major episode of infection requiring prescription anti-infective treatment 2 weeks prior to Screening.

    b. History of recurrent infections defined as 3 or more of the same type of infection in a 12-month rolling period. This does not include vaginal candidiasis or onychomycosis provided these are considered by the investigator to be well controlled.

    c. Herpes infection meeting at least one of the following criteria:

        - A herpes zoster episode ≤3 months prior to Screening;

        - History of recurrent (ie, more than one episode) herpes zoster;

        - History of a single episode of disseminated (multidermatomal) herpes zoster or herpes simplex.

    d. Positive human immunodeficiency virus (HIV) serological test at screening. Note: a documented negative HIV test within 3 months of Screening visit is acceptable and does not need to be repeated at Screening.

e. Evidence of active or latent infection of hepatitis B or hepatitis C based on screening tests (See Section 7.1.9). Subjects who are positive for hepatitis C virus antibody (HCV Ab) will be reflex-tested for hepatitis C virus ribonucleic acid (HCV RNA) and only if HCV RNA is negative, they may be considered for enrolled in this study.

f. Current or past history of either 1) active tuberculosis (TB) infection or 2) latent TB that was inadequately treated or where adequate treatment cannot be documented.

g. Clinically significantly abnormal chest X-ray per investigator opinion or evidence of active TB on chest X-ray. Subjects who had chest X-ray performed within 3 months prior to the Screening visit do not have to have chest X-ray performed, provided documentation is available.

13. Known hypersensitivity, intolerance or allergic reaction to the IP or placebo or any of its excipients, or history of severe hypersensitivity to monoclonal antibodies.

14. Known hypersensitivity or allergic reaction to pre- or post-infusion medications (corticosteroids, acetaminophen and antihistamines).

15. Known hypersensitivity or allergic reaction to Td or Trumenba vaccination.

16. Received any live virus or live-attenuated vaccines within 4 weeks prior to Screening, or expected during the study period (from Screening to subject's last visit).

17. Received plasmapheresis within 12 weeks prior to Screening or expected during the study period (from Screening to subject's last visit).

18. History of or planned organ transplant for the duration of the study (from Screening to subject's last visit).

19. Major surgery requiring use of general anesthesia within 6 weeks prior to Screening or planned or expected major surgery during the study period (from Screening to subject's last visit).

20. History of any malignancy within past 5 years prior to Screening (except adequately treated and removed basal and squamous cell carcinomas of the skin, and in situ cervical cancer intraepithelial neoplasia of the uterine cervix).

21. Subject abused drugs or consumed an excessive amount of alcohol in the past 12 months, based on the opinion of the investigator.

22. Presence of any of the following laboratory abnormalities at Screening:

- B-cell count at Screening below the lower limit of normal (LLN), defined as 80 cells/µl (obtained from CLIA certified central lab).

- Total serum IgG <5 mg/dl (or 5 g/l).
- Hemoglobin <10 g/dL (100 g/L).
- White blood cell count <2.5 x 10^9 /L (<2,500/mm^3).
- Platelet count <75 x 10^9/L per central laboratory results (75,000/mm^3).
- Neutrophil count <1.5 x 10^9/L (<1,500/mm^3).
- Aspartate aminotransferase (AST) **or** alanine aminotransferase (ALT) level ≥2.0 × upper limit of normal (ULN).
- Total bilirubin level ≥2.0 × ULN; subjects with a history of Gilbert's syndrome may have direct bilirubin measured and would be eligible for this study provided the direct bilirubin level is ≤ ULN.

Any abnormal results may be confirmed by a single repeat test, if deemed necessary by the investigator and approved by the sponsor medical monitor.

23. Pregnant female subjects; breastfeeding female subjects; fertile male subjects and female subjects of childbearing potential who are unwilling or unable to use one highly effective method of contraception as outlined in this protocol for the duration of the study and for at least three months after the last dose of investigational product.
24. Blood donation (excluding plasma donations) of approximately 1 pint (500 mL) or more within 60 days prior to dosing.
25. Unwilling or unable to comply with the criteria in the Lifestyle Requirements section of this protocol.

4.3. Randomization Criteria

Subjects will be randomized into the study provided they have satisfied all subject eligibility criteria. Subjects will be randomized within each cohort to receive either PF-06835375 or placebo. Both SLE and RA subjects will be enrolled into this study. There are no requirements for a minimum number of RA or SLE subjects in each cohort.

In order to mitigate any unanticipated acute safety risks, sentinel dosing will be employed for this study as described in Section 3.2.

4.4. Lifestyle Requirements

4.4.1. Contraception

PF-06835375 has not been studied in embryofetal studies and therefore may have potential teratogenicity/fetotoxicity. All fertile male subjects and female subjects who are of childbearing potential and who are, in the opinion of the investigator, sexually active and at

risk for pregnancy with their partner(s) must agree to use a highly effective method of contraception consistently and correctly for the duration of this study. In addition, based on contraception use recommendations from other similar agents that deplete B-cells, the sponsor strongly recommends that all subjects, who leave study, should use highly effective contraception for a minimum of 6 months following the last dose of IP. This time frame of 6 months after the last dose of IP is strongly recommended but not required. Male subjects who are sexually active must agree to use a condom to prevent potential transmission of investigational product in seminal fluid starting for the same duration.

The investigator or his or her designee, in consultation with the subject, will confirm that the subject has selected an appropriate method of contraception for the individual subject and his or her partner from the permitted list of contraception methods (see below) and will confirm that the subject has been instructed in its consistent and correct use. At time points indicated in the Schedule of Activities, the investigator or designee will inform the subject of the need to use highly effective contraception consistently and correctly and document the conversation and the subject's affirmation in the subject's chart (subjects needs to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the subject to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the subject or the partner.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (ie, perfect use) and include the following:

1. Established use of hormonal methods of contraception associated with inhibition of ovulation (eg, oral, inserted, injected, implanted, transdermal) provided the subject or male subject's female partner plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.

2. Correctly placed copper-containing intrauterine device (IUD).

3. Male sterilization with absence of sperm in the postvasectomy ejaculate.

4. Bilateral tubal ligation/bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).

NOTE: Sexual abstinence, defined as completely and persistently refraining from all heterosexual intercourse (including during the entire period of risk associated with the study treatments) may obviate the need for contraception ONLY if this is the preferred and usual lifestyle of the subject.

4.5. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the Shared Investigator Portal - Sponsor Contacts.

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

5. STUDY TREATMENTS

For the purposes of this study, and per International Conference on Harmonisation (ICH) guidelines, investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference/comparator in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33).

For this study, the investigational product is PF-06835375 or placebo.

5.1. Allocation to Treatment

Allocation of subjects to treatment groups will proceed through the use of an interactive response technology (IRT) system (interactive Web based response [IWR]). The unblinded dispensing personnel will be required to enter or select information including but not limited to the user's identification (ID) and password, the protocol number, and the subject number. The unblinded dispenser will then be provided with a randomization number, treatment assignment, and dispensable unit (DU) or container number when investigational product is being supplied via the IRT system. The IRT system will provide a confirmation report containing the subject number, randomization number, and DU or container number assigned. The confirmation report must be retained by the unblinded dispenser in the unblinded site files.

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

5.2. Breaking the Blind

The study will be subject and investigator blinded. To safeguard blinding of investigators, investigators will not be able to access potentially unblinding data (eg, individual B-cell counts), unless needed for safety.

At the initiation of the study, the investigator site will be instructed on the method for breaking the blind. The method will be an electronic process. Blinding codes should be broken only in exceptional circumstances when knowledge of the actual treatment code is absolutely essential for further management of the subject. Investigators are encouraged to discuss with the sponsor's medical monitor if they believe that unblinding is necessary. When the blinding code is broken, the reason must be fully documented and entered on the case report form (CRF).

5.3. Subject Compliance

All doses of investigational product will be administered by the appropriately designated study staff at the investigator site.

5.4. Investigational and Non-Investigational Product Supplies

Clinical Trial supplies will be shipped to the study sites by Pfizer Global Clinical Supply (GCS), Worldwide Research and Development (WRD), and will include a Drug Shipment and Proof of Receipt form. This form will be completed, filed, and the shipment confirmed as directed on the bottom of the Drug Shipment and Proof of Receipt form. The Investigator shall take responsibility for and take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

5.4.1. Dosage Form(s) and Packaging

5.4.1.1. PF-06835375 or Placebo

Investigational product PF-06835375 is supplied as a sterile solution, packaged in a single use, 6 mL clear glass vial sealed with a coated serum stopper and an aluminum overseal. Each vial contains 1.35 mL PF-06835375 investigational product at a nominal concentration of 50 mg/mL at pH 5.8, sufficient to deliver a 1 mL dose of PF-06835375 investigational product. The PF-06835375 investigational product solution is a colorless to slightly brown colored solution and is labeled according to local regulatory requirements.

Placebo for PF-06835375 injection is presented as a sterile solution for SC and IV administration. Each vial nominally contains 1 mL of placebo as an aqueous buffered solution, is sealed with a coated serum stopper and an overseal, and is labeled according to local regulatory requirements. Placebo Solution is supplied as a sterile solution, packaged in a single use, 6 mL clear glass vial sealed with a coated serum stopper and an aluminum over seal. Each vial of placebo contains 1.35 mL of volume sufficient to deliver a 1 mL dose of placebo solution. The placebo solution should be clear, colorless and free of visible particulates, and is labeled according to local regulatory requirements.

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5.4.2. Preparation

Within this protocol, preparation refers to the investigator site activities performed to make the investigational product ready for administration to the subject by qualified staff.

See the Investigational Product Manual (IP manual), for instructions on how to prepare the investigational product for administration. Investigational product should be prepared and dispensed by an 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. Vials are for single use only.

5.4.2.1. PF-06835375 or Placebo Preparation

PF-06835375 and placebo will be prepared by two qualified unblinded site personnel according to the IP manual. The investigational product will be administered in blinded fashion to the subject.

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5.4.3. Administration

All study treatments will be administered at the investigational site as detailed in the IP Manual.

5.4.3.1. PF-06835375 or Placebo Administration

5.4.3.1.1. Intravenous Administration

Blinded IV PF-06835375 or placebo will be administered at the investigative site or clinic an IV infusion, using a calibrated infusion pump. Please refer to the IP manual for specific instructions.

Subjects should have venous access maintained for at least 2 hours after the completion of the infusion. This will allow immediate administration of any IV medication deemed necessary by the investigator in the event of an infusion-related reaction.

5.4.3.1.1.1. Infusion Durations

Blinded IV PF-06835375 or placebo will be administered as an IV infusion at the investigative site or clinic using a calibrated infusion pump according to IP manual. The total infusion time will be **120 minutes ±10 minutes,** unless a different time is needed to manage symptoms typical of infusion reactions. In such a case, the entire duration of study drug infusion should not exceed ~4 hours unless a different time is communicated to the site by the sponsor (See Section 5.4.3.1.1.2). Once the infusion has completed, all subjects will be monitored according to the Schedule of Activities. Refer to the IP manual for specific instructions for administration.

5.4.3.1.1.2. Infusion Discontinuation

The following rules should be followed by infusion discontinuation:

- If a subject experiences symptoms typical of an allergic reaction, the study drug administration should be discontinued immediately and permanently.
- If a subject experiences symptoms typical of infusion reactions (eg, lightheadedness, nausea, chills, fever), the study drug infusion should be slowed down or stopped.
- If symptoms are resolved within 1 hour after the stop of infusion, the infusion can be restarted at the discretion of the investigator. If symptoms return, then the study drug administration should be discontinued immediately and permanently.

The entire duration of study drug infusion, from the initial start of infusion to the completion of infusion, should not exceed 4 hours unless a different time is communicated to the site by the sponsor.

5.4.3.1.2. Subcutaneous Administration

Blinded subcutaneous (SC) PF-06835375 or placebo will be administered at the investigative site or clinic. In Part B (MAD), the planned route of administration will be SC, however safety, tolerability, PK and PD data from the Part A (SAD) will be assessed prior to initiating Part B to determine route of administration. Please refer to the IP manual for specific instructions.

The preferred body location of the SC injections is in the abdomen. If abdominal injections are not possible, arm or thigh locations may also be used. If an arm is used for the SC injection, the opposite arm should be used for the blood sample collections for PK analyses.

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5.4.4. Investigational Product Storage

The investigator or an approved representative, eg, pharmacist, will ensure that all investigational products are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

Investigational products should be stored in their original containers and in accordance with the labels.

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

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated, and/or room-temperature products). This should be captured from the time of investigational product receipt throughout the study. Even for continuous-monitoring systems, a log or site procedure that ensures active evaluation for excursions should be available. The intent is to ensure that the minimum and maximum temperature is checked each business day to confirm that no excursion occurred since the last evaluation and to provide the site with the capability to store or view the minimum/maximum temperature for all non-working days upon return to normal operations. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure they are maintained in working order.

Any excursions from the product label storage conditions should be reported to Pfizer upon discovery. The site should actively pursue options for returning the product to the storage conditions described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to Pfizer.

Once an excursion is identified, the investigational product must be quarantined and not used until Pfizer provides permission to use the investigational product. It will not be considered a protocol deviation if Pfizer approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to Pfizer approval will be considered a protocol deviation. Specific details regarding information the site should report for each excursion will be provided to the site.

Receipt of materials, door opening and closing, and other routine handling operations where the products are briefly out of the temperature range described in the labeling are not considered excursions.

See the IP manual for complete information on storage conditions, handling and stability of the product.

5.5. Investigational Product Accountability

The investigator site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies. All investigational products will be accounted for using a drug accountability form/record.

5.5.1. Destruction of Investigational Product Supplies

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

5.6. Concomitant Treatment(s)

Subjects should abstain from initiating new treatments during the study, except for the treatment of adverse events and continued use of those medications as described in Appendix 3. Limited use of non-prescription medications that are not believed to affect subject safety or the overall results of the study is permitted based on Investigator's discretion.

All concomitant treatments taken during the study must be recorded with indication, daily dose, and start and stop dates of administration. All subjects will be questioned about concomitant treatment at each clinic visit.

Treatments taken within 28 days before the first dose of study investigational product will be documented as a prior treatment. Treatments taken after the first dose of study investigational product will be documented as concomitant treatments.

Females taking hormone replacement therapy may be eligible to participate in this study if they are willing to discontinue therapy at least 28 days prior to the first dose of study treatment and remain off hormonal therapy for the duration of the study.

5.6.1. Treatment Prior to IP Administration

Treatment with agents that deplete B-cells have the potential to cause serious and life threatening infusion reactions. Appropriate equipment and personnel to manage anaphylaxis or serious infusion reactions are required. Approximately 1 hour prior to the administration of IP, each subject will be pre-treated with 1000 mg oral acetaminophen and an oral antihistamine (eg, 25 mg of oral diphenhydramine).

Based on emerging safety/tolerability data, additional pre-treatment may be necessary to manage infusion or injection reactions, including administration of oral or IV corticosteroids.

Specific instructions for pre-medication will be communicated by the sponsor to sites and investigators based on available safety data (both at dose escalation review meetings and periodically during the study as needed).

5.6.2. Treatment Post-infusion/Injection

Based on discretion of the investigator, subjects may receive additional acetaminophen at 4 hours and 8 hours after administration of IP based on clinical symptoms.

In addition, subjects may be given anti-histamines, anti-pyretics and/or corticosteroids based on investigator's discretion to manage infusion and injection reactions, particularly in the higher dose cohorts. If none of these steps are successful in appropriately managing infusion reactions as determined by the investigator, the investigator should consider hospitalization of the subject for further management.

Specific instructions for post-infusion/injection medication will be communicated by the sponsor to sites and investigators based on available safety data, both at dose escalation review meetings and periodically during the study as needed.

5.6.3. Guidance for Investigators

Subjects who have been dosed and who experience an increase in disease activity (ie flare) should receive medication as needed based on the discretion of the Investigator. The subject should continue to be followed as per Schedule of Activities. If the subject requires medications inconsistent with the guidance in Appendix 2 and Appendix 3, a protocol deviation should be recorded and the sponsor clinician or medical monitor should be notified.

If medications inconsistent with the guidance in Appendix 2 and Appendix 3 are required to manage subject's increase in SLE or RA disease activity in Part B after the first dose of IP but prior to the second dose of IP, the second dose of IP should not be administered. The subject should continue to be followed as per Schedule of Activities (See Section 3.4.3).

6. STUDY PROCEDURES

Visits should occur when scheduled, within the time window indicated in the Schedule of Activities. Written informed consent must be obtained prior to performing any protocol-specific procedures.

Where possible the following order of activities (if applicable to a given visit) should be followed during the clinic visits:

1. The Columbia-Suicide Severity Rating Scale (C-SSRS).
2. Vital signs.
3. Physical exam.
4. Clinical scales (eg, CCI , ACR/EULAR, SLICC, CCI).
5. ECGs.

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7. Blood and Urine Sample Collection.

6.1. Screening

For screening procedures, see Schedule of Activities section. Screening assessments may be repeated within the allowed screening visit window, provided this was approved by the sponsor clinician or sponsor medical monitor. An approval is not needed when repeating 1) ECGs to rule out improper lead (see Section 7.1.8) or 2) Interferon gamma release assay once only after an indeterminate result (see Section 7.1.10.1).

If a subject has been screen-failed, this subject may be re-screened one time, provided this was approved by the sponsor clinician or sponsor medical monitor. All screening assessments must be repeated during re-screening, with the exception of chest X-ray, HIV, Hepatitis and TB testing, which do not have to be repeated, provided re-screening is done within 3 months of the initial screening visit and these assessments were performed during the initial screening visit.

If for scheduling or logistics reasons, subject cannot be randomized within the screening window as described in Schedule of Activities, screening window subject may be extended by up to 5 days, provided this was approved by the sponsor clinician or sponsor medical monitor.

In order to ensure sentinel dosing is implemented and that appropriate number of subjects is screened, sites need to obtain written approval from the sponsor clinician to proceed with screening and dosing of each subject in this study.

6.2. Study Period

For procedures during study period, see Schedule of Activities section. All subjects will be followed for a minimum of 16 weeks.

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If a subject has any clinically significant, study related abnormalities at the conclusion of a scheduled inpatient portion of the study (or at the end of outpatient Day 29 for Part B), it is at the investigator's discretion to ask the subject to remain in the clinical unit until it is safe for outpatient follow up. The investigator must promptly notify the sponsor clinician or medical monitor. If the subject is unable or unwilling to remain in the clinical unit, the investigator should make every effort to arrange follow up evaluations at appropriate intervals.

The study includes a Screening visit to assess eligibility and subsequent visits for a minimum of 16 weeks. Subjects who meet the end of study criteria (See Section 3.5) will have one follow-up phone call visit which will represent the end of study visit (unless additional follow up is needed for safety reasons or) Subjects, who do not meet the criteria to leave the study at Week 16, will continue with clinic visits every four weeks until Week 52 and then

every 12 weeks until they meet these criteria Week 52 and then every 12 weeks until they meet these criteria.

Subjects may be asked to return for additional follow up visits beyond the anticipated end of study visit for safety reasons as determined by the Investigator in consultation with the sponsor medical monitor.

6.3. Subject Withdrawal

Withdrawal of consent:

Subjects who request to discontinue receipt of study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him or her or persons previously authorized by the subject to provide this information. Subjects 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 investigational product 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 subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

Lost to follow-up:

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject after a minimum of 2 documented phone calls, faxes, or e-mails as well as lack of response by the subject to 1 registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use locally permissible methods to obtain the date and cause of death. If the investigator's use of a third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a sponsor-retained third-party representative to assist site staff with obtaining the subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If, after all attempts, the subject remains lost to follow-up, then the last-known-alive date as determined by the investigator should be reported and documented in the subject's medical records.

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety (see also the Withdrawal From the Study Due to Adverse Events section) or behavioral reasons, or the inability of the subject to comply with the protocol-required schedule of study visits or procedures at a given study site.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. The investigator or site staff should attempt to contact the subject twice. After 2 attempts, site staff may send a registered letter. If no response is received from the subject, the subject will be considered lost to follow-up. All attempts to contact the subject and information received during contact attempts must be documented in the subject's medical record. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request that the subject return for a final visit, if applicable, and follow up with the subject regarding any unresolved adverse events (AEs).

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

Subjects who withdraw from the study may be replaced at the discretion of the sponsor. A replacement subject will receive the same treatment as the withdrawn subject.

The early termination visit only applies to subjects who are randomized, receive at least one dose of study drug and then are prematurely withdrawn from the study. Subject should return to the clinic for final safety assessments to be scheduled as early as practically feasible following the decision to withdraw from the study. At the early termination visit, every effort must be made to complete as many the following assessments:

- Limited physical examination.
- Sitting single blood pressure, temperature and pulse rate measurements.
- Supine triplicate 12-lead ECG measurement.
- Blood and urine specimens for safety laboratory (hematology, chemistry and urinalysis).
- Urine pregnancy test for female of childbearing potential.
- Collect blood samples for viral surveillance, CCI [redacted], immunogenicity (ADA, neutralizing antibodies (NAb) and pharmacokinetic analysis.

7. ASSESSMENTS

Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside of the control of the investigator that may make it unfeasible to perform the test. In these cases the investigator will take all steps necessary to ensure the safety and well-being of the subject. When a protocol-required test cannot be performed, the investigator will document the reason for this and any corrective and preventive actions that

he or she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely manner.

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

7.1. Safety

7.1.1. Laboratory Tests

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

Table 3. Laboratory Tests

Hematology[a]	Chemistry[a]	Urinalysis[a]	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	Blood urea nitrogen (BUN) Creatinine Glucose (non-fasting) Calcium Sodium Potassium Chloride Total CO_2 (bicarbonate) AST ALT Total bilirubin Alkaline phosphatase Uric acid Albumin Total protein Creatine kinase	pH Glucose (qual) Protein (qual)[l] Blood (qual) Ketones Nitrites Leukocyte esterase Urobilinogen Urine bilirubin Microscopy[b] Creatinine[l]	FSH[c] β-hCG[d] CCI (TNF-α, IL6, IFN-γ) IGRA TB test HIV and hepatitis testing[f] Viral surveillance[g] Serum Ig[h] PK and Immunogenicity[i] CCI JCV
	Additional Tests (Needed for Hy's Law)		

	AST, ALT (repeat) Total bilirubin (repeat) Albumin (repeat) Alkaline phosphatase (repeat) Direct bilirubin Indirect bilirubin Creatine kinase (repeat) GGT PT/INR Total bile acids Acetaminophen drug and/or protein adduct levels		

a. Safety labs include hematology, chemistry and urinalysis. Fasting is not required.
b. Only if urine dipstick is positive for blood, protein, nitrites or leukocyte esterase.
c. At Screening only, in females who are amenorrheic for at least 12 consecutive months. If post-menopausal for ≥5 years, it is at the investigator's discretion whether to confirm post-menopausal status by FSH.
d. Serum or urine β-hCG for female subjects of childbearing potential.
e. [redacted]
f. At Screening only. Includes HepBsAg, HepBcAb and HCVAb. Only subjects who are positive for HCV Ab will be reflex-tested for hepatitis C virus ribonucleic acid (HCV RNA).
g. Includes testing for CMV, EBV, HSV-1, HSV-2and VZV.
h. Includes testing for total Ig and Ig subtypes (IgA, IgG, IgE and IgM).
i. See Section 7.2 and Section 7.3 for details.
j. See Section 7.6 for details.
k. See Section 7.1.14 for details.
l. Urinary protein to urinary creatinine ratio will be calculated for all subjects at screening. CCI [redacted]

Any remaining serum/plasma from samples collected for clinical safety laboratory measurements at baseline and at all times after dose administration may be retained and stored for the duration of the study. CCI [redacted]

7.1.2. Pregnancy Testing

For female subjects of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed according to Schedule of Activities.

A negative pregnancy test result is required before the subject may receive the study treatments. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected). Pregnancy tests may also be repeated if requested by institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations.

Urine pregnancy tests must be sensitive to at least 25 mIU/mL and will be conducted with the test kit provided by the central laboratory in accordance with instructions provided in its package insert. Subjects who have missed a menstrual period or who show an indeterminate

or positive result on the urine test may not further progress in the study until pregnancy is ruled out using further diagnostic testing (eg, a negative quantitative serum pregnancy test conducted at a certified laboratory).

In the case of a positive confirmed pregnancy, the subject will be withdrawn from administration of investigational product but may remain in the study.

7.1.3. Physical Examinations

Physical examinations may be conducted by a physician, trained physician's assistant, or nurse practitioner as acceptable according to local regulation. A full physical examination will include head, ears, eyes, nose, mouth, neck, throat, skin, heart and lung examinations, lymph nodes, and gastrointestinal, musculoskeletal, and neurological systems. The limited or abbreviated physical examination will be focused on general appearance, the respiratory and cardiovascular systems, and subject-reported symptoms.

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

Complete and brief physical examinations will be performed time points as described in Schedules of Activities.

7.1.4. Vital Signs

Sitting blood pressure (BP), pulse rate, and temperature will be measured after approximately 5 minutes of rest at times specified in the Schedule of Activities. It is preferred that the same measurement method be used consistently throughout the study. Additional collection times or changes to collection times will be permitted, as necessary to ensure appropriate collection of safety data. When the timing of these measurements coincides with a blood collection, it is preferred that vital signs be obtained prior to the nominal time of blood collection.

Sitting blood pressure will be measured with the subject’s arm supported at the level of the heart, and recorded to the nearest mmHg. It is preferred that the same arm (preferably the dominant arm) be used throughout the study.

The same properly sized and calibrated Blood Pressure (BP) cuff, will be used to measure BP each time. The use of automated devices for measuring BP and pulse rate is acceptable, although, when done manually, pulse rate will be measured in the brachial/radial artery for at least 30 seconds. When the timing of these measurements coincides with a blood collection, BP and PR should be obtained prior to the nominal time of the blood collection.

It is preferred that body temperature be measured orally. A second acceptable method is temporal (forehead). Same method must be used consistently throughout the study for the same subject. No eating, drinking, or smoking is allowed for 15 minutes prior to the measurement.

7.1.5. Medical History

Investigators should make all reasonable efforts to obtain an accurate and complete medical history and history of prior medication use when evaluating whether a subject is eligible for the study. The following will be collected at Screening: complete medical history, SLE/RA disease history (including disease duration, extent of disease, and prior treatments), cardiovascular disease history, venous thromboembolic event history, alcohol and tobacco use history.

If the status of a subject's medical history is in doubt or information pertaining to a critical variable is conflicting, every reasonable step to secure proper documentation of correct medical status should be attempted. Documentation of the medical and medication histories over the protocol defined time periods should be available for sponsor review during the source data verification process. Questions about prior medications or eligibility should be directed to the sponsor Clinician or Medical Monitor.

7.1.6. Height and Weight

Height and weight will be measured without the subject wearing shoes. Height and weight will be measured up to one decimal place and recorded in the source document at the baseline visit.

Height will be measured only at Screening. Weight will be assessed at times indicated in the Schedules of Activities.

7.1.7. Chest X-Ray

Subject must have a chest X-ray (posterior-anterior and lateral views) taken at Screening or within 3 months prior to the Screening visit and read by a qualified radiologist. Documentation of the official reading must be located and available in the source documentation.

7.1.8. Electrocardiogram

12-lead ECGs should be collected at times specified in the Schedule of Activities.

All scheduled ECGs should be performed after the subject has rested quietly for at least 10 minutes in a supine position and prior to any blood collection procedures.

ECGs will be collected in triplicate in Part A on Days 1 and 2, in Part B on Days 1, 2 and 29. Single ECGs will be collected at all other times. Triplicate 12-lead ECGs will be obtained approximately 2 to 4 minutes apart; the average of the triplicate ECG measurements collected pre-dose on Day 1 will serve as each subject's baseline QTc value.

The Day 1 ECG values will serve as each subject's baseline values. To ensure safety of the subjects, a qualified individual (investigator or sub-investigator) at the investigator site will make comparisons to baseline measurements. If the QTc interval is increased by ≥45 msec from the baseline, or an absolute QTc value is ≥500 msec for any scheduled ECG, then 2 additional ECGs will be collected, approximately 2 to 4 minutes apart, to confirm the

original measurement. If either of the QTc values from these repeated ECGs remains above the threshold value (ie, is ≥45 msec from the baseline, or is ≥500 msec), then a single ECG must be repeated at least hourly until QTc values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement.

If QTc values remain ≥500 msec (or ≥45 msec from the baseline) for greater than 4 hours (or sooner, at the discretion of the investigator), or QTc intervals get progressively longer, the subject should be referred to a cardiologist for consultation.

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 are placed in the same positions each time in order to achieve precise ECG recordings. If a machine-read QTc value is prolonged, as defined above, repeat measurements may not be necessary if a qualified medical provider's interpretation determines that the QTc values are in the acceptable range.

7.1.9. Hepatitis B and C Screening

At Screening, all subjects will be tested for hepatitis B surface antigen (HepBsAg), hepatitis B core antibody (HepBcAb) and hepatitis C virus antibody (HCV Ab). Subjects who are HepBsAg or HepBcAb positive will not be enrolled in the study. Subjects who are positive for HCV Ab will be reflex-tested for hepatitis C virus ribonucleic acid (HCV RNA) and if negative may be considered for enrollment into this study; subjects positive for HCV RNA will not be enrolled into this study.

7.1.10. Tuberculosis Screening and Monitoring

7.1.10.1. Interferon Gamma Release Assay Tuberculin Test

Subjects should be screened for tuberculosis (TB) using an Interferon gamma release assay (IGRA) per local guidelines. IGRA will be tested during Screening. QuantiFERON®-TB Gold In-tube test (QFT-G) will be used. Site personnel should follow the processing and analyses steps based on the assay chosen. Ensure incubation steps are followed as appropriate. Documentation of IGRA product used and the test result must be in the subject's source documentation.

If the results of the IGRA are indeterminate, the test may be repeated once without sponsor approval.

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

7.1.10.2. Additional Measures for Tuberculosis (TB) Monitoring

Additional testing for TB will take place as specified in Schedule of Activities. The following measures will be followed to ensure the continued safety of subjects and to further mitigate the risk of *Mycobacterium tuberculosis* infection:

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

- If a subject converts from a negative to positive TB test during the study, they are to be thoroughly evaluated. The sponsor medical monitor should be notified as soon as possible. Evaluations should include, and may not be limited, to a history, completion physical examination, repeat TB testing, and imaging, as appropriate. Referrals to an infectious disease and/or pulmonology specialists are to be considered on an individual basis. Such subjects are not to receive additional investigational product until the details have been discussed with the sponsor. Sponsor will evaluate these cases in consultation with infectious disease and/or pulmonology specialists.

- If it is confirmed that a subject has developed latent or active TB during the study based upon the above evaluations, the subject should not receive further doses of investigational product, and should be treated with standard antimycobacterial therapy. Investigators should consider such an event as medically important and report the event as an SAE in accordance with the process described in Section 8.

- If the results of the IGRA test are indeterminate at any time in the study, the test should be repeated, and if a negative test result is obtained, the subject may remain in the study and continue treatment. Subjects with a repeat indeterminate IGRA test result should be seen by an infectious disease and/or pulmonary specialist. The sponsor medical monitor should be immediately notified and may evaluate these cases in consultation with infectious disease and/or pulmonology specialists.

7.1.11. Monitoring for Infections

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

Treated infections are infections that:

- Require antimicrobial therapy by any route of administration or;

- Require any surgical intervention (eg, incision and drainage).

A subject, who experiences an infection associated with SAE should not receive further dose(s) of investigational product. Furthermore, a subject, who requires oral or parenteral antimicrobial therapy (with the exception of mild vulvovaginal/urogenital infections), should only be administered further dose(s) of investigational product after consultation with sponsor clinician or medical monitor.

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

7.1.12. Infusion Site Reactions

Subjects will be continuously monitored for infusion site reactions from the start of drug administration until the end of infusion and then at time points indicated in the Schedule of Activities. Infusion site reactions may be monitored beyond the time points indicated in the Schedule of Activities based on investigator's assessment.

Infusion reactions may include but are not limited to: rash, flushing, hypotension, tachycardia, throat irritation or discomfort, difficulty swallowing, fever, chills. Any signs or symptoms related to either an infusion or injection site reaction(s) should be treated according to the investigator's standard of care and reported as adverse events. See Appendix 7 for details regarding the grading of adverse events arising from infusion reactions. Infusion reactions will be categorized according to the following definitions:

1. Acute: From start of infusion to 2 hours after the infusion. Infusion reaction AEs that occur during this time period be further classified as follows:

    a. Serious: Infusion reactions that meet the criteria of an SAE.

    b. Dose interrupted: Associated with temporary or permanent interruption and/or modification in dose.

    c. Infusion reaction AEs based on investigator's judgment.

2. Immediate: 2 hours after the infusion to 24 hours after initiation of treatment. Infusion reaction AEs that occur during this time period can be further classified as follows:

    a. Serious: Infusion reactions that meet the criteria of an SAE.

    b. Infusion reaction AEs based on investigator's judgment.

3. Late (delayed): 2 days to 14 days after initiation of treatment:

    a. Serious: Infusion reactions that meet the criteria of an SAE.

    b. Infusion reaction AEs based on investigator's judgment.

Information regarding infusion reactions will be collected on the Adverse Event Record. If the infusion reaction requires a modification to the administration of test article, the information must be recorded on the Test Article Record. All infusion reactions that are considered SAEs should be reported as specified in Section 8.2.3.

7.1.13. Injection Site Reactions

Subjects will be monitored continuously for injection site reactions (ISR) for 30 minutes following study drug administration and then at time points indicated in the Schedule of Activities. Injection site reactions may be monitored beyond the time points indicated in the Schedule of Activities based on investigator's assessment.

An ISR is a relatively common adverse event (AE) that develops following administration of subcutaneous/intramuscular injectable therapies. ISR may include but are not limited to: erythema, induration, ecchymosis, pain, and pruritus. Any signs or symptoms related to injection site reaction(s) should be treated according to the investigator's standard of care and reported as adverse events. ISRs may be immediate or delayed. The reaction to subcutaneous injections is varied and usually occurs immediately following an injection and/or up to 2 days later. Injection site reactions (which are generally delayed or prolonged) need to be clearly differentiated from symptoms associated with the technique of administering subcutaneous injections (eg, local trauma due to the injection). An ISR may not be visible in 1 hour, therefore, the subject should be instructed to look for ISR symptoms (itching, redness, swelling, pain or skin ulceration) and report when the reaction occurred and describe it in detail. ISR will be graded for intensity as described in Appendix 8.

For the purposes of data collection, only reactions that begin within the first 4 hours and are persistent following an injection and/or occur more than or equal to 4 hours following an injection will be collected and the appropriate CRF form will be completed. The time period was selected as local reactions that are caused by mechanical injury generally abate within this time frame.

The examiner will indicate for each injection site reaction(s) the presence or absence of pre-defined symptoms such as itching, redness, swelling, pain or ulceration. Bruising and/or bleeding at the injection site will be recorded as adverse events associated with the injection procedure, not as an ISR. Resolution of an ISR will mean that, in the judgment of the examiner, the defined features (itching, pain, redness, swelling, ulceration) have resolved. Secondary changes, eg, hyperpigmentation, may be recorded as an adverse event but will not influence the assessment of resolution of ISR.

7.1.14. JC Virus (JCV) Monitoring and Progressive Multifocal Leukoencephalopathy (PML)

PML is an opportunistic infection of the brain caused by the JC virus (JCV) in immunosuppressed subjects, and has been observed in subjects receiving B-cell depleting agents, including rituximab, as well as with other immunosuppressive agents. Investigators should consider a diagnosis of PML in subjects who present with new-onset neurological manifestations, such as gait disturbances, memory loss, cognitive disorders, or visual

symptoms, and a neurology consult, brain MRI and lumbar puncture should be considered. There is no currently accepted screening test for PML. The disease course of PML is usually progressive and fatal. To monitor for the potential of PML, samples for JCV testing will be collected according to Schedule of Activities.

Reductions or discontinuation of concomitant immunosuppressive therapy and appropriate treatment including antiviral therapy should be considered. There are no known interventions that can reliably prevent PML or adequately treat PML if it occurs. The majority of patients who develop PML have a fatal outcome.

Any suspected case of PML should be reported as an SAE. If a confirmed or probable case of PML is observed in this or other ongoing PF-06835375 studies, the sponsor will hold dosing for all subjects until the benefit risk assessment of PF-06835375 is re-evaluated by the sponsor.

7.1.15. Viral Surveillance

Blood samples for possible analysis of cytomegalovirus (CMV), Epstein-Barr virus (EBV), herpes simplex virus type 1 & 2 (HSV-1, HSV-2) and varicella-zoster virus (VZV) will be collected according to the times outlined in the Schedule of Activities. Details regarding the collection, processing, storage and shipping of the blood samples will be provided in the lab manual.

Note: Due to delayed reporting times for these assays, the results might not be available along with the other study tests.

In addition to time points specified, a blood sample for viral surveillance sample may also be taken at the time of an AE, as clinically appropriate.

7.1.16. Suspected Herpetiform Rash

For any occurrence of a suspected herpetiform rash (eg, herpes simplex and herpes zoster), 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.

7.1.17. Assessment of Suicidal Ideation and Behavior

The Columbia Suicide Severity Rating Scale (C-SSRS) is an interview based rating scale to systematically assess suicidal ideation and suicidal behavior.[19] Versions are available for "Lifetime" and "Since Last Visit". The "Lifetime" evaluation is done at screening, and "Since Last Visit" is done at all other time points.

The C-SSRS should be collected at times specified in the Schedule of Activities section of this protocol by an appropriately trained clinical site staff member. The C-SSRS can also be administered at any time in the study at the discretion of the investigator based on any reasonable concern.

At each suicidality assessment as per Schedule of Activities, subjects felt to have significant suicidal ideation with actual plan and intent or suicidal behavior, must be evaluated by a clinician/mental health professional (MHP) skilled in the evaluation of suicidality in the subjects by virtue of training or experience (eg, psychiatrist, licensed clinical psychologist) who will determine if it is safe for the subject to participate/continue in the trial. Specific criteria that indicate a need for such an assessment are:

- Suicidal ideation associated with actual intent and/or plan in the past year; (a "YES" answer to C-SSRS questions 4 "some intent to act without specific plan" or 5 "specific plan and intent").

- Previous history of suicide behaviors in the past 10 years (a "YES" answer to any of the suicidal behavior items of the C-SSRS with the behavior occurring in the past 10 years).

- The presence of any current major psychiatric disorder that is not explicitly permitted in the inclusion/exclusion criteria and in the investigator's judgment would interfere with study participation.

- Any lifetime history of serious or recurrent suicidal behavior. [Non-suicidal self-injurious behavior is not a trigger for a risk assessment unless in the investigator's judgment it is indicated].

- In the investigators judgment a risk assessment or exclusion is warranted.

A written copy of the risk assessment should be included in the subject's source documentation.

Other possible suicidality adverse events or other clinical observations may, based on the judgment of the investigator, also trigger a risk assessment and require a narrative.

Suicidality adverse events or other clinical observations may, based on the judgment of the investigator and clinician/MHP, also trigger a risk assessment and a narrative using information from the C-SSRS, and available information, prior to screening and baseline information, and the clinician/MHP assessment. When there is a positive response to any question on the C-SSRS, the investigator should determine whether an adverse event has occurred.

7.2. Pharmacokinetics

7.2.1. Serum for Analysis of PF-06835375

During all study periods, blood samples for PK analysis will be collected at times specified in the Schedule of Activities. A serum separator tube should not be used.

The actual times may change but the number of samples will remain the same. All efforts will be made to obtain the PK samples at the exact nominal time relative to dosing. However, samples obtained within 10% of the nominal time (eg, within 6 minutes of a

60 minute sample) from dosing will not be captured as a protocol deviation, as long as the exact time of the sample collection is noted on the source document and data collection tool (CRF).

- Samples will be analyzed using a validated analytical method in compliance with Pfizer standard operating procedures. Placebo PK samples will not be analyzed.

- Details regarding the collection, processing, storage and shipping of the blood samples will be provided in the lab manual.

- The PK samples must be processed and shipped as indicated to maintain sample integrity. Any deviations from the PK processing steps, 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. Any sample deemed outside of established stability, or of questionable integrity, will be considered a protocol deviation.

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7.2.2. Shipment of Pharmacokinetic Samples

The shipment address and assay lab contact information will be provided to the investigator site prior to initiation of the study.

7.3. Immunogenicity

7.3.1. Serum for Analysis of Anti-PF-06835375 Antibodies and Neutralizing Anti-PF-06835375 Antibodies

Blood samples for the detection of Anti-PF-06835375 Antibodies (ADA) and Neutralizing Anti-PF-06835375 Antibodies (NAb) will be collected at the times specified in the Schedule of Activities.

Details regarding the collection, processing, storage and shipping of the blood samples will be provided in the lab manual.

7.3.2. Immunogenicity Analyses

The immunogenicity samples must be processed and shipped as indicated to maintain sample integrity. Any deviations from the immunogenicity processing steps, 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. Any sample deemed outside of established stability, or of questionable integrity, will be considered a protocol deviation.

Samples will be analyzed using validated analytical methods in compliance with sponsor standard operating procedures. Samples tested as ADA positive, (not just confirmed positive, but also with a titer positive result) will be further tested for NAb using validated NAb assays.

Samples collected for detecting ADA and NAb will be retained in accordance to local regulations and if not used within this timeframe, will be destroyed. CCI [redacted]

7.3.3. Shipment of Immunogenicity (ADA/NAb) Samples

The shipment address and assay lab contact information will be provided to the investigator site prior to initiation of the study.

CCI [redacted]

CCI [redacted]

DNA; however, the biospecimen may also be used to study other molecules (eg, RNA, proteins, and metabolites).

7.5. Rater Qualifications

For specific rating assessments, only qualified raters will be allowed to evaluate and/or rate subjects in this study. The minimum qualifications a rater must meet for each study rating assessment will be outlined in the Rater Assessment Manual provided to each participating site. The level of experience with the target population (or equivalent), specific scale experience (or equivalent), and certification required (if applicable) will be listed and used to

determine whether a rater is approved for a given assessment. Proposed raters who do not meet specific criteria but who may be qualified based on unique circumstances may be individually reviewed by the study clinical team to determine whether or not a waiver may be issued. The rater must become certified to perform selected study assessments before he or she can participate in the conduct of the study. For specifically defined assessments, rater training and standardization exercises may be conducted, and written and signed documentation will be provided by the site for each rater's certification. In return, each site will be provided written and signed documentation outlining each rater's certification for specific study assessments. Recertification may be required at periodic intervals during the study. The raters who administer specific study assessments will be documented in a centralized location and all site staff who administer ratings will be verified in the site study documentation during the conduct of the study.

7.6. Pharmacodynamics[redacted]

Blood samples for pharmacodynamics (PD) will be collected according to the Schedule of Activities. Details regarding the collection, processing, storage and shipping of the blood samples will be provided in the lab manual.

The PD samples must be processed and shipped as indicated to maintain sample integrity. Any deviations from the PD processing steps, 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. Any sample deemed outside of established stability or of questionable integrity will be considered a protocol deviation.

[redacted]

7.6.1. Samples Collected for All Subjects (both RA and SLE)

The following samples will be collected for all subjects

[redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

7.6.1.5. Erythrocyte Sedimentation Rate (ESR)

Blood samples for analysis of ESR will be collected at the visits specified in the Schedule of Activities. The ESR will be done locally.

7.6.1.6. B-cell Activating Factor (BAFF)

Blood samples for the analysis of B-cell activating factor (BAFF) will be collected according to times outlined in the Schedule of Activities. BAFF is also known as B Lymphocyte Stimulator (BLyS).

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

7.6.3. Samples Collected for Subjects with SLE

The following samples will be collected for subjects with SLE. In case a subject has diagnoses of both RA and SLE, both RA and SLE samples will be collected.

7.6.3.1. Anti-nuclear Antibodies

Blood samples will be collected for Anti-nuclear Antibodies (ANA), according to the times outlined in the Schedule of Activities.

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

7.7. Blood Volume

The total blood sampling volume for individual subjects in this study is as follows.

In Part A, during the first 16 weeks, the total blood volume will be approximately 820 mL. If subjects remain in the study in Part A beyond Week 16, the total blood volume every 12 weeks will be approximately 250 ml.

In Part B, during the first 16 weeks, the total blood volume will be approximately 900 mL. If subjects remain in the study in Part B beyond Week 16, the total blood volume every 12 weeks will be approximately 250 ml.

Additional blood samples may be taken for safety assessments or to repeat screening assessments (if appropriate) as described in the Schedule of Activities, provided the total volume taken during the study does not exceed 550 mL during any period of 30 consecutive days.

7.8. Diagnostic and Efficacy Assessments

7.8.1. American College of Rheumatology/European League Against Rheumatism Classification for RA

Eligibility for the study for subjects with RA will be evaluated according to the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) Classification Criteria for Rheumatoid Arthritis (See Appendix 6).[21] Subjects are required to have a score of 6 or greater at Screening, with symptom duration at least 6 months prior to Screening visit.

7.8.2. American College of Rheumatology/SLICC Criteria for the Classification of SLE

Eligibility for the study for subjects with SLE will be evaluated according to the American College of Rheumatology (ACR) / SLICC Criteria for the Classification of SLE (See Appendix 5).[22] These criteria require that subjects satisfy 4 of the clinical and immunologic criteria used in the SLICC classification criteria, including at least 1 clinical criterion and 1 immunologic criterion, OR that subject has biopsy-proven nephritis compatible with SLE in the presence of ANAs or anti-dsDNA antibodies.

In addition, subjects are also required to have symptoms at least 6 months prior to Screening visit.

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[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

CCI [redacted]

7.8.4.2. Patient's Global Assessment (PtGA) of Arthritis

This will be collected only for RA subjects. Subject will answer the following question, "Considering all the ways your arthritis affects you, how are you feeling today?" The subject's response will be recorded using a 100 mm visual analog scale (VAS) (See Appendix 10). This assessment must be performed early in the clinic visit and before the subject has extensive contact with site personnel and/or investigator and prior to dosing.

8. ADVERSE EVENT REPORTING

8.1. Requirements

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

Safety Event	**Recorded on the CRF**	**Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness**
SAE	All	All
Non-serious AE	All	None
Exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure	All (regardless of whether associated with an AE), **except occupational exposure**	Exposure during pregnancy, exposure via breastfeeding, occupational exposure (regardless of whether associated with an AE)

All observed or volunteered events regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following paragraphs.

Events listed in the table above that require reporting to Pfizer Safety on the CT SAE Report Form within 24 hours of awareness of the event by the investigator **are to be reported regardless of whether the event is determined by the investigator to be related to an investigational product under study**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer Safety must be made immediately, irrespective of the extent of available event information. This time frame also applies to additional new (follow-up) information on previously forwarded reports. In the rare situation that the investigator does not become immediately aware of the occurrence of an event, the investigator must report the event

within 24 hours after learning of it and document the time of his/her first awareness of the event.

For each event, the investigator must pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE (see the Serious Adverse Events section below). In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the CRF. In general, this 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 subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety. Any pertinent additional information must be reported on the CT SAE Report Form; additional source documents (eg, medical records, CRF, laboratory data) are to be sent to Pfizer Safety **ONLY** upon request.

As part of ongoing safety reviews conducted by the sponsor, any non-serious 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.

8.1.1. Additional Details On Recording Adverse Events on the CRF

All events detailed in the table above will be recorded on the AE page(s) of the CRF. 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.

8.1.2. Eliciting Adverse Event Information

The investigator is to record on the CRF all directly observed AEs and all AEs spontaneously reported by the study subject. In addition, each study subject will be questioned about the occurrence of AEs in a non-leading manner.

8.1.3. Withdrawal From the Study Due to Adverse Events (see also the Subject Withdrawal section)

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted below, and recorded on the CRF.

When a subject withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported, as appropriate, on the CT SAE Report Form, in accordance with the Requirements section above.

8.1.4. Time Period for Collecting AE/SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each subject begins from the time the subject provides informed consent, which is obtained before the subject's participation in the study (ie, before undergoing any study-related procedure and/or receiving investigational product), through and including and including a minimum of 90 calendar days after the last administration of the investigational product. For subjects who are in the study beyond 90 calendar days after the last administration of the investigational product (expected for most subjects), the end of study visit will be used as a minimum cut-off.

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

8.1.4.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a subject during the active collection period are reported to Pfizer Safety on the CT SAE Report Form.

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

Follow up by the investigator continues throughout and after the active collection period and until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

8.1.4.2. Recording Non-serious AEs and SAEs on the CRF

During the active collection period, both non-serious AEs and SAEs are recorded on the CRF.

Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

8.1.5. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship on the CRF, and report such an assessment in accordance with the SAE reporting requirements, if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor. If the investigator's causality assessment is "unknown but not related" to investigational product, this should be clearly documented on study records.

In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

8.1.6. Sponsor's Reporting Requirements to Regulatory Authorities

AE reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

8.2. Definitions

8.2.1. Adverse Events

An AE is any untoward medical occurrence in a study subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include, but are not limited to:

- Abnormal test findings;
- Clinically significant signs and symptoms;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Drug abuse;
- Drug dependency.

Additionally, AEs may include signs and symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;

- Occupational exposure.

8.2.2. Abnormal Test Findings

Abnormal objective test findings should be recorded as AEs when any of the following conditions are met:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result 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; and/or
- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require recording as an AE.

8.2.3. Serious Adverse Events

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Or that is considered to be:

- An important medical event.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are 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.

8.2.4. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility, or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit is assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same-day surgeries (as outpatient/same-day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of a persistent pretreatment laboratory abnormality);
- Social admission (eg, subject has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;

- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual subject.

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as SAEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an SAE. For example, an acute appendicitis that begins during the reporting period should be reported if the SAE requirements are met, and the resulting appendectomy should be recorded as treatment of the AE.

8.3. Severity Assessment

If required on the AE page of the CRF, the investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:	
MILD	Does not interfere with subject's usual function.
MODERATE	Interferes to some extent with subject's usual function.
SEVERE	Interferes significantly with subject's usual function.

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

8.4. Special Situations

8.4.1. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported to Pfizer Safety by the investigator as described in previous sections, and will be handled as SAEs in the safety database.

8.4.2. 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 subjects, transaminase elevations are a harbinger of a more serious potential outcome. These subjects fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as drug-induced liver injury (DILI). Subjects who experience a transaminase elevation above 3 times the upper limit of normal (× ULN) should be monitored more frequently to determine if they are an “adaptor” or are “susceptible.”

In the majority of DILI cases, elevations in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) precede total bilirubin (TBili) elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same lab sample).

In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the subject's individual baseline values and underlying conditions. Subjects 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:

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

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

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

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

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

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

In addition to repeating measurements of AST and ALT and TBili, laboratory tests should include albumin, creatine kinase (CK), direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/international normalized ratio (INR), total bile acids, alkaline phosphatase and acetaminophen drug and/or protein adduct levels. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen (either by itself or as a coformulated product in prescription or over-the-counter medications),

recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the 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.

8.4.3. Exposure to the Investigational Product During Pregnancy or Breastfeeding, and Occupational Exposure

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

8.4.3.1. Exposure During Pregnancy

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

- A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the investigational product;

  An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

- A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a subject or subject's partner becomes or is found to be pregnant during the subject's treatment with the investigational product, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) to Pfizer Safety using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The

information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

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

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

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

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

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 subject with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the subject was given the Pregnant Partner Release of Information Form to provide to his partner.

8.4.3.2. Exposure During Breastfeeding

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

8.4.3.3. Occupational Exposure

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

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

8.4.4. Medication Errors

Other exposures to the investigational product under study may occur in clinical trial settings, such as medication errors.

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

8.4.4.1. Medication Errors

Medication errors may result from the administration or consumption of the investigational product by the wrong subject, or at the wrong time, or at the wrong dosage strength.

Medication errors include:

- Medication errors involving subject exposure to the investigational product.
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.
- The administration of an incorrect dosage.

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

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

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

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

9. DATA ANALYSIS/STATISTICAL METHODS

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

The final analysis will be conducted when all subjects have completed all study visits. In addition, unblinded data will be analyzed when all subjects have completed the Week 16 Visit or discontinued. This analysis may take place prior to the enrollment of the optional cohort.

9.1. Sample Size Determination

The sample size was primarily based on the clinical consideration to provide sufficient safety and tolerability data. In addition, the need to obtain PK/PD data and minimize number of RA/SLE subjects exposed to PF-06835375 was taken into consideration. The sample size is not based on any statistical considerations. No formal inferential statistics will be applied to the safety or PK data.

CCI [redacted]

[redacted]

9.3. Pharmacokinetic Analysis

9.3.1. Analysis Population

The PK concentration population is defined as enrolled subjects who received at least one dose of PF-06835375 and have at least 1 concentration. The PK parameter analysis population is defined as all enrolled subjects who received at least one dose of PF-06835375 and that have at least 1 of the PK parameters of interest. Samples from subjects who received the placebo will not be analyzed routinely. Subjects who withdraw from the study may be replaced at the discretion of the sponsor. A replacement subject will receive the same treatment as the withdrawn subject.

9.3.2. Derivation of Pharmacokinetic Parameters

PK parameters for PF-06835375 following single and multiple dose administration will be derived from the concentration-time profiles by non-compartmental analysis as described in Table 5 and Table 6. Additional PK analyses may be performed if deemed appropriate. The PK parameters will be calculated using actual time and summarized descriptively by dose and regimen in accordance with Pfizer data standards. Details of the analysis will be provided in the SAP.

Table 5. PF-06835375 Serum Pharmacokinetic Parameters for Single Ascending Dose (SAD) Phase

Parameter	Definition	Method of Determination
C_{max}	Maximum serum concentration	Observed directly from data
T_{max}	Time at which C_{max} occurred	Observed directly from data as time of first occurrence
CCI	[redacted]	[redacted]
AUC_{last}	Area under the concentration-time profile from time 0 to the time of the last quantifiable concentration (C_{last})	Linear/log trapezoidal method
AUC_{inf} [a]	Area under the concentration-time profile from time 0 extrapolated to infinite time	$AUC_{last} + (C_{last}*/k_{el})$, where $C_{last}*$ was the predicted serum concentration at the last quantifiable time point estimated from the log-linear regression analysis
CCI	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
AUC_{last} (dn)	Dose normalized AUC_{last}	AUC_{last}/dose
AUC_{inf} (dn)[a]	Dose normalized AUC_{inf}	AUC_{inf}/dose
CCI	[redacted]	[redacted]

a. If data permitted.
Abbreviations: CCI [redacted]; dn = Dose normalized to 1 mg; DOF = Duration of the IV infusion dose; IV = Intravenous.

PK parameters following multiple dose administration will be derived from the concentration time profiles of the repeat dose cohorts as follows:

Table 6. PF-06835375 Serum Pharmacokinetic Parameters for Multiple Ascending Dose (MAD) Phase

Parameter	Definition	Method of Determination
AUC_{tau}	Area under the concentration-time profile from time 0 to time $_{tau}$, the dosing interval, where $_{tau}$= 28 days	Linear/log trapezoidal method
AUC_{last}	Area under the concentration-time profile from time 0 to T_{last}	Linear/log trapezoidal method
[redacted]	[redacted]	[redacted]
C_{max}	Maximum serum concentration during the dosing interval	Observed directly from data
T_{max}	Time at which C_{max} occurred	Observed directly from data as time of first occurrence
$t_{½}$[a]	Terminal half-life	$Log_e(2)/k_{el}$, where k_{el} was the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve
[redacted]	[redacted]	[redacted]
AUC_{last} (dn)	Dose normalized AUC_{last}	AUC_{last}/dose
[redacted]	[redacted]	[redacted]
C_{min}	Lowest concentration observed during the dosing interval	Observed directly from data
[redacted]	[redacted]	[redacted]
R_{ac}	Observed accumulation ratio	MD AUC_{τ}/Day 1 AUC_{τ}
R_{ac}, C_{max}	Observed accumulation ratio for C_{max}	MD C_{max}/Day 1 C_{max}
PTF	Peak-to-trough fluctuation at steady state	$(C_{max} - C_{min})/C_{av}$

a. If data permitted.
Abbreviations: dn = dose normalized to 1 mg, DOF = duration of the IV infusion dose, IV = intravenous, MAD = multiple ascending dose, SC = subcutaneous.

9.4. Pharmacodynamic Analysis

The pharmacodynamic (PD) analysis population is defined as all randomized subjects treated who have at least one PD assessment in at least one cohort. PD assessments will include, but not limited to, [redacted] soluble protein analytes, whole-blood RNA (inflammation and disease-related) and responses to vaccines. The data will be summarized and plotted by treatment group and sampling time. Further details will be documented in the SAP.

CCI [redacted]

CCI [redacted]

9.6. Safety Analysis

Adverse events, ECGs, blood pressure, pulse rate, oral temperature, continuous cardiac monitoring, and safety laboratory data will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of subjects. Any clinical laboratory, ECG, vital sign abnormalities of potential clinical concern will be described. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

Immunogenicity (ADA, NAb) results will be listed and summarized by cohorts and time points. Subject level immune response will also be summarized by cohorts. Effect of positive ADA and neutralizing immune response on safety, PD and PK may be assessed, if appropriate.

Incidence of viral infections or change in baseline of viral loads (CMV, VZV, EBV,and HSV-1/2) if they occur, will be summarized by treatment group.

Medical history and physical examination and neurologic examination information, as applicable, collected during the course of the study will be considered source data and will not be required to be reported, unless otherwise noted. However, any untoward findings identified on physical and/or neurologic examinations conducted during the active collection period will be captured as an adverse event, if those findings meet the definition of an adverse event. Data collected at Screening that are used for inclusion/exclusion criteria, such as laboratory data, ECGs and vital signs will be considered source data, and will not be required to be reported, unless otherwise noted. Demographic data collected at Screening will be reported.

9.6.1. Electrocardiogram (ECG) Analysis

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

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

Table 7. Safety QTc

	Borderline (msec)	Prolonged (msec)
Absolute Value	≥450 - <480	≥480
Absolute Change	30-<60	≥60

In addition, the number of subjects with corrected and uncorrected QT values ≥500 msec will be summarized.

If more than one ECG is collected at a nominal time after dose administration (for example, triplicate ECGs), the mean of the replicate measurements will be used to represent a single observation at that time point. If any of the three individual ECG tracings has a QTc value ≥500 msec, but the mean of the triplicates is not ≥500 msec, the data from the subject's individual tracing will be described in a safety section of the CSR in order to place the ≥500 msec value in appropriate clinical context. However, values from individual tracings within triplicate measurements that are ≥500 msec will not be included in the categorical analysis unless the average from the triplicate measurements is also ≥500 msec. Changes from baseline will be defined as the change between postdose QTc value and the average of the pre-dose triplicate values on Day 1. The average of the pre-dose triplicate QTc values on Day 1 will serve as each subject's baseline QTc value. Standard algorithms and reporting formats will be applied.

In addition, an attempt may be made to explore and characterize the relationship between serum concentration and appropriately corrected QT interval length. The results from this analysis will be reported separately from CSR.

9.7. Interim Analysis

No formal interim analysis will be conducted for this study. However, as this is a sponsor-open study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating dose-escalation decisions, facilitating PK/PD modeling, and/or to support clinical development.

9.8. Data Monitoring Committee

This study will not use a data monitoring committee. Ongoing safety reviews in support of dose escalation and during the study will be conducted by blinded and unblinded personnel as described in Section 3.4.

10. QUALITY CONTROL AND QUALITY ASSURANCE

Pfizer or its agent will conduct periodic monitoring visits during study conduct to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate

regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

During study conduct and/or after study completion, the investigator site may be subject to review by the IRB/EC, and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

The investigator(s) will notify Pfizer or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its agents to prepare the investigator site for the inspection and will allow Pfizer 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 subject's medical records. The investigator will promptly provide copies of the inspection findings to Pfizer or its agent. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its agents with an opportunity to review and comment on responses to any such findings.

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.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital or the physician subject chart. In these cases, data collected on the CRFs must match the data in those charts.

In some cases, the CRF may also serve as the source document. In these cases, a document should be available at the investigator site and at Pfizer that clearly identifies those data that will be recorded on the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to the ICH guidelines, according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or an independent third party arranged by Pfizer.

Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Institutional Review Board/Ethics Committee

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the investigator file. Copies of IRB/EC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/EC and Pfizer in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, legal and regulatory requirements, and the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), ICH Guideline for Good Clinical Practice, and the Declaration of Helsinki.

12.3. Subject Information and Consent

All parties will ensure protection of subject personal data and will not include subject names or other identifiable data in any reports, publications, or other disclosures, except where required by law.

When study data are compiled for transfer to Pfizer and other authorized parties, subject names, addresses, and other identifiable data will be replaced by numerical codes based on a numbering system provided by Pfizer in order to de-identify study subjects. The investigator site will maintain a confidential list of subjects who participated in the study, linking each subject's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subjects' personal data consistent with applicable privacy laws.

The informed consent documents and any subject recruitment materials must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent documents used during the informed consent process and any subject recruitment materials must be reviewed and approved by Pfizer, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study subject, is fully informed about the nature and objectives of the study and possible risks associated with participation.

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject before any study-specific activity is performed. The investigator will retain the original of each subject's signed consent document.

12.4. 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 investigational product, Pfizer should be informed immediately.

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

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in a Member State

End of trial in a Member State of the European Union is defined as the time at which it is deemed that a sufficient number of subjects have been recruited and completed the study as stated in the regulatory application (ie, clinical trial application [CTA]) and ethics application in the Member State. Poor recruitment (recruiting less than the anticipated number in the

CTA) by a Member State is not a reason for premature termination but is considered a normal conclusion to the study in that Member State.

13.2. End of Trial in All Other Participating Countries

End of trial in all other participating countries is defined as last subject last visit (LSLV), which may be determined by the point at which the dose-escalation and study stopping rules (Section 3.4) have been met.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or investigational product safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of PF-06835375 at any time.

If a study is prematurely terminated, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating subjects and the hospital pharmacy (if applicable) within a time period set by Pfizer. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations.

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

www.clinicaltrials.gov

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

PCD is defined as the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the prespecified protocol or was terminated.

EudraCT

Pfizer posts European Union (EU) Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the PCD for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

www.pfizer.com

Pfizer posts Public Disclosure Synopses (clinical study report synopses in which any data that could be used to identify individual patients has been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

15.2. Publications by Investigators

Pfizer supports the exercise of academic freedom and has no objection to publication by the principal investigator (PI) of the results of the study based on information collected or generated by the PI, whether or not the results are favorable to the Pfizer product. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure of the results of the study (collectively, "publication") before it is submitted or otherwise disclosed.

The investigator will provide any publication to Pfizer at least 30 days before it is submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer product-related information necessary to the appropriate scientific presentation or understanding of the study results.

If the study is part of a multicenter study, the investigator agrees that the first publication is to be a joint publication covering all investigator sites, and that any subsequent publications by the PI will reference that primary publication. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, the investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, the institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the CSA between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the CSA.

If there is any conflict between the CSA and any attachments to it, the terms of the CSA control. If there is any conflict between this protocol and the CSA, this protocol will control as to any issue regarding treatment of study subjects, and the CSA will control as to all other issues.

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Appendix 1. Abbreviations

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

Abbreviation	Term
Abs	Absolute
AE	Adverse event
ACPA	Anti- Citrullinated Peptide Antibody
ACR	American College of Rheumatology
ADA	Anti-drug antibody
ADCC	Antibody-dependent cellular cytotoxicity
ALT	Alanine aminotransferase
ANA	Anti-nuclear antibodies
ANC	Absolute neutrophil count
ANCA	Anti-neutrophil cytoplasmic antibody
Anti-dsDNA	Anti-double-stranded deoxyribonucleic acid
APS	Antiphospholipid antibody syndrome
AST	Aspartate aminotransferase
AUC	Area under the curve
BA	Bioavailability
CCI	[redacted]
CCI	[redacted]
BE	Bioequivalence
β-hCG	Beta-human chorionic gonadotropin
BLyS	B Lymphocyte Stimulator
BMI	Body mass index
BP	Blood pressure
Bpm	Beats per minute
BUN	Blood urea nitrogen
Cav	Average observed concentration
CDC	Centers for Disease Control and Prevention
CK	Creatine kinase
CL	Clearance
CLIA	Clinical Laboratory Improvement Amendments
Cmax	Maximum observed concentration
CMV	Cytomegalovirus
CNS	Central nervous system
CO2	Carbon dioxide (bicarbonate)
CRF	Case report form
CRP	C-reactive protein
CRU	Clinical research unit
CSA	Clinical study agreement
csDMARDs	Conventional synthetic Disease-modifying antirheumatic drugs
CSF	Cerebrospinal fluid

Abbreviation	Term
CSR	Clinical study report
C-SSRS	The Columbia Suicide Severity Rating Scale
CT	Clinical Trial
CTA	Clinical trial application
CTCAE	Common Terminology Criteria for Adverse Events
cTfh	Circulating follicular T helper-like
CXCL13	C-X-C Motif Chemokine Ligand 13
CXCR5	C-X-C chemokine receptor type 5
DILI	Drug-induced liver injury
DMARDs	Disease-modifying antirheumatic drugs
DMC	Data monitoring committee
DNA	Deoxyribonucleic acid
CCI [redacted]	[redacted]
DU	Dispensable unit
EBV	Epstein Barr virus
EC	Ethics committee
ECG	Electrocardiogram
E-DMC	External data monitoring committee
EDP	Exposure during pregnancy
EDR	Extemporaneous dispensing record
EDTA	Edetic acid (ethylenediaminetetraacetic acid)
eGFR	Estimated Glomerular Filtration Rate
CCI [redacted]	[redacted]
ePPND	Enhanced pre- and postnatal development study
ESR	Erythrocyte sedimentation rate
EU	European Union
EULAR	European League Against Rheumatism
EudraCT	European Clinical Trials Database
fHBP	Factor H binding protein
FIH	First in human
FSH	Follicle-stimulating hormone
GC	Germinal center
GCP	Good Clinical Practice
GCS	Global Clinical Supply
GGT	Gamma-glutamyl transferase
GLP	Good Laboratory Practice
hCG	Human chorionic gonadotropin
HepBcAb	Hepatitis B core antibody
HepBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HCVAb	Hepatitis C antibody
HED	Human equivalent dose

Abbreviation	Term
HIV	Human immunodeficiency virus
CCI [redacted]	[redacted]
HSV	herpes simplex virus
ICH	International Conference on Harmonisation
ID	Identification
Ig	Immunoglobulin
IgG	Immunoglobulin G
IGRA	Interferon gamma release assay
IND	Investigational new drug application
INR	International normalized ratio
IP	Investigational product
IRB	Institutional review board
IRC	Internal review committee
IRT	Interactive response technology
ISR	Injection site reactions
IUD	Intrauterine device
IV	Intravenous
IWR	Interactive Web-based response
JCV	JC virus
CCI [redacted]	[redacted]
LFT	Liver function test
LLN	Lower limit of normal
LSLV	Last subject last visit
mAb	Monoclonal antibody
MAD	Multiple Ascending Dose
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCP	Metacarpophalangeal
MCV	Mean corpuscular volume
CCI [redacted]	[redacted]
MHP	Mental health professional
N/A	Not applicable
Nab	neutralizing antibodies
NK	Natural killer
NOAEL	No observed adverse effect level
NSAIDS	Nonsteroidal anti-inflammatory drugs
PBMCs	Peripheral blood mononuclear cells
PCD	Primary completion date
PD	Pharmacodynamic(s)
PGx	Pharmacogenomic(s)
pH	Potential of hydrogen
PI	Principal investigator

Abbreviation	Term
PIB	Powder in bottle
PIP	Proximal interphalangeal
PK	Pharmacokinetic(s)
PML	Progressive Multifocal Leukoencephalopathy
PR	Pulse rate
PT	Prothrombin time
PtGA	Patient's Global Assessment of Arthritis
QFT-G	QuantiFERON®-TB Gold In-tube test
QTc	Corrected QT
qual	Qualitative
RA	Rheumatoid arthritis
RBC	Red blood cell
RF	Rheumatoid factor
RNA	Ribonucleic acid
CCI [redacted]	[redacted]
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SCr	Serum creatinine
SIE	Serious infectious event
CCI [redacted]	[redacted]
SLE	Systemic lupus erythematosus
CCI [redacted]	[redacted]
SOP	Standard operating procedure
CCI [redacted]	[redacted]
SRSD	Single reference safety document
TB	Tuberculosis
TBili	Total bilirubin
Td	Tetanus and Diphtheria
CCI [redacted]	[redacted]
Tfh	Follicular T helper
THC	Tetrahydrocannabinol
TK	toxicokinetics
TMCs	Tonsillar mononuclear cells
TNF	Tumor necrosis factor
ULN	Upper limit of normal
Upr/Ucr	Urinary protein to urinary creatinine ratio
US	United States
WBC	White blood cell
WNL	Within normal limits
WoCBP	Women of childbearing potential

Abbreviation	Term
WRD	Worldwide Research and Development
VAS	Visual analog scale
Vss	Volume of distribution at steady state
VZV	Varicella zoster virus

Appendix 2. List of SLE/RA-related Prohibited Medications (Immunosuppressants & Immunomodulators)

These medications are prohibited starting from specified period prior to Screening until the subject's end of study visit. If subject requires any prohibited medication during the study, the Investigator should contact sponsor medical monitor or Clinician. Subject should remain in the study and be followed per Schedule of Activities in the event of receiving a prohibited medication for disease-flare.

Drug/class	Timeframe of restriction prior to Screening
B cell depleting agents (eg, Rituximab)	52 weeks
Intravenous immunoglobulin [IVIG]	16 weeks
TNF-α inhibitors (ie, etanercept, adalimumab, infliximab) including investigational TNF-a biosimilars	8 weeks
Belimumab	12 weeks
Cyclophosphamide	24 weeks
Abatacept	8 weeks
Tofacitinib, Baricitinib or other JAK inhibitors	4 weeks
Calcineurin inhibitors (eg, cyclosporine, tacrolimus)	8 weeks
IL-6 or IL-6 receptor targeting agents (eg, sarilimab, tocilizumab)	8 weeks
Intravenous corticosteroids (ie, methylprednisolone)	8 weeks
Oral corticosteroids[a]	4 weeks
Intramuscular corticosteroids[b]	4 weeks
Any other immunosuppressant or immunomodulating drugs, including biologic and/or non-biologic therapies.	8 weeks

a. Use of oral corticosteroids greater than prednisone 20 mg (or equivalent) is not permitted within 4 weeks of Screening. As noted in Appendix 3, oral prednisone (10 mg or less) is allowed during the study, but must be at a stable dose for 4 weeks prior to Day 1.

b. Use of intramuscular corticosteroids is not permitted within 4 weeks of screening and during the study.

Appendix 3. List of Allowed SLE/RA-related and Chronic Medications

All allowed medications must be taken as described in the table below at stable doses, defined as no more than 20% change in dose. This applies from the timeframe specified in the table until the subject's end of study visit. If subject requires any of the below medications at higher doses during the study, investigator should contact sponsor to determine if the subject should be discontinued from the study.

Only one drug from each of the classes below (immunosuppressants, anti-malarials and corticosteroids) is allowed.

Drug/class	Timeframe of restriction prior to Day 1 visit	Maximum allowed dose (stable)	Other restrictions
Immunosuppressants & Immunomodulators			
Methotrexate	8 weeks	25 mg/week	N/A
Leflunomide	8 weeks	20 mg/day	N/A
Sulfasalazine	8 weeks	3 g/day	N/A
Azathioprine	8 weeks	1 mg/kg/day	N/A
Mycophenolate	8 weeks	1.5 g/day	N/A
Anti-malarial			
Hydroxychloroquine	8 weeks	400 mg/day	Only oral formulations permitted
Chloroquine	8 weeks	250 mg/day	Only oral formulations permitted
Corticosteroids			
Oral	4 weeks	10 mg/day prednisone equivalent	N/A
Intra-articular injections	2 weeks	20 mg triamcinolone equivalent per joint	N/A
Drugs to treat chronic medical conditions	4 weeks	N/A	N/A

Appendix 4. Oral Corticosteroids, Systemic Equivalencies[25]

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

Appendix 5. SLICC Classification Criteria for SLE

A subject is classified as having SLE if he or she satisfies 4 of the clinical and immunologic criteria used in the SLICC classification criteria, including at least 1 clinical criterion and 1 immunologic criterion, OR if he or she has biopsy-proven nephritis compatible with SLE in the presence of ANAs or anti-dsDNA antibodies.

The criteria do not need to be present concurrently. A criterion should only be judged as fulfilled if better explained by other causal relationships (eg, other disease, drug-site effects).[22]

2012 SLICC SLE Criteria		
Clinical Criteria		
Has the subject ever experienced any of the following clinical criteria?		
1. Acute Cutaneous Lupus		
Lupus malar rash (do not count if malar discoid)	Yes	No
Bullous lupus	Yes	No
Toxic epidermal necrolysis variant of SLE	Yes	No
Maculopapular lupus rash	Yes	No
Photosensitive lupus rash in the absence of dermatomyositis	Yes	No
Subacute cutaneous lupus (nonindurated psoriasiform and/or annular polycyclic lesions that resolve without scarring, although occasionally with postinflammatory dyspigmentation or telangiectasias)	Yes	No
2. Chronic Cutaneous Lupus		
Localized classical discoid rash (above the neck)	Yes	No
Generalized classical discoid rash (above and below the neck)	Yes	No
Hypertrophic (verrucous) lupus	Yes	No
Lupus panniculitis (profundus)	Yes	No
Mucosal lupus	Yes	No
Lupus erythematosus tumidus	Yes	No
Chillblains lupus	Yes	No
Discoid lupus/lichen planus overlap	Yes	No
3. Oral or nasal ulcers in the absence of other causes, such as vasculitis, Behcet's disease/syndrome, infection (herpes), inflammatory bowel disease, reactive arthritis, and acidic foods		
Palate	Yes	No
Buccal	Yes	No
Tongue	Yes	No
Nasal	Yes	No

4. Non-scarring alopecia (diffuse thinning or hair fragility with visible broken hairs) in the absence of other causes such as alopecia areata, drugs, iron deficiency and androgenic alopecia	Yes	No
5. Synovitis involving 2 or more joints, characterized by swelling or effusion OR tenderness in 2 or more joints and thirty minutes or more of morning stiffness	Yes	No
6. Serositis		
Typical pleurisy for more than 1 day	Yes	No
Pleural effusions	Yes	No
Pleural rub	Yes	No
Typical pericardial pain (pain with recumbency improved by sitting forward) for more than 1	Yes	No
Pericardial effusion	Yes	No
Pericardial rub	Yes	No
Pericarditis by ECG in the absence of other causes, such as infection, uremia, and Dressler's pericarditis	Yes	No
7. Renal		
Urine protein/creatinine ratio (or 24 hour urine protein) representing ≥500 mg of protein/24hr	Yes	No
Red blood cell casts	Yes	No
8. Neurologic		
Seizures	Yes	No
Psychosis	Yes	No
Mononeuritis multiplex in the absence of other known causes such as primary vasculitis	Yes	No
Myelitis	Yes	No
Peripheral or cranial neuropathy in the absence of other known causes such as primary vasculitis, infection, and diabetes mellitus	Yes	No
Acute confusional state in the absence of other causes, including toxic-metabolic, uremia, drugs	Yes	No
9. Hemolytic anemia	Yes	No
10. Leukopenia		
Leukocytes <4000/mm^3 at least once in the absence of other known causes such as Felty's syndrome, drugs, and portal hypertension	Yes	No
Lymphocytes <1000/mm^3 at least once in the absence of other known causes such as corticosteroids, drugs and infection	Yes	No
11. Thrombocytopenia (<100,000/mm^3) at least once in the absence of other known causes such as drugs, portal hypertension, and thrombotic thrombocytopenic purpura (TTP)	Yes	No
Immunological criteria		
1. ANA above laboratory reference range increase	Yes	No
2. Anti-dsDNA antibody above laboratory reference range, except enzyme-linked immunosorbent assay (ELISA): twice above laboratory reference range	Yes	No
3. Anti-Sm	Yes	No

4. Antiphospholipid antibody		
Lupus anticoagulant	Yes	No
False-positive rapid plasma regain (RPR)	Yes	No
Medium or high titer anticardiolipin antibody level (IgA, IgG, or IgM)	Yes	No
Anti-β2 glycoprotein I (IgA, IgG, or IgM)	Yes	No
5. Low complement		
Low C3	Yes	No
Low C4	Yes	No
Low CH50	Yes	No
6. Direct Coombs test in the absence of hemolytic anemia	Yes	No

Appendix 6. The 2010 American College of Rheumatology/European League Against Rheumatism Classification Criteria for Rheumatoid Arthritis[21]

	Score
Target population (Who should be tested?): Patients who Have at least 1 joint with definite clinical synovitis (swelling)*	
With the synovitis not better explained by another disease†	
Classification criteria for RA (score-based algorithm: add score of categories A-D; a score of ≥6/10 is needed for classification of a patient as having definite RA)‡	
Joint involvement§	
1 large joint¶	0
2-10 large joints	1
1-3 small joints (with or without involvement of large joints)#	2
4-10 small joints (with or without involvement of large joints)	3
>10 joints (at least 1 small joint)**	5
Serology (at least 1 test result is needed for classification)††	
Negative RF and negative ACPA	0
Low-positive RF or low-positive ACPA	2
High-positive RF or high-positive ACPA	3
Acute-phase reactants (at least 1 test result is needed for classification)‡‡	
Normal CRP and normal ESR	0
Abnormal CRP or abnormal ESR	1
Duration of symptoms§§	
<6 weeks	0
≥6 weeks	1

*The criteria are aimed at classification of newly presenting patients. In addition, patients with erosive disease typical of rheumatoid arthritis (RA) with a history compatible with prior fulfillment of the 2010 criteria should be classified as having RA. Patients with longstanding disease, including those whose disease is inactive (with or without treatment) who, based on retrospectively available data, have previously fulfilled the 2010 criteria should be classified as having RA.

†Differential diagnoses vary among patients with different presentations, but may include conditions such as systemic lupus erythematosus, psoriatic arthritis, and gout. If it is unclear about the relevant differential diagnoses to consider an expert rheumatologist should be consulted.

‡Although patients with a score of <6/10 are not classifiable as having RA, their status can be reassessed and the criteria might be fulfilled cumulatively over time.

§Joint involvement refers to any *swollen* or *tender* joint on examination, which may be confirmed by imaging evidence of synovitis. Distal interphalangeal joints, first carpometacarpal joints, and first metatarsophalangeal joints are *excluded from assessment*. Categories of joint distribution are classified according to the location and number of involved joints, with placement into the highest category possible based on the pattern of joint involvement.
¶"Large joints" refers to shoulders, elbows, hips, knees, and ankles.
#"Small joints" refers to the metacarpophalangeal joints, proximal interphalangeal joints, second through fifth metatarsophalangeal joints, thumb interphalangeal joints, and wrists.
**In this category, at least 1 of the involved joints must be a small joint; the other joints can include any combination of large and additional small joints, as well as other joints not specifically listed elsewhere (eg, temporomandibular, acromioclavicular, sternoclavicular, etc.).
†† Negative refers to IU values that are less than or equal to the upper limit of normal (ULN) for the laboratory and assay; low-positive refers to IU values that are higher than the ULN but ≤3 times the ULN for the laboratory and assay; high-positive refers to IU values that are >3 times the ULN for the laboratory and assay. Where rheumatoid factor (RF) information is only available as positive or negative, a positive result should be scored as low-positive for RF. ACPA = anti-citrullinated protein antibody.
‡‡Normal/abnormal is determined by local laboratory standards. CRP = C-reactive protein; ESR = erythrocyte sedimentation rate.
§§ Duration of symptoms refers to patient self-report of the duration of signs or symptoms of synovitis (eg, pain, swelling, tenderness) of joints that are clinically involved at the time of assessment, regardless of treatment status.

Appendix 7. Common Terminology Criteria For Adverse Events (Infusion Reactions)

		Grade				
Adverse Event	Short Name	1	2	3	4	5
Allergic reaction/ Hypersensitivity (including drug fever)	Allergic Reaction	Transient flushing or rash; drug fever <38°C (<100.4°F)	Rash; flushing; urticaria; dyspnea; drug fever ≥38°C (≥100.4°F)	Symptomatic bronchospasm, with or without urticaria; parenteral medication(s) indicated; allergy-related edema/angioedema; hypotension	Anaphylaxis	Death
Remark: Urticaria with manifestations of allergic or hypersensitivity reaction is graded as Allergic reaction/hypersensitivity (including drug fever).						
Hypertension	Hypertension	Asymptomatic, transient (<24 hrs) increase by >20 mmHg (diastolic) or to >150/100 if previously WNL; intervention not	Recurrent or persistent (≥24 hrs) or symptomatic increase by >20 mmHg (diastolic) or to >150/100 if previously WNL; monotherapy may be indicated	Requiring more than one drug or more intensive therapy than previously	Life-threatening consequences (eg, hypertensive crisis)	Death
Hypotension	Hypotension	Changes, intervention not indicated	Brief (<24 hrs) fluid replacement or other therapy; no physiologic consequences	Sustained (≥4 hrs) therapy, resolves without persisting physiologic consequences	Shock (eg, acidemia; impairment of vital organ	Death
Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10^9/L)	Fever	38.0 to 39.0°C (100.4 to 102.2°F)	>39.0 to 40.0 degrees C (102.3 to 104.0°F)	>40.0°C (>104.0°F) for ≤24 hrs	>40.0°C (>104.0°F) for >24 hrs	Death
Remark: The temperature measurements listed are oral or tympanic.						
Rigors/chills		Mild	Moderate, narcotics indicated	Severe or prolonged, not responsive to narcotics	--	--
Cytokine release syndrome/acute infusion reaction	Cytokine release	Mild reaction; infusion interruption not indicated; intervention not indicated	Requires therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates)	Life-threatening; pressor or ventilatory support indicated	Death

Remark: Cytokine release syndromes/acute infusion reactions are different from Allergic/hypersensitive reactions, although some of the manifestations are common to both AEs. An acute infusion reaction may occur with an agent that causes cytokine release (eg, monoclonal antibodies or other biological agents). Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hrs of completion of infusion. Signs/symptoms may include: Allergic reaction/hypersensitivity (including drug fever); Arthralgia (joint pain); Bronchospasm; Cough; Dizziness; Dyspnea (shortness of breath); Fatigue (asthenia, lethargy, malaise); Headache; Hypertension; Hypotension; Myalgia (muscle pain); Nausea; Pruritis/itching; Rash/desquamation; Rigors/chills; Sweating (diaphoresis); Tachycardia; Tumor pain (onset or exacerbation of tumor pain due to treatment); Urticaria (hives, welts, wheals); Vomiting.

Appendix 8. Antigen Local Reactivity Due to IP or Vaccine Challenges

All local reactions at the site of IP injection or antigen injections [redacted] will be recorded as AEs. Antigen injection sites will be monitored for pain, tenderness, erythema and swelling using the intensity grading scheme presented below

Injection Site Reaction Grading Scheme

	Intensity Grading			
Reaction	**Mild**	**Moderate**	**Severe**	**Potentially Life-threatening**
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	Emergency room visit or hospitalization
Erythema/redness	2.5 to 5 cm	5.1 to 10 cm	>10 cm	Necrosis or exfoliative dermatitis
Induration/swelling	2.5 to 5 cm and does not interfere with activity	5.1 to 10 cm or interferes with activity	>10 cm or prevents daily activity	Necrosis

CCI [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

Appendix 10. Patient's Global Assessment (PtGA) of Arthritis

CONSIDERING ALL THE WAYS YOUR ARTHRITIS AFFECTS YOU, HOW ARE YOU FEELING TODAY?

(PLEASE MAKE AN X MARK ON THE LINE BELOW.)

Very Well _____ Very Poorly

[Note: Scale will be 100 mm in length]

CCI

[redacted]