CLINICAL PHARMACOLOGY PROTOCOL

A PHASE 1, RANDOMIZED, DOUBLE-BLIND, SPONSOR-OPEN, PLACEBO -CONTROLLED, FIRST-IN-HUMAN TRIAL TO EVALUATE THE SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF PF-06755347 AFTER SINGLE ASCENDING INTRAVENOUS AND SUBCUTANEOUS DOSING IN HEALTHY ADULT MALE PARTICIPANTS AND OPEN-LABEL AFTER SINGLE SUBCUTANEOUS DOSING IN MALE AND FEMALE PARTICIPANTS WITH PERSISTENT OR CHRONIC PRIMARY IMMUNE THROMBOCYTOPENIA

Investigational Product Number:	PF-06755347
Investigational Product Name:	Not Applicable (N/A)
United States (US) Investigational New Drug (IND) Number:	CCI [redacted]
European Clinical Trials Database (EudraCT) Number:	CCI [redacted]
Protocol Number:	B7801001
Phase:	1

Short Title: A Phase 1 randomized, placebo-controlled study to evaluate safety, tolerability, and PK of PF-06755347 after SAD IV or SC dosing in HPs and open-label by SC dosing in participants with persistent or chronic primary ITP.

Protocol Amendment Summary of Changes Table

Amendment 8 25 July 2022

Overall Rationale for the Amendment to incorporate changes requested by the Czech Republic Regulatory Agency, add CCI biomarker collection and clarify rescue medications to be consistent with BRC.

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 10.12 Appendix 12 Country Specific Requirements	Added specific Czech Republic requirements to Appendix 12	Regulatory request	Substantial
Section 6.6 Dose Progression	Added specific Czech Republic enrollment requirements for female participants	Regulatory request	Substantial
CCI [redacted]	[redacted]	[redacted]	[redacted]
Rescue Medication 6.5.1.1 and 6.5.1.2	Provided specific guidance to investigators regarding rescue therapy for CRS and for bleeding in participants with ITP	Regulatory request for clarity and RMC requirement	Nonsubstantial
4.2.1.3.2. Subcutaneous Administration in Healthy Participants Table 7	Added updated values of Observed Human Exposures and Safety Margins Following Single SC Administration of PF-06755347	Makes data table current	Nonsubstantial
Section 5.3 Inclusion Criteria for Participants with ITP	Added references for the established guidelines for ITP	Corroborates with the inclusion criterion for ITP	Nonsubstantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 1.1 Protocol Overview Cohort Overview for IV and SC Administration	Added numbers of participants dosed	Makes data table current	Nonsubstantial
Section 4.1 Overall Design	Included changes implemented with PACL dated 01 Apr 2022	To explain the reason that the safety and tolerability of PF-06755347 is not being evaluated in healthy female participants prior to administration to female participants with ITP in B7801001	Nonsubstantial
Section 10.13 Appendix 13 Protocol Amendment History	Moved protocol amendment history to new Appendix 13	Updated per Sponsor's revised SOP protocol template	Nonsubstantial

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

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

SCHEDULE OF ACTIVITIES

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

Table 1. Schedule of Activities for IV cohorts

Protocol Activity	**Screen**		**Clinical Confinement**																**Outpatient Follow-Up Visits**						
Study Day/Visit Window (days) **Abbreviations used in this table may be found in 10.14. Appendix 14: Abbreviations**	**-56 to -2**	**-1[a]**	**1**										**2**	**3**		**4**	**6**	**8**	**11 ±2**	**15 ±2**	**22 ±2**	**29 ±2**	**36[a] ±3**	**50[a] ±3**	**71[a] ±3 or ET**
Hour(s) Post Dose			**0 pre-dose**	**0.5**	**1 or EOI[b]**	**3 or EOI[c]**	**3.5**	**4**	**5**	**6**	**8**	**12**	**24**	**36**	**48**	**72**	**120**	**168**	**240**	**336**	**504**	**672**	**840**	**1176**	**1680**
Informed consent	X																								
Demography (including Height)	X																								
Outpatient Visit	X																		X	X	X	X	X[a]	X[a]	X[a]
Study Site Confinement		X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X							
Discharge																		X							
Chest X-ray[d]	X																								
QuantiFERON-TB Gold test	X																								
HIV, HepBsAg, HepBcAb, HCVAb tests	X																								
Test for anti-cardiolipin antibody, rheumatoid factor, anti-nuclear antibody, Total IgG and Total IgA, TSH, thyroxine (free T4), and triiodothyronine (free T3) and TSAb. Lipid profile.	X																								
Inclusion/Exclusion	X	X																							
Medical history; history of illegal drug, alcohol & tobacco use	X	X[e]																							
Medication history	X	X[e]																							
Weight	X	X																					X[f]		X[f]
Urine drug screening	X	X																							
Review contraception use	X	X																X	X	X	X	X	X	X	X
Physical examination[g]	X	X																X	X	X	X	X	X	X	X

Table 1. Schedule of Activities for IV cohorts

Protocol Activity	Screen		Clinical Confinement																Outpatient Follow-Up Visits						
Study Day/Visit Window (days) **Abbreviations used in this table may be found in 10.14. Appendix 14: Abbreviations**	-56 to -2	-1[a]	1										2	3		4	6	8	11 ±2	15 ±2	22 ±2	29 ±2	36[a] ±3	50[a] ±3	71[a] ±3 or ET
Hour(s) Post Dose			0 pre-dose	0.5	1 or EOI[b]	3 or EOI[c]	3.5	4	5	6	8	12	24	36	48	72	120	168	240	336	504	672	840	1176	1680
Hematology & Coagulation (PT, INR, PTT, D-dimer & fibrinogen) Safety Labs	X	X			X[m,n]	X[n]			X[n]		X[n]	X[n]	X		X[n]	X	X	X	X	X	X	X	X	X	X
Chemistry/Urinalysis/Other Safety Labs	X	X			X[m,n]								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		X		X		X
Telemetry		X[i]	X[i]	→	→	→	→	→	→	→	X														
Vital signs (BP, pulse rate, temperature)[j]	X		X	X	X	X	X[n]	X[n]	X	X[n]	X	X	X	X	X	X	X	X	X	X	X	X[n]	X	X[n]	X
Pulse Oximetry	X		X	X	X	X	X[n]	X[n]	X	X[n]	X	X	X	X	X	X	X	X	X	X	X	X[n]	X	X[n]	X
ADA blood sampling	X[o]	X																X		X			X		X
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]																						
IV administration			X[l]	→	X	X																			
Infusion site assessment			X	X	X	X	X[n]	X[n]	X	X[n]	X	X	X					X[n]		X[n]			X[n]		X[n]
PK blood sampling (IV Cohorts 1 and 2 only)			X		X	X			X		X	X	X	X	X	X	X	X							
PK blood sampling (IV Cohorts 3-5)			X		X	X			X		X	X	X		X	X	X	X		X	X	X	X	X	X
PK blood sampling (IV Cohorts 5 exp. 6-9, and optional IV cohorts)			X		X[m,n]	X	X[n]	X[n]	X	X[n]	X	X	X		X	X	X	X		X	X	X	X	X	X
Serious and non-serious Adverse Event monitoring	X	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X
Prior/Concomitant treatments	X	X	X									X	→	→	→	→	→	→	→	→	→	→	→	→	X

Abbreviations: →= ongoing/continuous; ADA= anti-drug antibody; BP = blood pressure; ECG = electrocardiogram; EOI = end of infusion; HepBsAg = hepatitis B surface antigen; HepBcAb = hepatitis B core antibody; HCVAb = hepatitis C antibody; HIV = human immunodeficiency virus; IgA = immunoglobulin A; IgG = immunoglobulin G; INR = international normalized ratio; IV = intravenous; PK = pharmacokinetics; PT = prothrombin time; PTT = partial thromboplastin time; RNA = ribonucleic acid; TB = tuberculosis; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid stimulating hormone; TSAb = thyroid stimulating antibodies.

a. Admission may be on Day -2 or Day -1 at the discretion of the Investigator. Cohorts with proposed doses ≤1 mg/kg by intravenous (IV) administration will complete the study on approximately Day 36. Remaining visit(s)/assessments are not applicable if participant has completed the study. Cohorts with proposed doses >1 mg/kg by IV administration will complete the study at approximately Day 71. If a participant discontinues early they should, when possible, return to complete assessments outlined at Day 71. The follow-up period may be extended if any participant in a particular cohort is tested positive for anti-drug antibody to PF-06755347 or has detectable concentration of PF-06755347 at final study visit. If there is an early termination (ET), the Day 71 schedule will be followed.

b. Immediately prior to end of infusion (PEOI) for cohorts with targeted infusion duration of approximately 1 hour. If the infusion is interrupted and restarted, the infusion duration will not exceed 2 hours.

c. Immediately prior to end of infusion (PEOI for cohorts with targeted infusion duration of 3 hours. If the infusion is interrupted, the infusion duration will not exceed 4 hours.

d. Chest X-ray results within 3 months of screening visit otherwise a chest X-ray must be performed at screening and results obtained prior to admission.

e. Update alcohol and nicotine use since screening.

f. Weight should be measured at Day 36 for participants on a dose of ≤1 mg/kg and on Day 71 only for participants on a dose of >1 mg/kg.

g. Full physical examination (PE) may be done at screening or may be deferred to admission at the discretion of the investigator. If a full PE is performed at screening, a limited PE may be performed at admission. Limited PE may be performed at discharge or at any outpatient visit at the discretion of the investigator.

h. Single electrocardiogram (ECG) at screening and scheduled outpatient visits; triplicate ECG at all other time points (including unscheduled, early termination, or extended immune follow-up visit).

i. Baseline for at least 2 hours between admission and prior to dosing while awake.

j. Vital signs measurement (including BP, pulse rate & temperature) triplicate at pre-dose only, at the discretion of the investigator triplicate assessments may be taken at other timepoints. Oral or tympanic method for temperature determination is allowed, however must be used consistently for each participant.

k. Banked biospecimen may be collected on admission or Day 1 (prior to dosing). If not collected on the designated collection day, collect at the next available time point when biospecimens are being collected in conjunction with a participant visit.

l. Start of infusion time.

m. Samples for safety laboratory and pharmacokinetics (PK) at 1 h will not be collected in participants with targeted infusion duration ≥3 h.

n. Procedures updated from amendment 2.

o. No screening anti-drug antibody (ADA) blood sample is needed for participants in Cohort 5 expansion and in Cohorts 6-11.

Table 2. Schedule of Activities for SC Cohorts of Healthy Participants

Protocol Activity **Abbreviations used in this table may be found in 10.14. Appendix 14: Abbreviations**	**Screen**		**Clinical Confinement**																**Outpatient Follow-Up Visits**						
Study Day/Visit Window (days)	**-56 to -2**	**-1[a]**	**1**										**2**	**3**		**4**	**5**	**6**	**8**	**11 ±2**	**15 ±2**	**22 ±2**	**29 ±2**	**36 ±3**	**50 ±3**	**71 ±3 or ET**
Hour(s) Post Dose			**0 pre-dose**	**0.5**	**1**	**3**	**3.5**	**4**	**5**	**6**	**8**	**12**	**24**	**36**	**48**	**72**	**96**	**120**	**168**	**240**	**336**	**504**	**672**	**840**	**1176**	**1680**
Informed consent	X																									
Demography (including Height)	X																									
Outpatient Visit	X																			X	X	X	X	X	X	X
Study Site Confinement		X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X							
Randomization			X																							
Discharge																			X							
Chest X-ray[b]	X																									
QuantiFERON-TB Gold test	X																									
HIV, HepBsAg, HepBcAb, HCVAb tests	X																									
Test for rheumatoid factor, anti-nuclear antibody, Total IgG and Total IgA, TSH, thyroxine (free T4), and triiodothyronine (free T3) TSAb; Lipid profile.	X																									
Inclusion/Exclusion	X	X																								
Medical history; history of illegal drug, alcohol & tobacco use	X	X[c]																								
Medication history	X	X[c]																								
Weight	X	X																						X		X
Urine drug screening	X	X																								
Review contraception use	X	X																	X	X	X	X	X	X	X	X
Physical examination[d]	X	X																	X	X	X	X	X	X	X	X
Hematology & Coagulation (PT, INR, PTT, D-dimer & fibrinogen) Safety Labs	X	X										X	X		X	X		X	X	X	X	X	X	X	X	X
Chemistry/Urinalysis/Other Safety Labs	X	X										X	X		X	X		X	X	X	X	X	X	X	X	X
ECG[e]	X		X							X		X	X		X	X		X	X	X		X		X		X
Telemetry[h]		X	X	→	→	→	→	→	→	→	X															

Table 2. Schedule of Activities for SC Cohorts of Healthy Participants

Protocol Activity **Abbreviations used in this table may be found in 10.14. Appendix 14: Abbreviations**	**Screen**		**Clinical Confinement**																**Outpatient Follow-Up Visits**						
Study Day/Visit Window (days)	**-56 to -2**	**-1[a]**	**1**										**2**	**3**		**4**	**5**	**6**	**8**	**11 ±2**	**15 ±2**	**22 ±2**	**29 ±2**	**36 ±3**	**50 ±3**	**71 ±3 or ET**
Hour(s) Post Dose			**0 pre-dose**	**0.5**	**1**	**3**	**3.5**	**4**	**5**	**6**	**8**	**12**	**24**	**36**	**48**	**72**	**96**	**120**	**168**	**240**	**336**	**504**	**672**	**840**	**1176**	**1680**
Vital signs (BP, pulse rate, temperature)[f]	X		X							X		X	X	X	X	X		X	X	X	X	X	X	X	X	X
Pulse Oximetry	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X
ADA blood sampling		X																	X		X			X[i]		X
CCI		[redacted]																								
SC Administration			X																							
SC Injection site assessment			X	X	X	X	X	X	X	X	X	X	X						X		X			X		X
PK blood sampling (SC cohorts)			X							X		X	X		X	X	X	X	X	X	X	X	X	X	X	X
Serious and non-serious Adverse Event monitoring	X	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X
Prior/Concomitant treatments	X	X	X									X	→	→	→	→	→	→	→	→	→	→	→	→	→	X

Abbreviations: →= ongoing/continuous; ADA= anti-drug antibody; BP = blood pressure; ECG = electrocardiogram; EOI = end of infusion; HepBsAg = hepatitis B surface antigen; HepBcAb = hepatitis B core antibody; HCVAb = hepatitis C antibody; HIV = human immunodeficiency virus; IgA = immunoglobulin A; IgG = immunoglobulin G; INR = international normalized ratio; PK = pharmacokinetics; PT = prothrombin time; PTT = partial thromboplastin time; RNA = ribonucleic acid; SC = subcutaneous; TB = tuberculosis; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid stimulating hormone; TSAb = thyroid stimulating antibodies.

a. Admission may be on Day -2 or Day -1 at the discretion of the Investigator. If a participant discontinues early they should, when possible, return to complete assessments outlined at Day 71. The follow up period may be extended if any participant in a particular cohort is tested positive for anti-drug antibody to PF-06755347 or has detectable concentration of PF-06755347 at final study visit. If there is an early termination (ET), the Day 71 schedule will be followed.

b. Chest X-ray results within 3 months of screening visit otherwise a chest X-ray must be performed at screening and results obtained prior to admission.

c. Update alcohol and nicotine use since screening.

d. Full physical examination (PE) may be done at screening or may be deferred to admission at the discretion of the investigator. If a full PE is performed at screening, a limited PE may be performed at admission. Limited PE may be performed at discharge or at any outpatient visit at the discretion of the investigator.
e. Single electrocardiogram (ECG) at screening and scheduled outpatient visits; triplicate ECG at all other time points (including unscheduled, early termination, or extended immune follow up visit).
f. Vital signs measurement (including BP, pulse rate & temperature) triplicate at pre dose only, at the discretion of the investigator triplicate assessments may be taken at other timepoints. Either oral or tympanic method for temperature determination is allowed; however the method should be used consistently for each participant.
g. Banked biospecimen may be collected on admission or Day 1 (prior to dosing). If not collected on the designated collection day, collect at the next available time point when biospecimens are being collected in conjunction with a participant visit.
h. Only participants dosed prior to acceptance of protocol amendment 6 will have telemetry performed.

Table 3. Schedule of Activities for SC Cohorts of ITP Participants

Protocol Activity Abbreviations used in this table may be found in 10.14. Appendix 14: Abbreviations	**Screen**		**Clinical Confinement**																**Outpatient Follow-Up Visits**						
Study Day/Visit Window (days)	**-56 to -2**	**-1[a]**	**1**										**2**	**3**		**4**	**5**	**6**	**8**	**11 ±2**	**15 ±2**	**22 ±2**	**29 ±2**	**36 ±3**	**50 ±3**	**71 ±3 or ET**
Hour(s) Post Dose			**0 pre-dose**	**0.5**	**1**	**3**	**3.5**	**4**	**5**	**6**	**8**	**12**	**24**	**36**	**48**	**72**	**96**	**120**	**168**	**240**	**336**	**504**	**672**	**840**	**1176**	**1680**
Informed consent	X																									
Demography (including Height)	X																									
Outpatient Visit	X																			X	X	X	X	X	X	X
Study Site Confinement		X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X							
Randomization			X																							
Discharge																			X							
Chest X-ray[b]	X																									
QuantiFERON-TB Gold test	X																									
HIV, HepBsAg, HepBcAb, HCVAb tests	X																									
Test for rheumatoid factor, anti nuclear antibody, Total IgG and Total IgA, TSH, thyroxine (free T4), and triiodothyronine (free T3) TSAb; Lipid profile	X																									
Inclusion/Exclusion	X	X																								
Medical history; history of illegal drug, alcohol & tobacco use	X	X[c]																								
Medication history	X	X[c]																								
Weight	X	X																						X		X
Urine drug screening	X	X																								
FSH[h]	X																									
Serum Pregnancy[i]	X	X																								
Review contraception use	X	X																	X	X	X	X	X	X	X	X
Physical examination[d]	X	X																	X	X	X	X	X	X	X	X
Hematology & Coagulation (PT, INR, PTT, D-dimer & fibrinogen) Safety Labs	X	X										X	X		X	X		X	X	X	X	X	X	X	X	X
Chemistry/Urinalysis/Other Safety Labs	X	X										X	X		X	X		X	X	X	X	X	X	X	X	X

Table 3. Schedule of Activities for SC Cohorts of ITP Participants

Protocol Activity Abbreviations used in this table may be found in 10.14. Appendix 14: Abbreviations	Screen		Clinical Confinement																	Outpatient Follow-Up Visits						
Study Day/Visit Window (days)	**-56 to -2**	**-1[a]**	**1**										**2**	**3**		**4**	**5**	**6**	**8**	**11 ±2**	**15 ±2**	**22 ±2**	**29 ±2**	**36 ±3**	**50 ±3**	**71 ±3 or ET**
Hour(s) Post Dose			**0 pre-dose**	**0.5**	**1**	**3**	**3.5**	**4**	**5**	**6**	**8**	**12**	**24**	**36**	**48**	**72**	**96**	**120**	**168**	**240**	**336**	**504**	**672**	**840**	**1176**	**1680**
ECG[e]	X		X							X		X	X		X	X		X	X	X		X		X		X
Vital signs (BP, pulse rate, temperature)[f]	X		X							X		X	X	X	X	X		X	X	X	X	X	X	X	X	X
Pulse Oximetry	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X
ADA blood sampling		X																	X		X			X		X
CCI																										
SC Administration			X																							
SC Injection site assessment			X	X	X	X	X	X	X	X	X	X	X						X		X			X		X
PK blood sampling			X							X		X	X		X	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test[j]			X																					X		X
Serious and non-serious Adverse Event monitoring	X	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X
Prior/Concomitant treatments	X	X	X									X	→	→	→	→	→	→	→	→	→	→	→	→	→	X

Abbreviations: →= ongoing/continuous; ADA= anti-drug antibody; BP = blood pressure; ECG = electrocardiogram; HepBsAg = hepatitis B surface antigen; HepBcAb = hepatitis B core antibody; HCVAb = hepatitis C antibody; HIV = human immunodeficiency virus; IgA = immunoglobulin A; IgG = immunoglobulin G; INR = international normalized ratio; PK = pharmacokinetics; PT = prothrombin time; PTT = partial thromboplastin time; RNA = ribonucleic acid; SC = subcutaneous; TB = tuberculosis; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid stimulating hormone; TSAb = thyroid stimulating antibodies.

a. Admission may be on Day -2 or Day -1 at the discretion of the Investigator. If a participant discontinues early they should, when possible, return to complete assessments outlined at Day 71. The follow-up period may be extended if any participant in a particular cohort is tested positive for anti-drug antibody to PF-06755347 or has detectable concentration of PF-06755347 at final study visit. If there is an ET, the Day 71 schedule will be followed.

b. Chest X-ray results within 3 months of screening visit otherwise a chest X-ray must be performed at screening and results obtained prior to admission.

c. Update medication history, alcohol and nicotine use since screening.

d. Full PE may be done at screening or may be deferred to admission at the discretion of the investigator. If a full PE is performed at screening, a limited PE may be performed at admission. Limited PE may be performed at discharge or at any outpatient visit at the discretion of the investigator.

e. Single ECG at screening and scheduled outpatient visits; triplicate ECG at all other time points (including unscheduled, early termination, or extended immune follow up visit).

f. Vital signs measurement (including BP, pulse rate & temperature) triplicate at pre dose only, at the discretion of the investigator triplicate assessments may be taken at other timepoints. Either oral or tympanic method for temperature determination is allowed; however the method should be used consistently for each participant.

g. Banked biospecimen may be collected on admission or Day 1 (prior to dosing). If not collected on the designated collection day, collect at the next available time point when biospecimens are being collected in conjunction with a participant visit.

h. Serum FSH will be performed to confirm postmenopausal status for females (at the investigator's discretion whether to confirm post-menopausal status by FSH if greater than 5 years since last menses.

i. Serum pregnancy test will be conducted at a local lab. For female participants of childbearing potential, 2 negative pregnancy tests are required prior to dose on Day 1 (1 negative serum pregnancy test at Screening and 1 negative urine pregnancy test on Day 1). Results of serum pregnancy test from Day -1 are not required prior to dosing.

j. Urine pregnancy test will be conducted locally in females of ITP cohorts.

1. PROTOCOL SUMMARY

1.1. Synopsis

Short Title: A Phase 1 randomized, placebo controlled study to evaluate safety, tolerability, and PK of PF-06755347 after SAD IV or SC dosing in HPs and open-label by SC dosing in participants with persistent or chronic primary ITP.

Rationale

PF-06755347 is a fusion protein comprised of a recombinant human IgG1 Fc and IgG2 hinge. The investigational product is designed to form Fc multimers in order to enhance avidity to low avidity Fcγ receptors and C1q. It is being developed for the treatment of primary immune thrombocytopenia (ITP), chronic inflammatory demyelinating polyneuropathy (CIDP) and rare autoimmune diseases that respond to human immunoglobulin.

The purpose of this first in human study is to evaluate the safety, tolerability, PK and potentially PD of PF-06755347 following dosing by single IV infusion and SC injection in healthy adult male participants and by SC injection in adult male or female participants with persistent or chronic primary ITP.

Objectives and Endpoints

Primary Objective:	**Primary Endpoints:**
• To evaluate safety and tolerability following a single dose of PF-06755347 in the study population.	• Assessment of adverse events (AEs), clinical laboratory tests, vital signs, body temperature, cardiac telemetry (where collected) and 12-lead electrocardiogram (ECG).
Secondary Objective:	**Secondary Endpoints:**
• To characterize the plasma PK profile following a single dose of PF-06755347 in the study population.	• PK parameters derived from plasma PF-06755347 concentration: C_{max}, T_{max}, AUC_{last}, $t_{½}$, if data permit.
• To evaluate the immunogenicity profile following a single dose of PF-06755347 in the study population.	• Incidence of the development of antidrug antibody to PF-06755347.
• CCI [redacted]	[redacted].
Tertiary Objective:	**Tertiary Endpoints:**
• To further characterize the plasma PK profile following a single dose of PF-06755347 in the study population.	• PK parameters derived from plasma PF-06755347 concentration: C_{max} (dn), AUC_{last} (dn), AUC_{inf} (dn), CL, V_{ss}, CL/F, and V_z/F, if applicable.
• CCI [redacted]	• Collection of biospecimens unless prohibited by local regulations or ethics committee decision. Additional information on collection

	and potential use is provided in the Biospecimens section.

Overall Design

This is a Phase 1, randomized, double-blind, Sponsor-open, placebo-controlled, first-in-human SAD study to evaluate the safety, tolerability, and PK of PF-06755347 in healthy adult male participants by IV and SC administration and in adult male or female participants with persistent or chronic primary ITP by SC administration.

A schematic of the overall study design is provided in Figure 1.

A total of approximately 75 healthy adult male participants are planned to be randomized to either receive PF-06755347 or placebo by IV or SC administration in a 3:1 allocation ratio. Emerging clinical data from the IV cohorts supporting the transition to SC dosing are summarized in the IB, Section 6. The cohorts planned in this study are listed in Table 4. If cohort numbers are expanded, then the total number of participants randomized will not exceed 87.

Table 4. Cohort Overview for IV and SC Administration

Cohort	Population	Optional	Number of Participants Dosed	SC Administration Number of Participants Planned
1 - 4	HP		16	
5	HP		4	
6	HP		5	
7	HP		4	
8	HP		8	
9	HP		8	
10	HP	X	In progress	8
11	HP	X	ND	8
12	Japanese	X	ND	4 - 8
13	ITP		ND	3 - 6
14	ITP		ND	3 - 6

For all cohorts, participants will be dosed sequentially, with a minimum of 72-hour safety data (96-hour for SC administration) for each participant being reviewed by the team before dosing the next participant. There will be a minimum interval of 96-hours for IV administration or 120-hours for SC administration between dosing of consecutive participants. Screening evaluation will occur within 56 days prior to dosing. Eligible participants who meet the entry criteria will be admitted on Day -1 and are required to stay overnight through completion of Day 8 evaluations. At the discretion of the study site, participants may be admitted on Day -2. Participants will return for outpatient visits through approximately Day 36 (≤1 mg/kg IV dose level) or Day 71 (>1 mg/kg IV dose level and all

subcutaneous dose levels) for a total of approximately 5 or 10 weeks study participation, respectively from first dose to follow-up, excluding screening.

Dose Escalation and Study Stopping

Clinical tolerability, safety, PK CCI [redacted] data will be reviewed by a dose escalation subteam to establish whether each dose level is considered safe and well tolerated. These criteria may lead to a pause to evaluate participants at a given dose level, to repeat a dose, or to dose escalation. Unless a specific pause criterion is met, a review of all available safety, PK, cytokine and complement data will occur after each cohort has completed and dose escalation will proceed if the last dose was considered to be well tolerated. In the event of dosing pause, all available safety, cytokine, and complement data for the participants will be reviewed by the dose escalation subteam. The subteam should determine whether clinical signs and symptoms, including laboratory findings, associated with the pause criteria have resolved and whether it is safe to continue dosing.

Data Monitoring Committee:

This study will not use an external data monitoring committee. However, the dose escalation subteam will include an external Sponsor-independent safety reviewer.

Statistical Methods

No formal inferential statistics will be applied to the pharmacokinetic data.

The plasma concentration of PF-06755347 will be listed and summarized descriptively by nominal PK sampling time and treatment group. Individual participant, mean and median profiles of the plasma concentration time data will be plotted by treatment group using actual and nominal times, respectively. Mean and median profiles will be presented on both linear and log scales.

Baseline and change from baseline in cytokines and complement components will be summarized descriptively and plotted by dose.

Platelet counts for participants in the ITP Cohorts will be listed and summarized descriptively as absolute values and change from baseline.

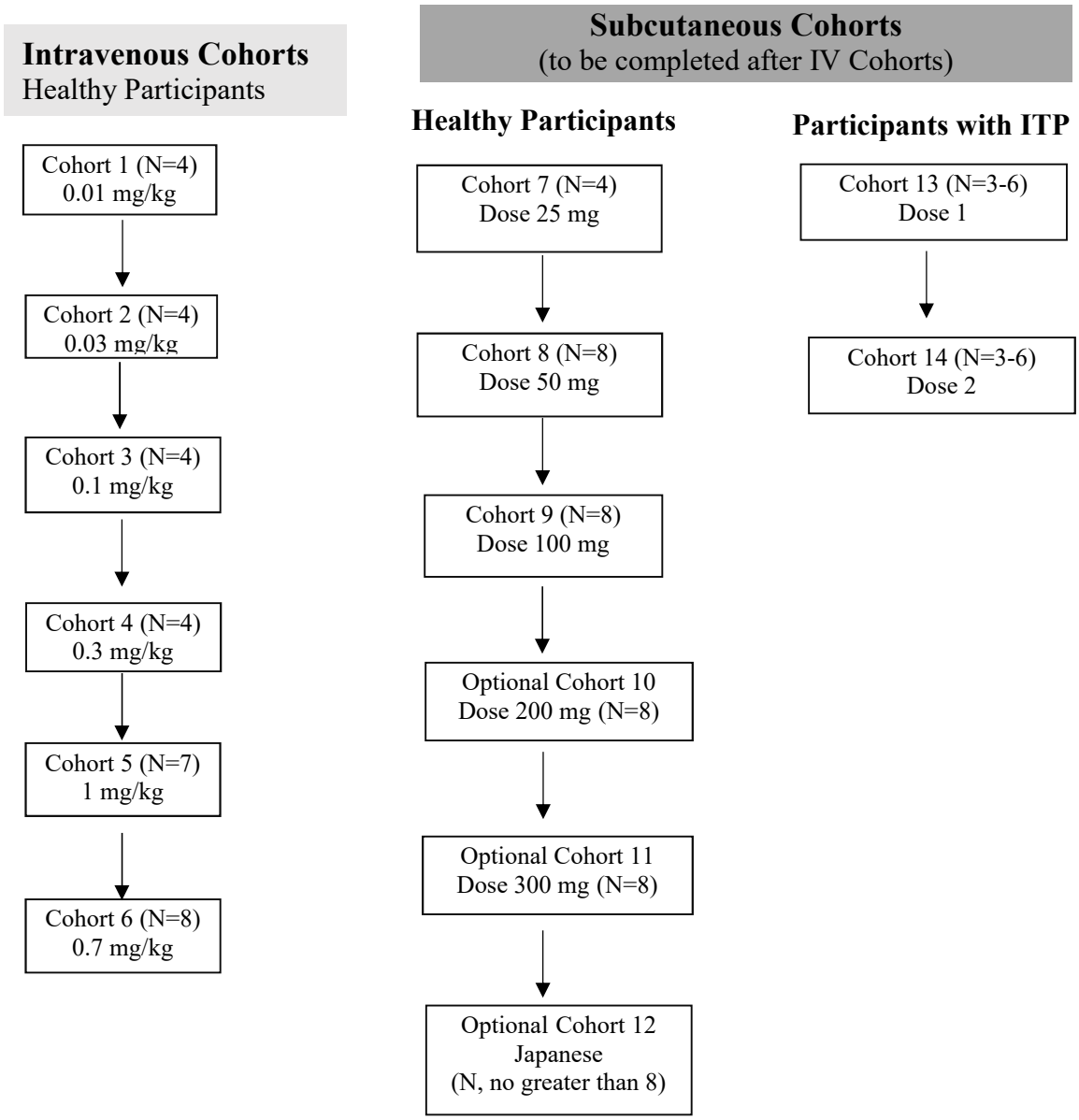
Immunogenicity (anti-drug antibody [ADA]) results will be listed (including titers) and summarized by treatment group and time points. Participant level immune response will also be summarized by treatment. Effect of positive ADA on safety, PD and PK will be assessed, if appropriate.

CCI [redacted]

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

1.2. Schema

Figure 1. Study Schematic



<u>Within</u> cohort sequential dosing scheme for IV and SC:

For all cohorts, participants will be dosed sequentially, one at a time. A safety review of the post-dose 72-hour data (96-hour for SC) will occur for each participant in order to proceed with dosing the next participant. There will be a minimum of 96-hours (120-hours for SC administration) between dosing of consecutive participants.

Actual dose levels are subject to change. See Section 4.2.

2. INTRODUCTION

PF-06755347 is a recombinant human IgG1 Fc fusion protein comprised of a recombinant human IgG1 Fc and IgG2 hinge. The drug candidate is designed to form multimers in order to enhance avidity to Fcg receptors and C1q. PF-06755347 is being developed as a treatment for primary ITP, CIDP, and rare autoimmune diseases that respond to human immunoglobulin.

2.1. Study Rationale

The current study is the first clinical trial with PF-06755347. It is designed to evaluate the safety, tolerability, PK and CCI following IV infusion and SC injection to healthy adult male participants and SC injection in adult male or female participants with persistent or chronic primary ITP.

Platelet count response in ITP is a robust, objective, validated biomarker for efficacy for IVIg. An increase in platelet count would be informative for the clinical development of PF-06755347 in ITP and CIDP. Participants with persistent and chronic primary ITP are chosen to ensure a low likelihood of spontaneous resolution of the platelet count. Participants with moderate to severe ITP (30 – 75 x 10^9 platelet count) who have no acute need for therapy are selected to minimize undue risk to the participant (see IB, Section 6.2.1.1), including bleeding at the injection site.

PF-06755347 modulates the production of pro- and anti-inflammatory cytokines and the production of complement activation products in vitro and in nonclinical species. A maximum tolerated dose of 0.3 mg/kg by intravenous infusion has been identified, with Grades 1 and 2 CRS observed at higher doses of 0.7 and 1 mg/kg. No further IV dosing will occur. (see Investigator Brochure Section 6.2). Moving forward, the safety, tolerability, and PK of PF-06755347 will be assessed following SC administration.

In ITP, bleeding may occur due to low numbers of platelets, circulating cell fragments that clump together to form plugs in blood vessel injuries.

The study design with single escalating IV and SC doses of PF-06755347 is ongoing with review of safety, PK and CCI. To permit an unbiased assessment of safety, the administration of active PF-06755347 versus placebo in each healthy participant cohort will be double-blinded to site staff (except those involved in preparation of doses) and participants. All participants in the ITP cohorts will receive PF-06755347. To allow for real-time review of the safety, tolerability, PK and cytokine/complement data, a designated limited number of Sponsor colleagues will be unblinded, with careful measures exercised to limit degree of unblinding. Refer to Section 9.9 for details. An independent and medically qualified reviewer, external to Sponsor and with authority to pause dose escalation to the subsequent cohort, will also be included as an unblinded member of the dose-escalation subteam.

This study includes rigorous in-clinic monitoring of study participants. Safety labs, urinalysis, telemetry (for participants prior to amendment 6), thorough ECG and vital sign assessments and adverse event monitoring will provide data to evaluate the safety and tolerability of PF-06755347. A sequential dosing design (see Section 4.1), will be used for all participants. This design ensures no concurrent dosing of multiple participants at a given dose level before a sufficient amount of safety information for a given dose level is acquired. In total there will be a minimum of 96 hours for IV administration between each participant to allow for review of 72-hr safety data and a minimum of 120 hours for SC administration to allow for review of 96-hour safety data. In addition, the proposed dose progression and escalation rules (see Section 6.6 and Section 6.7) will minimize the risk to study participants and ensure close and controlled safety, tolerability and PK monitoring in advance of escalating the dose level. Blood samples will also be analyzed for anti-drug antibodies following administration of PF-06755347.

The study will specifically screen and exclude potential participants with evidence of latent infections (eg, with chest X-rays and -QuantiFERON-TB Gold test for TB, HIV and hepatitis) to minimize the potential risk of infection even though there is no evidence of treatment related infections in nonclinical studies, or from the proposed immune-modulatory effect of PF-06755347. Additionally, given the rare thromboembolic events associated with intravenous (IVIg) and subcutaneous immunoglobulin (SCIg) treatment, lipid profiling (total cholesterol, low density lipoprotein [LDL], high density lipoprotein [HDL], triglycerides [TG], and apolipoprotein B100 [ApoB100]) will be conducted to exclude the participants who may be at higher risk of an event.

CCI

CCI

CCI [redacted]

2.1.1. Drug Development Rationale

PF-06755347 is being developed for the treatment of rare autoimmune diseases, specifically primary ITP and CIDP.[1,8,9] Primary ITP is characterized by a peripheral blood platelet count of $<100 \times 10^9$/L in the absence of another cause/disorder to explain the deficit. The main clinical concern is an increased risk of bleeding due to insufficient numbers of platelets, circulating cell fragments that clump together to form plugs in blood vessel injuries. CIDP is a rare polyneuropathy typically affecting both motor and sensory nerves. Plasma derived IVIg is an approved therapy for both of these indications. Similar to IVIg, the therapeutic goal of the PF-06755347 program is to increase platelet levels in ITP patients, and to improve the balance of pro- and anti-inflammatory factors involved in autoimmunity and inflammation that occur in CIDP patients.

PF-06755347 has been demonstrated to have enhanced potency compared to IVIg in multiple preclinical autoimmune disease models. These data suggested that lower doses of PF-06755347 may be sufficient for efficacy in autoimmune disease patients, enabling lower administration volumes and shorter administration times compared to those required for IVIg.

It has been shown that the Fc component of IVIg preparations is primarily responsible for the therapeutic activity of IVIg in several autoimmune disease models. IVIg preparations in which the Fab component was removed demonstrated similar efficacy to whole IVIg in the passive idiopathic thrombocytopenic purpura (ITP) model in mice,[2] and in the rat experimental autoimmune neuritis (EAN) model of CIDP.[3] In clinical ITP studies, it has been shown that the Fc component of IVIg rescued platelet numbers, similar to that seen with unmodified IVIg preparations.[14] There are multiple potential mechanistic pathways involving discrete Fc receptors and different cell types that may contribute to the anti-inflammatory and immune-modulatory activities of the Fc portion of IVIg. However it is not currently possible to identify a single molecular and cellular pathway that is responsible for clinical efficacy.[2]

PF-06755347 is a recombinant human IgG1 multimeric Fc fusion protein that is being developed for the treatment of autoimmune disorders currently treated with IVIg, including ITP and CIDP. It is designed to form a drug product comprising multimerized Fc species (including the homodimer) which display enhanced avidity to Fc receptors. The multimeric structure of PF-06755347 is hypothesized to reproduce the functional activity of high molecular weight Fc containing immune aggregates in IVIg for the treatment of various autoimmune diseases. Internal studies demonstrated that multimerization drives a 2-3 order of magnitude greater avidity for the FcγRs than IVIg and increased potency has been demonstrated in several cell-based assays of FcγR activation and immune cell functional

activity. PF-06755347 and its murine analogue M045, demonstrated efficacy in several independent autoimmune disease animal models including those for CIDP, ITP, rheumatoid arthritis, and myasthenia gravis. In studies where a direct comparison was done with human IVIg, the recombinant material was similarly effective at a 25-fold lower dose. The proposed mechanism of action of PF-06755347, the Fc-dependent efficacy of IVIg in autoimmune diseases, and the PF-06755347 driven efficacy in autoimmune disease rodent models at doses significantly lower than IVIg together suggest a utility for PF-06755347 in the treatment of rare autoimmune diseases such as ITP and CIDP.

2.2. Background

2.2.1. Nonclinical Pharmacology

PF-06755347 demonstrated high binding avidity (apparent $K_d \leq 1.45E^{-10}$ M) to a panel of available recombinant human FcγRs. These binding avidity values were 2-3 orders of magnitude lower than that seen with IVIg for all FcγRs except for the high avidity receptor, FcγRI. Similar, but lower (compared to FcγRs) binding to the neonatal Fc receptor (FcRN) was observed with PF-06755347 and IVIg ($K_d \leq 3.61E^{-05}$ M). PF-06755347 bound with high avidity to available recombinant human, cynomolgus monkey, rat and mouse FcγRs, providing rationale for further studies in rodent and monkey efficacy and toxicology studies.

The consequence of PF-06755347 binding to these receptors was demonstrated by its inhibition of immune complex binding to Chinese Hamster Ovary (CHO) cells engineered to express FcγRs and its inhibition of FcγR-mediated macrophage phagocytosis of antibody-opsonized immune cells. Also, PF-06755347 induced signaling downstream of ligand binding to human FcγRIIA and FcγRIIIA receptors on Jurkat cells in a reporter assay. In primary human blood-derived neutrophil preparations, PF-06755347 inhibited neutrophil chemotaxis induced by C5a with a mean IC_{50} in the range of 0.2-1 µg/mL, and inhibited neutrophil transendothelial migration induced by IL-8 with a mean IC_{50} in the range of 1-25 µg/mL. These cell-based functional activity assays demonstrated the immunomodulatory activity induced by PF-06755347.

In healthy human whole blood samples, PF-06755347 modulated a panel of pro- and anti-inflammatory cytokines and chemokines, and was shown to bind Complement component 1q (C1q), preventing the initiation of complement -dependent cytotoxicity (CDC). Additional studies demonstrated that PF-06755347 induces self-limited complement activation that is governed by Factors H and I and results in the generation of proteolytically inactive product of complement component 3b (iC3b) which is associated with the induction of tolerance.[10] Together these in vitro data demonstrated that PF-06755347 binds to multiple FcγRs expressed on different immune cell subtypes and to C1q and affects several activities associated with an immuno-modulatory role that is also seen with IVIg but at higher concentrations.

The anti-autoimmune activity of PF-06755347 was evaluated in the rat EAN model, a well characterized model of CIDP induced by administration of bovine myelin. PF-06755347 ameliorated the neurological disease score in rats with EAN. Although an ED_{50} was not calculated in this model, efficacy was achieved at 25-fold lower doses than for IVIg

(40 mg/kg vs 1000 mg/kg respectively). Additional measures included body weight and Rotarod scores (measures balance and endurance), which correlated with the improvement in the neurological disease scores seen with PF-06755347.[4]

The mouse collagen -induced arthritis (CIA) model is a well characterized model of rheumatoid arthritis and is used as a model of immune complex -mediated autoimmune disorders. PF-06755347 ameliorated the CIA disease score, body weight loss and histopathology endpoints at doses 25-40 fold lower than the dose of IVIg administered. The data from the mouse CIA model, in which PF-06755347 demonstrated an amelioration of the disease with a dose-responsive trend, was incorporated into the projections of the human therapeutic systemic drug concentration modeling.

2.2.2. Nonclinical Pharmacokinetics and Metabolism

After single-dose IV administration of PF-06755347 to mice (pharmacology species), rats, and monkeys (toxicology species), the PK of PF-06755347 were characterized by low systemic clearance (CL) and low to moderate apparent volumes of distribution at steady-state (V_{ss}). Mean terminal elimination half-life ($t_{½}$) values for PF-06755347 were 313 hours (approximately 13 days) in mice, 42 to 91 hours in rats, and 34 to 84 hours in monkeys.

After weekly IV administration of PF-06755347 for up to 6-weeks in rats and monkeys, there were no apparent sex-related differences in systemic exposure (as assessed by maximum observed plasma concentration [C_{max}] and area under the concentration-time curve from time 0 to 168 hours [AUC_{168}]). Mean systemic exposure increased with increasing dose in an approximately dose-proportional or slightly higher than dose-proportional manner. The overall incidence of ADA induction to PF-06755347 was 11% (22/199 animals) in rats and 62% (24/39 animals) in monkeys for all PF-06755347 dosed animals assessed. In monkeys, PF-06755347 serum exposures were generally similar in ADA-positive animals compared to ADA-negative animals.

No in vitro or in vivo PK drug interaction studies have been performed to date. PF-06755347 is expected to have immuno-modulatory activity, affecting various cytokines. Cytokines have been shown to modulate expression of CYP enzymes and transporters.[5,6] Therefore, treatment with PF-06755347 could theoretically affect CYP enzyme and transporter levels through normalization of inflammatory states, and consequently modulate the clearance of concomitant medications that are substrates for these enzymes or transporters. However, cytokine mediated- drug interactions observed with clinically immuno-modulatory drugs have been modest in magnitude, resulting in less than a 2x change in the exposure of coadministered- small molecule drugs.[7]

The primary clearance mechanism of PF-06755347 is via nonspecific catabolic degradation with some evidence of target-mediated disposition in monkeys. At expected therapeutic doses, target-mediated disposition is predicted to be modest and therefore, it is unlikely that concomitant medication will significantly alter the clearance of PF-06755347, even if target expression is affected.

2.2.3. Nonclinical Safety

The nonclinical safety profile of PF-06755347 has been evaluated using in vitro assays to measure cytokine and complement cascade modulation, cardiovascular (CV) safety pharmacology studies and toxicology studies of up to 6 weeks in duration in rats and cynomolgus monkeys. In vivo studies primarily used a complex, stepped IV infusion paradigm.

In vitro, PF-06755347 increased the release of pro-inflammatory cytokines IL-6, IFNγ, and TNFα in human whole blood, and complement component C4a in human and cynomolgus monkey serum, in a concentration-dependent manner. The EC20 values were calculated for these experiments and presented in Table 5.

Table 5. In Vitro PF-06755347 Potency for Increases in Cytokines and Complement Component

Analyte (Species)	EC_{20} (µg/mL)	95% Reference Interval
IL6 (Human)	1.95	0.78 – 4.89
IFNγ (Human)	5.30	1.24 – 22.67
TNFα (Human)	6.33	1.87 – 21.47
C4a (Human)	9.89	3.57 – 27.42
C4a (Cynomolgus monkey)	4.35	2.38 – 7.94

Cardiovascular safety pharmacology studies were conducted in rats and cynomolgus monkeys that were surgically implanted with telemetry devices. These studies were conducted across a range of IV infusion rates and concentrations. In rats, doses from 1 to 160 mg/kg were infused over a range of durations from 1 to 5.5 hours. Small increases in heart rate, BP and body temperature were observed that did not demonstrate dose dependence.

In cynomolgus monkeys, multiple safety pharmacology studies were conducted. Variable infusion rates and durations allowed a wide dose range (0.1 to 990 mg/kg) and different infusion regimens to be assessed. The first pivotal study evaluated doses of 25, 224, and 750 mg/kg and the second assessed doses of 0.1, 10, and 50 mg/kg. Hemodynamic changes including both increases and decreases in BP and heart rate were noted. Antihistamine premedication was utilized in the initial high dose range studies in cynomolgus monkeys but was not used in the subsequent studies to ensure the pharmacology of PF-06755347 could be fully evaluated. In the 2 pivotal cardiovascular studies, cynomolgus monkeys demonstrated a low incidence of emesis and retching at doses ≥10 mg/kg, as well as minimally increased heart rate and decreased BP that showed no dose dependency. At 50 mg/kg, the high dose in the second pivotal study, emesis was observed in 1/4 cynomolgus monkeys with minimal cardiovascular changes and no change in body temperature. At 50 mg/kg in the safety pharmacology study, the C_{max} was 966 µg/mL, which is 5680x the predicted human C_{max} of 0.17 µg/mL at the anticipated human starting dose of 0.01 mg/kg.

Multiple rat and cynomolgus monkey repeat-dose toxicity studies were conducted. The first set of toxicity studies used relatively high dose ranges while the second set of studies employed a lower dose range as described.

In the initial non-pivotal rat toxicity study, PF-06755347 was tolerated at doses of 160, 508, and 1611 mg/kg/week although it produced changes in a number of parameters. However, these effects were considered to be non-adverse due to low incidence and/or magnitude of the effects. Based on these results, the doses selected for the initial high dose range pivotal study in rats were 160, 566, and 2000 mg/kg/week.

In the initial pivotal higher dose range study in rats, a single dose of 2000 mg/kg/week was not tolerated. Therefore, the high dose of 2000 mg/kg was lowered to 1200 mg/kg/week for the second weekly dose and the remainder of the study. A total of 10 animals were euthanized in a moribund condition due to hind limb dysfunction associated with extravasation of the test article (6 rats at 2000 mg/kg, 3 rats at 566 mg/kg/week, and 1 rat at 160 mg/kg/week). These euthanized animals demonstrated clinical signs (swollen and limited use of the hind limb, swollen inguinal region), macroscopic findings (enlarged tarsus or swollen foot pad joint, thickened tissue or mass at the catheter/infusion sites), and microscopic findings (chronic-active inflammation of hind limb or at the catheter/infusion sites) that were associated with extravasation of the test article. After 7 weekly doses, there were no adverse findings in surviving animals.

These hind limb findings were not reproduced in the second pivotal rat study. In this lower dose range toxicity study, doses of 1, 10, or 160 mg/kg/week were administered over 6 weeks (7 weekly doses). There were no PF-06755347-related effects on mortality, clinical signs, body weights, food consumption, ophthalmology, hematology, coagulation, clinical chemistry, or urinalysis parameters, immunophenotyping parameters (other than spleen activated dendritic cells), changes in concentrations of total cell count (TCC), or organ weight, macroscopic or microscopic changes. PF-06755347 did produce non-adverse changes in cytokines (IL-6, IL-10, IL-13, IL-17, and TNF-α) at $\geq$1 mg/kg and IL-4 at $\geq$10 mg/kg. The no observed adverse effect level (NOAEL) was considered to be 160 mg/kg/week (selected on the basis that this dose had no increased mortality relative to controls), with a Day 36 mean C_{max} of 2210 µg/mL and mean AUC_{168} of 64000 µg·hr/mL.

In the non-pivotal toxicity study in cynomolgus monkeys, test article -related increases in cytokines IL-6, IL-10, and IL-1RA as well as complement activation products were observed at $\geq$150 mg/kg/week and were reversible. In the initial higher dose range pivotal cynomolgus monkey study, doses of 50, 224, and 1000 mg/kg/week were administered over 6 weeks (7 weekly doses). No adverse test article-related effects were noted at <224 mg/kg although PF-06755347 induced changes in immune cell subtypes, cytokines, and complement activation products. In the second, lower dose range pivotal toxicity study, doses of 0.1, 10, or 50 mg/kg/week were administered over 6 weeks (7 weekly doses). In this study, there were no PF-06755347-related effects on mortality, clinical observations, ophthalmic observations, body weight parameters, electrocardiography parameters, organ weight parameters, urinalysis, coagulation test parameters, macroscopic observations, and microscopic findings. In addition, no test article -related changes were observed in the

numbers of peripheral blood leukocyte subsets of T cells, helper T cells, cytotoxic T cells, B cells, myeloid dendritic cells (mDC), or CD14+ monocytes, or in the percentage of CD14+ monocytes, mDC, or B cells expressing markers of activation, or in CD14 expression (MFI) on monocytes. Test article -related, non-adverse decreases in peripheral blood CD3-CD159a+ natural killer (NK) cells (0.14x-0.41x baseline) and regulatory T cells (0.45x-0.62x baseline) were observed for males and females administered 50 mg/kg/week of PF-06755347. The decreases of CD3-CD16+ NK cells observed for all animals administered 10 or 50 mg/kg/week are likely due to the inability of the flow cytometry antibody to bind CD16 in the presence of the test article. Non-adverse test article related findings for cytokines and complement activation products included increases in IL-10, sC5b-9, and Bb concentrations at ≥0.1 mg/kg and increases in IL-1RA, IL-6, C3a, and C4a concentrations at ≥10 mg/kg. The NOAEL in this study is the highest dose of 50 mg/kg which corresponded to mean C_{max} and AUC_{168} values of 1130 µg/mL and 34000 µg·hr/mL, respectively, on Day 36 of the dosing phase.

Mortality occurred in the rat toxicity studies. The causes of mortality/morbidity for animals found dead or euthanized for humane reasons were attributed to procedural issues arising from long term infusion and were not considered to be due to PF-06755347. These included blocked catheters, retracted catheters, complications from blood collection, extravasation of test article, infection, trauma of undetermined origin, air in infusion line, and complications during re-catheterization surgery.

In the second, lower dose range pivotal rat toxicity study, 6 of the 9 deaths occurred during or as a result of repair surgery and are not considered to be due to test article. One animal was euthanized on Day 39 in a moribund condition resulting from infection at catheter site resulting in sepsis. The 2 undetermined deaths, 1 control and one 1 mg/kg/week, are considered to be incidental and not due to the test article as there was no deaths at 10 and 160 mg/kg/week.

The variability of cytokine and complement activation product concentrations in untreated rats and monkeys is not available in the published literature. Therefore, these data were compiled from vehicle control and pre-dose baseline samples across a number of the nonclinical studies. These control cytokine and complement activation products data allowed comparison between cytokine and complement activation product concentrations at lowest observed effect level (LOEL) doses and untreated control samples. Many, but not all, of the concentrations for these parameters at the LOEL doses were within the control range thereby proving additional support for the conclusion that these increases were not adverse. In addition, although PF-06755347 increased cytokines and complement activation factors across a wide range of doses in both rat and cynomolgus monkeys the dose response curve was relatively flat. No meaningful increase in cytokine levels were observed beyond 10 mg/kg/week. For the 2 cynomolgus monkey studies, the overall NOAEL is considered to be 224 mg/kg/week. This conclusion is based on the euthanasia of 2 animals in the 1000 mg/kg/week dose group and 1 animal in the control group that was attributed to infection and not to test article. However, in order to eliminate the uncertainty related to the possible test article -related causation of these deaths, the next lower dose of 224 mg/kg/week is determined to be the overall cynomolgus monkey NOAEL. Thus,

systemic exposure (C_{max} and AUC_{168}) at the NOAEL dose of 224 mg/kg/week in cynomolgus monkeys was 5870 µg/mL and 215000 µg·hr/mL, respectively.

In considering the 5 pivotal 6-week toxicology studies as a whole, the overall lowest NOAEL is concluded to be the 160 mg/kg/week dose in the second, lower dose rat study. This dose had no increased mortality relative to controls. The systemic exposure (C_{max} and AUC_{168}) at this overall NOAEL in rats was 2210 µg/mL and 64000 µg·hr/mL, respectively.

The proposed starting clinical dose of 0.01 mg/kg is expected to yield a C_{max} of 0.17 µg/mL. This value is similar to the human in vitro cytokine release assay EC_3 for IL-6 for the most sensitive endpoint for cytokine release or complement activation product and also corresponds to a projected 1% B cell receptor occupancy. This estimated C_{max} of 0.17 µg/mL at the proposed starting clinical dose of 0.01 mg/kg is 13000x and 6647x lower than the C_{max} exposures at the NOAELs in rats (160 mg/kg/week) and cynomolgus monkeys (50 mg/kg/week), respectively. The PK stopping limits proposed in the first in human (FIH) study were chosen based on the exposures of PF-06755347 achieved at the NOAEL dose of 50 mg/kg/week on Day 36 (1130 µg/mL) from the 6-week lower dose range cynomolgus monkey toxicity study.

The exposure margins at the starting dose are robust and, therefore considered sufficiently broad to compensate for the greater human in vitro sensitivity to cytokine release when compared to monkey.

In summary, the nonclinical program with PF-06755347 identified the expected pharmacological effects including modulation of cytokine release, detection of complement activation products and changes in immune cell subtypes. These changes were generally transient over the 24 hrs post-start of infusion interval and not associated with microscopic changes at the NOAEL doses of 160 mg/kg/week (rats) and 224 mg/kg/week (cynomolgus monkeys) although there were monitorable and reversible effects on BP, heart rate, and body temperature. The nonclinical program supports clinical trials with PF-06755347 up to 6 weeks in duration.

2.3. Benefit/Risk Assessment

PF-06755347 is not expected to provide any clinical benefit to healthy participants but it may provide a transient increase in platelet count in participants with persistent or chronic ITP. This study is designed primarily to generate safety, tolerability, and pharmacokinetic data that will support further clinical development.

PF-06755347 has been shown to cause transient elevation in pro-inflammatory cytokines. Symptoms associated with CRS vary greatly and may be difficult to distinguish from other conditions. The more common symptoms include fever, nausea, headache, tachycardia, hypotension, rash and shortness of breath. The severity of symptoms can be mild to life threatening and thus there should be a high suspicion for CRS if these symptoms occur. Cytokines will be analyzed to determine if cytokine elevation consistent with CRS is observed (see Section 10.10). The severity of CRS will be assessed according to the most

recent consensus grading from the American Society for Transplantation and Cellular Therapy (ASTCT).[2]

For study participants with ITP, there is an increased risk of procedure-related bleeding/bruising from subcutaneous injections, mitigated by the lower bound of platelets in the eligibility criteria. An increased risk of thrombosis has also been reported in ITP.[15] High dose single IV administration of PF-06755347 may transiently lower platelet counts in healthy participants, while repeat IV administration in non-clinical studies may also lower platelet counts. The predicted C_{max} with SC administration in ITP participants is approximately 6 fold lower than observed C_{max} at 1 mg/kg at which the reduction in platelet count was observed in healthy participant (see Table 6). More detailed information about the known and expected benefits and risks and reasonably expected adverse events of PF-06755347 may be found in the investigators brochure, which is the SRSD for this study.

Each study site should have a COVID-19 risk mitigation policy (RMP), which documents the site's COVID-19 virus testing strategy for participants and staff, social distancing measures, and management of COVID-19-like symptoms.

To account for the widespread deployment of COVID-19 vaccine during the COVID-19 pandemic, the benefit/risk analysis has assessed both the impact of PF-06755347 on risk of COVID-19 disease in study participants who may become infected with SARS-CoV-2 and the efficacy of COVID-19 vaccines.

The benefit/risk analysis for study participants for COVID-19 related illness during the COVID-19 pandemic is similar to the benefit/risk prior to COVID-19. PF-06755347 is proposed to be an immunomodulator similar to IVIg, and so its safety in humans can reasonably be predicted from clinical experience with IVIg. PF-06755347 is not an immunosuppressant that might render an individual more susceptible to the impact of COVID-19. IVIg has been used in COVID-19 infected individuals because of its known immunomodulatory effects and is reported in uncontrolled trials to be helpful in critically ill individuals. There are currently no reports of injury because of the immunomodulatory effects of IVIg in COVID-19 infected individuals.

In contrast, the benefit/risk analysis for study participants who are scheduled to receive or have received a COVID-19 vaccine suggests that appropriate interval between vaccination and administration of PF-06755347 is prudent because of the potential for an immunomodulatory effect to interfere with development of the intended immune response to the vaccine. While this has not be been studied for PF-06755347, extrapolation from other immunodulatory/immunosuppressive agents suggests at least a 28 day interval after completion of the vaccination course should be sufficient to allow a desired immune response.

By the time of discharge after study confinement on Day 8, approximately 3 terminal half-lives of the study drug will have elapsed. Coupled with the rapidity of the cytokine response to study drug, longer duration of confinement for additional observation appears unnecessary. The on-site follow up requirements for the study are standard timelines for participant safety.

3. OBJECTIVES AND ENDPOINTS

Primary Objective:	Primary Endpoints:
• To evaluate safety and tolerability following a single dose of PF-06755347 in the study population.	• Assessment of AEs, clinical laboratory tests, vital signs, body temperature, cardiac monitoring and cardiac telemetry (where collected) and 12-lead ECG.
Secondary Objective:	**Secondary Endpoints:**
• To characterize the plasma PK profile following a single of PF-06755347 in the study population.	• PK parameters derived from plasma PF-06755347 concentration:[a] C_{max}, T_{max}, AUC_{last}, AUC_{inf}, $t_{½}$, if data permit.
• To evaluate the immunogenicity profile following a single dose of PF-06755347 in the study population.	• Incidence of the development of anti-drug antibody to PF-06755347.
• CCI [redacted]	[redacted]
Tertiary Objective:	**Tertiary Endpoints:**
• To further characterize the plasma PK profile following a single dose of PF-06755347 in the study population.	• PK parameters derived from plasma PF-06755347 concentration:[a] C_{max} (dn), AUC_{last} (dn), AUC_{inf} (dn), CL, V_{ss}, CL/F, and V_z/F, if applicable.
• CCI [redacted]	• Collection of biospecimens unless prohibited by local regulations or ethics committee decision. Additional information on collection and potential use is provided in the Biospecimens section.

a. For a complete definition of all PK parameters, refer to Section 9.5.1.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 1, randomized, double-blind, Sponsor-open, placebo -controlled, first-in-human single -ascending dose study to evaluate the safety, tolerability, and PK of PF-06755347 in healthy adult male participants by IV and SC administration and in male or female participants with persistent or chronic ITP by SC administration. Personnel, trained in advanced cardiac life support, emergency resuscitative equipment and the management of anaphylaxis, are immediately available to treat systemic reactions under the supervision of a physician. IV fluids, epinephrine, antihistamine and methylprednisolone will be available for immediate parenteral use in the event of an anaphylactic reaction.

A schematic of the overall study design is provided in Section 1.2 (note actual dose levels to be administered beyond the starting dose are subject to change, see Section 4.2.1.3). A total of approximately 75 healthy adult male participants are planned to be randomized to either receive PF-06755347 or placebo by intravenous or subcutaneous administration in a 3:1 allocation ratio. All participants with ITP will receive PF-06755347. Clinical data from the IV cohorts supporting the transition to SC dosing are summarized in the IB, Section 6. SC Cohorts 7-14 are planned, Cohort 7 will have 4 male participants (3 active and 1 placebo)

and Cohorts 9-11 will have 8 male participants (6 active and 2 placebo). Cohort 12 (optional Japanese cohort) will include approximately 4-8 male Japanese healthy participants and Cohorts 13 and 14 combined will include a maximum of 12 male or female participants with ITP. The total number of participants randomized will not exceed 87. The ITP cohort dosing will start after completion of the 50 mg dose cohort in HPs.

Participants within each cohort will be dosed using a sequential dosing scheme. For all cohorts, only a single participant will be dosed at any given time. Based on the emerging safety data to date with IV dosing, cytokine and laboratory abnormalities reach their peak levels within the first few hours following PF-06755347 C_{max} and are resolved within 24 hours. The C_{max} was predicted to be 24 -48 hours with SC administration, however preliminary data from Cohort 7 supports increasing the monitoring period to 96-hr for safety.

A safety review of the post-dose 72-hour data (96-hour for SC administration) will occur for every participant in order to proceed with dosing the next participant. A minimum of 96-hours (120-hours for SC administration) between dosing of consecutive participants. A safety review evaluation meeting may be required in order to proceed with dosing the next participant. The safety review period can be extended if deemed necessary at the discretion of any PI (in consultation with the Sponsor medical monitor). Dose levels selected for optional cohorts will be selected based on the assumption that resulting clinical exposures will not exceed protocol defined PK stopping limits.

Only males will be enrolled in the healthy participant cohorts in an attempt to reduce overall variability because there are significant gender variations in immune responses.[16] Healthy Participants will be screened to ensure that they do not have any autoimmune disease or immune deficiency prior to enrollment. Participants with ITP that have active autoimmune disease in the opinion of the investigator will be excluded. Participants with a history of migraine will also be excluded so as not to confound pro-inflammatory adverse event assessments using the Common Terminology Criteria for Adverse Events (CTCAE) criteria. The age range will be 18-55 years in order to ensure adequate renal function and reduce the risk of thrombo-embolic events. Screening evaluation will occur within 56 days prior to dosing.

Male and female participants will be enrolled in the ITP cohorts. In adults, ITP is more common in females than in males. Therefore, it is important to allow for assessment of safety, tolerability and PK in both males and females.

PF-06755347 has been administered to male and female cynomolgus monkeys by IV infusion and SC bolus injection across a wide range of doses in multiple studies. PF-06755347 PK parameters (C_{max}, T_{max}, AUC_{168}) were similar between male and female cynomolgus monkeys at all doses. Additionally, incidence and magnitude of IL-6 or IL-1RA release was similar between the sexes. Therefore, nonclinical data support the expectation that no dose adjustment is needed in female participants in B7801001.

Eligible participants who meet the entry criteria will be admitted on Day -1 and are required to stay overnight through completion of Day 8 evaluations. At the discretion of the study site participants may be admitted on Day -2. Participants will return for outpatient visits per the Schedule of Activities (SoA) through approximately Day 36 (≤1 mg/kg IV dose level) or Day 71 (>1 mg/kg IV dose level and all subcutaneous dose levels for a total of approximately 5 or 10 weeks study participation, respectively from first dose to final follow-up, excluding screening. The follow-up period may be extended for a participant and/or a cohort if any participant in the cohort tests positive for anti-drug antibody to PF-06755347 at the scheduled follow-up visit, or has detectable concentration of PF-06755347 at final follow-up visit.

If a participant discontinues during the study, the participant may be replaced at the discretion of the Sponsor in consultation with the PI. Doses in the dose escalation sequence may be repeated or adjusted depending on the results obtained during the study to explore different doses and/or infusion/dosing rates as needed. The total number of participants including the subcutaneous and optional cohorts will not exceed 87.

Some of the cohorts in the study may not be conducted if study objectives are deemed accomplished or if directed by emergent data. Participants in any cohort may be confined for a period beyond what is required in the SoA at the discretion of the investigator for safety reasons and/or to accommodate the frequency of required outpatient visits.

CCI [redacted]

4.2. Dose Justification

4.2.1. Human Predictions

4.2.1.1. Prediction of Human Pharmacokinetics

The PK data from cynomolgus monkeys were characterized using a 2-compartmental model incorporating linear and non-linear clearance (V_{max}/K_m model), to describe the observed non-linear PK. Subsequently, a human PK model was established by allometrically scaling the PK parameters from monkey to human. The scaling was performed to be the most conservative (produce the highest exposure) by using scaling factor of 0.75 for V_{max} and 1 for K_m. In humans the projected serum CL and V_{ss} for the linear process were 0.11 mL/hr/kg and 87 mL/kg respectively, and the parameters for non-linear clearance mechanism (V_{max} and K_m) were predicted to be 385 µg/kg/hr and 942 nM, respectively. The terminal half-life was estimated to be approximately 8-9 days.

4.2.1.2. Prediction of Human Efficacious Exposure

The data obtained from the pharmacology study in a CIA mouse model were fitted using a direct effect I_{max} model where either average concentration (C_{av}) or trough concentration (C_{min}) were assumed to drive the response (% normalized disease score). The human efficacious concentration (C_{eff}) was defined as the C_{av} or C_{min} to achieve the expected IC_{90}s in human, which was calculated based on the mouse IC_{90}s after correcting for the mouse-human potency difference. The potency correction was based on the in vitro FcγRIIB and FcγRIIIA binding assays, which suggests a more than 10x higher binding avidity for human FcγRIIB and FcγRIIIA compared to mouse. The projected C_{eff} is 37 µg/mL for C_{av} (or 6 µg/mL for C_{min}).

4.2.1.3. Clinical Dose Selection

4.2.1.3.1. Intravenous Administration in Healthy Participants

The starting dose of PF-06755347 proposed for this study was 0.01 mg/kg (IV). Subsequent dose escalation was to proceed to either the highest dose deemed to be well tolerated with an acceptable safety profile or the achievement of plasma exposure equivalent to the PK stopping limits. The PK stopping limits proposed in this study were chosen based on the Day 36 exposures of PF-06755347 achieved at the NOAEL (50 mg/kg weekly) from the 6-week lower dose range monkey toxicity study (see Section 2.2.3). Human PK parameters and efficacious exposure predicted for PF-06755347, along with the toxicokinetic data, and anticipated binding and pharmacological activity, were used to establish the dose range to be studied. The dose range in this study aimed to bracket the expected clinically efficacious exposure range in humans, while allowing for uncertainty in the prediction of targeted efficacious concentration and PK.

Table 6. Observed Human Exposure and Safety Margin Following Single IV Administration of PF-06755347

Dose (mg/kg)	Human Exposure of Plasma PF-06755347[a]		Observed Safety Margin[b]	
	C_{max} (µg/mL)	AUC_{168} (µg·hr/mL)	C_{max}	AUC_{168}
0.01	0.112	1.41	10089	24113
0.03	0.446	10.5	2534	3238
0.1	1.65	45.2	685	752
0.3	4.70	139.0	240	245
0.7	12.4	281.0	91	121
1	24.7	490.0	46	69

a. C_{max} and AUC_{168} are observed exposure levels following IV administration. Please refer to Investigator's Brochure for additional details.
b. Safety margins for C_{max} and AUC are calculated using the exposure limiting criteria (NOAEL in lower dose range monkey toxicity study: C_{max} = 1130 µg/mL and AUC_{168} = 34000 µg·hr/mL); and equal to the ratio of limiting criteria/observed C_{max} or AUC_{168}.

The starting IV dose of 0.01 mg/kg was projected to be safe with anticipated level of Fc-gamma receptor occupancy estimated at 1% and minimal associated pharmacological activity. Non-clinical human pharmacology and non-human primate (NHP) toxicology studies suggested that this dose would achieve greater than 5000-fold safety margin over the NOAEL, and would not be associated with any clinical symptoms or vital sign changes. The dose was predicted to be associated with low level transient systemic IL-6 release, but was

not expected to be associated with elevated levels of other cytokines or with any evidence of complement activation.

The observed C_{max} (0.112 µg/mL; Table 6) at the starting IV dose was approximately 10-fold lower than the C_{max} achieved at the lowest dose level tested in the 6-week pivotal toxicity study in cynomolgus monkeys (0.1 mg/kg, 1.77 µg/mL), and was similar to the C_{max} on Day 1 of the investigative monkey study (8384439/18GR088) at the 2 lowest doses tested of 0.005 (0.097 µg/mL) and 0.01 mg/kg (0.168 µg/mL). All doses, 0.005, 0.01 and 0.05 mg/kg, produced minimal transient elevations in IL-6 but not in TNFα or INFα or complement. This IL-6-only response at ≤0.05 mg/kg was less than that observed at 0.1 mg/kg in monkeys, where non-adverse, minimal changes in cytokine and complement activation products were observed. There were no effects on immune cells, or changes in clinical signs, other laboratory parameters or macroscopic and microscopic observations at 0.1 mg/kg in monkeys. Minimal changes in heart rate were observed at 0.1 mg/kg in NHP, with no other hemodynamic changes (more details can be found in the accompanying IB). Thus the safety data package supports the choice of the proposed starting dose of 0.01 mg/kg.

A receptor occupancy calculation was also performed. Since PF-06755347 binds to multiple FcγRs on multiple cells, the apparent K_d was determined using in vitro human whole blood. PF-06755347 exhibited the greatest binding avidity towards B cells, with an apparent K_d of 13.95 µg/mL. Using this most conservative apparent K_d value, the predicted peak receptor occupancy achieved at the starting dose of 0.01 mg/kg was expected to be approximately 1%, which also represents an EC_3 for in vitro IL-6 release in human whole blood, the most sensitive functional assay.

Furthermore, the 0.01 mg/kg starting dose is 1/200,000th of the prescribed loading dose of 2 g/kg for IVIg (based on Gamunex®-C US prescribing information [USPI][9] for CIDP) on a mg/kg basis (or 1/200th to 1/2000th of an estimated loading dose of IVIg, if corrected for the approximately 100-1000x higher human FcγR binding avidity for PF-06755347 vs. IVIg).

Dose escalation beyond the starting dose will be dictated by the criteria summarized in Section 6.7 and will aim to occur in incremental increases of no more than half-log (ie, 3.3 fold) based on predicted exposure, with smaller increments if required due to emerging safety data or once the expected PF-06755347 exposure approaches the PK stopping limit. The actual doses to be evaluated in the escalation sequence as well as the number of dose levels to be evaluated may be adjusted according to emerging safety, tolerability and PK data, provided the dose escalation criteria specified in Section 6.6 and Section 6.7 are not violated. These criteria are applicable to both IV and SC administration.

A body weight-based dosing approach (mg/kg) was used in this study for the IV cohorts with the goal of reducing inter-individual variations in IV infusion/dosing rate and PK exposure. PF-06755347 was administered as a single infusion over 60 minutes for the starting dose of 0.01 mg/kg. Based on emerging safety data of cytokine elevation at the 1 mg/kg dose level, the infusion duration was increased to 3 hours for an expansion cohort at 1 mg/kg. (Section 6.1.1.1). The increase in infusion duration was expected to modulate the tolerability of PF-06755347. Safety data from the 1 mg/kg expansion cohort showed that an increase in

infusion duration to 3 hours did not modulate the tolerability profile of PF-06755347 and subsequently, the next cohort used 0.7 mg/kg infused over 1 hour. Guidelines for the proposed infusion rate at each dose level are provided in Section 6.1.1.1. However, the actual dosing rate could have been reduced and/or the overall infusion time increased at the discretion of the PI and upon the review of the available safety data. The overall infusion time was not to exceed 4 hrs. If deemed appropriate by the PI, concomitant medications (such as acetaminophen and diphenhydramine) coupled with adjustment of dosing rate could have been implemented to manage possible emerging symptoms that may have been related to transient pro-inflammatory activity.

4.2.1.3.2. Subcutaneous Administration in Healthy Participants

Following IV administration of PF-06755347, the observed safety data to date has shown Grades 1 and 2 CRS associated with IV doses of 1.0 and 0.7 mg/kg, respectively. Cytokine (eg, IL-6) elevation peaked within the first few hours following IV administration and returned to baseline levels within 24 hours. These results may suggest that the degree of cytokine release is dose dependent and potentially correlated with PF-06755347 C_{max} and the rate of rise to achieve C_{max}. SC dosing of PF-06755347 offers the potential to blunt the severity of CRS by reducing the C_{max} and delaying the time to achieve C_{max} (T_{max}). The observed C_{max} (0.895 µg/mL) at the proposed starting SC dose of 25 mg is approximately 5-fold lower than the observed mean C_{max} (4.7 µg/mL) achieved at the highest tolerated IV dose level of 0.3 mg/kg (Table 6), with a safety margin of 1263 for C_{max} and 345 for AUC_{168}. Observed C_{max} values in subsequent dose levels of 50 and 100 mg were of 1.37 and 2.64 µg/mL respectively; approximately 3.5-fold and 1.8-fold lower than the values observed at the 0.3 mg/kg IV dose level. The SC dose level of 300 mg will only be explored when SC doses up to 200 mg levels are deemed to be safe and well tolerated and within the PK stopping limit criteria.

In order to support subcutaneous delivery of PF-06755347, a toxicology study (Study 14MA141, IB Section 5.3.7) in NHP was conducted with a single 250 mg/kg SC dose and the results showed that the drug was tolerated.

The dose for the optional Japanese SC Cohort 12, if conducted, will be the highest dose from Cohorts 7-11 that is found to be safe and well tolerated.

Table 7. Observed/Predicted Human Exposures and Safety Margins Following Single SC Administration of PF 06755347

Dose (mg)[a]	Human Exposure of Plasma PF-06755347		Safety Margin[b]	
	C_{max} (µg/mL)	AUC_{576} or AUC_{168} (SC) (µg·hr/mL)	C_{max}	AUC
25 mg SC[c]	0.895	98.5	1263	345
50 mg SC[c]	1.37	159	825	214
100 mg SC[c]	2.64	315	428	108
200 mg SC	5.28	630	214	54
300 mg SC	7.92	945	143	36

a. Depending on the safety and PK data available, dose escalation may be adjusted to doses other than those outlined above while following dose progression and stopping rules outlined in Section 6.6 and Section 6.7.
b. Safety margins for C_{max} and AUC are calculated using the exposure limiting criteria (NOAEL in lower dose range monkey toxicity study: C_{max} = 1130 µg/mL and AUC_{168} = 34000 µg·hr/mL); and equal to the ratio of limiting criteria/projected C_{max} or AUC_{168} or AUC_{576} (SC).
c. Observed exposures and safety margins are reported for 25 mg, 50 mg and 100 mg SC dose.

4.2.1.3.3. Subcutaneous Administration in Participants with ITP

The starting dose of the ITP cohorts will be dependent on the equivalent dose levels in healthy participants having been studied and been deemed to be safe and well tolerated.

The dose levels to be tested in participants with ITP may include SC doses of 25 mg, 50 mg or 100 mg. The observed mean C_{av} after administration of a single 25 mg SC dose in HP was 0.586 ug/ml. This C_{av} is approximately 2-fold higher than the C_{av} of 0.25 ug/ml for ≥90% receptor occupancy for human FcγR. Thus it is expected that the lowest proposed dose in participants with ITP in this study could have pharmacological activity after a single dose.

The starting dose for participants with ITP will be 25 mg based upon the safety and tolerability data in HP.

Dosing progression and escalation are outlined in Section 6.6 and 6.7.

4.3. End of Study Definition

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

5. STUDY POPULATION

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

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

5.1. Inclusion Criteria for Healthy Participants

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

Age and Sex:

1. Healthy male participants who, at the time of screening, are between the ages of 18 and 55 years, inclusive. Healthy is defined as no clinically relevant abnormalities identified by a detailed medical history, full physical examination, including temperature, BP and pulse rate measurement, pulse oximetry, 12-lead ECG or clinical laboratory tests.

Type of Participant and Disease Characteristics:

2. Participants who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, and other study procedures.

3. Chest X-ray with no evidence of current, active TB or previous inactive TB, general infections, heart failure, malignancy, or other clinically significant abnormalities taken at Screening or within 3 months prior to Screening and read by a qualified radiologist.

4. Additional criterion for participants to be enrolled in Japanese cohort only: Japanese participants who have four Japanese biologic grandparents born in Japan.

Weight:

5. Body Mass Index (BMI) of 17.5 to 30.5 kg/m2 and a total body weight >50 kg such that the calculated total volume of the IV infusion of PF-06755347 will not exceed 1 liter.

Informed Consent

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

5.2. Exclusion Criteria for Healthy Participants

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

Medical Conditions

1. Evidence or history of clinically significant hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurologic, or

allergic disease (but excluding untreated, asymptomatic, seasonal allergies at the time of dosing).

Diagnostic assessments

2. A positive urine drug screen.

3. Participants with a history of autoimmune disorders and other conditions that compromise or impair the immune system (including but not limited to: Crohn's Disease, rheumatoid arthritis, scleroderma, systemic lupus erythematosus, Graves' disease, and asthma) or have a current positive result for the following; rheumatoid factor, anti-nuclear antibody, or abnormal free triiodothyronine (T3), free thyroxine (T4), thyroid stimulating hormone (TSH), or thyroid stimulating antibody (TSAb) suggestive of thyroid disease.

4. Participants with a history of autoimmune deficiency or current evidence of total immunoglobulin G (IgG) or total immunoglobulin A (IgA) deficiency.

5. Participants with a history of migraine.

6. Participants with a history or current evidence from lab safety tests of clinically significant dyslipidemia in the opinion of the investigator.

7. Participants with a history of allergic or anaphylactic reaction to any drug including immunoglobulin.

8. Participants with a fever or skin rash within 7 days prior to dosing.

9. History of active infections within 28 days prior to the screening visit.

10. Participants with a history of or current positive results for any of the following serological tests: Hepatitis B surface antigen (HepBsAg), Hepatitis B core antibody (HepBcAb), Hepatitis C antibody (HCVAb) or HIV.

11. Participants with a history of thromboembolic events.

12. Participants with a history of cyclic neutropenia.

13. History of TB or active, latent or inadequately treated TB infection. All positive TB test result(s) are exclusionary.

Other exclusions

14. History of regular alcohol consumption exceeding 14 drinks/week for male participants (1 drink = 5 ounces [150 mL] of wine or 12 ounces [360 mL] of beer or 1.5 ounces [45 mL] of hard liquor) within 6 months before Screening.

15. Use of tobacco or nicotine containing products in excess of the equivalent of 5 cigarettes per day.

16. Exposure to live vaccines within the 28 days prior to the screening visit.

17. Treatment with an investigational drug within 30 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of investigational product (IP) (whichever is longer). An approved COVID-19 vaccine is considered a concomitant medication . Due to the potential for interference with vaccine efficacy, the last dose of an approved COVID-19 vaccine must be completed 28 days prior to dosing with PF-06755347.

18. Screening supine BP ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic), following at least 5 minutes of supine rest. If BP is ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic), the BP should be repeated 2 more times and the average of the 3 BP values should be used to determine the participants eligibility.

19. Screening supine 12-lead ECG demonstrating a corrected QT (QTc) interval >450 msec or a QRS interval >120 msec. If QTc exceeds 450 msec, or QRS exceeds 120 msec, the ECG should be repeated 2 more times and the average of the 3 QTc or QRS values should be used to determine the participants eligibility.

20. Participants with **ANY** of the following abnormalities in clinical laboratory tests at screening or on admission, as assessed by the study specific laboratory and confirmed by a single repeat tests, if deemed necessary:

    - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) level >1.25 × upper limit of normal (ULN);

    - Total bilirubin level >1.0 × ULN; participants with a history of Gilberts syndrome may have direct bilirubin measured and would be eligible for this study provided the direct bilirubin level is ≤ ULN;

    - Creatinine levels >1.0 × ULN;

    - eGFR of <90 mL/min/1.73m^2.

21. Male participants with partners currently pregnant; fertile male participants who are unwilling or unable to use a condom or whose female partners are unable or unwilling to use a highly effective method of contraception as outlined in this protocol for the duration of the study through final study release of the participant (inclusive of final extended immune follow-up visit, if required), or through at least 28 days after the last dose of IP (whichever is longer).

22. Blood donation (excluding plasma donations) of approximately 1 pint (500 mL) or more within 60 days prior to dosing.

23. Unwilling or unable to comply with the criteria in the Lifestyle Considerations section of this protocol.

24. Participants who are 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 participants who are Pfizer employees, including their family members, directly involved in the conduct of the study.

25. Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality (including prothrombin time [PT]/international normalized ratio [INR], partial thromboplastin time [PTT], Ddimer, fibrinogen, hematology and ionogram) 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 participant inappropriate for entry into this study.

Prior/Concomitant Therapy

26. Use of prescription or nonprescription drugs and dietary supplements within 7 days or 5 half-lives (whichever is longer) prior to the first dose of IP. As an exception, acetaminophen/paracetamol may be used at doses of ≤1 g/day. Limited use of nonprescription treatments that are not believed to affect participant safety or the overall results of the study may be permitted on a case-by-case basis following approval by the Sponsor.

27. Herbal supplements must have been discontinued at least 28 days prior to the first dose of investigational product.

28. Due to the potential for interference with vaccine efficacy, the last dose of an approved COVID-19 vaccine must be at least 28 days prior to dosing with PF-06755347.

Prior/Concurrent Clinical Study Experience:

29. Participation in a previous cohort in the current study.

5.3. Inclusion Criteria for Participants with ITP

1. Male and female participants ages 18-55 years at time of ICD signature. Female participants may be of non-childbearing or childbearing potential.

2. Diagnosis of Primary ITP. ITP must be diagnosed in accordance with established guidelines.[17,18]

   - Persistent (>3 months and ≤12 months) OR Chronic (>12 months).

     AND

- Platelet count 30-75 x 10^9/L (inclusive) with criteria achieved on 2 qualifying counts
    - The first platelet count must be taken within approximately 10 days prior to dosing. The second platelet count must be taken at the time of admission.
    - There must be at least 5 days between the 2 platelet counts

3. Participants must have received and responded to IVIg or corticosteroids as treatment for ITP (response is defined as achievement of platelet count >50 x 10^9/L and doubling of platelet count from baseline).

4. Willing and able to comply with all scheduled visits, treatment plan, lab tests, lifestyle considerations and other study procedures.

5. BMI of 17.5 to 30.5 kg/m2 and a total body weight >40 kg (88 lbs).

6. Capable of giving informed consent, including compliance with requirements and restrictions in ICD and in the protocol.

5.4. Exclusion Criteria for Participants with ITP

Medical Conditions:

1. Evidence or history of clinically significant hematological (other than ITP), renal, endocrine, metabolic, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurologic, or allergic disease (but excluding untreated, asymptomatic, seasonal allergies at the time of dosing).

2. Chest X-ray with evidence of current, active TB, previous inactive TB, general infections, heart failure, malignancy, or other clinically significant abnormalities. Chest x-ray must be taken at Screening or within 3 months prior to Screening and read by a qualified radiologist.

3. Any bleeding event requiring medical evaluation or treatment in the 4 weeks prior to screening.

4. Any current bleeding event that, in the opinion of the investigator, requires treatment.

5. Scheduled or anticipated invasive procedures (eg, surgery, dental procedures) within 28 days following PF-06755347 dosing.

6. Splenectomy within ≤180 days prior to PF-06755347 dosing or splenectomy planned during the period of the study.

Diagnostic Assessments:

7. Positive urine drug test.

8. History of any active autoimmune disorder (other than ITP) or other conditions that may compromise or impair the immune system (including but not limited to: Crohn's Disease, rheumatoid arthritis, scleroderma, systemic lupus erythematosus, Graves' disease, and asthma).

9. Participants with a history or current evidence from lab safety tests of clinically significant dyslipidemia in the opinion of the investigator.

10. History of immune deficiency or current evidence of total IgG or total IgA deficiency.

11. History of allergic or anaphylactic reaction to any drug including immunoglobulin.

12. Fever or skin rash within 7 days prior to dosing.

13. History of active infections within 28 days prior to the screening visit.

14. History of Hepatitis B, Hepatitis C or HIV or current positive results for any of the following serological tests - HBsAg, HBcAb, HCVAb or HIV.

15. History of thromboembolic events. For participants in the Czech Republic, see Appendix 12: Country Specific Requirements.

16. History of cyclic neutropenia.

17. Any evidence of latent or active tuberculosis infection.

18. Hemoglobin <9 g/dL.

19. Positive Direct Coombs test.

Other Exclusions:

20. History of regular alcohol consumption for male participants exceeding 14 drinks/week and for female participants, 7 drinks/week (1 drink = 5 ounces [150 mL] of wine or 12 ounces [360 mL] of beer or 1.5 ounces [45 mL] of hard liquor) within 6 months before Screening.

21. Male participants with partners currently pregnant; fertile male participants who are unwilling or unable to use a condom or whose female partners are unable or unwilling to use a highly effective method of contraception as outlined in this protocol for the duration of the study through final study release of the participant (inclusive of final extended immune follow-up visit, if required), or through at least 28 days after the last dose of study intervention (whichever is longer).

22. Pregnant female participants; breastfeeding female subjects; and female participants of childbearing potential who are unwilling or unable to use a highly effective method of contraception as outlined in this protocol for the duration of the study through final study release of the participant (inclusive of final extended immune follow up visit, if

required), or through at least 28 days after the last dose of study intervention (whichever is longer).

23. Exposure to live vaccines within the 28 days prior to the screening visit.

24. Treatment with an investigational drug within 30 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of IP (whichever is longer).

    a. An approved COVID-19 vaccine is considered as a concomitant medication. Due to the potential for interference with vaccine efficacy the last dose of an approved COVID-19 vaccine must be completed 28 days prior to dosing with PF-06755347.

25. Screening supine BP ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic), following at least 5 minutes of supine rest. If BP is ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic), the BP should be repeated 2 more times and the average of the 3 BP values should be used to determine participant eligibility.

26. Screening supine 12-lead ECG demonstrating a corrected QT (QTc) interval >450 msec or a QRS interval >120 msec. If QTc exceeds 450 msec, or QRS exceeds 120 msec, the ECG should be repeated 2 more times and the average of the 3 QTc or QRS values should be used to determine participant eligibility.

27. **ANY** of the following abnormalities in clinical laboratory tests at screening or on admission, as assessed by the study-specific laboratory and confirmed by a single repeat tests, if deemed necessary:

    - AST or ALT ≥1.5 x upper limit of normal); If currently taking eltrombopag, AST or ALT >3 × ULN;
    - Total bilirubin ≥1.25 x upper limit of normal); If currently taking eltrombopag, total bilirubin level >1.5 × ULN (Participants with a history of Gilberts syndrome may have direct bilirubin measured and would be eligible for this study provided the direct bilirubin level is ≤ ULN);
    - Serum creatinine >1.5 x ULN;
    - eGFR <60 ml/min/1.73m^2 by CKD-EPI Formula.

28. Participants who are 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 participants who are Pfizer employees (including their family members) directly involved in the conduct of the study.

29. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

30. Participation in a previous cohort in the current study.

Prior/Concurrent Therapy for ITP:

31. ≤28 days prior to PF-06755347 dosing:

    - Treatment with IVIg or an anti-Rh D antigen agent (eg, WinRho®).

    - Treatment with high-dose pulse corticosteroid therapy (eg, dexamethasone 40mg/day for 4 days or methylprednisolone 30 mg/kg/day for 3 days).

    - Other Anti-inflammatory Drugs, including NSAIDS for Cox-1 and Cox-2 (eg, Ibuprofen, naproxen, aspirin, diclofenac) or anti-IL-6 agents tocilizumab or siltuximab.

32. Within 3 months prior to PF-06755347 dosing:

    - Treatment with cytotoxic agents (eg, cyclophosphamide, vincristine).

    - Plasmapheresis.

33. Within 6 months prior to PF-06755347 dosing:

    - Treatment with rituximab (or any other anti-CD20 agent).

Concomitant Therapy:

34. If receiving corticosteroids, the dose must be <1 mg/kg prednisone per day or equivalent, must have been stable or decreasing for ≥28 days prior to PF-06755347 dosing and must be expected to remain stable or to decrease for the duration of the study.

35. If receiving any of the medications shown below, the dose must have been stable for ≥28 days prior to PF-06755347 dosing and must be expected to remain stable for the duration of the study:

    - Avatrombopag, eltrombopag, fostamatinib, or romiplostim.

    - Adjunct immunosuppressives cyclosporine, azathioprine, mycophenolate, or 6-mercaptopurine.

5.5. Lifestyle Considerations

The following guidelines are provided:

5.5.1. Meals and Dietary Restrictions

- Participants must abstain from all food and drink (except water) at least 4 hours prior to any safety laboratory evaluations (minimum of 12 hrs for lipid profile at screening). Participants will not be required to fast on Day 1 for post-dose laboratory safety tests. Water may be consumed without restriction throughout the study.

- On dosing days, a standard breakfast will be provided approximately 1 hour prior to the start of dosing and last approximately 20 minutes. Standard breakfast will be provided on other in-patient stay days.

- Lunch will be provided approximately 4 hours after the start of dosing.

- Dinner will be provided approximately 9 to 10 hours after the start of dosing.

- An evening snack may be permitted.

- While confined, the total daily nutritional composition should be approximately 55% carbohydrate, 30% fat and 15% protein. The daily caloric intake per participant should not exceed approximately 3200 kcal.

5.5.2. Caffeine, Alcohol and Tobacco

- Participants will abstain from alcohol for 24 hours prior to admission and continue abstaining from alcohol until discharge, as well as 24 hours prior to outpatient visits. Participants may undergo an alcohol breath, blood or urine test at the discretion of the investigator.

- Healthy participants will abstain from caffeine-containing products for 24 hours prior to the start of dosing or until collection of the final PK sample prior to discharge on Day 8. Caffeine is allowed for participants with ITP.

- Healthy participants will abstain from the use of tobacco- or nicotine-containing products for 24 hours prior to dosing and during confinement in the research unit. Nicotine-containing products are allowed for participants with ITP.

5.5.3. Activity

- Participants will be confined to the procedure room/participant room, as appropriate, for the first 8 hours after the start of dosing on Day 1 during continuous cardiac monitoring, except for lunch and to use the bathroom. After this, if the equipment setup allows, participants may be ambulatory during the continuous cardiac monitoring period, but should not engage in strenuous activities. If equipment does not allow ambulation, appropriate accommodations will be made by the investigator

site to facilitate continuous monitoring (eg, bedside urinals should be provided to accommodate participants' excretory needs).

- Participants will abstain from strenuous exercise (eg, heavy lifting, weight training, calisthenics, aerobics) for at least 48 hours prior to each blood collection for clinical laboratory tests. Walking at a normal pace will be permitted.

5.5.4. Contraception

The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual participant and his/her partner(s) from the permitted list of contraception methods (see Appendix 4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the SoA, the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participants affirmation in the participants chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or the participant's partner.

5.6. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to investigational product/entered in the study. Screen failure data are collected and remain as source and are not reported to the clinical database.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once and must meet all inclusion/exclusion criteria. Rescreened participants will be re-consented. All screening assessments must be repeated during rescreening.

6. STUDY INTERVENTION

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

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

6.1. Study Intervention(s) Administered

For this study, the investigational product is PF-06755347 and its non-matching placebo.

PF-06755347 and non-matching placebo will be supplied by Pfizer as solution for injection in sterile vials for preparation of intravenous infusion and subcutaneous injections at the study site.

PF-06755347 1000 mg/vial Solution for Injection (50 mg/mL) is presented as a sterile solution for intravenous and subcutaneous administration. Each vial of PF-06755347 contains a sufficient amount of product to ensure an extractable volume of 20 mL of aqueous buffered solution, is sealed with a coated stopper and an overseal, and is labeled according to local regulatory requirements.

Placebo for PF-06755347 Solution for Injection is presented as a sterile solution for intravenous and subcutaneous administration. Each vial contains 20 mL of placebo as an aqueous buffered solution, is sealed with a coated stopper and an overseal, and is labeled according to local regulatory requirements.

Sterile vials will be supplied as individual vials packaged in an open-label fashion in units of multiple vials in a carton.

6.1.1. Administration

Healthy Participants

Participants will start receiving IP in a blinded fashion at approximately 08:00 hours (plus or minus 3 hours). Blinded investigator site personnel will administer IP for each participant according to the IP Manual. The IV infusion will be on the opposite arm from PK sampling and start and stop time of the infusion will be recorded. The preferred site for subcutaneous injection(s) will be on the abdomen.

Participants with ITP

Participants will receive open-label IP at approximately 08:00 hours (plus or minus 3 hours). Investigator site personnel will administer IP for each participant according to the IP Manual. The preferred site for subcutaneous injection(s) will be on the abdomen.

6.1.1.1. Guideline on Intravenous Infusion

PF-06755347 or placebo will be administered by continuous IV infusion. The infusion rate and duration depends on the dose and the volume to be infused. Table 8 provides guidelines on infusion scheme for each proposed dose; however the actual infusion rate may be lowered and/or infusion duration may be increased to mitigate infusion-related symptoms at the discretion of the PI (see Section 6.6 and Section 6.7). The overall infusion time will not exceed 4 hrs. The infusion scheme will also be adjusted appropriately if doses other than those proposed are used.

Table 8. Guideline on Intravenous Infusion Scheme

Target Dose (mg/kg)	Infusate Drug concentration (mg/mL)	Infusion Rate (mL/kg/min)	Dosing Rate (mg/kg/min)	Infusion Duration[c](min)	Dose per Interval (mg/kg)
0.01	0.03	0.006	0.00018	60	0.01
0.03	0.03	0.017	0.00051	60	0.03
0.1	0.05	0.02	0.001	30	0.03
	0.05	0.04	0.002	35	0.07
0.3	0.15	0.02	0.003	30	0.09
	0.15	0.04	0.006	35	0.21
1[a]	0.5	0.02	0.01	30	0.3
	0.5	0.04	0.02	35	0.7
1[b]	0.5	0.011	0.0055	180	1
2	0.5	0.022	0.011	180	2
4	1.5	0.015	0.023	180	4
8	1.5	0.03	0.045	180	8
16	2.5	0.036	0.09	180	16

a. Infusion rates for the first 3 participants in Cohort 5 (1 mg/kg IV).
b. Infusion rates for the 4 participants in Cohort 5 (1 mg/kg IV) expansion.
c. Infusion duration of 180 minutes (±18 minutes).

6.1.1.2. Guideline on Subcutaneous Injection

For participants receiving a SC injection, the number of injections will be recorded. Time 0 for the SC injection will be the time of the first injection. The preferred body location for the SC injection is the abdomen but the 5 cm area around the navel should be avoided. 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 PK blood sample collections. For doses that require more than one injection, individual injections should be administered approximately 3 cm away from the site of the previous injection (ie, the abdomen, same arm or thigh). Avoid umbilicus area and skin with tattoos and scarring. The maximum volume for an individual injection is 1.5 ml. Since the drug product concentration is 50 mg/mL, the maximum number of injections will be approximately 4. At SC doses that require greater than the maximum number of injections, a SC infusion will be used.

If a participant experiences an infusion or injection site reaction during the administration period, then treatment administration should be paused for that participant and supportive care should be provided according to the Investigator's standard practice (eg, treatment with an antihistamine). Treatment administration may resume at the discretion of the Investigator if there are no systemic symptoms and if the reaction resolves.

Consult the IP Manual for detailed instructions regarding study drug preparation, stability and administration. Per the drug stopping rules (Section 6.6 and Section 6.7), dosing will be paused for the entire cohort, for any serious adverse event (SAE) that occurs in a participant receiving active treatment until causality is fully assessed by the PI and Sponsor.

6.2. Preparation/Handling/Storage/Accountability

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

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

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

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

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

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

7. See the IP Manual for storage conditions of the study intervention once prepared.

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

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

6.2.1. Preparation and Dispensing

Within this protocol, preparation refers to the investigator site activities performed to make the investigational product ready for administration or dispensing to the participant by qualified staff. Dispensing is defined as the provision of investigational product, concomitant treatments, and accompanying information by qualified staff member(s) to a healthcare provider or participant in accordance with this protocol. Local health authority regulations or investigator site guidelines may use alternative terms for these activities.

See the IP Manual for instructions on how to prepare and blind the investigational product for administration.

PF-06755347 and placebo should be prepared by an appropriately qualified unblinded site personnel (ie, pharmacist) according to the IP manual 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. Dose preparation must be performed with locally accepted sterile handling technique and the investigational product will be administered in blinded fashion to the participant.

PF-06755347 and placebo vials are single use.

All dosing and administration calculations and dose preparation must be performed and checked by one qualified clinical site personnel and verified by a qualified and experienced second clinical site personnel (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist). The site will take all necessary precautions to maintain the investigator and other site personnel blind.

6.3. Measures to minimize bias: Randomization and blinding

An Interactive Response Technology (IRT) system will be programmed with blind-breaking instructions. Refer to subsections 6.3.1 Allocation to Investigational Product and 6.3.2 Breaking the Blind for further details.

6.3.1. Allocation to Investigational Product

Allocation of participants to treatment groups will proceed through the use of an interactive response technology (IRT) system (interactive Web-based response [IWR]). The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's identification (ID) and password, the protocol number, and the participant number. The site personnel will then be provided with a

treatment assignment and randomization number, when investigational product is being supplied via the IRT system. The IRT system will provide a confirmation report containing the participant number, randomization number, and treatment assignment.. The confirmation report must be stored in the site's files.

Investigational product will be dispensed at Day 1 inpatient visit.

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

6.3.2. Breaking the Blind (for HP cohorts only)

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. The IRT will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination.

If the investigator decides that unblinding is warranted in the interest of the safety of a participant, the investigator should make every effort to contact the Sponsor prior to unblinding a participant's treatment assignment unless this could delay further management of the participant. However, discussion with the Sponsor in advance of unblinding is not required. If a participant's treatment assignment is unblinded, the Sponsor must be notified within 24 hours after breaking the blind.

When the blinding code is broken, the reason must be fully documented and entered on the data collection tool (DCT).

Blood specimens will be obtained from all participants for PK analysis to maintain the study blind at the investigator site. The investigator site staff and blinded study monitor, if assigned, will be blinded to IP. A designated limited number of Sponsor colleagues within the study team will be unblinded to participant treatments in order to permit real-time interpretation of the safety and PK data and provide information necessary to potentially alter the dose-escalation sequence (see Section 9.9). Specimens from participants randomized to placebo will not be routinely analyzed. To minimize the potential for bias, treatment randomization information will be kept confidential by Pfizer unblinded personnel and will not be released to the blinded investigator or blinded investigator site personnel until the study database has been locked or the investigator requests unblinding for safety reasons.

6.4. Study Intervention Compliance

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

6.5. Concomitant Therapy

Healthy participants will abstain from all concomitant therapies except those required for the treatment of adverse events.

Participants with ITP will be permitted to continue any medications that they routinely receive for treatment of ITP or any other co-existing medical conditions, so long as their use does not violate any inclusion or exclusion criteria. They will also be permitted to receive concomitant therapies required for the treatment of adverse events.

Acetaminophen/paracetamol, nonsteroidal anti-inflammatory drugs (for HPs only) and diphenhydramine are permitted to manage adverse events and infusion or injection related reactions.

Limited use of nonprescription treatments that are not believed to affect participant safety or the overall results of the study may be permitted on a case-by-case basis following approval by the Sponsor.

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

Treatments taken within 56 days before the first dose of investigational product will be documented as a prior treatment. Treatments taken after the first dose of investigational product will be documented as concomitant treatments.

6.5.1. Rescue Medication

6.5.1.1. Rescue Therapy for CRS

Rescue therapy for CRS should be immediately available including oral paracetamol, oral NSAIDs, IV normal saline, IV corticosteroids, oxygen.

An ICU should be available for additional support and administration of vasopressors if appropriate. The availability of anti-IL-6 agents is optional.

See Section 10.10 for further guidance.

6.5.1.2. Rescue Therapy for Bleeding Events in ITP Participants

Rescue therapy for bleeding events in ITP participants should be carried out in accordance with each country's/site's standard procedures and practices.[19]

6.6. Dose Progression

The participants within each cohort will be dosed using a sequential dosing scheme. For all cohorts, a single participant will be dosed at a given time, followed by a minimum of 72-hour (for IV) and 96-hours (for SC) safety monitoring period. In total there will be a minimum of 96 hours between each IV participant dosed and 120 hours for each SC participant dosed.

The following rules will be applied when considering dosing of the next participant in the cohort.

Sequential dosing may **proceed** only if no adverse events are reported OR all of the following criteria are met:

1. Any pro-inflammatory events are < Grade 2 Per CTCAE criteria in Appendix 9.
2. All other adverse events are deemed mild or moderate in severity, regardless of relatedness.
3. Any laboratory, ECG or vital sign changes are considered not clinically significant.
4. No other pause or stop criteria are met.
5. For participants with ITP, in addition to the above criteria, no participant has greater than a 30% decrease in platelet count – defined from the immediate pre-dosing platelet count to the lowest postdosing platelet count. Dose progression will be independent of dose progression from HP cohorts at higher dose levels.

Sequential dosing should be **paused** if any criterion below is met in a participant receiving active drug:

1. Grade 2 (Objective) pro-inflammatory event (vomiting, diarrhea, hypotension or hypoxia) (see Appendix 9).
2. Adverse event which is considered to be severe (Grade 3 or higher) AND is deemed related to study intervention.
3. A moderate event (Grade 2) AND is deemed related to study intervention not otherwise identified as a proinflammatory event or AE of special interest, that in the opinion of the PI and Sponsor are of concern and warrant further investigation before additional dosing.
4. For participants with ITP, platelet count of <30 x 109/L AND a decrease from baseline ≥30%, or a platelet count decrease from baseline of ≥50%, defined from the immediate pre-dosing platelet count to the lowest post-dosing platelet count, or a bleeding or bruising-related AE CTCAE 4.03 Grade 2 or higher (except metrorrhagia Grade 3 or higher).

Sequential dosing should be **stopped** at the current dose level if any criterion below is met in participant receiving active drug:

1. Grade 3 or greater pro-inflammatory event.
2. Serious adverse event that is deemed related to study intervention.

3. A single occurrence of confirmed drug induced liver injury (see Appendix 6) or confirmed drug induced kidney injury (see Section 7.1) will be reported as a serious adverse event, and therefore, will be considered dose limiting.

In the event of a dose **pause**, all available safety, PK (if available), cytokine, and complement data for the participants will be reviewed by the dose escalation subteam. The subteam should determine whether clinical symptoms associated with the pause criteria have resolved and determine whether IL-6 has returned to near baseline levels ie that the event is reversible. IL-6 has been selected as the surrogate marker for decision making purposes as it appears to be the most sensitive cytokine pathways from the non-human primate and human in vitro data. However, TNF-α, IFN-γ cytokine and complement data will be available at the time of review. If the dose escalation subteam determines that dosing may resume, a plan that mitigates risks to participants with the resumption of dosing may be implemented. Such a plan could include a revision of inclusion/exclusion criteria, repeating or reducing the dose, reducing infusion/dosing rate or adding appropriate safety monitoring or prophylactic treatment. This mitigation plan may need to be discussed with the Institutional Review Board (IRB) or Regulatory Authority as appropriate. The ultimate decision to continue dosing of study participants rests with the PI. Sponsor dose escalation subteam cannot overrule PI decision/clinical judgement.

If the decision is to **stop** dose progression this will also stop any further dose escalation.

6.7. Dose Escalation

After each cohort has completed, a batched level review of all available safety, PK, cytokine and complement data will occur. For purposes of dose escalation, a completer is defined as a participant that has finished the clinical confinement up to Day 8. Dose escalation can proceed if the last dose was considered to be safe and well tolerated in all participants up to Day 8. Dose escalation may be stopped if it is determined that the limits of safety and/or tolerability or PK stopping criteria have been reached. This decision will be made after a discussion takes place between the Sponsor study team and each site's investigator or delegate. The Sponsor study team may not overrule the investigators 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.

Dose escalation may **progress** when one of the following criterion is met:

- Sequential dosing was completed successfully for the cohort and the last dose was considered to be safe and well tolerated.

- In the event that a dosing pause criteria has been met for the cohort (see Section 6.6), the dose escalation subteam confirmed that, after review of all data, it is safe to progress. Any requested mitigations must be applied eg, reduction in infusion rate.

- Dose escalation from the first to second ITP cohort will occur when the first dose is deemed safe and tolerable in ITP participants AND the second ITP cohort dose is deemed safe and tolerable in HPs, ie, dependent upon HP data.

For sites in the Czech Republic, the participation of females with ITP should commence only following approval by the Sponsor's dose escalation subteam. Please refer to Appendix 12: Country Specific Requirements for further details.

The dose escalation will be **terminated** if any of the following criterion is met:

- If 50% or more of the participants receiving active drug at a given dose level (but not participants receiving placebo) develop similar clinically significant laboratory, ECG, or vital sign abnormalities, in the same organ class, indicating dose-limiting intolerance.
- Severe nonserious AEs, considered as, at least, possibly related to study intervention administration, in 2 participants at a given dose level (but not participants receiving placebo), independent of within or not within the same system organ class, indicating dose limiting intolerance.
- It is determined that the limit of safety and/or tolerability has been reached. This decision will be made following discussions between the study team and the investigator.
- Other findings that, at the discretion of the study team and investigators, indicate that dose escalation should be halted.
- Sequential dosing was stopped based on the criteria in Section 6.6.
- At any dose level, the exposure reaches or exceeds the PK stopping limits in any individual participant (AUC_{168} of 34000 µg·hr/mL and/or C_{max} of 1130 µg/mL).
- Based on the observed data, the C_{max} or AUC_{168} of the next planned dose is projected to exceed the escalation limits in any individual participant, that dose will not be explored. Modified doses may be explored if they are not expected to exceed PK stopping criteria.

If following an internal safety review, it is appropriate to restart the trial, a substantial amendment will be submitted to CAs and ECs. The trial will not restart until the amendment has been approved by CAs and ECs.

Progression to the next dose will occur if the last dose was well tolerated and after satisfactory review of the available safety and PK data.

6.8. Infusion or Injection Site Reactions (ISR)

ISR is a type of hypersensitivity reaction that may be immediate, although it usually appears within 24-48 hrs after injection. ISR, by definition, includes the following: erythema, induration ecchymosis, pain and pruritus at the infusion or injection site.

Infusion or injection-related reactions will be assessed and managed based on the CTCAE severity scale for infusion reactions (see Appendix 11).

- Grade 1 reaction (Mild): Participant will be monitored closely at bedside while infusion or injection continues. For IV dosing, the PI may slow the infusion rate, based on medical judgement.

- Grade 2 (Moderate): Infusion may be paused, and symptomatic treatment (such as antihistamine, acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs) may be administered. For IV dosing, if the infusion is paused, once symptoms subside, infusion may be restarted at a 50% reduction in infusion rate. Infusion rate may be increased after 30 minutes if participant is stable.

- Grade 3 (Severe) or 4 (life-threatening): FoIV dosing, the infusion will be stopped promptly. Participant will be followed until symptoms resolve, and no further follow-up regarding the AEs is needed in the opinion of the PI.

- For IV dosing, acute infusion reactions of mild-moderate severity (Grade 1 or Grade 2) which fully resolve following dose interruption and/or the administration of antihistamines/antipyretics with subsequent resumption and safe completion of dosing will not be considered dose limiting.

6.9. Intervention After the End of the Study

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

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Discontinuation of Study Intervention

Potential Cases of Acute Kidney Injury

Abnormal values in serum creatinine (SCr) concurrent with presence or absence of increase in blood urea nitrogen (BUN) that meet the criteria below, in the absence of other causes of kidney injury, are considered potential cases of acute kidney injury and should be considered important medical events.

An increase of ≥0.3 mg/dL (or ≥26.5 µmol/L) in SCr level relative to the participants own baseline measurement should trigger another assessment of SCr as soon as practically feasible, preferably within 48 hours from awareness.

If the second assessment (after the first observations of ≥0.3 mg/dL [or ≥26.5 µmol/L] in SCr relative to the participants own baseline measurement) is ≥0.4 mg/dL (or ≥35.4 µmol/L), adequate, immediate, supportive measures taken to correct apparent acute kidney injury.

Participants should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the second assessment confirming abnormal SCr result. This evaluation should include laboratory tests, detailed history, and physical assessment. In addition to repeating SCr, laboratory tests should include serum BUN, serum creatine kinase, and serum electrolytes (including at a minimum potassium, sodium, phosphate/phosphorus, and calcium), in addition to urinary dipstick, urine microscopic examination, and urinary indices. Continued follow-up per protocol as well as any additional specific investigations/management required to manage the kidney injury is required until resolution.

All cases confirmed on repeat testing as meeting the laboratory criteria for acute kidney injury, with no other cause(s) of laboratory abnormalities identified, should be considered potential cases of drug-induced kidney injury irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal SCr. If ≥2 healthy participants in a given cohort are noted to have 2 *consecutive* SCr results of ≥0.3 mg/dL (or ≥26.5 µmol/L), an assessment of whether the finding may be considered an adverse drug reaction should be undertaken.

7.1. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study at any time at his own request.

Reasons for discontinuation from the study include the following:

- Refused further follow-up;
- Lost to follow-up;
- Death;
- Study terminated by Sponsor.

If a participant discontinues during the trial, the participant may be replaced at the discretion of the Sponsor in consultation with the PI.

At the time of discontinuing from the study, if possible, an early termination visit with assessments from Day 71 should be conducted. See the SoA for assessments to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

The early discontinuation visit applies only to participants who are enrolled/randomized and then are prematurely withdrawn from the study. Participants should be questioned regarding their reason for withdrawal. The participant will be permanently discontinued both from the study intervention and from the study at that time.

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

If the participant withdraws from the study and also withdraws consent (see Section 7.1.1) 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.

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

7.1.1. Withdrawal of Consent

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

7.2. Lost to Follow up

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

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

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

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

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

Participants will be screened within 56 days prior to administration of the investigational product to confirm that they meet the study population criteria for the study. The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study-specific procedures.

A participant who qualified for this protocol but did not enroll from an earlier cohort/group may be used in a subsequent cohort/group without rescreening, provided laboratory results obtained prior to the first dose administration meet eligibility criteria for this study. In addition, other clinical assessments or specimen collections, eg, banked biospecimens, may be used without repeat collection, as appropriate.

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

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

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

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

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

If an IV catheter is utilized for blood sample collections, ECGs and vital sign assessments (pulse rate and BP) should be collected prior to the insertion of the catheter or if not, ensure adequate rest is achieved prior to the collection of vital signs.

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.

To prepare for study participation, participants will be instructed on the information in the Lifestyle Considerations and Concomitant Therapy sections of the protocol.

8.1. Efficacy Assessments

Not Applicable.

8.2. Safety Assessments

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

8.2.1. Physical Examinations

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

A brief physical examination will include, at a minimum, assessments of general appearance, the respiratory and cardiovascular systems, and participant reported symptoms.

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

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

8.2.2. Vital Signs

Supine BP will be measured with the participants arm supported at the level of the heart, and recorded to the nearest mm Hg after approximately 5 minutes of rest. The same arm (preferably the dominant arm) will be used throughout the study. Blood pressure should be taken from the contralateral arm to that receiving infusion. Participants should be instructed not to speak during measurements.

The same properly sized and calibrated BP cuff will be used to measure BP each time. The use of an automated device for measuring BP and pulse rate is acceptable, however, 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 pulse rate should be obtained prior to the nominal time of the blood collection. Triplicate vital signs measurement (including oral temperature) at the times specified in the SoA should be collected approximately 2 minutes apart.

Additional collection times, or changes to collection times, of BP and pulse rate will be permitted, as necessary, to ensure appropriate collection of safety data.

Normal range for vital sign measurements are defined as: 90 mmHg ≤ systolic BP ≤139 mmHg; 50 mmHg ≤ diastolic BP ≤89 mmHg; 40 bpm ≤ heart rate ≤100 bpm; 35.4°C ≤ oral temperature ≤37.5°C.

8.2.2.1. Respiratory Rate

Not Applicable.

8.2.2.2. Temperature

Temperature will be measured using either an oral or tympanic method. The same collection method for each participant is required throughout the study. No eating and drinking is allowed for 15 minutes prior to the measurement.

8.2.3. Electrocardiogram

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

Triplicate 12-lead ECGs will be obtained approximately 2 to 4 minutes apart; the average QTc value from the triplicate ECG measurements collected at each nominal time point on Day -1 will serve as each participant's time-controlled baseline QTc value.

To ensure safety of the participants, a qualified individual at the investigator site will make comparisons to baseline measurements. Additional ECG monitoring will occur if a) the mean value from the triplicate measurements for any postdose QTc interval is increased by ≥30 msec from the baseline **and** is >450 msec; or b) an absolute QTc value is ≥500 msec for any scheduled ECG. If either of these conditions occurs, then a single ECG measurement must be repeated at least hourly until QTc values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement.

If a postdose QTc interval remains ≥30 msec from the baseline **and** is >450 msec; or b) an absolute QTc value is ≥500 msec for any scheduled ECG for greater than 4 hours (or sooner, at the discretion of the investigator), or c) QTc intervals get progressively longer, the participant should undergo continuous ECG monitoring. A cardiologist should be consulted if QTc intervals do not return to less than the criterion listed above after 8 hours of monitoring (or sooner, at the discretion of the investigator).

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

qualified medical providers interpretation determines that the QTc values are in the acceptable range.

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

8.2.3.1. Continuous Cardiac Monitoring by Telemetry

All abnormal rhythms will be recorded and reviewed by the study physician for the presence of rhythms of potential clinical concern. The time, duration, and description of the clinically significant event will be recorded in the DCT. In addition, a printed record of the tracing(s) of the clinically significant rhythm(s) will be made and retained with other source documents.

Telemetry should be collected using a centralized system that also allows for the storage and advanced analysis of all recorded data in order to preserve important events for future evaluations. Holter monitoring should not be used in parallel with continuous telemetry, unless it is the only means of data storage available at the investigator site, or verifiable arrhythmia quantification is required. To establish a baseline, telemetry should be recorded for at least 2 hours before dosing. This may be done immediately prior to dosing or at some 2-hour continuous interval between admission and prior to dosing, as long as the recording is performed when the participant is awake. Telemetry may be stopped within a reasonably short period of time prior to dosing, in order to avoid interference with study operations conducted immediately before dosing. However, it is expected that the telemetry leads will be in place and the system connected prior to dosing.

8.2.4. Clinical Safety Laboratory Assessments

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

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

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

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

See Appendix 6 for suggested actions and follow-up assessments in the event of potential drug-induced liver injury.

8.2.5. Pulse Oximetry

Saturation level of oxygen in blood (Sp02) will be measured as outlined in the SoA using Pulse Oximetry and can be obtained in a supine position. Additional collection times, or changes to collection times will be permitted, as necessary, to ensure appropriate collection of safety data.

8.2.6. Pregnancy Testing

Pregnancy tests may be urine or serum tests, but must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the SoA. Following a negative pregnancy test result at screening, appropriate contraception must be commenced and a second negative pregnancy test result will be required at the baseline visit prior to the participant's receiving PF-06755347. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) and at the end of the study. Pregnancy tests may also be repeated if requested by IRBs/ECs or if required by local regulations. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded if the serum pregnancy result is positive.

8.3. Adverse Events and Serious Adverse Events

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

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

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

Each participant will be questioned about the occurrence of AEs in a nonleading manner.

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

Assessment of adverse events will include the type, incidence, severity (CTCAE version 4.03, Appendix 11) timing, seriousness, and relatedness for injection site reactions. The severity of CRS will be assessed according to the grading described by the ASTCT and Lee et al. (2019, see Appendix 10).[12]

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

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

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.

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

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

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

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

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.3.1 are reported to Pfizer Safety on the CT SAE Report Form immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

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

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

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

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

8.3.2. Method of Detecting AEs and SAEs

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

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

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.2).

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

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

8.3.4. Regulatory Reporting Requirements for SAEs

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

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

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

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

8.3.5. Exposure 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.

8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

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

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

- If EDP occurs in a participant or a participant's partner, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancies will be collected after the start of study intervention and until at least 5 terminal half-lives after the last dose.
- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the CT SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP Supplemental Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural

integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs. Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

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

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

8.3.5.2. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

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

The investigator must report exposure during breastfeeding to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the CT SAE Report Form. When exposure during breastfeeding occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study**,** so the information is not recorded on a CRF. However, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

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, the SAE is reported together with the exposure during breastfeeding.

8.3.5.3. 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.

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

8.3.6. Cardiovascular and Death Events

Not applicable.

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

Not applicable.

8.3.8. Adverse Events of Special Interest

All adverse events of special interest (AESIs) must be reported as an AE or SAE following the procedures described in Section 10.3. An AESI is to be recorded as an AE or SAE on the CRF. In addition, an AESI that is also an SAE must be reported using the CT SAE Report Form.

8.3.8.1. Lack of Efficacy

This section is not applicable because efficacy is not expected in the study population.

8.3.9. Medical Device Deficiencies

Not applicable.

8.3.10. Medication Errors

Medication errors may result from the administration or consumption of the investigational product by the wrong participant, or at the wrong time, or at the wrong dosage strength, or noncompliance as described in Section 6.4.

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

Medication errors include:

- Medication errors involving participant 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 study participant.

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

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

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

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

8.4. Treatment of Overdose

For this study, any dose of investigational product greater than that prescribed at each dose level will be considered an overdose.

Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities for at least 5 half-lives or 28 calendar days after the overdose of PF-06755347 (whichever is longer).
3. Obtain a blood sample for PK analysis within 2 days from the date of the last dose of study intervention if requested by the medical monitor (determined on a case-by-case basis).

4. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.

5. Overdose is reportable to Safety **only when associated with an SAE.**

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

8.5. Pharmacokinetics

8.5.1. Analysis of PF-06755347

Blood samples (2 mL) to provide approximately 0.5 mL plasma for pharmacokinetic analysis will be collected into appropriately labeled tubes containing dipotassium ethylene diamine tetraacetic acid (K_2EDTA) at times specified in the SoA.

The actual times may change but the number of samples will remain the same. All efforts will be made to obtain the pharmacokinetic 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 (eg, DCT). Collection of samples more than 10 hours after dose administration that are obtained ≤1 hour away from the nominal time relative to dosing will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and data collection tool (eg, DCT). This protocol deviation window does not apply to samples to be collected more than 10 hours after dose administration at outpatient/follow-up visits with visit windows.

Samples will be analyzed using a validated analytical method in compliance with Pfizer standard operating procedures.

The PK samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the PK sample handling procedure (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the Sponsor. On a case-by-case basis, the Sponsor may make a determination as to whether sample integrity has been compromised. Any deviation from the specified sample handling procedure resulted in compromised sample integrity will be considered a protocol deviation.

As part of understanding the pharmacokinetics of the IP, samples may be used for metabolite identification and/or evaluation of the bioanalytical method, CCI [redacted] These data will not be included in the clinical study report (CSR).

8.5.2. Analysis of Anti-Drug Antibodies

Blood samples (4 mL) to provide approximately 1.5 mL serum for the assessment of antidrug (anti-PF-06755347) antibodies will be collected into appropriately labeled tubes containing no anticoagulant or gel serum separator at visits specified in the SoA.

The ADA sample analysis will follow a tiered approach of screening, confirmation, and titer determination. Samples will be analyzed using a validated analytical method in compliance with Pfizer standard operating procedures.

The ADA samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the immunogenicity sample handling procedure (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the Sponsor. On a case-by-case basis, the Sponsor may make a determination as to whether sample integrity has been compromised. Any deviation from the specified sample handling procedure resulting in compromised sample integrity will be considered a protocol deviation.

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [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]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

9. STATISTICAL CONSIDERATIONS

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

9.1. Statistical Hypotheses

No formal statistical hypothesis testing will be performed in this study.

9.2. Sample Size Determination

No formal sample size calculation was performed. For cohorts that include healthy participants, cohort size of approximately 4 (3 active, 1 placebo) to 8 (4 active, 2 placebo) participants has been chosen to ensure appropriate sample size to provide adequate safety, toleration and PK information at each dose level and to provide a placebo comparison group, while minimizing exposure to humans of a new biologic entity. ITP Cohorts will not include placebo. ITP cohort size will be approximately 3 to 6 participants to reflect the number dosed receiving PF-06755347 in HP cohorts. Participants who discontinue during the trial may be replaced at the discretion of the Sponsor and Investigator.

9.3. Populations for Analysis

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign the ICD.
PK Population	The PK concentration population is defined as randomized participants who received at least one dose and have at least 1 concentration. The PK parameter analysis population is defined as all randomized participants who received at least one dose and have at least 1 of the PK parameters of interest.
PD Population	The PD analysis population is defined as all randomized participants treated who have at least one PD assessment in at least one cohort.
Safety	All participants randomly assigned to investigational product and who receive at least 1 dose of investigational product. Participants will be analyzed according to the product they actually received.

9.4. Statistical Analyses

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

9.4.1. Efficacy Analyses

An efficacy analysis is not applicable to this study.

9.5. Pharmacokinetic Analysis

9.5.1. Derivation of Pharmacokinetic Parameters

PK parameters following single dose administration will be derived from the plasma PF-06755347 concentration-time profiles as defined in Table 10 for each participant and treatment, as applicable, using noncompartmental analysis of concentration-time data. Samples below the lower limit of quantitation will be set to zero for analysis. Actual sample collection times will be used for the pharmacokinetic analysis.

Table 10. Plasma Pharmacokinetic Parameter Definition

Parameter	Definition	Mode of Determination
C_{max}	Maximum plasma concentration	Observed directly from data
C_{max} (dn)	Dose normalized C_{max}	C_{max}/Dose
T_{max}	Time for C_{max}	Observed directly from data as time of first occurrence
AUC_{last}	Area under the plasma concentration-time profile from time zero to the time of last quantifiable concentration (C_{last})	Linear/Log trapezoidal method
AUC_{last}(dn)	Dose normalized AUC_{last}	AUC_{last}/Dose
AUC_{inf} [a]	Area under the plasma concentration-time profile from time zero extrapolated to infinite time	$AUC_{last} + (C_{last}*/k_{el})$, where $C_{last}*$ is the predicted plasma concentration at the last quantifiable time point estimated from the log-linear regression analysis
AUC_{inf} (dn)[a]	Dose normalized AUC_{inf}	AUC_{inf}/Dose
$t_{½}$[a]	Terminal half-life	$Log_e(2)/k_{el}$, where k_{el} is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve. Only those data points judged to describe the terminal log-linear decline will be used in the regression.
CL (IV)[a]	Systemic Clearance	Dose/AUC_{inf}
V_{ss} (IV)[a]	Volume of distribution at steady-state	CL*MRT where MRT=($AUMC_{inf}$/AUC_{inf})–(DOI/2)
CL/F (SC)	Apparent clearance	Dose/AUC_{inf} for SC route
Vz/F (SC)	Apparent volume of distribution	Dose / (AUC_{inf} *kel) for SC route
F (SC)	bioavailability	F = $AUC_{inf,sc}$/ $AUC_{inf,iv}$

a. If data permit.
Abbreviation: AUMC = area under the first moment plasma concentration curve; dn=dose normalized to a 1 mg dose; DOI = duration of infusion; MRT = mean residence time.
Actual PK sampling times will be used in derivation of PK parameters.

The supporting data from the estimation of $t_{½}$ will also be reported: the terminal phase rate constant (k_{el}); the first, last, and number of time points used for the log-linear regression ($k_{el,t(lo)}$, $k_{el,t(hi)}$, and $k_{el,t(n)}$); the goodness-of-fit statistic from the regression (r^2); and the percent of the area under the plasma concentration-time curve from time zero to infinite time, AUC_{inf}, obtained by forward extrapolation (AUC_{extrap}%).

9.5.1.1. Statistical Methods

No formal inferential statistics will be applied to the pharmacokinetic data.

The plasma concentration of PF-06755347 will be listed and summarized descriptively by nominal PK sampling time and treatment group. Individual participant, mean and median profiles of the plasma concentration-time data will be plotted by treatment group using actual and nominal times, respectively. Mean and median profiles will be presented on both linear and log scales.

If data allows, PK parameters will be descriptively summarized and plotted by treatment group.

If data permits, dose normalized (to 1 mg) AUC_{inf}, AUC_{last} and C_{max} will be plotted against dose (using a logarithmic scale), and will include individual participant values and the geometric means for each dose. These plots will be used to help understand the relationship between the plasma PK parameters and dose.

9.6. Pharmacodynamic Analysis

Baseline and change from baseline in cytokines and complement components will be summarized descriptively and plotted by dose. CCI [redacted] Further details will be documented in the SAP.

9.7. Analysis of Other Endpoints

Immunogenicity (ADA) results will be listed (including titers) and summarized by treatment group and time points. Participant level immune response will also be summarized by treatment. Effect of positive ADA on safety, PD and PK will be assessed, if appropriate.

Pharmacogenomic data will be collected and retained for future analyses, but will not be analyzed, specifically, for this study.

9.8. Safety Analysis

Adverse events, ECGs, BP, pulse rate, pulse oximetry, continuous cardiac monitoring by telemetry, and safety laboratory data will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of participants. Any clinical laboratory, ECG, BP, pulse rate or oxygen saturation abnormalities of potential clinical concern will be described. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

Medical history and physical 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 examinations conducted during the active collection period will be captured as an AE, if those findings meet the definition of an AE. Data collected at Screening that is 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.

9.8.1. Electrocardiogram Analysis

Absolute values and changes from baseline for the ECG parameters, heart rate, QT interval, QTcF interval, PR interval and QRS interval will be summarized by treatment and time. Baseline will be average of triplicate measurement at pre-dose on Day 1.

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

Table 11. Categories for Safety QTcF

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

In addition, the number of participants 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 participants 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 the postdose QTc value and the average of the pre-dose triplicate values on Day 1.

In addition, an attempt will be made to explore and characterize the relationship between plasma concentration and QT interval length using a PK/PD modeling approach. If a PK/PD relationship is found, the impact of participant factors (covariates) on the relationship will be examined.

9.9. Interim Analysis

No formal interim analysis will be conducted for this study.

However, as this is a Sponsor-open study, the Sponsor will 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.

Unblinded results will be reviewed by a designated limited number of Sponsor colleagues within the study team and an independent consulting safety reviewer. The Data Blinding Plan will delineate study team members who will be involved in these unblinded reviews as well as steps to be instituted ahead of initiation of any unblinded review to ensure study integrity is maintained.

9.10. Data Monitoring Committee

This study will not use an external data monitoring committee. However, the dose escalation subteam will include an external, independent safety reviewer (refer to Section 9.9).

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

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

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines;

- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines;

- Applicable laws and regulations, including applicable privacy laws.

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

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

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;

- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;

- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

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

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the 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 participants against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

10.1.2. Informed Consent Process

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

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

The investigator must ensure that each study participant is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participants personal data.

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

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

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

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

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

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

A participant who is rescreened is required to sign another ICD even if the rescreening occurs within 56 days from the previous ICD signature date.

CCI [redacted] Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. CCI [redacted] Participants who decline to participate in this optional research will not provide this separate signature.

10.1.3. Data Protection

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

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

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

10.1.4. Dissemination of Clinical Study Data

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

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

www.clinicaltrials.gov

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

PCD is defined as the date that the final participant 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 (CSR synopses in which any data that could be used to identify individual participants have 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

Documents within marketing authorization packages/submissions

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

Data Sharing

Pfizer provides researchers secure access to patient-level data or full CSRs for the purposes of “bona-fide scientific research” that contribute to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials 24 months after study completion. Patient-level data will be anonymized in accordance with

applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

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

10.1.5. Data Quality Assurance

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

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

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic form and are password protected to prevent access by unauthorized third parties.

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

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

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

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

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for a minimum of 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the

Sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

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

The investigator(s) will notify the Sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the Sponsor or its agents to prepare the investigator site for the inspection and will allow the Sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participants medical records. The investigator will promptly provide copies of the inspection findings to the Sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the Sponsor or its agents with an opportunity to review and comment on responses to any such findings.

10.1.6. Source Documents

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

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

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

10.1.7. Study and Site Closure

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

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

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

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the Sponsors procedures, or GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

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

10.1.8. Publication Policy

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

The investigator agrees to refer to the primary publication in any subsequent publications such as secondary manuscripts, and submits all manuscripts or abstracts to the Sponsor 30 days before submission. This allows the Sponsor to protect proprietary information and to provide comments and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer-intervention related information necessary for the appropriate scientific presentation or understanding of the study results.

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

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

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

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

10.1.9. Sponsors Qualified Medical Personnel

The contact information for the Sponsors appropriately qualified medical personnel for the study is documented in the study contact list located in the clinical trial management system (CTMS) and study team on demand (SToD) system.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card. The contact card contains, at a minimum, protocol and investigational product identifiers, participant numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the participants 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.

10.2. Appendix 2: Clinical Laboratory Tests

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

Table 12. Safety Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count MPV WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN/Urea Creatinine Glucose (fasting) Calcium Sodium Potassium Chloride Total CO2 (Bicarbonate) AST, ALT Total Bilirubin Alkaline phosphatase Uric acid Albumin Total protein CRP Ferritin	pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Urobilinogen Urine bilirubin Microscopy[a]	Urine drug screen[b] HIV, HepBsAg, HepBc Ab and HCVAb tests[c] QuantiFERON-TB Gold test[c] eGFR (CKD-EPI) RF[c] ANA[d] Free T3[c], free T4[c], TSH[c], TSAb[c] Total IgA[c], Total IgG[c] Lipid Profile[f] (total cholesterol, LDL, HDL, TG, and ApoB100)
Coagulation		**Pregnancy**	**Cytokines[e]**
D-dimer Fibrinogen PT/INR PTT		(β hCG)[g] FSH[h]	IL-6 TNF-α IFNγ Complement (C3a, Bb, C5a)

a. Only if urine dipstick is positive for blood, protein, nitrites or leukocyte esterase.

b. At Screening and Day -1. The minimum requirement for drug screening includes cocaine, tetrahydrocannabinol (THC), opiates/opioids, benzodiazepines, and amphetamines.

c. At Screening only applicable to all cohorts.

d. Applicable to healthy participant cohorts only.

e. Ad hoc cytokines for local or central lab evaluation will be collected if CRS is suspected and coincides with a day pharmacodynamic samples are not collected per the SoA. Local lab evaluation of cytokine is only required if the site require this information for safety management.

f. Clinically significant dyslipidemia for all participants is to be determined by investigator judgment.

g. Urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/EC. Serum or urine b-hCG tests are for female participants of childbearing potential at a local lab.

h. For confirmation of postmenopausal status only.

- Participants may undergo random urine drug testing at the discretion of the investigator. Drug testing conducted prior to dosing must be negative for participants to receive IP.

- 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] These data will not be included in the CSR. Samples to be used for this purpose will be shipped to either a Pfizer approved BBS facility or other designated laboratory and retained for up to 1 year following the completion of the study.

Investigators must document their review of each laboratory safety report.

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

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as

an AE/SAE unless it is an intentional overdose taken with possible suicidal/self harming intent. Such overdoses should be reported regardless of sequelae.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition

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

10.3.2. Definition of SAE

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

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

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

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

AE and SAE Recording/Reporting

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

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

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Nonserious AE	All	None

Exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure	All AEs/SAEs associated with exposure during pregnancy or breastfeeding Occupational exposure is not recorded.	All (and exposure during pregnancy [EDP] supplemental form for EDP)

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

Assessment of Intensity

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

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as “serious” when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the Sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as

possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare professionals.

- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool

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

SAE Reporting to Pfizer Safety via CT SAE Report Form

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

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

10.4.1. Male Participant Reproductive Inclusion Criteria

Male participants are eligible to participate if they agree to the following requirements for the duration of the study through final study release of the participant (inclusive of final extended immune follow-up visit, if required), or through at least 28 days after the last dose of IP (whichever is longer).

- Refrain from donating sperm.

PLUS either**:**

- Be abstinent from heterosexual intercourse with a female of childbearing potential as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

  OR

- Must agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person.

- In addition to male condom use, a highly effective method of contraception must be considered in WOCBP partners of male participants (refer to the list of highly effective methods below in Section 10.4.1).

10.4.2. Female Participant Reproductive Inclusion Criteria

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

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

  OR

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), as described below, during the intervention period and for at least 28 days or 5 terminal half-lives (whichever duration is longer) after the last dose of study intervention, which corresponds to the time needed to eliminate any reproductive safety risk of the study intervention. If a highly effective method that is user dependent is chosen, a second effective method of contraception, as described in Section 10.4.4, must also be used. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

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

10.4.3. Woman of Childbearing Potential

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

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

Women in the following categories are not considered WOCBP:

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

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

      Note: Documentation for any of the above categories can come from the site personnel's review of the participants medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participants medical record for the study.
3. Postmenopausal female.
    - A postmenopausal state is defined as age 60 years or older or no menses for 12 months without an alternative medical cause.
        - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT).
        - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.4. Contraception Methods

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

2. Intrauterine device.

3. Intrauterine hormone-releasing system.

4. Bilateral tubal occlusion (eg, bilateral tubal ligation).

5. Vasectomized partner.

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

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

    - Oral;

    - Intravaginal;

    - Transdermal.

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

    - Oral;

    - Injectable.

8. Sexual abstinence.

    - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

One of the following effective barrier methods must be used in addition to the highly effective methods listed above that are user dependent:

- Male or female condom with or without spermicide;

- Cervical cap, diaphragm, or sponge with spermicide;

- A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods).

Collection of Pregnancy Information

For both unapproved/unlicensed products and for marketed products, an 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 partners pregnancy.

If a participant's partner becomes or is found to be pregnant during the participants 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 participant reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) to Pfizer Safety using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

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

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

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

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the 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 participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

10.5. Appendix 5: Genetics

Use/Analysis of DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Therefore, where local regulations and IRBs/ECs allow, a blood sample will be collected for DNA analysis.

- Genetic research may consist of the analysis of 1 or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).

- The samples may be analyzed as part of a multistudy assessment of genetic factors involved in the response to study intervention or study interventions of this class to understand treatments for the disease(s) under study or the disease(s) themselves.

- The results of genetic analyses may be reported in the CSR or in a separate study summary, or may be used for internal decision making without being included in a study report.

- The Sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

- The samples will be retained as indicated:

    - Samples for banking (see Section 8.7.2 and 8.8.4) will be stored indefinitely or other period as per local requirements.

- Participants may withdraw their consent for the storage and/or use of their banked biospecimens at any time by making a request to the investigator; in this case, any remaining material will be destroyed. Data already generated from the samples will be retained to protect the integrity of existing analyses.

- Banked biospecimens will be labeled with a code. The key between the code and the participants personally identifying information (eg, name, address) will be held at the study site and will not be provided to the sample bank.

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

Potential Cases of Drug-Induced Liver Injury

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

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

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

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

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

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

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

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

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

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

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

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

10.7. Appendix 7: ECG Findings of Potential Clinical Concern

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

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

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

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

ECG Findings That Qualify as Serious Adverse Events

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

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

10.8. Appendix 8: Alternative Measures During Public Emergencies

The alternative study measures described in this section are to be followed during public emergencies, including the COVID-19 pandemic. This appendix applies for the duration of the COVID-19 pandemic and will become effective for other public emergencies only upon written notification from Pfizer.

Use of these alternative study measures are expected to cease upon the return of business as usual circumstances (including the lifting of any quarantines and travel bans/advisories).

10.8.1. Eligibility

While SARS-CoV-2 testing is not mandated for this study, local clinical practice standards for testing should be followed. A participant should be excluded if they have a positive test result for SARS-CoV-2 infection, is known to have asymptomatic infection, or are suspected of having SARS-CoV-2. Participants with active infections are excluded from the study. When the infection resolves, the participant may be considered for re-screening.

10.8.2. Telehealth Visits

In the event that in-clinic study visits cannot be conducted, every effort should be made to follow up on the safety of study participants at scheduled visits per the SoA or unscheduled visits. Telehealth visits may be used to continue to assess participant safety and collect data points. Telehealth includes the exchange of healthcare information and services via telecommunication technologies (eg, audio, video, video-conferencing software) remotely, allowing the participant and the investigator to communicate on aspects of clinical care, including medical advice, reminders, education, and safety monitoring.

The following assessments must be performed during a telehealth visit:

- Review and record study intervention(s), including compliance and missed doses.
- Review and record any AEs and SAEs since the last contact.
- Review and record any new concomitant medications or changes in concomitant medications since the last contact.
- Review and record contraceptive method and results of pregnancy test. Confirm that the participant is adhering to the contraception method(s) required in the protocol. Refer to Section 10.4.

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

10.8.2.1. Laboratory Testing

If a study participant is unable to visit the site for protocol-specified safety laboratory evaluations, testing may be conducted at a local laboratory if permitted by local regulations. The local laboratory may be a standalone institution or within a hospital. The following safety laboratory evaluations may be performed at a local laboratory as indicated in Section 10.2. If a local laboratory is used, qualified study site personnel must order, receive, and review results. Site staff must collect the local laboratory reference ranges and certifications/accreditations for filing at the site. Laboratory test results are to be provided to the site staff as soon as possible. The local laboratory reports should be filed in the participant's source documents/medical records. Relevant data from the local laboratory report should be recorded on the CRF.

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

10.8.2.2. Electrocardiograms

If the participant is unable to visit the study site for ECGs, the participant may visit an alternative facility to have the ECGs performed. Qualified study site personnel must order, receive, and review results.

10.8.3. Adverse Events and Serious Adverse Events

If a participant has COVID-19 during the study, this should be reported as an AE or SAE and appropriate medical intervention provided. It is recommended that the investigator discuss temporary or permanent discontinuation of study intervention with the Sponsor before continuing treatment.

10.9. Appendix 9: Grading System for Pro-Inflammatory-Related Adverse Events

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Vomiting	1 - 2 episodes (separated by 5 minutes) in 24 hrs	3 - 5 episodes (separated by 5 minutes) in 24 hrs	≥6 episodes (separated by 5 minutes) in 24 hrs; tube feeding, TPN or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase of ≥7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death

Abbreviations: ADL = activities of daily living; TPN = total parenteral nutrition.

10.10. Appendix 10: CRS Grading System and Management

CRS is a non-antigen-specific cytokine-associated toxicity that occurs as a result of high-level immune activation. Cytokine release with fever and headache have been reported to occur with IVIg infusion and meets current criteria for Grade 1 CRS; it may occur with PF-06755347 administration.[11] Based upon the mechanism of action of PF-06755347, CRS, if it occurs, is expected to be manageable through awareness and supportive care.

Early recognition and intervention should be undertaken at the first signs or symptoms of CRS; signs may include pyrexia, shivering/rigors, tachycardia, tachypnea and/or hypotension and symptoms may include headache, nausea, chills, vomiting, and back ache when temporally related to PF-06755347 administration in the absence of alternative etiologies.

Grading by the more recent ASTCT CRS criteria[12] (Table 13) will be captured on the CRS CRF.

Table 13. ASTCT CRS Revised Grading System[12]

CRS parameter:	Fever*	With Hypotension	And/or† Hypoxia
Grade 1	Temp. ≥38°C	None	None
Grade 2	Temp. ≥38°C	Not requiring vasopressors	Requiring low-flow‡ nasal cannula, low-flow‡ facemask or blow-by
Grade 3	Temp. ≥38°C	Requiring a vasopressor with or without vasopressin	Requiring high-flow‡ nasal cannula, high-flow‡ facemask, nonrebreather mask, or Venturi mask
Grade 4	Temp. ≥38°C	Requiring multiple vasopressors (excluding vasopressin)	Requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)

Organ toxicities associated with CRS should still be graded according to CTCAE v4.03 and do not influence CRS grading.

* Fever is defined as temperature ≥38°C and not attributable to any other cause. In patients who have CRS then receive antipyretic therapy, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

† CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5°C hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.

‡ Low-flow nasal cannula or facemask is defined as oxygen delivered at ≤6 L/min. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula or facemask is defined as oxygen delivered at >6 L/min. This is modified from original ASTCT criteria to differentiate between low-flow and high-flow facemask.

Abbreviations: ASTCT = American Society for Transplantation and Cellular Therapy; BiPAP = bilevel positive airway pressure; CPAP = continuous positive airway pressure; CRS = cytokine release syndrome; CTCAE = Common Terminology Criteria for Adverse Events.

CRS identification and management (adapted from Neelapu et al[13])

- Monitor vital signs (temperature, blood pressure, pulse and SpO_2) according to SoA and at a minimum, every 1 hour until vital signs have returned to baseline levels. If clinical symptoms suggestive of CRS are reported by the participant outside of the scheduled windows of the SoA, close monitoring of vital signs should be conducted as above.

Fever (body temperature ≥38.0°C)

- Acetaminophen/paracetamol and cooling blanket for the treatment of fever.
- Non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen/naproxen can be used as second treatment option for fever if not contraindicated.
- Assess for infection using blood and urine cultures and nasal swab for COVID-19 as indicated.
- Initiate oral or IV fluids for hydration as tolerated. Increase fluid rate from the existing IV catheter.

Hypotension (Systolic Blood Pressure <90 mmHg or a decrease of 20% from baseline levels in either systolic or diastolic blood pressure whichever is lower).

- IV fluid 500 ml of normal saline given as rapidly as the existing safety IV cannula can tolerate.
- May give a second 500 ml of normal saline if participant remains hypotensive or participant's symptoms of hypotension do not resolve.

Corticosteroid Use:

- Up to a total of hydrocortisone 200 mg or dexamethasone 10 mg or methylprednisolone 125 mg IV. should be used if IV fluid does not stabilize blood pressure. At the investigator's discretion, this dose may be split in half, with the first half given during the first Normal Saline infusion and the second half given if symptoms and signs do not improve within one hour. If participant remains hypotensive after full dose of corticosteroids and fluid is administered or is otherwise not responding to therapy, or at investigator's discretion, initiate transfer to ICU for consideration of vasopressors or optional anti-IL-6 agents (tocilizumab 8 mg/kg (maximum dose 800 mg) IV or siltuximab 11 mg/kg IV).

Hypoxia

- If SpO_2 <94%, initiate supplemental oxygen via nasal cannula or low flow mask, and increase flow to maintain SpO_2 to ≥94%.
- Initiate transfer to ICU at investigator's discretion, or if oxygen flow rate exceeds 6 L/min or mask with fraction of inspired oxygen (FiO2) >40%.

10.11. Appendix 11: CTCAE (version 4.03) Grading System for Infusion-Related Reactions

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Infusion related reaction	Mild transient reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDS, narcotics, IV fluids); [a]prophylactic medications indicated for ≤24 hrs	Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Life-threatening consequences; urgent intervention indicated	Death

a. Investigator may pause the infusion if needed in the case of an infusion related reaction, and apply prophylactic treatment after the event has resolved, order to mitigate against additional infusion related symptoms if/once the infusion was restarted.
Abbreviations: NSAID = non-steroidal anti-inflammatory drug; IV = intravenous.

10.12. Appendix 12: Country Specific Requirements

10.12.1. Czech Republic

Schedule of Activities Error! Not a valid bookmark self-reference.

Table 14. Schedule of Activities for SC Cohorts of ITP Participants- Czech Republic ONLY

Protocol Activity	Screen			Clinical Confinement																Outpatient Follow-up Visits						
Study Day/Visit Window (days)	-56 to -2	-1[a]	1										2	3		4	5	6	7	8	11 ±2	15 ±2	22 ±2	29 ±2	36 ±3	50 ±3	71 ±3 or ET
Hour(s) Post Dose			0 pre-dose	0.5	1	3	3.5	4	5	6	8	12	24	36	48	72	96	120		168	240	336	504	672	840		
Informed consent	X																										
Demography (including Height)	X																										
Outpatient Visit	X																				X	X	X	X	X	X	X
Study Site Confinement		X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X							
Randomization			X																								
Discharge																				X							
Chest X-ray[b]	X																										
QuantiFERON-TB Gold test	X																										
HIV, HepBsAg, HepBcAb, HCVAb tests	X																										
Test for rheumatoid factor, anti-nuclear antibody, Total IgG and Total IgA, TSH, thyroxine (free T4), and triiodothyronine (free T3) TSAb; Lipid profile.	X																										
Inclusion/Exclusion	X	X																									
Medical history; history of illegal drug, alcohol & tobacco use	X	X[c]																									
Medication history	X	X[c]																									
Weight	X	X																							X		X
Urine drug screening	X	X																									
FSH[h]	X																										
Serum Pregnancy[i]	X	X																									
Review contraception use	X	X																		X	X	X	X	X	X	X	X
Physical examination[d]	X	X	X							X			X		X	X	X	X	X	X	X	X	X	X	X	X	X

Protocol Activity	Screen			Clinical Confinement																Outpatient Follow-up Visits						
Study Day/Visit Window (days)	-56 to -2	-1[a]	1										2	3		4	5	6	7	8	11 ±2	15 ±2	22 ±2	29 ±2	36 ±3	50 ±3	71 ±3 or ET
Hour(s) Post Dose			0 pre-dose	0.5	1	3	3.5	4	5	6	8	12	24	36	48	72	96	120		168	240	336	504	672	840		
Hematology & Coagulation (PT, INR, PTT, D-dimer & fibrinogen) Safety Labs	X	X										X	X		X	X		X		X	X	X	X	X	X	X	X
Chemistry/Urinalysis/Other Safety Labs	X	X										X	X		X	X		X		X	X	X	X	X	X	X	X
ECG[e]	X		X							X		X	X		X	X	X	X	X	X	X		X		X		X
Vital signs (BP, pulse rate, temperature)[f]	X		X							X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pulse Oximetry	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ADA blood sampling		X																		X		X			X	X	X
CCI [redacted]		[redacted]	[redacted]						[redacted]			[redacted]	[redacted]		[redacted]		[redacted]			[redacted]		[redacted]			[redacted]		
SC Administration			X																								
SC Injection site assessment			X	X	X	X	X	X	X	X	X	X	X							X		X			X		X
PK blood sampling			X							X		X	X		X	X	X	X		X	X	X	X	X	X	X	X
Urine pregnancy test[j]			X																						X		X
Serious and non-serious Adverse Event monitoring	X	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X
Prior/Concomitant treatments	X	X	X									X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X

a. Admission may be on Day -2 or Day -1 at the discretion of the Investigator. If a participant discontinues early they should, when possible, return to complete assessments outlined at Day 36. The follow-up period may be extended if any participant in a particular cohort is tested positive for anti-drug antibody to PF-06755347 or has detectable concentration of PF-06755347 at final study visit. If there is an ET, the Day 36 schedule will be followed.

b. Chest X-ray results within 3 months of screening visit otherwise a chest X-ray must be performed at screening and results obtained prior to admission.

c. Update medication history, alcohol and tobacco use since screening.

d. Full PE may be done at screening or may be deferred to admission at the discretion of the investigator. If a full PE is performed at screening, a brief PE may be performed at admission. Limited PE may be performed at discharge or at any outpatient visit at the discretion of the investigator. Additional PE to be performed in Czech Republic at investigator's discretion. Post dose day 1 PE to be performed at a consistent time for each of their participants.

e. Single ECG at screening and scheduled outpatient visits; triplicate ECG at all other time points (including unscheduled, early termination, or extended immune follow up visit).

f. Vital signs measurement (including BP, pulse rate & temperature) triplicate at pre dose only, at the discretion of the investigator triplicate assessments may be taken at other timepoints. Either oral or tympanic method for temperature determination is allowed; however the method should be used consistently for each participant.

g. Banked biospecimen may be collected on admission or Day 1 (prior to dosing). If not collected on the designated collection day, collect at the next available time point when biospecimens are being collected in conjunction with a participant visit.

h. Serum FSH will be performed to confirm postmenopausal status for females (at the investigator's discretion whether to confirm post-menopausal status by FSH if greater than 5 years since last menses.

i. Serum pregnancy test will be conducted at a local lab. For female participants of childbearing potential, 2 negative pregnancy tests are required prior to dose on Day 1 (1 negative serum pregnancy test at Screening and 1 negative urine pregnancy test on Day 1). Results of serum pregnancy test from Day -1 are not required prior to dosing.

j. Urine pregnancy test will be conducted locally in females of ITP cohorts.

Section 5.4 Exclusion Criteria for Participants with ITP

Exclusion number 15.) History of thromboembolic events:

Participants who in the opinion of the investigator, based upon medical history, have predisposing factors other than ITP for the development of thromboembolic disease (eg, Factor V Leiden mutation, long-term use of hormonal contraception, history of thromboembolic events, antiphospholipid antibody), are prohibited from entering the study.

Section 6.5.1 Rescue Medication:

For any event of bleeding associated with ITP it is expected that rescue therapies be administered to the participant according to the local standard procedures of the centre in accordance with the recommended procedures of the Czech Society of Haematology.

Given this is a single time administration, if a participant requires rescue therapy for any event, then they remain eligible to continue participation in the study in order to document adequate assessment of the safety profile.

Section 6.7 Dose Escalation:

Administration of PF-06755347 to female participants in the Czech Republic will be deferred until the safety data used for dose escalation decisions from at least 6 female participants (from other participating countries) has been reviewed by the Sponsor's members of the dose escalation subteam according to the criteria outlined in Section 6.7 of the protocol and found to be consistent with healthy male participant data.

The dose escalation subteam will perform a review of safety, PK, cytokine, and complement data of the first 6 female participants with ITP who receive study drug to assess immunologic response similarity to males.

Section 10.4.3. Women of Childbearing Potential

The definition of postmenopausal women will be in accordance with point 1.1 of the CTFG Recommendations.

> *For the purpose of this document, a woman is considered of childbearing potential (WOCBP), ie, fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.*
>
> *A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.*

10.13. Appendix 13 Protocol Amendment History

Amendment 7	16 December 2021	1. Section 2.1 Study Rationale Change: added context Rationale: explain the rationale for the inclusion of participants with ITP 2. Section 4.1 Overall Design Change: specified timing for the initiation of ITP cohorts Rationale: clarify dosing details 3. Section 4.2.1.3.3 Subcutaneous Administration in Participants with ITP Change: added demonstration of pharmacologic activity at doses for ITP cohorts Rationale: justify dose selection 4. Sections 6.6. and 6.7 Dose Progression and Escalation rules Change: added information unique to ITP cohorts Rationale: clarify rules 5. Section 10.4.4 Contraception Methods Change: added second effective contraception methods Rationale: to be consistent with CTFG guidance
Amendment 6	27 October 2021	1. Updated appropriate sections throughout the protocol to include cohorts of participants with ITP. Rationale: to obtain safety, tolerability, and PK data in participants with chronic and persistent ITP.

		2. Added Randomization at Day 1 to SoA Tables 2 & 3. Rationale: to clarify timing. 3. Updated the SoA for HP SC Table 2 with the following: • Anti- cardiolipin antibody: removed screening assessment. Rationale: Single values for anti-cardiolipin antibodies are uninformative for mitigation of thromboembolic risk associated with Ig products and by extension PF-06755347. • Cytokine and complement biomarkers: Added 96-hour (Day 5) and removed 1, 3 & 8 hour collections. • PK blood sampling: Added 96-hour (Day 5) collection. Rationale: Sample timepoints capture observed T_{max} and C_{max} of SC administration. • Telemetry: footnote added to indicate only participants dosed prior to acceptance to amendment 6 will have telemetry performed. Rationale: IV administration with significantly higher concentrations demonstrated no safety concern. • Chemistry, Urinalysis, Hematology and Coagulation Labs: Removed hour 6 collection. Rationale: Minimize unnecessary blood draws while maintaining safety for both populations; and is uninformative for SC cohorts. 4. Extended the dose progression safety monitoring data acquisition time from 72 to 96 hours post dose for SC administration.

		Rationale: Sample timepoints capture observed T_{max} and C_{max} of SC administration. 5. Added a separate SoA Table 3 for SC in participants with ITP. This includes serum and urine pregnancy, FSH, and Randomization on Day 1, and to remove screening autoantibodies, including anti-cardiolipin antibody. Rationale: female participants are included in the ITP cohorts thus requiring pregnancy testing; autoimmune disease will be assessed by the judgment of the PI in that active disease will be exclusionary. Exclusion will not be based on an autoantibody lab value. 6. Removed language in Section 1.1 Overall Design that described the implementation of additional safety monitoring that was incorporated into Amendment 5. Rationale: to delete redundancy. 7. Simplified the language of study participants in the Synopsis and Section 3. Rationale: to improve readability. 8. Updated 4.2.1.3 Clinical Dose Selection to separate into HP IV, HP SC and ITP SC subsections. Deleted “to allow for dose escalation” in 4.2.1.3.3. Rationale: easier to read; and allow for testing the most appropriate doses in participants with ITP. 9. Updated 5.2 Exclusion Criterion #6 in HP SC to exclude only clinically significant dyslipidemia in the opinion of the investigator, and removed Exclusion Criterion # 11 for a positive anti cardiolipin antibody. Rationale: Aligned identified risk factors for Ig products and by extension PF-06755347. Clinically significant dyslipidemia is a known risk factor for thromboembolic events. Single

		values for anti-cardiolipin antibodies are uninformative for mitigation of thromboembolic risk in study population. 10. Updated 5.5.2 to allow participants with ITP to have caffeine and tobacco, and to allow all sites to screen for alcohol in breath, blood and/or urine. Rationale: to not add additional recruitment difficulty; avoids aerosol testing during COVID-19 pandemic. 11. Added female contraception text in Section 10.4.2 Female Participant Reproductive Inclusion Criteria and pregnancy testing text in Section 8.2.6 Pregnancy Testing. Rationale: these requirements are necessary now with the inclusion of females in the ITP cohorts; to ensure consistency with Clinical Trial Facilitation Group document with the definition of highly effective contraception methods. 12. Updated to Section 6.6 Dose Progression Pause Criteria. Rationale: added specific guidance for participants with ITP. 13. Updated footnotes within 10.2 Appendix 2 Clinical Laboratory Tests Table 12 and removed anti-cardiolipin antibody. Rationale: to make a clear distinction which screening labs apply to specific cohorts. 14. Added of Appendix 8 Section 10.8 Alternative Measures During Public Emergency. Rationale: to accommodate ongoing global pandemic. 15. Updated the term ‘participant’ throughout the protocol.

		Rationale: consistent use of terms.
Amendment 5	15 March 2021	1. Section 1.1 Overall Design: updated to include specific doses for subcutaneous (SC) cohorts 7-12. Rationale: to provide clarity on subcutaneous dosing strategy. 2. Section 1.2 Schema: all cohorts including the optional Japanese are to dose in a sequential manner. Table 3: updated to move the optional Japanese cohort to the SC group. Rationale: implementation of sequential dosing for all cohorts including the optional Japanese will enhance safety monitoring. 3. Section 2.1 Study Rationale: updated to note that a maximum tolerated dose with IV has been achieved with Grades 1 and 2 CRS observed at doses of 0.7 and 1 mg/kg therefore no further IV dosing will occur. Going forward, evaluation of the safety, tolerability and PK of PF-06755347 will be conducted via the SC administration route. Rationale: The proposal is to re-start the study as described in this amendment with SC dosing. 4. Section 4.1 Overall Design: updated total number of participants and specification of dose levels for SC cohorts Rationale: to summarize the approximate total number of participants in IV and SC cohorts and to specify planned dose levels for SC administration. 5. Section 4.2 Dose Justification: updated Table 5 with observed human exposure, added Table 6 to provide drug exposure projections for SC dosing and included language in the Clinical Dose Selection Section 4.2.1.3.

		Rationale: to provide predicted exposures for planned SC dose levels. 6. Section 5.2 Exclusion Criteria: added language to #17 that an approved COVID-19 vaccine is considered a concomitant medication. Language has been added that participants that have received an approved vaccine should allow 28 days prior to dosing with PF-06755347. Rationale: to provide clarity on vaccine administration during the pandemic. 7. Section 6.5.1 Rescue Medication: updated to include language regarding the availability of specific medications and an ICU. Rationale: added per regulatory feedback. 8. Section 6.6 Dose Progression: stop criteria was updated. Rationale: The previous protocol amendment stated in Section 6.6 Dose Progression included stopping criteria where the study would be stopped. The clinical findings to date with the IV route illustrate an understanding of the time course of adverse events, CRS and laboratory abnormalities. As a result, the proposal is to restart the study with SC administration because it is anticipated that the severity of CRS is potentially related to C_{max}. Therefore, the SC route is predicted to decrease the C_{max} by about 4-fold; thus reducing the risk to participants and the need to stop the study. 9. Section 10.8 Appendix 8 removed hypoxia and hypotension from the Grading System of Pro-Inflammatory-Related Adverse Events table. Rationale: to minimize confusion as these events are part of the CRS grading table in Section 10.9 Appendix 9. 10. Section 10.9 Appendix 9: CRS Grading System and Management Guidelines: updated to be

		more specific for the management of CRS and use of medication. Rationale: to provide clarification and clearer expectations. 11. PACL dated 29 Sept 2020: clarifications were implemented into Section 1.2 Study Schematic to include a footnote referring to Section 4.2 stating that actual dose levels are subject to change. Rationale: to be consistent with language stated in Section 4.2 and 4.3.1.3 regarding dose adjustment.
Amendment 4	24 July 2020	1. Section 2.3 Benefit/Risk Assessment updated to include language during COVID-19 pandemic. Rationale: Added information relevant to benefit/risk assessment of this compound including the drug mechanism of action, long half-life, duration of in-house observation and follow-up requirements during the COVID-19 pandemic. 2. Section 5.2 Exclusion Criteria #21 condom and highly effective method of contraception are required. Rationale: to ensure consistency with Clinical Trial Facilitation Group document with the definition of highly effective contraception methods. 3. Section 6.7 Dose Escalation deletion of bullet 3 due to redundancy in Section 6.6. Rationale: clarification of protocol language to make clear that a single serious adverse reaction will result in termination of escalation. 4. Section 6.8 Infusion or Injection Site Reaction Grade 3 serious changed to 'life-threatening'. Rationale: to clarify the distinction between intensity and seriousness of adverse events. 5. Section 7 Potential Cases of Acute Kidney Injury updated to include follow up

		management language, Section 7.1 changed discontinuation visit to 'early termination' visit per SoA. Rationale: clarified that continued follow-up within the protocol instead of the current language requiring withdrawal from the study. 6. Appendix 9 Section 10.9 CRS Grading and Management Guidelines updated to include detailed management guidelines, improved context introduction and deletion of reference to management 'at investigator's discretion'. Rationale: provided guidance on the management of cytokine release syndrome. 7. Appendix 4 Section 10.4.4 Contraception Methods removed methods #9-12. Rationale: consistency with Clinical Trial Facilitation Group document for clarification of effective methods of contraception.
Amendment 3	30 June 2020	1. Schedule of Activities (SoA) was updated to include: a. additional hours post dose timepoints (3.5, 4 & 6) for assessing Vital signs, Pulse oximetry and PK; and additional 8 &12 hour post dose timepoints for cytokines and complement. Rationale: to enhance participant safety monitoring, and aligning with the cytokine complement biomarker timepoints. b. the addition of 'discharge from site' at Day 8. Rationale: to provide clarity. c. separation of Safety Labs into two separate activities: Hematology/Coagulation Safety and Chemistry/Urinalysis/Other Safety Labs. Removal of Chemistry labs at post dose time points 1 & 3 hours.

		Rationale: Additional hematology/coagulation labs have additional collection times to monitor safety compared with chemistry labs and thus they were separated in the protocol. d. addition of Day 11 outpatient visit. Rationale: Correction of Inadvertent omission e. addition of Hematology/Coagulation Safety lab assessments post dose timepoints (1, 3, 5, 8, 12 & 240 hours). Rationale: increase safety surveillance. f. update to body temperature determination by allowing both oral and tympanic methods. Rationale: acceptable as long as consistent. g. addition of subcutaneous (SC) to the site assessment and PK blood sampling, and removed footnote regarding infusion site reactions (ISR), added a footnote regarding cytokine release syndrome (CRS) assessment and 1h safety and PK required only for infusion durations <2 hours. Rationale: properly reflects cohort update and expectations. 2. Section 2 Introduction updated to include both ITP and CIDP indications consistent with clinical development plan. 3. Section 3 Objectives and Endpoints updated to include three subcutaneous cohorts. Rationale: to explore PK/PD in SC route of administration for future clinical development. 4. Section 2.1 Drug Development Rationale was updated Rationale: to align with recently updated April 2020 IB.

		5. Section 1.2 Study Schema was updated to a two-fold increment of ascending doses at cohort 6 instead of cohort 8; also includes the addition of up to three subcutaneous cohorts. Rationale: to increase participant safety due to emerging safety data on cytokine release and to determine PK following SC administration. 6. Section 4.3 Table 3 Predicted Exposure was updated. Rationale: Based on emerging safety, dosing increments were amended and thus predicted exposure reflects the updated dose levels. 7. Section 5.2 Exclusion Criteria #3 (positive ADA antibody result) was removed. Rationale: The recommendations by health authority in 2017 were misinterpreted by the Sponsor and upon further review of the FAMHP meeting minutes it became clear that pre-existing ADA was not a suggested exclusion criterion for the study. Rationale: to add safety precaution and ensure specific exclusion criterion. 8. Section 6.1 added guidelines on SC injections. Rationale: required with the addition of SC cohorts. 9. Section 6.3 Randomization and Blinding updated to include IRT system. Rationale: required with the addition of external sites. 10. Section 6.4 Study Intervention compliance The content of one Protocol Administrative Clarification Letter (PACL) 24Feb2020 was added to define medication error. Rationale: to provide clarity.

		11. Section 6.5.1 Cytokine Release Syndrome and Section 6.8 Infusion or Injection Site Reaction details were added. Rationale: required per associated risk with the IP. 12. Section 6.6 Dose Progression added language that any mitigation plan may need to be discussed with the Institutional Review Board (IRB) or Regulatory Authority as appropriate; removed grade 1 fever, pause criteria were clarified. Rationale: Cytokine release syndrome (CRS) guidelines have been updated in the protocol and reflect that a Grade 1 fever alone is indicative of a Grade 1 toxicity for CRS. Language added to make decision tree clearer. Dose Progression section has been updated to reflect the updated guidelines. 13. Section 6.7 Dose Escalation included the maximum exposure observed in individual participants within a cohort rather than the mean exposure should be taken into account for dose escalation, moving this language from Section 6.6. Rationale: Per HMR UK site request, the PK rule for stopping escalation has been updated per site request. 14. Section 8.10.4 Banked Biospecimens for Biomarkers was updated. Rationale: the protocol was updated to be consistent with template. 15. Section 8.11 Blood Volume Table updated to reflect increased safety lab surveillance and SC cohorts. Rationale: to accurately reflect changes made to protocol 16. Section 9.5.1 Derivation of PK parameters Table 6 was updated with definitions.

		Rationale: SC dosing will be explored and therefore different PK parameters will be assessed. 17. Section 10.2 Appendix 2 Clinical Laboratory Tests Table 8 was updated with a separate Coagulation and Cytokine/complement section. Rationale: to clarify the specific tests required for the Coagulation panel and the Cytokine/complement panel labs. 18. Section 10.9 Appendix 9 added Cytokine Release Syndrome Mitigation and Table 9 ASTCT CRS revised grading system. Rationale: required per identified IP risk. 19. Additionally typographical errors were corrected. 20. Section 6.6 Deleted "Two participants or more develop similar clinically significant laboratory, electrocardiogram (ECG), or vital sign abnormalities, in the same organ class, indicating dose-limiting intolerance". Rationale: this text is deleted from Section 6.6 and moved to section 6.7; where it is applicable to the entire cohort: "If 50% or more of the participants receiving active drug at a given dose level (but not participants receiving placebo) develop similar clinically significant laboratory, ECG, or vital sign abnormalities, in the same organ class, indicating dose-limiting intolerance".
Amendment 2	10 October 2019	Schedule of Activities, Section 8. Study Assessments and Procedures and Section 8.1. Screening. To enable continuous screening and to assist with participant scheduling for all planned cohorts the overall screening window has been increased for 28 days to 56 days. Reference to the Pfizer Clinical Research Unit (CRU) has been removed throughout the protocol and where appropriate the text refers simply to

		"site", so as to allow this protocol to be used at multiple centres, if required. Section 4.2 Scientific Rationale for Study Design, Section 5.1 Inclusion Criteria # 1. The age range for this study has been changed from 18-40 to 18-55. The overall risk benefit profile remains unchanged. Section 5.1 Inclusion criteria: • Inclusion criteria # 5: The body weight criteria has been modified to >50 kg so as to broaden the pool of participants that are eligible for enrolment. However, the overall infusion volume based on weight must not exceed 1L. • Inclusion Criteria # 21. The AST/ALT criteria has been amended to AST or ALT level >1.25 × upper limit of normal (ULN) which more adequately reflects the variability of AST/ALT seen in healthy participants whilst maintaining a suitable threshold to exclude participants with potential pre-existing liver issues. • Section 5.2 Exclusion Criteria: • Exclusion # 1. Duplicate language around drug allergies has been removed. Section 6.1.1. Administration. To allow greater flexibility in scheduling the administration window has been increase for 08:00 (plus or minus 2 hours) to 08:00 (plus or minus 3 hours). Section 8.4.6. Continuous Cardiac Monitoring by Telemetry. As admission may occur as early as Day-2, the language has been updated to allow earlier measurements of cardiac function replacing "in the 24 hours prior to dosing" with "between admission and dosing".
Amendment 1	03 October 2018	The primary reason for Amendment 1 is to revise the Dose range and the Dose Escalation criteria to

		address FAMHP guidance. Sections revised include: General updates: New global protocol template used. Section 2.23: Non clinical safety: Updated with low dose non-human primate data Section 3: Objectives and Endpoints: Fluorescence-activated cell sorter (FACS) analysis of immune cell subsets, RNA biomarkers, phagocytosis and complement-dependent cytotoxicity (CDC) biomarkers removed. Section 4: Study Design. Updated to include two lower dose cohorts of 0.01 mg/kg and 0.03 mg/kg. The 45 mg/kg dose cohort has been removed. Section 4.3.1.3: Clinical dose. Updated the safety margins based on the non-human primate data removing reference to the rat data. Section 5: Female participants removed with all associated text. Study will be conducted in male participants only. Table 6: Intravenous infusion guidance updated to include the two lower dose cohorts of 0.01 mg/kg and 0.03 mg/kg. Section 6.6 and 6.7: Dose progression and Dose Escalation: Updated to reflect the use of a sequential dosing scheme.
Original protocol	14 June 2017	N/A

10.14. Appendix 14: Abbreviations

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

Abbreviation	Term
AE	adverse event
Abs	absolute
ADA	anti-drug antibody
ADL	activities of daily living
AESI	adverse event of special interest
ALT	alanine aminotransferase
ApoB100	apolipoprotein B100
ANOVA	analysis of variance
AST	aspartate aminotransferase
ASTCT	American Society for Transplantation and Cellular Therapy
AUC	area under the curve
AUC_{168}	area under the concentration-time curve from time 0 to 168 hours
AUC_{inf}	area under the concentration-time curve from time 0 to infinity
AUC_{last}	area under the concentration-time curve from time 0 to the time of the last quantifiable concentration
AUMC	area under the first moment plasma concentration curve
Bb	activated factor B
BBS	Biospecimen Banking System
BiPAP	bilevel positive airway pressure
BMI	body mass index
BP	blood pressure
BPM	beats per minute
BRC	Benefit Risk Committee
BUN	blood urea nitrogen
C1q	Complement component 1q
C3a	Complement 3a
C5a	Complement 5a
C_{av}	average concentration
CA	Competent Authority
CDC	complement-dependent cytotoxicity
CDS	core data sheet
C_{eff}	efficacious concentration
CFR	Code of Federal Regulations
CHO	Chinese Hamster Ovary
CI	confidence interval
CIA	Collagen-Induced Arthritis
CIDP	chronic inflammatory demyelinating polyneuropathy
CK	creatine kinase
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL	clearance
CL/F	apparent clearance
C_{max}	peak or maximum observed concentration
CO_2	carbon dioxide (bicarbonate)
COVID-19	Corona virus disease 2019
CPAP	continuous positive airway pressure
CRF	case report form
CRO	contract research organization
CRS	cytokine release syndrome

Abbreviation	Term
CSA	clinical study agreement
CSF	cerebrospinal fluid
CSR	clinical study report
CT	Clinical Trial
CTA	clinical trial application
CTC	Common Terminology Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CTFG	Clinical Trials Facilitation and co-ordination Group
CTMS	Clinical Trial Management System
CV	cardiovascular
DAI	Dosing Administration Instructions
DCT	data collection tool
DILI	drug-induced liver injury
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DOI	duration of infusion
EAN	experimental autoimmune neuritis
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic CRF
EDCMS	electronic data capture and management system
EDMC	external data monitoring committee
EDP	exposure during pregnancy
EDR	Extemporaneous Dispensing Record
EDTA	edetic acid (ethylenediaminetetraacetic acid)
eGFR	estimated glomerular filtration rate
EIU	exposure in utero
EMA	European Medicines Agency
EOI	end of infusion
ERB	external review board
ET	Early termination
EU	European Union
EudraCT	European Clinical Trials Database
FcγRs	Fcγ receptors
FDA	Food and Drug Administration (United States)
FDAAA	Food and Drug Administration Amendments Act (United States)
FFPE	formalin-fixed paraffin-embedded
FIH	first-in-human
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GLP	Good Laboratory Practices
hCG	human chorionic gonadotropin
HDL	high density lipoprotein
HDL-C	high density lipoprotein cholesterol
HCVAb	hepatitis C antibody
HepBsAg	hepatitis B surface antigen
HepBcAb	hepatitis B core antibody
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HP	Healthy participant
HR	heart rate

Abbreviation	Term
Hr	hour
HRT	hormone replacement therapy
HSV-1	Herpes Simplex Virus 1
HSV-2	Herpes Simplex Virus 2
IB	investigators brochure
iC3b	inactive product of complement component 3b
ICD	Informed consent document
ICE	IGIV-C CIDP efficacy
ICH	International Conference on Harmonisation
ID	Identification
IEC	independent ethics committee
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgG2	Immunoglobulin G2
IND	investigational new drug application
INR	international normalized ratio
IFNγ	Interferon gamma
IL-1RA	Interleukin-1 receptor antagonist
IL-6	Interleukin-6
IP	investigational product
IRB	institutional review board
IRC	internal review committee
IRT	interactive response technology
ISR	infusion site reaction
ITP	idiopathic thrombocytopenic purpura or immune thrombocytopenia
IUD	intrauterine device
IUS	Intrauterine system
IV	intravenous
IVIg	intravenous immunoglobulin
IWR	interactive Web-based response
K_2EDTA	dipotassium ethylene diamine tetraacetic acid
LDL	low density lipoprotein
LDL-C	low density lipoprotein-cholesterol
LFT	liver function test
LOEL	lowest observed effect level
LPD	local product document
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MHRA	Medicines and Healthcare products Regulatory Agency
mDC	myeloid dendritic cells
MedDRA	medical Dictionary for Regulatory Activities
MRT	mean residence time
MTD	maximum tolerated dose
N/A	not applicable
ND	Not done
NHP	non-human primate
NK	natural killer
NOAEL	no observed adverse effect level
NOEL	no observed effect level
NSAID	non-steroidal anti-inflammatory drug
PACL	protocol administration clarification letter

Abbreviation	Term
PCV	premature ventricular complexes
PD	Pharmacodynamics
PE	physical examination
PEOI	prior to end of infusion
PG	Pharmacogenomics
PI	principal investigator
PK	Pharmacokinetics
PT	prothrombin time
PTT	partial thromboplastin time
QC	quality control
QTc	corrected QT
QW	weekly
RBC	red blood cell
RMC	Risk Management Committee
RNA	ribonucleic acid
SAD	single ascending dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SC	subcutaneous
SC Ig	Subcutaneous immunoglobulin
SCr	serum creatinine
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SoA	Schedule of Activities
SOP	standard operating procedure
SPC	summary of product characteristics
SRSD	single reference safety document
SToD	Study team on demand
SUSAR	suspected unexpected serious adverse reactions
$t_{½}$	terminal half-life
T3	triiodothyronine
T4	thyroxine
TB	tuberculosis
Tbili	total bilirubin
TCC	total cell count
TG	triglycerides
T_{max}	time to reach maximum concentration
TNF-α	Tumor necrosis factor alpha
THC	tetrahydrocannabinol
TPN	Total parenteral nutrition
TSAb	Thyroid stimulating antibodies
TSH	Thyroid stimulating hormone
UA	urinalysis
ULN	upper limit of normal
US	United States
USPI	United States prescribing information
V_{ss}	volumes of distribution at steady-state
V_z	volume of distribution
V_z/F	apparent volume of distribution
WBC	white blood cell
WOCBP	Woman of child bearing potential

11. REFERENCES

1. Hugues RA, Donofrio P, Bril V, et al. Intravenous immune globulin (10% caprylatechromatography purified) for the treatment of chronic inflammatory demyelinating polyradiculoneuropathy (ICE study): a randomised placebo-controlled trial. Lancet Neurol 2008; 7(2):136-44.-

2. Lunemann JD, Nimmerjahn F, Dalakas MC. Intravenous immunoglobulin in neurology--mode of action and clinical efficacy. Nat Rev Neurol 2015; 11(2):80-9.

3. Lin HH, Wang MX, Spies JM, et al. Effective treatment of experimental autoimmune neuritis with Fc fragment of human immunoglobulin. J Neuroimmunol 2007; 186(1-2):133-40.

4. Niknami M, Wang MX, Nguyen T, et al. Beneficial effect of a multimerized immunoglobulin Fc in an animal model of inflammatory neuropathy (experimental autoimmune neuritis). J Peripher Nerv Syst 2013; 18(2):141-52.

5. Mahmood I, Green MD. Drug interaction studies of therapeutic proteins or monoclonal antibodies. J Clin Pharmacol 2007; 47(12):1540-54.

6. Lee JI, Zhang L, Men AY, et al. CYP-mediated therapeutic protein-drug interactions: clinical findings, proposed mechanisms and regulatory implications. Clin Pharmacokinet 2010; 49(5):295-310.

7. Evers R, Dallas S, Dickmann LJ, et al. Critical review of preclinical approaches to investigate cytochrome P450-mediated therapeutic protein drug-drug interactions and recommendations for best practices: a white paper. Drug Metab Dispos 2013; 41(9):1598-1609.

8. Andresen I, Kovarik JM, Spycher M, et al. Product equivalence study comparing the tolerability, pharmacokinetics, and pharmacodynamics of various human immunoglobulin-G formulations. J Clin Pharmacol 2000; 40(7):722-30.

9. Grifols [Internet]. GAMUNEX-C prescribing information, 3/2017revision. [Cited 17 September 2018] Available from: https://www.gamunex-c.com/documents/27482625/27482925/Gamunex-C+Prescribing+Information.pdf/9258bd0f-4205-47e1-ab80-540304c1ff8e.

10. Zhou H, Olsen H, So E, et al. A fully recombinant human IgG1 Fc multimer (GL-2045) inhibits complement-mediated cytotoxicity and induces iC3b. Blood Advances 2017; 1(8):504-515.

11. Bagdasarian A, Tonetta S, Harel W, Mamidi R, Uemura Y. IVIG adverse reactions: potential role of cytokines and vasoactive substances. Vox Sang. 1998;74(2):74-82.

12. Lee DW, Santomasso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. Biol Blood Marrow Transplant 2019; 25(4):625-38.

13. Neelapu SS. Managing the toxicities of CAR T-cell therapy. Hematol Oncol. 2019;37 Suppl 1:48-52., Neelapu SS, Tummala S, Kebriaei P, Wierda W, Gutierrez C, Locke FL, et al. Chimeric antigen receptor T-cell therapy - assessment and management of toxicities. Nat Rev Clin Oncol. 2018;15(1):47-62.

14. Debre M, Bonnet MC, Fridman WH, et al. Infusion of Fc gamma fragments for treatment of children with acute immune thrombocytopenic purpura. Lancet 1993; 342(8877):945-9.

15. Doobaree IU, Nandigam R, Bennette D, et al; Thromboembolism in adults with primary immune thrombocytopenia: a systematic literature review and meta-analysis. Eur J Haematol. 2016;97(4):321–30.

16. Markle JG, Fish EN. SeXX matters in immunity. Trends Immunol. 2014;35(3):97-104.

17. Provan D, Arnold DM, Bussel JB, et al. Updated international consensus report on the investigation and management of primary immune thrombocytopenia. Blood Adv. 2019;3(22):3780-817.

18. Neunert C, Terrell DR, Arnold DM, et al. American Society of Hematology 2019 guidelines for immune thrombocytopenia. Blood Adv. 2019;3(23):3829-66.

19. Provan D, Arnold DM, Bussel JB, et al. Updated international consensus report on the investigation and management of primary immune thrombocytopenia. Blood Adv. 2019;3(22):3780-817.