Official Title: A Phase 2B, Multicenter, Randomized, Double-Blind, Placebo-Controlled Dose-Ranging Study to Evaluate the Efficacy, Safety, And Pharmacokinetics of PF-06480605 in Adult Participants with Moderate to Severe Ulcerative Colitis

NCT Number: NCT04090411

Document Date: Protocol Amendment Version 3: 15-Mar-2022

16.1.1. PROTOCOL

16.1.1.1. B7541007 Protocol Administrative Change Letter 19 August 2022

16.1.1.2. B7541007 Protocol Amendment 3 Clean 15 March 2022

19 Aug 2022

RE: Protocol Administrative Changes and Clarifications for Study B7541007, A Phase 2b, Multicenter, Randomized, Double-Blind, Placebo-Controlled Dose-Ranging Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of PF-06480605 in Adult Participants with Moderate to Severe Ulcerative Colitis

Dear Investigator,

This Protocol Administrative Change Letter (PACL) is to notify you of the following administrative changes and clarifications to the B7541007 protocol; Protocol Amendment 3, March 15, 2022.

The planned change is not considered substantial by Pfizer Inc. because there is no significant impact to the safety or physical or mental integrity of the trial participant, the scientific value of the trial, the conduct or management of the trial, or the quality or safety of any investigational medicinal product used in the trial, and therefore is not part of a formal amendment.

As noted in Protocol Appendix 4, Section 10.4.4 Collection of Pregnancy Information, if a pregnancy occurs during the study, investigators are to follow the pregnancy until completion, assessing the structural integrity of the neonate at the time of birth. Further follow-up of birth outcomes is to be handled on a case-by-case basis. This PACL clarifies that part of the case-by-case basis will include following the outcomes (for both the mother and the child) until 12 months after delivery to ensure that an abnormal pregnancy outcome has not occurred. Accordingly, the following sentence in Appendix 4 is modified as indicated with additional text in bold font:

> "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) **and will include following the outcomes for both the mother and the child for 12 months after delivery to ensure that a normal pregnancy outcome has occurred**."

Rationale:

Study drug PF-06480605 is a fully human neutralizing monoclonal antibody (mAb) in the early stages of clinical development. Presently, in pre-clinical studies in rabbits and mice (PF-06480605 Investigator's Brochure June 2022 Version 5.0 Section 5.3.8) PF-06480605 crosses the placental barrier but no toxicity was observed for embryo-fetal development, and clinical data is lacking. It is recognized that additional data on the effect of mAb exposure during pregnancy is required per FDA guidelines. The addition of the 12-month post-birth follow-up may assist with a better understanding of mAb exposure during pregnancy and satisfies FDA regulations.

In addition, the new proposed language does not change the intent, operatives, or logistics of the protocol nor the analysis, but rather adds clarification through a specified 12-month time period surrounding requested pregnancy follow-up completed by the investigator. At this time, the study does not have any pregnant participants, study enrollment is complete, and all participants received their last dose of study drug and have entered the 12-week Follow-up Period. The study is on target for last participant last visit to occur in October 2022.

If the protocol requires substantial changes in the future that apply globally to all sites, the nonsubstantial changes described in this letter will be incorporated into the amended protocol.

Review/approval by institutional review board/ethics committee (IRB/EC) is not required prior to PACL implementation. Please inform your IRB/EC of these changes, as required.

Sincerely,

[redacted]

B7541007 [redacted]
[redacted], MD
cc: Trial Master File

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Subject CN	TAIGLE LLC
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Issuer DN	CN=Entrust Class 3 Client CA - SHA256,OU=(c) 2015 Entrust, Inc. - for authorized use only,OU=See www.entrust.net/legal-terms,O=Entrust, Inc.,C=US
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19 Aug 2022 10:34:002-0400	[redacted] UUID : [redacted] Email : [redacted] IP Address : [redacted]	Started	The custodian composed the ePak succesfully. Subject: B7541007 Protocol Administrative Change Letter 19 Aug 2022 ePak UUID: [redacted]
19 Aug 2022 10:34:002-0400	[redacted] UUID : [redacted] Email : [redacted]	RequestSent	Sign request sent to ePak recipient.
19 Aug 2022 12:23:024-0400	[redacted] UUID : [redacted] Email : [redacted] IP Address : [redacted]	DocumentViewed	Document viewed by signer.
19 Aug 2022 12:23:053-0400	[redacted] UUID : [redacted] Email : [redacted] IP Address : [redacted]	Signed	The recipient signed the document with no comments. Comments: None Reason: None Consent: I understand that my Electronic Signature is Equivalent to my Handwritten Signature and is therefore legally binding. My Electronic Signature will remain unique to me, and under no circumstance I am allowed to disclose my password to any individual which may allow unauthorized access to system. I understand that I am accountable and responsible for all actions associated with my Electronic Signature.
19 Aug 2022 12:23:053-0400	[redacted] UUID [redacted] Email : [redacted]	Completed	The ePak is completed successfully.

A PHASE 2B, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED DOSE-RANGING STUDY TO EVALUATE THE EFFICACY, SAFETY, AND PHARMACOKINETICS OF PF-06480605 IN ADULT PARTICIPANTS WITH MODERATE TO SEVERE ULCERATIVE COLITIS

Investigational Product Number:	PF-06480605
Investigational Product Name:	Not Applicable (N/A)
United States (US) Investigational New Drug (IND) Number:	[redacted]
European Clinical Trials Database (EudraCT) Number:	2019-002698-74
Protocol Number:	B7541007
Phase:	2B

SHORT TITLE: A study to evaluate the efficacy and safety of PF-06480605 in adult participants with moderate to severe ulcerative colitis

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary of Changes and Rationale**
Amendment 3	15 Mar 2022	The rationale for this protocol amendment is to incorporate changes from multiple previously written Protocol Administration Change Letter (PACL) 7, 8, 9, and 10. Typographical and spelling errors as well as cross references corrected throughout the document. Sections 1.1 Synopsis, 3.0 Objectives, Estimands, and Endpoints and 9.1.1 Estimands: Modified estimands to permit exclusion of participants with missed visits due to COVID–19 from analysis. Added Chronic Therapy Period secondary endpoint change from baseline for fecal calprotectin, hsCRP, and sTL1A biomarkers in order to better understand the full trajectory over time; tertiary endpoint for [redacted] to assess the impact of drug on a clinically meaningful threshold and more details around histopathology endpoints. Sections 1.1 Synopsis and 9.4.1 Efficacy Analyses: Modified analysis methods to align with similar analysis of binary endpoints, and to allow comparison with historical data from other studies and publications with similar endpoints on treatment effect. Sections 1.1 Synopsis, 9.5 Interim Analyses and 9.5.1 Data Monitoring Committee: Modified first interim analysis language to 100% of participants, second interim analysis to approximately 100% of participants, and removed futility assessment by IRC due to quicker than expected enrollment. Included Pfizer

		template language regarding how IRC recommendations will be processed. Sections 1.1 Synopsis, 1.3 SoA footnote "u", 4.1 Overall Design, 7.1 Discontinuation of Study Intervention, 7.2 Participant Discontinuation/ Withdrawal from Study, and 8.1.1 Colonoscopy/Sigmoidoscopy: Modified language to clarify participants who withdraw from the treatment period should be followed for 3 study visits (one being the Early Withdrawal Visit) for a total of 12 weeks from the last dose of investigational product. Section 1.3 Scheduled of Activities (SoA): Removed return stool diary data collection tool from Early Withdrawal visit due to administrative error. Sections 1.3 SoA footnote "v", 8.2.6 Hepatitis, and Appendix 2.1: Altered reference from Appendix 2.1 to Section 8.2.6 in SoA footnote "v", modified language in Section 8.2.6 to align with footnote "v" and incorporate Appendix 2.1 language, and removed Appendix 2.1 to clarify Hepatitis B study requirements. Section 7.2: Modified language to clarify when protocol deviations are not required for early withdrawal procedures. Section 9.3 Populations for Analysis: Updated Evaluable Population to include Intention–To–Treat (ITT) and modified Intention–To–Treat (mITT) in order to distinguish between Induction and Chronic Period, and provided clarification for Biomarker Analysis Population and clarified biomarker analysis population.

		Section 9.4.2.1 Adverse Events: Modified safety endpoint language to align with updated Pfizer Data Standards. Country Specific: Appendix 15 Alternative Measures During Public Emergencies: Added alternative approach language to home health visits for Germany and Japan.
Amendment 2	01 Sep 2020	The rationale for this protocol amendment is to incorporate non-substantial changes from multiple previously written PACL 1, 2, 3, 4, 5, and 6. The most current revision is noted in the protocol. Typographical and spelling errors as well as cross references corrected throughout the document. Sections 1.1, 3.0 and 9.1.1: Clarified estimands regarding primary induction and chronic therapy period, related to what is considered a non responder regarding early treatment discontinuation. Estimands section updated to reflect and clarify how a patient who discontinues study treatment prior to week 12 will be allocated regarding responder and non responder. Section 1.3 Schedule of Activities Changes implemented: Hep Virus, chest x-ray, colonoscopy, participant stool diary updates within table and/or footnotes. Urine drug screen as indicated in Appendix 2. Fecal microbiome and fecal metabolomics will be collected at screening prior to the bowel preparation, (not Visit 1). Fecal calprotectin, fecal microbiome and fecal

		metabolomics will be collected at the early Withdraw Visit, to collect final specimens if participant withdraws. Serum protein profiling to be collected at Visit 17, was inadvertently removed during formatting. Blood for PBMC single cell sequencing removed Week 4, 12, 28, 52, and 60 as no longer required. The letter "g" was removed from Study Visits 1 and 15 for Injection Site Reactions, as reference to the footnote is provided in the Treatment Procedure column of the table. Targeted medical exam removed at Visit 15 as complete physical exam is required and already present. Footnote "w" added to Day 1 (baseline) [redacted] to clarify that participants should select option for "no change" since starting the study medication. Footnote "x" added to banked biospecimens that if not collected on the designated day to collect at the next scheduled visit. Partial Mayo Score: The Partial Mayo Score is comprised of the sum of the participant's stool frequency, rectal bleeding and physician's global assessment, (PGA). While it is necessary for the participant to collect [redacted] stool frequencies, and rectal bleeding during the screening period, the PGA should not be assessed until Day 1. Therefore the schedule of assessments table will have Partial Mayo Score assessment "X" removed at screening.

		Dispensing of stool kits will be removed at study Visits 4 and 15. Section 1.3, Schedule of Activities, and/or Section 8.8.10.1, Exploratory Banked Biospecimens; Prep B1.5 and Prep B2.5 changed to Prep B1 and Prep B2 as this represents the larger collection tubes. Other Changes throughout the protocol: Section 5.1, Inclusion Criterion Weight, BMI removed as investigational drug is not dosed based on weight. Section 5.2, Exclusion Criterion #17: Corrected error in expressing unit conversion for both ALC and ANC. Section 6.1: Added to Table 4: see investigational product manual for dosing. Section 6.2.1: Preparation and Dispensing: Protocol wording changed from "administered to blinded participants" to "will be administered in a blinded manner to participants." Section 6.2.1, Preparation and Dispensing: corrected text from "investigational product will be dispensed using an IRT system for each visit from Visit 1 to Visit 15" to "investigational product will be dispensed using an IRT system from Visit 1 to Visit 15 with the exception of Visit 5." Sections 6.5 and 8.1.7: Added anti-IL 12/23 to the list of conmeds to be consistent with inclusion criterion #5. Section 6.5.1: Added clarifications to the wording under permitted medications.

		Section 8.1.1: Updated the order of the biopsies to be collected to be consistent between both paragraphs. 8.1.1: Provided enhanced instructions on activating Trialweb at Visit 5 or Visit 16. Section 8.2.3: added "or an expert of lung disease" in addition to qualified radiologist. Section 1.3, 8.2.6 and Appendix 2 Hepatitis results clarified. Section 8.3:Updates to May 2020 template. Section 8.3.1 Time period for collecting AE and SAE information: Protocol wording states, "through and including Visit 20"; this is corrected to Visit 18. Section 8.3.7 Updated section to May 2020 template and added information related to lack of efficacy. [redacted] Section 1.1 and 9.4.1: Efficacy Analyses: Additional details provided for estimating the odds ratio and associated 2 sided 90% confidence intervals. Section 10.1.3 and 8.3, removed legally acceptable representative throughout the section, as all participants must be able to read to answer the [redacted]electronic diary.

		Appendix 8, Prohibited Medications: Clarified text regarding prohibited corticosteroid doses. Appendix 8, [redacted] Changed to "Prohibited Time Period". Appendix 8, Prohibited concomitant medications: [redacted] Appendix 8, Prohibited concomitant medications: [redacted] Country specific: [redacted] [redacted] Appendix(s) 8 and 9, Prohibited and Permitted Medications Clarifications completed to make the time required to be off of prohibited drugs and established time required for stable dosing. Appendix 10, Updated Mayo Scoring system for assessment of ulcerative colitis: the modified endoscopic scoring system will be used in this study. Friability was

		removed from endoscopic subscore of 1 and placed into the endoscopic subscore 2. Added Appendix 15: Alternative measures to be taken during public emergencies; added to note alternative methods may be used to continue the currently enrolled participants in the study, in case of a resurgence of COVID-19.
Amendment 1	10 Feb 2020	Japan Country Specific Amendment: Added HBV DNA testing at screening and (if applicable every 12 weeks during treatment) per PMDA Regulations. HBV DNA testing was added to Section 1.3, (added HBV testing to footnote "m" to be performed locally and added footnote "v" specific to Japan participants). Added HBV DNA testing to section 8.2.6, Appendix 2 (Table 5) and Appendix 2.1. Added HBV DNA testing to abbreviations.
Original protocol	18 July 2019	Not applicable (N/A)

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

TABLE OF CONTENTS

LIST OF TABLES

1. PROTOCOL SUMMARY

1.1. Synopsis

Short Title: A study to evaluate the efficacy and safety of PF-06480605 in adult participants with moderate to severe ulcerative colitis.

Rationale:

Treatment with PF-06480605 was safe and well tolerated in a Phase 1 study in healthy participants and a Phase 2a study in participants with moderate to severe active Ulcerative Colitis, (UC). Furthermore, PF-06480605 was efficacious in treatment of UC.

This Phase 2b, multicenter, randomized, double-blind, placebo-controlled dose-ranging study examines varying subcutaneous, (SC) doses of investigational product, (IP) administered every 4 weeks in participants with moderate to severe active UC to characterize safety, efficacy, pharmacokinetics (PK), and immunogenicity and to inform subsequent Phase 3 design.

Objectives, Estimands, and Endpoints Primary and Secondary Endpoints

Objectives	Endpoints	Estimands
Induction Period: Primary		
• To evaluate the efficacy of PF-06480605 in induction of clinical remission at Week 14 in participants with moderate to severe active UC.	• Proportion of participants achieving clinical remission (defined as a Total Mayo Score ≤2, with no individual subscore >1) at Week 14.	E1: This estimand is defined as a population average treatment difference between PF-06480605 and placebo in the proportion of participants who met the binary endpoint without discontinuing treatment prior to Week 12 visit. Treatment: PF-06480605, Placebo. Population: Participants with moderate to severe active UC as defined by inclusion/exclusion criteria. Variable: clinical remission at Week 14. Intercurrent Events: Treatment discontinuation prior to Week 12 visit. If a study participant discontinued the treatment prior to Week 12 visit but didn't attend the early withdrawal visit, the participant will be considered as a non-responder for the binary remission endpoint at Week 14 for the primary analysis

		unless reason for missed visit was due to COVID-19. Population level summary: treatment difference between PF-06480605 and placebo in proportions of responders using the binary endpoint.
• To evaluate the safety and tolerability of PF-06480605 during the induction period (from baseline to Week 14) in participants with moderate to severe active UC.	• Incidence and severity of treatment emergent adverse events (TEAEs) during the induction period. • Incidence of serious adverse events (SAEs) during the induction period. • Incidence of AEs or SAEs leading to discontinuation during the induction period. • Incidence of clinically significant abnormalities in vital signs, electrocardiograms, (ECGs) and laboratory values during the induction period.	There is no defined estimand for these endpoints and they will be analyzed using Pfizer data standards as applicable.
Induction Period: Secondary		
• To evaluate the efficacy of PF-06480605 in inducing remission at Week 14 in participants with moderate to severe active UC.	• Proportion of participants achieving remission Food and Drug Administration, ((FDA) definition 1 - defined as endoscopic subscore = 0 or 1, stool frequency subscore = 0, and rectal bleeding subscore = 0) at Week 14.	This composite estimand is defined the same as the Estimand E1 except the definition of the binary endpoint.
	• Proportion of participants achieving remission (FDA definition 2 - defined as endoscopic subscore = 0 or 1, ≥1-point decrease from baseline to achieve a stool frequency subscore = 0 or 1, and rectal bleeding subscore = 0) at Week 14.	This composite estimand is defined the same as the Estimand E1 except the definition of the binary endpoint.
• To evaluate the efficacy of PF-06480605 on endoscopic appearance at Week 14 in participants with	• Proportion of participants achieving endoscopic improvement (defined as endoscopic subscore = 0 or 1) at Week 14.	This composite estimand is defined the same as the Estimand E1 except the definition of the binary endpoint.

moderate to severe active UC during the induction period.	• Proportion of participants achieving endoscopic remission (defined as endoscopic subscore = 0) at Week 14.	This composite estimand is defined the same as the Estimand E1 except the definition of the binary endpoint.
• To characterize the PK of PF-06480605 in participants with moderate to severe active UC during the induction period.	• PF-06480605 trough concentrations during the induction period through Week 14.	There is no defined estimand for these endpoints and they will be analyzed descriptively. Missing data will not be included in the analysis.
• To evaluate disease and pathway related biomarkers (ie, hsCRP and fecal calprotectin and serum sTL1A) during the induction period.	• Change from screening in fecal calprotectin during the induction period through Week 14. • Change from baseline in hsCRP during the induction period through Week 14. • Change from baseline in serum sTL1A during the induction period through Week 14.	There is no defined estimand for these endpoints and they will be analyzed descriptively. Missing data will not be included in the analysis.
• To characterize the immunogenicity of PF-06480605 in participants with moderate to severe active UC during the induction period.	• Incidence of development of anti-drug antibodies (ADAs) and neutralizing antibodies (NAbs) during the induction period through Week 14.	There is no defined estimand for these endpoints and they will be analyzed descriptively. Missing data will not be included in the analysis.
Chronic Therapy Period - Primary		
• To evaluate the safety and tolerability of PF-06480605 during the chronic therapy period (from Week 14 to the End of Study Visit) in participants with moderate to severe active UC during the chronic therapy period.	• Incidence and severity of treatment emergent adverse events (TEAEs) during the chronic therapy period. • Incidence of serious adverse events (SAEs) during the chronic therapy period. • Incidence of AEs or SAEs leading to discontinuation during the chronic therapy period. • Incidence of clinically significant abnormalities in vital signs, ECGs and laboratory values during the chronic therapy period.	There is no defined estimand for these endpoints and they will be analyzed using Pfizer data standards as applicable.

Chronic Therapy Period – Secondary		
• To evaluate the efficacy of chronic therapy of PF-06480605.	• Proportion of participants achieving clinical remission (defined as a Total Mayo Score ≤2, with no individual subscore >1) at Week 56.	E2: This estimand is defined as a population average treatment difference between PF-06480605 and placebo in the proportion of participants who met the binary endpoint without discontinuing treatment prior to Week 52 Visit. Treatment: PF-06480605, Placebo. Population: Participants with moderate to severe active UC as defined by inclusion/exclusion criteria, and participants who met the binary endpoint at Week 14 but did not continue to the chronic therapy period will be excluded. Variable: Clinical Remission at Week 56. Intercurrent Events: Treatment discontinuation prior to Week 52 Visit. If a study participant discontinued the treatment prior to Week 52 Visit but didn't attend the early withdrawal visit, the participant will be considered as a non-responder for the binary remission endpoint at Week 56 for the secondary analysis unless reason for missed visit was due to COVID-19. Population level summary: treatment difference between PF-06480605 and placebo in proportions of responders using the binary endpoint.
	• Proportion of participants achieving sustained clinical remission (ie, clinical remission at both Week 14 and Week 56).	This composite estimand is defined the same as the Estimand E2 except that the binary endpoint is sustained clinical remission.
	• Proportion of participants achieving remission (FDA definition 1 - defined as endoscopic subscore = 0 or 1, stool frequency subscore = 0, and rectal bleeding subscore = 0) at Week 56. • Proportion of participants achieving sustained remission-FDA definition 1	This composite estimand is defined the same as the Estimand E2 except that the binary endpoint is remission (FDA definition 1) at Week 56 or sustained remission (FDA definition 1).

	(ie, remission-FDA definition 1 at both Week 14 and Week 56).	
	• Proportion of participants achieving remission (FDA definition 2 - defined as endoscopic subscore = 0 or 1, ≥1-point decrease from baseline to achieve a stool frequency subscore = 0 or 1, and rectal bleeding subscore = 0) at Week 56. • Proportion of participants achieving sustained remission-FDA definition 2 (ie, remission-FDA definition 2 at both Week 14 and Week 56).	This composite estimand is defined the same as the Estimand E2 except that the binary endpoint is remission (FDA definition 2) at Week 56 or sustained remission (FDA definition 2).
	• Proportion of participants achieving endoscopic improvement (defined as endoscopic subscore = 0 or 1) at Week 56. • Proportion of participants achieving sustained endoscopic improvement (ie, endoscopic improvement at both Week 14 and Week 56).	This composite estimand is defined the same as the Estimand E2 except that the binary endpoint is endoscopic improvement at Week 56 or sustained endoscopic improvement.
	• Proportion of participants achieving endoscopic remission (defined as endoscopic sub-score = 0) at Week 56. • Proportion of participants achieving sustained endoscopic remission (ie, endoscopic remission at both Week 14 and Week 56).	This composite estimand is defined the same as the Estimand E2 except that the binary endpoint is endoscopic remission at Week 56 or sustained endoscopic remission.
• To characterize the PK of PF-06480605 in participants with moderate to severe UC during the chronic therapy period.	• PF-06480605 concentration from Week 14 through the End of Study Visit.	There is no defined estimand for these endpoints and they will be analyzed descriptively. Missing data will not be included in the analysis.
• To evaluate disease and pathway related biomarkers (ie, hsCRP and fecal calprotectin and serum sTL1A during	• Change from Week 14 in fecal calprotectin during the chronic therapy period through the End of Study Visit.	There is no defined estimand for these endpoints and they will be analyzed descriptively. Missing data will not be included in the analysis.

the chronic therapy period.	• Change from Week 14 in hsCRP during the chronic therapy period through the End of Study Visit. • Change from week 14 in serum sTL1A during the chronic therapy period through the End of Study Visit. • Change from baseline through the End of the Study Visit in fecal calprotectin. • Change from baseline through the End of the Study Visit in hsCRP. • Change from baseline through the End of Study Visit in serum sTL1A.	
• To characterize the immunogenicity of PF-06480605 in participants with moderate to severe UC during the chronic therapy period.	• Incidence of development of anti-drug antibodies (ADAs) and neutralizing antibodies (NAbs) from Week 14 through the End of Study Visit.	There is no defined estimand for these endpoints and they will be analyzed descriptively. Missing data will not be included in the analysis.

Overall Design

This is a Phase 2b multi-center, parallel group, placebo-controlled, double-blind, randomized study in participants with moderate to severe active UC. An internal review committee will be used.

Number of Participants

A maximum of approximately 240 participants will be randomly assigned to investigational product, such that approximately 216 evaluable participants complete the study.

Intervention Groups and Duration

This study will occur over 4 periods; screening, induction, chronic therapy and follow-up. The first screening period may last up to 6 weeks to assess eligibility. During the 12-week induction period, participants will receive 50 mg, 150 mg, 450 mg, or matched placebo by subcutaneous administration every 4 weeks. During the 40-week chronic therapy period, all participants will receive active drug: 50 mg, 150 mg, or 450 mg by subcutaneous administration every 4 weeks. During the 12-week follow-up period, final safety assessments will be made. The final follow-up period will be 12 weeks in duration. Overall the study participation for each participant will be up to 70 weeks. Participants that discontinue at any time during the study will proceed into the follow-up period with an early withdrawal visit. Any participant who prematurely withdraws from the treatment period

(after being randomized and during active study intervention) should be followed for 3 study visits (one being the Early Withdrawal Visit) for a total of 12 weeks from the last dose of interventional product.

Data Monitoring Committee

This study will use an internal review committee (IRC). An external data monitoring committee will not be utilized. An IRC charter will be developed to govern the details of any IRC operations.

Statistical Methods

The primary estimand for the primary endpoint of clinical remission at Week 14 will be the population average treatment difference between PF-06480605 and placebo in the proportion of participants with moderate to severe active ulcerative colitis who achieve the binary remission endpoint without discontinuing treatment prior to the Week 12 Visit. If a study participant discontinues treatment prior to Week 12 Visit but did not attend the early study withdrawal visit, then the participant will be considered as a non-responder for the primary analysis unless reason for missed visit was due to COVID-19.

The primary endpoint of this study is the proportion of participants achieving clinical remission at Week 14. The proportions responding and the risk difference between the treatment arms and the placebo arm will be analyzed using an unconditional exact method: risk differences and corresponding 2 sided unconditional exact 90% confidence intervals will be computed using the Chan and Zhang[24] method.

Two interim analyses may be conducted for the study. The first analysis will be conducted when 100% of participants have completed or have the opportunity to complete the Week 14 Visit. The second interim analysis may be conducted when all participants have completed or have the opportunity to complete the induction period and approximately 100% of them have completed or have the opportunity to complete at least 6 months of chronic therapy. Interim analysis results may be used for internal decisions regarding future study planning.

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined in Section 9 and further detailed in a statistical analysis plan (SAP), which will be maintained by the sponsor.

1.2. Schema

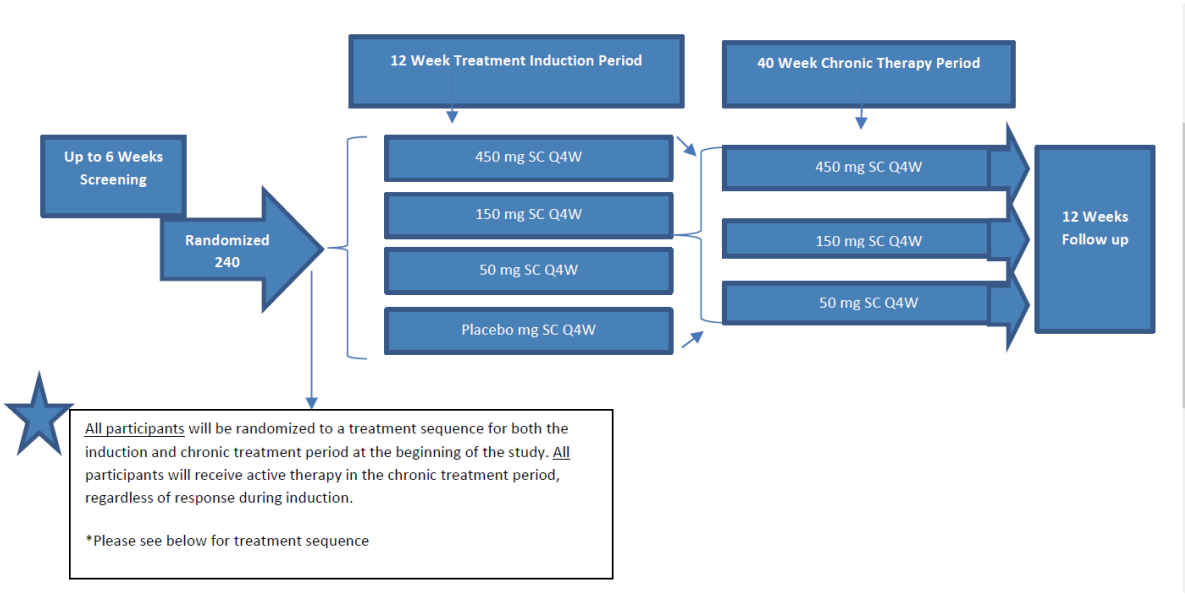
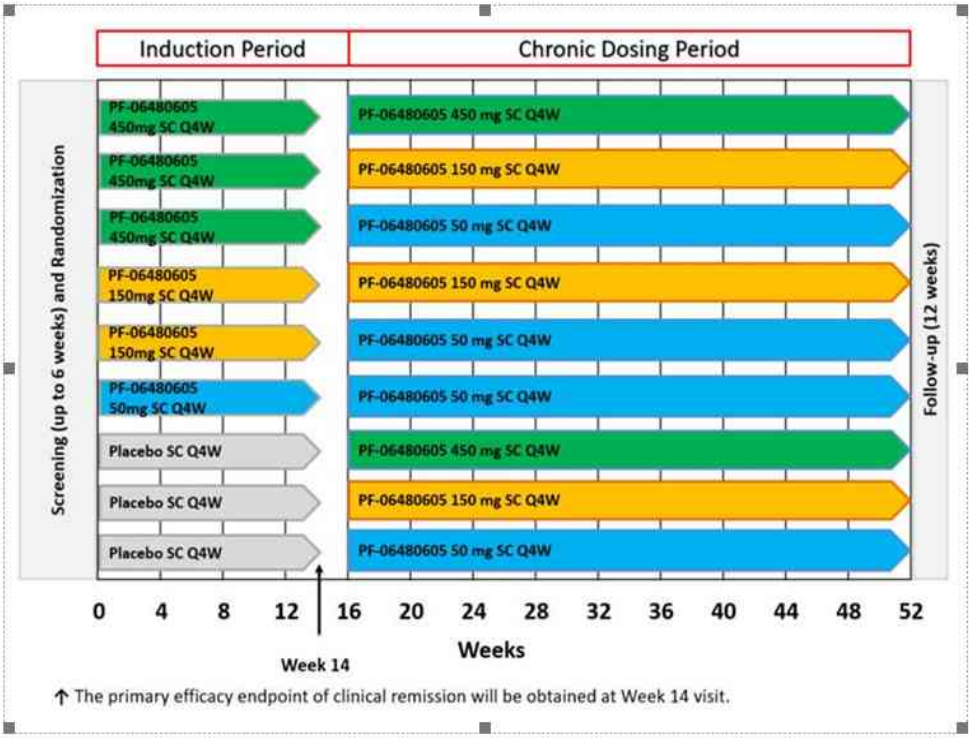


Table 1. View of the Schematic



1.3. Schedule of Activities (SoA)

The SoA table provides an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed in the SoA table, in order to conduct evaluations or assessments required to protect the well-being of the participant.

B7541007 Screening, Treatment, Follow-up Period and Early Withdraw Visit (if applicable):

	Screening	Induction Treatment Period				Primary Endpoint	Chronic Therapy Period										Follow-up Period			
		Treatment Period					Treatment Period													
Study Visit																				
Study Week																				
Study Day																				
Visit Window	**N/A**	**N/A**	**±3days**																	
Enrollment procedures																				
Informed consent	X																			
Inclusion/ Exclusion criteria	X	X																		
Demographics, Medical History, UC Medical History, UC Medication History	X																			
Medical Procedures																				
Complete Physical examination[a]	X					X										X			X	X
Targeted Physical examination[b]		X	X	X	X		X	X	X	X	X	X	X	X	X		X	X		
Height (in or cm)[c]	X																			
Weight (lbs. or kg)[c]	X	X				X										X			X	X

	Screening	Induction Treatment Period				Primary Endpoint	Chronic Therapy Period										Follow-up Period			
		Treatment Period					Treatment Period													
Study Visit																				
Study Week																				
Study Day																				
Visit Window	N/A	N/A	±3days																	
12-Lead ECG	X	X[d]	X		X	X					X					X			X	X
BP and Pulse[e] (after sitting for 5 minutes)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Temperature[e] (oral, tympanic or axillary) [C° or F°]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chest X-ray or Chest CT Scan[f]	X																			
Treatment procedures																				
Randomization (After all screening procedures completed and eligibility confirmed)		X																		
Investigational treatment administration		X	X	X	X		X	X	X	X	X	X	X	X	X	X				
Injection site reaction[g]		X	X	X	X		X	X	X	X	X	X	X	X	X	X				
Contraception check	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior and Concomitant medication and treatment(s)	X	X	X	X	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	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

	Screening	Induction Treatment Period				Primary Endpoint	Chronic Therapy Period										Follow-up Period			
		Treatment Period					Treatment Period													
Study Visit	[redacted]																			
Study Week																				
Study Day																				
Visit Window	N/A	N/A	±3days																	
PRO																				
[redacted]		X	X	X	X	X			X							X			X	X
		X[w]	X	X	X	X			X		X		X			X			X	X
		X	X			X			X							X			X	X
		X	X			X			X							X			X	X
Colonoscopy																				
Colonoscopy or flexible sigmoidoscopy[i]	X					X											X			X
Intestinal tissue biopsies[j]	X					X											X			X
Disease Activity Analysis																				
Stool Diary Instructions	X	X																		
Partial Mayo Score		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Total Mayo Score[k]		X				X											X			X
Review [redacted] Stool Diary Collection tool, (eDiary)[l]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Return Stool Diary Data Collection Tool (eDiary)																			X	
Laboratory (Safety)																				
Serology: HIV[m] HBsAg, HBcAb, HBsAb, HBV DNA, HCVAb, HCV RNA[m]	X[v]				X[v]				X[v]			X[v]			X[v]			X[v]		

	Screening	Induction Treatment Period			Primary Endpoint	Chronic Therapy Period											Follow-up Period			
		Treatment Period				Treatment Period														
Study Visit	[redacted]																			
Study Week																				
Study Day																				
Visit Window	N/A	N/A	±3days																	
Tuberculosis Test: IGRA per local guidelines[n]	X																			
Hematology/ chemistry/UA,° PT/PTT/INR	X[o,y]	X	X	X	X[o,y]	X	X	X	X	X	X	X	X	X	X	X[o,y]	X	X	X	X
Urine Drug Screen	X																			
Urine Pregnancy Test WOCBP		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum Pregnancy test or FSH testing[p]	X																			
[redacted]	X																			
Biomarkers																				
Dispense stool collection kit	X	X	X	X		X	X	X	X	X	X	X	X	X	X		X	X		
[redacted]	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	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		X	X
	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

	Screening	Induction Treatment Period				Primary Endpoint	Chronic Therapy Period										Follow-up Period		
		Treatment Period					Treatment Period												
Study Visit	[redacted]																		
Study Week																			
Study Day																			
Visit Window	N/A	N/A	±3days																
[redacted]																			
Banked Biospecimens																			
Genomic Banked biospecimen Prep D1[x]		X																	
[redacted]																			
Pharmacokinetics																			
PK[t]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]																			

Abbreviations: [redacted] BP=blood pressure; C°=Celsius; [redacted] cm=centimeters; CRF=case report form; ECG=electrocardiogram; eDiary=electronic hand held diary to collect UC symptoms; [redacted] F°=Fahrenheit; FSH=follicle stimulating hormone;; HBsAg=hepatitis B surface antigen; total HBcAb=hepatitis B core antibody; HBV DNA =hepatitis B virus deoxyribonucleic acid, HCVAb=hepatitis C antibody; HEENT=Head, Eyes ears, nose throat; HIV=human immunodeficiency virus; [redacted] IGRA=interferon gamma release assay; in=inches; INR=international normalized ratio; kg=kilograms;lbs=pounds; N/A=Not Applicable; [redacted] PK=pharmacokinetics; PPD=purified protein derivative; PRO=patient reported outcome; PT=Promthrombin time; PTT=Partial thromboplastin time; [redacted] UA=urine analysis;UC=Ulcerative Colitis;WONCBP=Women of non-childbearing potential.

a. Complete physical exam includes review of the following body systems: general appearance, skin, HEENT= (head, eyes, ears, nose and throat), heart, lungs, breast (optional), abdomen, external genitalia (optional), extremities, neurologic function, back and lymph nodes.

b. Targeted physical exam includes the review of the following body systems: skin, heart, lungs, abdomen and examination of body systems where there are symptom complaints by the participant.

c. Height and weight measured without shoes and multiple layers of clothing.

d. Day 1 dosing; ECG will be performed in triplicate prior to dosing.

e. At dosing visits, vital signs will be collected approximately 30 minutes prior to dosing and 30 minutes after dosing.

f. A previous Chest x-ray or Chest CT Scan may be used if taken up to 12 weeks prior to the screening visit. Official reading must be located in the source documentation. If no previous results, a Chest x-ray or CT-Scan may be performed during the screening period.

g. Assess participant for injection site reaction after dosing administration for 60 minutes. If no issues, participant may be monitored for 30 minutes after next dosing administrations as per investigator discretion.

h. [redacted]

i. Colonoscopy/sigmoidoscopy should be completed for a participant within approximately, preferably [redacted] days prior to baseline (Day 1) to allow stool data collection for Mayo score calculation and to obtain endoscopic subscore report from the Central Reader. The endoscopic subscore from the Central Reader will be used to determine eligibility.

j. At each colonoscopy or flexible sigmoidoscopy, [redacted] biopsies should be taken for the analyses described: [redacted] (See Section 8) for additional details.

k. Total Mayo Score will be based on the centrally-read endoscopic subscore, stool frequency, rectal bleeding and physician's global assessment.

l. The participant stool diary (eDiary) will be used to collect [redacted] stool frequency, rectal bleeding, and [redacted] score.

m. Per local regulations. Confirmation and documentation of a negative HIV test result within 12 months prior to screening will be accepted. HIV testing can be conducted locally or centrally. Hepatitis testing (HBsAg, HBcAb, HBsAb, HCV Ab, and HCV RNA will be performed by the central laboratory). Per Country Requirement: HBV DNA testing may be performed locally or centrally

n. TB testing if assayed locally, IGRA official reading and method or test must be located in the source documentation. Please see the lab manual.

o. Screening laboratory tests with abnormal results (if considered by the investigator to be transient and inconsistent with the participant's clinical condition) may be repeated within the screening window to confirm abnormal results. If results return to protocol acceptable limits within the screening period, the participant may enter the study.

p. Serum pregnancy testing at screening and urine pregnancy testing at other scheduled visits are required only for female participants of childbearing potential. Follicle stimulating hormone (FSH) test to be performed at screening to confirm postmenopausal status in female participants who have been amenorrheic for at least 12 consecutive months.

q. [redacted]

r.

s.

t. At dosing visits, samples will be collected preferably after vital signs data and within approximately 30 minutes prior to SC dosing.

u. Any participant who prematurely withdraws from the treatment period (after being randomized and taking IP) should be followed for 12 weeks from the last dose of investigational product. The Early Withdrawal Visit replaces Visit 16 (see Section 7.1).

v. For participants who enroll from Japan or countries where DNA testing is required for Hepatitis: Participants who are negative for all 3 serology tests may be eligible. Participants who are HBsAg positive will be excluded; participants who are HbsAg negative, HBcAb positive and HBsAb negative will be excluded. Participants who are HBsAg negative, HBcAb negative, and HBsAb positive and provide documentation of prior HBV vaccination, may be eligible for the study and will not require HBV DNA monitoring during the study. Participants who are HBsAg negative, HBcAb negative, and HBsAb positive without documentation of prior HBV vaccination AND participants who are HBsAg negative, HBcAb positive, and HBsAb positive, will have HBV DNA assessed at screening. If HBV DNA is detectable, participants will be excluded. If HBV DNA is not detectable, participants may be eligible. If enrolled, HBV DNA will also be assessed at Week 12 and repeated every 12 Weeks: Also see Section 8.2.6.

w. Participant to mark “no change” for Day 1 [redacted] as the question is not applicable to Day 1.

x. If not collected on the designated collection day, collect at the next available time point when biospecimens are being collected in conjunction with a participant visit.

y. Coagulation tests, PT/PTT/INR will be collected at screening, Week 12, and Week 52.

2. INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic inflammatory condition of the gastrointestinal tract that affects 5 million people worldwide. IBD presents as 1 of 2 major forms, ulcerative colitis (UC) or Crohn's disease (CD). UC is characterized by continuous inflammation that is localized to the colon. Medical therapy is available, but surgical resection of the entire colon can provide a definitive cure. CD is characterized by discontinuous inflammation that affects the entire gastrointestinal tract from mouth to anus and long-term debilitating sequelae, such as fistulae and intestinal strictures. Although the exact causes of UC and CD remain unclear, inhibition of pro-inflammatory cytokines and adhesion molecules have proven to deliver some therapeutic benefit.

The incidence of UC reported in the past 20 years varies by location. Reported rates in North America range from about 8-19, in South America from 1.5-2.6, in Asia and the Middle East from 0.6-4.4, in Western Europe from 2.3-17.5, in Eastern Europe from 0.8-5.9, and in Australia/New Zealand, from 7.6-17.4 per 100,000 person-years. The prevalence of UC in the same time period, by geographic region, ranged from 155.8-248.6 in North America, was 76.1 in a single report from South America, from 4.9-168.3 in Asia and the Middle East, from 4.9-294 in Northern and Western Europe, from 2.42-101 in Eastern Europe and 145 in Australia and New Zealand per 1,000,000 persons. Globally there does not appear to be a gender difference in incidence of UC.[1]

Although UC can occur at any age, the incidence peaks between 15 to 25 years with a second peak between 55 to 65 years.[2] UC is a lifelong condition with a serious effect on the quality of life.

Current IBD treatments include aminosalicylates, corticosteroids, immunosuppressants, monoclonal antibodies against tumor necrosis factor (TNF)-α or α4β7 integrin, and JAK inhibitors. Despite multiple therapies being available, limitations remain in the treatment of IBD, and patients continue to have symptoms or develop intolerance to or side effects from their treatment regimens.

The investigational product (IP) PF-06480605 is a fully human neutralizing monoclonal antibody against TL1A currently in development for the treatment of IBD. The mechanism of action of PF-06480605 is to neutralize the binding and subsequent signaling of TL1A to its functional receptor DR3 on immune cells of the innate and adaptive immune system.

2.1. Study Rationale

Treatment with PF-06480605 was safe and well tolerated in a Phase 1 study in healthy participants and a Phase 2a study in participants with moderate to severe active UC. Furthermore, PF-06480605 was efficacious in treatment of UC.

This Phase 2b, multicenter, randomized, double-blind, placebo-controlled dose-ranging study examines varying SC doses of IP administered every 4 weeks in participants with moderate to severe active UC to characterize safety, efficacy, pharmacokinetics (PK), and immunogenicity and to inform subsequent Phase 3 design.

2.2. Background

The tumor necrosis factor family member TNF-like factor 1A (TL1A), encoded by the *TNFSF15 gene*, is a cytokine implicated in wide-ranging pro-inflammatory and pro-fibrotic processes.[3] TL1A mediates immune effects through its cognate receptor, Death Receptor 3 (DR3) *(TNFRSF25).* TL1A can also bind a soluble decoy receptor, DcR3 *(TNFRSF6B),* which also interacts with LIGHT *(TNFSF14)* lymphotoxin-related inducible ligand and Fas ligand. TL1A is commonly expressed under pro-inflammatory conditions on monocytes, macrophages, and dendritic cells (DCs), whereas DR3 is primarily expressed on T cells, NK cells, and innate lymphoid cells (ILCs), and possibly to a lesser degree also on B cells and macrophages.[3]

TL1A has been reported to play a central role in amplification of a broad spectrum of inflammatory responses. For instance, TL1A promotes interleukin, (IL)-2 signaling in T cells by simultaneously increasing IL-2 production and expression of IL-2RA and IL-2RB.[4,5] TL1A acts in synergy with IL-12, IL-15, and IL-18 on T cells and natural killer, (NK) cells to produce multiple cytokines, including interferon gamma, (IFN-γ), IL-6, IL-13, and granulocyte-macrophage colony-stimulating factor, (GM-CSF).[6,7] Furthermore, TL1A has been shown to have costimulatory effect on ILCs, where TL1A synergizes with IL-25 and IL-33 in stimulating the secretion of IL-5 and IL-13 from ILC2s,[8] and with IL-1β and IL-23 to induce IL-22 secretion from ILC3s.[9]

Human genetic evidence first highlighted a potentially critical role for TL1A in IBD pathogenesis. An initial genome wide association studies (GWAS) in a Japanese cohort implicated 12 single nucleotide polymorphisms (SNPs) in the *TNFSF15* gene as CD risk alleles.[10] 5 of these SNPs were validated as risk alleles in a subsequent United Kingdom, (UK) cohort.[10] Many *TNFSF15* GWAS studies have since emerged. A recent meta-analysis of 15 such studies demonstrated that 6 different SNPs are significantly associated with CD, while 3 SNPs are significantly associated with UC.[11] Additionally, SNPs in the decoy receptor TNFRSF6B gene (DcR3) have been shown to be a risk factor for pediatric IBD.[12,13] One of these TNFSF15 risk alleles is associated with diagnosis at the age of 16 or younger, ileocolonic location, and stricturing or penetrating behavior in a Japanese CD cohort.[14]

Follow-up human studies have further corroborated the potentially critical role for TL1A in IBD pathogenesis. TL1A expression studies have demonstrated high expression levels of *TNFSF15* (TL1A) gene in the inflamed intestinal mucosa of patients with CD, when compared to their non-inflamed intestinal regions and compared with non-IBD controls.[15-17] Moreover, increased serum TL1A levels were reported in both CD and UC patients with active disease compared with controls.[17,18]

Transgenic mice overexpressing TL1A in a cell specific manner have further elucidated the role of TL1A in intestinal inflammation. These mice constitutively express TL1A in T cells under the control of the CD2 promoter, in dendritic cells under the control of the CD11c promoter, and on myeloid cells under the control of the CSF-1R promoter (*c-fms*).[19-21] In all of these models the mice spontaneously develop mild intestinal inflammation that appears to be dependent on IL-13 and has a fibrotic component to it. Consistent with a pro-fibrotic role

for TL1A, it has been recently shown that DR3-signaling on intestinal myofibroblasts leads to increased collagen and *IL31RA* expression.[22] Finally, *in vivo* mouse models have highlighted the exciting promise of TL1A blockade as a therapeutic strategy in IBD. Administration of TL1A Ab led to a significant lowering of disease activity index (DAI) as compared with the isotype antibody in both adaptive T-cell transfer model of colitis and chronic-dextran sulphate sodium, (DSS) model of colitis.[22] Furthermore, the treatment with TL1A Ab reversed colonic fibrosis back to the original pre-inflamed levels in both models.[22]

Taken together, these observations suggest that TL1A may be a promising therapeutic target for IBD. PF-06480605, a fully human neutralizing monoclonal antibody against TL1A, is being used to further explore this potential in IBD treatment.

Study B7541002 was a Phase 2a study to assess the efficacy of PF-06480605 in participants with moderate to severe active UC. The study showed statistically significant results in the primary endpoint with an endoscopic improvement (a Mayo endoscopic subscore of 0 or 1 at Week 14) rate of 38.2% (95% CI:23.8%-53.7%). Based on this and other additional efficacy metrics, PF-06480605 is now being examined in a subsequent Phase 2b study in participants with moderate to severe active UC.

2.2.1. Clinical Overview

PF-06480605 has been explored in a Phase 1 study in healthy participants (Study B7541001) and a Phase 2a (Study B7541002) with participants diagnosed with moderate to severe active ulcerative colitis. PF-06480605 or placebo has been administered to a total of 142 participants, 92 healthy volunteers (60 participants in single ascending dose SAD and 32 participants in the multiple ascending dose MAD periods) by subcutaneous and intravenous routes. In study B7541002, 50 participants with moderate to severe ulcerative colitis were treated with intravenous, (IV) PF-06480605 administered every 2 weeks.

2.2.1.1. Clinical Safety

In the B7541001 study the primary objectives of this study were to evaluate the safety and tolerability of escalating single intravenous doses and multiple subcutaneous and intravenous doses of PF-06480605 administered to healthy participants.

A total of 92 healthy participants, 60 and 32 participants in the SAD and MAD periods, respectively, were assigned to and received investigational product (PF-06480605 or placebo). Single doses up to 800 mg and multiple doses up to 500 mg (3 doses every 2 weeks) were administered.

There were no deaths, SAEs, severe adverse events, (AEs), AEs resulting from anti-drug antibodies or neutralizing antibodies (ADA/NAbs), or participants with dose reductions or temporary discontinuations due to AEs during the first in human, (FIH) study with PF-06480605. Additionally, there were no clinically significant abnormalities in laboratory assessments abnormalities, vital signs, or electrocardiograms, (ECGs).

Overall, headache was the most commonly reported all causality (7 PF-06480605 participants and 3 placebo participants) and treatment-related (5 PF-06480605 participants) treatment emergent adverse events, (TEAE). The second most commonly reported treatment-related TEAE was abdominal pain which was reported by 3 PF-06480605 participants and 1 placebo participant.

The majority of TEAEs were mild in severity. There was a higher incidence of moderate severity TEAEs reported by participants in the MAD cohorts compared with SAD cohorts. The study's only treatment-related moderate severity TEAE, abdominal pain, was reported by a participant from the 300 mg MAD cohort. There were no severe TEAEs reported.

There were no participants from the SAD cohorts who discontinued from the study due to an AE. In the MAD cohorts, there was 1 participant who discontinued from the study due to a treatment- unrelated AE, pyuria, on study Day 14. The event was determined to be mild and the participant recovered in 1 day.

In the B7541002 study, a total of 50 participants were enrolled and treated with PF-06480605 500 mg IV every 2 weeks for a total of 7 doses. Among the 50 participants treated, 33 (66.0%) participants reported at least 1 all-causality treatment-emergent adverse events (TEAEs). The most frequently (≥3) reported TEAEs were arthralgia and UC exacerbation in 6 (12.0%) participants. Abdominal pain, alopecia, back pain, nasopharyngitis, nausea, and pharyngitis occurred in 3 (6.0%) participants.

Eight (8; 16.0%) participants among the 33 participants reported treatment related TEAEs. The treatment related, TEAEs reported were abdominal pain, acrochordon, increase in alanine aminotransferase alopecia, arthralgia, increase in aspartate aminotransferase, back pain, diastolic hypertension, haematoma, headache, hypertension, infusion site bruising, muscle spasms, nausea, oedema peripheral, oropharyngeal pain, pruritus, and vertigo.

Among the 50 participants treated with PF-06480605, [redacted]

One participant discontinued treatment after 1 dose of investigational product due to worsening UC. This participant also discontinued the study. One participant discontinued treatment related to a serious adverse event, alopecia. This participant did continue into the follow up portion of the study.

There were 4 SAEs reported in the B7541002 study; 3 resulted from worsening underlying disease activity, and the fourth was a case of alopecia/baldness, which was considered treatment related by the investigator. There were no deaths reported in either study.

No significant clinical findings have emerged from the completed Phase 1 FIH study or the completed Phase 2a study that would impact participant safety. There were no immunogenicity associated safety signals, thus, standard safety monitoring (ie, clinical evaluation, clinical laboratory tests, cardiac parameters, and testing for ADA) will be included in subsequent studies.

2.2.1.2. Clinical Pharmacokinetics

2.2.1.2.1. Study B7541001

Following single IV infusion dosing, PF-06480605 exposure based on mean area under the curve (AUC_{inf}) trended toward a greater than dose proportional increase with increasing doses across the 1-mg to 800-mg dose range, while the maximum observed concentration (C_{max}) appeared to increase in approximately dose proportional manner. The mean terminal half-life ($t_{½}$) values ranged between 6 and 23 days. Mean clearance (CL) estimates ranged between 0.00688 L/hr and 0.0180 L/hr across all doses. Volume of distribution at steady state (V_{ss}) was low with mean values ranging between 3.4 to 5.5 L across all doses, indicating that drug is localized mainly to the vascular compartment.

Following multiple SC doses ranging from 30 mg to 300 mg, absorption from the site of injection was slow and variable and exposure of Day 1 (as measured by geometric mean area under the curve over the dosing interval [AUC_{τ}] and C_{max}) increased in a dose proportional manner with an increase in dose, while exposures on Days 15 and 29 trended toward greater than dose proportional increases across the 30-mg and 300-mg SC doses. Estimated bioavailability (F) values based on geometric mean AUC_{τ} for the 30 mg, 100 mg, and 300 mg SC doses on Day 1 were 47%, 44%, and 42%, respectively, relative to the corresponding IV doses ($AUC_{14\ days}$) from the SAD portion of the study. No unexpected accumulation occurred based on the accumulation ratios (R_{ac}). Mean $t_{1/2}$ values for the SC doses on Day 29 ranged between 8.7 and 21 days.

Following multiple dose administration of a 500 mg IV dose once every 2 weeks for a total of 3 doses, higher geometric mean AUC_{τ} values were observed on Days 15 and 29 compared to Day 1 with similar C_{max} values observed across all dosing days. Mean $t_{1/2}$ was 20 days.

2.2.1.2.2. Study B7541002

Following multiple dose IV administration of 500 mg PF-06480605 Q2W for a total of 7 doses in participants with moderate to severe UC, C_{max} values ranged between 99300 and 1240000 ng/mL across all participants dosed, with a geometric mean of 263400 ng/mL. After the attainment of C_{max}, PF-06480605 serum concentration exhibited a biphasic decline over time, with mean $t_{½}$ of 19.3 days. Geometric mean area under the concentration-time profile from time 0 to time τ (τ), the dosing interval (AUC_{τ}) of 14 days (336 hours) was 57610000 ng•hr/mL and geometric mean peak-to-trough ratio at steady state (PTR) was 3.0. The geometric mean CL value was 0.00868 L/hr. Volume of distribution at steady state (Vss) was low (geometric mean value = 4.69 L), indicating that PF-06480605 was primarily distributed in the plasma volume.

[redacted]

2.3. Benefit/Risk Assessment

2.3.1. Overall Risk-Benefit Assessment for Study

Despite the expanding number of available medical therapies, a significant number of UC patients are unable to achieve or maintain remission. Whereas surgical resection of the colon offers definitive treatment, the long-term complications make this a therapy of last-resort. Taken together, development of novel medical medicines still remains a critical unmet need for UC patients.

2.3.2. Potential Benefits

The Phase 2 study assessed the efficacy of PF-06480605 500 mg IV every 2 weeks in 50 participants with moderate to severe active UC. The study showed statistically significant results in the primary endpoint with an endoscopic improvement (a Mayo endoscopic subscore of 0 or 1 at Week 14) rate of 38.2% (95% confidence interval, (CI):23.8%-53.7%). This finding suggests that participants in this study could benefit through control of their disease. Furthermore, participants may also benefit from learning about their health, as confirmed by study tests and assessments.

2.3.3. Potential Risks

A total of 142 participants have been exposed to PF-06480605 or placebo across 2 studies.

The Phase 1 study was a single ascending, multiple ascending dose study in 92 healthy participants. All adverse events were reported as mild or moderate. The most common adverse events reported were headache and stomach pain.

The Phase 2 study assessed the efficacy of PF-06480605 500 mg IV every 2 weeks in 50 participants with moderate to severe active UC. Eighteen adverse events were reported as related to PF-06480605. Most of these adverse events were mild (12), 5 were moderate and 1 was severe (hair loss). There were 4 SAEs reported during the study. Three SAEs were related to underlying UC disease activity and were not considered related to the study drug by the investigator. One SAE (hair loss) was considered severe in severity. The investigator felt that this event could not be ruled out as not being related to the study drug.

Toxicity studies with PF-06480605 in pregnant rabbits demonstrated no observed adverse effects in the highest dose tested (500 mg/kg). It is not known whether the study drug can affect male fertility or whether PF-06480605 is secreted in human milk. Because of the investigational nature PF-06480605 should not be administered to pregnant women or women who are nursing an infant.

The current PF-06480605 Investigator's Brochure (dated March 2019) appropriately describes the known benefits and risks of PF-06480605. Safety and efficacy data will continue to be closely monitored in all clinical trials, and any new safety concerns will be promptly reported.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of PF-06480605 may be found in the investigator's brochure, which is the single reference safety document (SRSD) for this study.

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

Objectives	Endpoints	Estimands
Induction Period: Primary		
• To evaluate the efficacy of PF-06480605 in induction of clinical remission at Week 14 in participants with moderate to severe active UC.	• Proportion of participants achieving clinical remission (defined as a Total Mayo Score ≤2, with no individual subscore >1) at Week 14.	E1: This estimand is defined as a population average treatment difference between PF-06480605 and placebo in the proportion of participants who met the binary endpoint without discontinuing treatment prior to Week 12 Visit Treatment: PF-06480605, Placebo. Population: Participants with moderate to severe active UC as defined by inclusion/exclusion criteria Variable: clinical remission at Week 14. Intercurrent Events: Treatment discontinuation prior to Week 12 Visit. If a study participant discontinued the treatment prior to Week 1 Visit but didn't attend the early withdrawal visit, the participant will be considered as a non-responder for the binary remission endpoint at Week 14 for the primary analysis unless reason for missed visit was due to COVID-19. Population level summary: treatment difference between PF-06480605 and placebo in proportions of responders using the binary endpoint.
• To evaluate the safety and tolerability of PF-06480605 during the induction period (from baseline to Week 14) in participants with moderate to severe active UC.	• Incidence and severity of treatment emergent adverse events (TEAEs) during the induction period. • Incidence of serious adverse events (SAEs) during the induction period. • Incidence of AEs or SAEs leading to discontinuation during the induction period. • Incidence of clinically significant abnormalities in vital signs, ECGs and laboratory values during the induction period.	There is no defined estimand for these endpoints and they will be analyzed using Pfizer data standards as applicable.

Induction Period: Secondary		
• To evaluate the efficacy of PF-06480605 in inducing remission at Week 14 in participants with moderate to severe active UC.	• Proportion of participants achieving remission (FDA definition 1 - defined as endoscopic subscore = 0 or 1, stool frequency subscore = 0, and rectal bleeding subscore = 0) at Week 14.	This composite estimand is defined the same as the Estimand E1 except the definition of the binary endpoint.
	• Proportion of participants achieving remission (FDA definition 2 - defined as endoscopic subscore = 0 or 1, ≥1-point decrease from baseline to achieve a stool frequency subscore = 0 or 1, and rectal bleeding subscore = 0) at Week 14.	This composite estimand is defined the same as the Estimand E1 except the definition of the binary endpoint.
• To evaluate the efficacy of PF-06480605 on endoscopic appearance at Week 14 in participants with moderate to severe active UC during the induction period.	• Proportion of participants achieving endoscopic improvement (defined as endoscopic subscore = 0 or 1) at Week 14.	This composite estimand is defined the same as the Estimand E1 except the definition of the binary endpoint.
	• Proportion of participants achieving endoscopic remission (defined as endoscopic subscore = 0) at Week 14.	This composite estimand is defined the same as the Estimand E1 except the definition of the binary endpoint.
• To characterize the PK of PF-06480605 in participants with moderate to severe active UC during the induction period.	• PF-06480605 trough concentrations during the induction period through Week 14.	There is no defined estimand for these endpoints and they will be analyzed descriptively. Missing data will not be included in the analysis.
• To evaluate disease and pathway related biomarkers (ie, hsCRP and fecal calprotectin and serum sTL1A) during the induction period.	• Change from screening in fecal calprotectin during the induction period through Week 14. • Change from baseline in hsCRP during the induction period through Week 14. • Change from baseline in serum sTL1A during the induction period through Week 14.	There is no defined estimand for these endpoints and they will be analyzed descriptively. Missing data will not be included in the analysis.

• To characterize the immunogenicity of PF-06480605 in participants with moderate to severe active UC during the induction period.	• Incidence of development of anti-drug antibodies (ADAs) and neutralizing antibodies (NAbs) during the induction period through Week 14.	There is no defined estimand for these endpoints and they will be analyzed descriptively. Missing data will not be included in the analysis.
Chronic Therapy Period - Primary		
• To evaluate the safety and tolerability of PF-06480605 during the chronic therapy period (from Week 14 to the End of Study Visit) in participants with moderate to severe active UC during the chronic therapy period.	• Incidence and severity of treatment emergent adverse events (TEAEs) during the chronic therapy period. • Incidence of serious adverse events (SAEs) during the chronic therapy period. • Incidence of AEs or SAEs leading to discontinuation during the chronic therapy period. • Incidence of clinically significant abnormalities in vital signs, ECGs and laboratory values during the chronic therapy period.	There is no defined estimand for these endpoints and they will be analyzed using Pfizer data standards as applicable.
Chronic Therapy Period – Secondary		
• To evaluate the efficacy of chronic therapy of PF-06480605.	• Proportion of participants achieving clinical remission (defined as a Total Mayo Score ≤2, with no individual subscore >1) at Week 56.	E2: This estimand is defined as a population average treatment difference between PF-06480605 and placebo in the proportion of participants who met the binary endpoint without discontinuing treatment prior to Week 52 Visit. Treatment: PF-06480605, Placebo. Population: Participants with moderate to severe active UC as defined by inclusion/exclusion criteria, and participants who met the binary endpoint at Week 14 but did not continue to the chronic therapy period will be excluded. Variable: Clinical Remission at Week 56. Intercurrent Events: Treatment discontinuation prior to Week 52 Visit. If a study participant discontinued the treatment prior to

		Week 52 Visit but didn't attend the early withdrawal visit, the participant will be considered as a non-responder for the binary remission endpoint at Week 56 for the secondary analysis unless reason for missed visit was due to COVID-19. Population level summary: treatment difference between PF-06480605 and placebo in proportions of responders using the binary endpoint.
	• Proportion of participants achieving sustained clinical remission (ie, clinical remission at both Week 14 and Week 56).	This composite estimand is defined the same as the Estimand E2 except that the binary endpoint is sustained clinical remission.
	• Proportion of participants achieving remission (FDA definition 1 - defined as endoscopic subscore = 0 or 1, stool frequency subscore = 0, and rectal bleeding subscore = 0) at Week 56. • Proportion of participants achieving sustained remission-FDA definition 1 (ie, remission-FDA definition 1 at both Week 14 and Week 56).	This composite estimand is defined the same as the Estimand E2 except that the binary endpoint is remission (FDA definition 1) at Week 56 or sustained remission (FDA definition 1).
	• Proportion of participants achieving remission (FDA definition 2 - defined as endoscopic subscore = 0 or 1, ≥1-point decrease from baseline to achieve a stool frequency subscore = 0 or 1, and rectal bleeding subscore = 0) at Week 56. • Proportion of participants achieving sustained remission-FDA definition 2 (ie, remission-FDA definition 2 at both Week 14 and Week 56).	This composite estimand is defined the same as the Estimand E2 except that the binary endpoint is remission (FDA definition 2) at Week 56 or sustained remission (FDA definition 2).
	• Proportion of participants achieving endoscopic improvement (defined as endoscopic subscore = 0 or 1) at Week 56. • Proportion of participants achieving sustained endoscopic	This composite estimand is defined the same as the Estimand E2 except that the binary endpoint is endoscopic improvement at Week 56 or sustained endoscopic improvement.

	improvement (ie, endoscopic improvement at both Week 14 and Week 56).	
	• Proportion of participants achieving endoscopic remission (defined as endoscopic sub-score = 0) at Week 56. • Proportion of participants achieving sustained endoscopic remission (ie, endoscopic remission at both Week 14 and Week 56).	This composite estimand is defined the same as the Estimand E2 except that the binary endpoint is endoscopic remission at Week 56 or sustained endoscopic remission.
• To characterize the PK of PF-06480605 in participants with moderate to severe active UC during the chronic therapy period.	• PF-06480605 concentration from Week 14 through the End of Study Visit.	There is no defined estimand for these endpoints and they will be analyzed descriptively. Missing data will not be included in the analysis.
• To evaluate disease and pathway related biomarkers (ie, hsCRP and fecal calprotectin and serum sTL1A during the chronic therapy period.	• Change from Week 14 in fecal calprotectin during the chronic therapy period through the End of Study Visit. • Change from Week 14 in hsCRP during the chronic therapy period through the End of Study Visit. • Change from week 14 in serum sTL1A during the chronic therapy period through the End of Study Visit. • Change from baseline through the End of Study Visit in fecal calprotectin. • Change from baseline through the End of Study Visit in hsCRP. • Change from baseline through the End of Study Visit in serum sTL1A.	There is no defined estimand for these endpoints and they will be analyzed descriptively. Missing data will not be included in the analysis.
• To characterize the immunogenicity of PF-06480605 in participants with moderate to severe active UC during	• Incidence of development of anti-drug antibodies (ADAs) and neutralizing antibodies (NAbs) from Week 14 through the End of Study Visit.	There is no defined estimand for these endpoints and they will be analyzed descriptively. Missing data will not be included in the analysis.

the chronic therapy period.		
Induction Period/Chronic Therapy Period: Tertiary		
• To evaluate the effect of PF-06480605 on clinical outcomes and quality-of-life in participants with moderate to severe active UC during the induction period and chronic therapy period.	• Proportion of participants achieving clinical response (defined as ≥3 point and ≥30% decrease from baseline in Total Mayo Scores, with an accompanying ≥1 point decrease in rectal bleeding subscore or absolute rectal bleeding subscore = 0 or 1) at Week 14 and Week 56, and sustained clinical response (ie, clinical response at both Week 14 and Week 56). • Proportion of participants achieving symptomatic remission (defined as a Total Mayo Score ≤2 with no individual subscore >1 and both rectal bleeding and stool frequency subscores of 0) at Week 14 and Week 56, and sustained symptomatic remission (ie, symptomatic remission at both Week 14 and Week 56). • Proportion of participants achieving deep remission (defined as a Total Mayo Score ≤2 with no individual subscore >1 and both endoscopic and rectal bleeding subscores of 0) at Week 14 and Week 56, and sustained deep remission (ie, deep remission at both Week 14 and Week 56). • Change from baseline in Partial Mayo scores over time. • Change from baseline in diary UC Symptoms over time. • Change from baseline in [redacted] over time. • Change from baseline in [redacted]	No estimands are defined for tertiary endpoints. Analyses details for these endpoints will be documented in the statistical analysis plan (SAP) or biomarker statistical analysis plan (bSAP).

	[redacted] over • The proportion of participants with [redacted] total score ≥170 over time. • Change from baseline in [redacted] over time. • Change from baseline in [redacted] over time.	
• [redacted]	• [redacted]	
• To collect non-banked samples [redacted] for RNA analysis) for exploratory research, unless prohibited by local regulations or ethics committee decision.	• Collection of non-banked exploratory samples unless prohibited by local regulations or ethics committee decision.	
• To enable exploratory research through collection of banked biospecimens, unless prohibited by local regulations or ethics committee decision.	• Potential results from exploratory analysis of banked biospecimens (these results may or may not be generated in the context of the present study).	
• [redacted]	• [redacted]	

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 2b, multi-center, randomized, double-blind, placebo controlled, parallel group study design, to assess the efficacy, safety and pharmacokinetics of PF-06480605 in participants with moderate to severe active UC. Approximately 240 participants will be randomized, and 216 of them are expected to complete the induction period, assuming a 10% drop out rate. Participants will be randomly assigned to 1 of 9 treatment sequences using an allocation ratio of [redacted]. The numbers of planned participants for the 9 treatment sequences (A-I) are listed in Table 2. Randomization will be stratified according to whether or not the participants have prior exposure to anti-TNFs in order to achieve a balanced proportion of participants with prior exposure to anti-TNFs across different treatment sequences.

This study will occur over 4 periods; screening, induction, chronic therapy, and follow-up. The first screening period may last up to 6 weeks to assess eligibility and may occur over a few study visits. During the screening period, eligibility will be assessed by review of the medical history, current/prior medications, and a colonoscopy/sigmoidoscopy to confirm moderate to severe active UC disease. (Please see the SoA for all assessments). The induction part of the study will be 12 weeks in duration, and all participants will be assigned to a treatment regimen. At the beginning of this period (baseline visit, or Day 1), participants will be randomly assigned to 1 of 9 treatment sequences (Table 2) according to a predefined randomization schedule. During the 12-week induction period, participants will receive 50 mg, 150 mg, 450 mg, or matched placebo. Participants will receive blinded induction treatment administered SC once every 4 weeks at their scheduled study visit according to the assigned treatment sequence. During this time participants will also collect UC symptoms (Partial Mayo Score) on a [redacted] eDiary. Other assessments will be completed at the scheduled visits such as safety labs, PK collection, and the completion of UC scales by the participants. Once the induction treatment is completed (Week 12), all participants will have a colonoscopy or sigmoidoscopy at Week 14. At Week 16, dosing will resume for all participants. During the chronic therapy period all participants will be on active drug, (50 mg, 150 mg, or 450 mg administered SC every 4 weeks). Treatment will continue through Week 52. Participants will continue to collect [redacted] UC symptoms on the eDiary, as well as report for scheduled study visits every 4 weeks, where safety labs PK, and UC scales will be completed by the participants. All participants will return for Week 56 so that the final colonoscopy or sigmoidoscopy is completed. The last 2 scheduled visits are a part of the follow-up portion of the study where safety assessments are collected, and many of the prohibited treatments are now permitted. The final follow-up period will be 12 weeks in duration. The [redacted] UC symptoms will continue to be collected until the end of the study. Overall the study participation for each participant is approximately up to 70 weeks. Please see Section 1 for the study design schema.

Participants that discontinue at any time during the study will proceed into the follow-up period with an early withdrawal visit (see Section 7.1).

Table 2. Treatment Sequence

Treatment Sequence	Treatment Sequence Description	
	Induction Period	**Chronic Therapy Period**
A	PF-06480605 450 mg SC Q4W	PF-06480605 450 mg SC Q4W
B	PF-06480605 450 mg SC Q4W	PF-06480605 150 mg SC Q4W
C	PF-06480605 450 mg SC Q4W	PF-06480605 50 mg SC Q4W
D	PF-06480605 150 mg SC Q4W	PF-06480605 150 mg SC Q4W
E	PF-06480605 150 mg SC Q4W	PF-06480605 50 mg SC Q4W
F	PF-06480605 50 mg SC Q4W	PF-06480605 50 mg SC Q4W
G	Placebo SC Q4W	PF-06480605 450 mg SC Q4W
H	Placebo SC Q4W	PF-06480605 150 mg SC Q4W
I	Placebo SC Q4W	PF-06480605 50 mg SC Q4W

4.2. Scientific Rationale for Study Design

Study B7541002, a Phase 2A, Multicenter, Single Arm, Open-Label, Two-Stage, Study to Evaluate the Efficacy, Safety, Tolerability, and Pharmacokinetics of PF-06480605 in Participants with Moderate to Severe Ulcerative Colitis has demonstrated PF-06480605 to be safe, well-tolerated, and efficacious following administration of 500 mg IV every 2 weeks (Q2W) for 12 weeks.

The induction period will inform Phase 3 dose selection. Subcutaneous administration every 4 weeks (Q4W) was considered for this study since it is the intended route of administration and the population PK/PD model-predicted P_{90} (proportion of subjects maintaining minimum target coverage ≥90%) values of for the 450 mg Q4W SC (highest dose to be evaluated in this study) and the efficacious 500 mg Q2W IV doses, respectively, supports both the route of administration and frequency of dosing.

The chronic therapy period will enable the characterization of long-term immunogenicity. Given the high immunogenicity observed in healthy volunteers (Study B7541001) and participants with Ulcerative Colitis (Study B7541002), capturing the trough at each PK visit is required to evaluate the impact of immunogenicity on drug concentration over the course of the study.

In the definitive embryo-fetal development, (EFD) study, PF-06480605 was intravenously administered by bolus injection to pregnant New Zealand White female rabbits once daily on Gestation Days (GD) 7 and 14 at 0, 60, 180, or 500 mg/kg/dose. The maternal and developmental no-observed-adverse-effect level (NOAEL) for PF-06480605 in rabbits was the highest dose tested, 500 mg/kg/dose, based on a lack of test article-related effects. Also, there were no findings in male or female reproductive organs in the 3- or 6-month toxicity studies in mice and cynomolgus monkeys, respectively. It is not known whether PF-06480605 can affect male fertility or whether PF-06480605 is secreted in human milk. Because of the investigational nature of this product, PF-06480605 should not be administered to pregnant women or women who are nursing an infant. Giving the unlikely risk of human teratogenicity/fetal toxicity all acceptable effective methods of contraception will be required for approximately 5 half -lives (3 months), following the last dose of IP. (See Appendix 4). The potential risk of exposure to PF-06480605 in a sexual partner of a male participant in this study via ejaculate is low, and therefore no contraception (condom) use in male participants is warranted. The calculated safety margin of 34,852 is >100-fold between the estimated partner exposure due to seminal transfer and the NOAEL for serious manifestations of developmental toxicity in nonclinical studies. The safety margin of 100-fold is based on applying a 10-fold safety factor for interspecies extrapolation and a 10-fold safety factor for susceptible populations.[23]

Banked biospecimens will be collected for exploratory [redacted] and retained in the Biospecimen Banking System (BBS), which makes it possible to better understand the investigational product's mechanism of action and to seek explanations for differences in, for example, exposure, tolerability, safety, and/or efficacy not anticipated prior to the beginning of the study.

4.3. Justification for Dose

[redacted]

[redacted]

[redacted]

[redacted]

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including; screening, induction phase, chronic therapy period, and the follow-up portion of the study up through and including visit (Visit 18), approximately 12 weeks post last dose of IP. The end of the study is defined as the date of the last visit (Visit 18), by the last participant across all sites globally.

5. STUDY POPULATION

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

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

5.1. Inclusion Criteria

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

Age and Sex:

1. Male or female participants ≥18 years, or (the minimum country specific age of consent if >18) to ≤75 years of age at the time of informed consent signing.

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

Type of Participant and Disease Characteristics:

2. A diagnosis of UC for ≥3 months. Endoscopy and pathology reports supporting the diagnosis, disease duration, and extent of disease (eg, proctosigmoiditis, left-sided colitis, or pancolitis) must be available in the source documentation.

3. Participants with moderate to severe active UC as defined by a Total Mayo Score of ≥6, and an endoscopic subscore of ≥2. See Section 8 for details.

4. Active disease beyond the rectum (>15 cm of active disease from the anal verge at the screening endoscopy).

5. Participants must have failed or be intolerant (discontinued the medication due to an adverse event as determined by the investigator) of at least 1 of the following treatments for UC:

   - Steroids;
   - Immunosuppressants (azathioprine [AZA], 6-mercaptopurine [6-MP], or methotrexate [MTX]);
   - Anti-TNF inhibitors (eg, infliximab, adalimumab, or golimumab);
   - Anti-integrin inhibitors (eg, vedolizumab);
   - Anti-IL-12/23 inhibitors (eg, ustekinumab);
   - JAK inhibitors (eg, tofacitinib).

   Please note: Participants currently receiving treatments for UC are eligible providing they have been and are anticipated to be on stable dose for the duration of the study. (See Appendix 9) for details.

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

Informed Consent:

7. 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

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

Medical Conditions:

1. Participants with a diagnosis of ischemic colitis, infectious colitis, radiation colitis, microscopic colitis, indeterminate colitis, or findings suggestive of Crohn's disease (eg, skip lesions, fistulae/perianal disease, non-necrotizing granulomas, etc.).

2. Participants displaying clinical signs of fulminant colitis or toxic megacolon.

3. Participants with an imminent need for surgery or with elective surgery scheduled to occur during the study.

4. Participants with evidence of colonic dysplasia, adenomas, or neoplasia per local guidelines.

5. Participants who meet either of the 2 criteria below are considered at risk for colonic dysplasia, adenomas, or neoplasia and must have a colonoscopy prior to randomization:

    a. If the participant has had extensive (ie greater than left sided) colitis for ≥8 years or disease limited to left side of colon (ie distal to splenic flexure) for ≥10 years, regardless of age, a colonoscopy within 1 year of screening visit is required to survey for dysplasia.

    b. If the participant is ≥50 years of age, a colonoscopy within 10 years of screening is required to exclude adenomatous polyps. Participants with adenomatous polyps identified on screening endoscopy will be eligible after complete polypectomy and follow-up surveillance per local guidelines is negative.

    The colonoscopy and pathology reports (if biopsies obtained) must be available in the source documentation.

6. Clinically significant infections within 6 months of baseline (eg those requiring hospitalization or parenteral antimicrobial therapy, or opportunistic infections), or a history of any infection otherwise judged by the investigator to have the potential for exacerbation by participation in the study.

7. Cancer or history of cancer or lymphoproliferative disease within 5 years of baseline (with the exception of participants with adequately treated or excised non-metastatic basal cell or squamous cell carcinoma of the skin or cervical carcinoma in situ).

8. Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or or laboratory abnormality that t may increase the risk associated with study participation 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:

9. See Section 6.5 and Appendix 8 for details regarding prohibited prior/concomitant medications.

10. Known exposure to anti-TL1A (PF-06480605) or any type of anti-TL1A therapy.

Prior/Concurrent Clinical Study Experience:

11. Previous administration 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 used in this study (whichever is longer). Note: local regulations or other factors may require more than 30 days.

Diagnostic Assessments:

12. A 12-lead electrocardiogram (ECG) that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results (eg, baseline corrected QT Fridericia method[QTcF] >450 msec, complete left bundle branch block [LBBB], signs of an acute or indeterminate-age myocardial infarction, ST-T interval changes suggestive of myocardial ischemia, second- or third-degree atrioventricular [AV] block, or serious bradyarrhythmias or tachyarrhythmias). If QTcF exceeds 450 msec, or QRS exceeds 120 msec, the ECG should be repeated 2 more times and the average of the 3 QTcF or QRS values should be used to determine the participant's eligibility.

13. Chest Radiograph or computed tomography scan showing abnormalities: The study will accept a Chest x-ray or computed tomography scan of the chest examination performed up to 12 weeks prior to screening if available. See Section 8.

14. Infected with tuberculosis, (TB): Any evidence of untreated latent or active TB infection. Please see Section 8 and Appendix 2.

15. Presence of active enteric infections: Known pathogenic bacterial, parasitic, fungal infections, including [redacted] Please see Appendix 2.

16. Infected with human immunodeficiency virus, (HIV), Hepatitis B or C viruses, please see Appendix 2.

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

    - Hemoglobin <8.0 g/dL or hematocrit <30% (<0.30 v/v);
    - Absolute lymphocyte count (ALC) <0.8 x 10^9/L (<800/mm^3);
    - Absolute neutrophil count (ANC) <1.2 x 10^9/L (<1200/mm^3);
    - Platelet count <100 x 10^9/L (<100,000/mm^3);
    - Aspartate aminotransferase, (AST) or alanine aminotransferase, (ALT) ≥2.0 times the upper limit of normal (ULN);
    - Total bilirubin level ≥1.5 times the ULN; participants with a history of Gilbert's syndrome may have a direct bilirubin measured and would be eligible for this study provided the direct bilirubin in ≤ ULN;
    - Screening laboratory tests with abnormal results (if considered by the investigator to be transient and inconsistent with the subject's clinical condition) may be repeated within the screening window to confirm abnormal results. If results return to protocol acceptable limits within the screening period, the subject may enter the study.

Other Exclusions:

18. History of alcohol or drug abuse (per the investigator's discretion) that would prevent the participant from being compliant with study visits and required procedures.

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

5.3. Lifestyle Considerations

5.3.1. Contraception

The investigator or his or her designee, in consultation with the participant, will confirm that female participants have selected an appropriate method of contraception from the permitted list of contraception methods (see Appendix 4 Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the schedule of activities (SoA), the investigator or designee will inform the participant of the

need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to receive investigational product or entered into the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

A participant who qualified for this study but did not enroll within the protocol prescribed screening period may be re-screened. All screening procedures must be repeated, and the participant assigned a new 8-digit study-specific participant identification (SSID) number.

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 IP is compound PF-06480605 and matching placebo administered SC; and will be administered SC once every 4 weeks (Q4W). To maintain the blind, every participant will receive [redacted] SC injections at all visits where participants are receiving investigational administration according to the SoA.

Table 4. Study Intervention(s) Administered

Intervention Name	PF-06480605 Solution for Injection, 100 mg/mL.	Placebo.
ARM Name	Induction, Maintenance.	Induction.
Type	Biologic.	Biologic.
Dose Formulation	Solution for Injection.	Solution for Injection.
Unit Dose Strength(s)	100 mg/mL, [redacted]mL extractable volume.	Placebo to match, [redacted]mL extractable.
Dosage Level(s)	50 mg, 150 mg, 450 mg.	Placebo.
Route of Administration	Subcutaneous.	Subcutaneous.

Investigational Medicinal Product (IMP) and Noninvestigational Medicinal Product (NIMP)	IMP.	IMP.
Sourcing	Provided centrally by the sponsor. Please reference the Investigational Product Manual for details on Drug ordering.	Provided centrally by the sponsor. Please reference the Investigational Product Manual for details on Drug ordering.
Packaging and Labeling	Study intervention will be provided in vials packaged in individual cartons. Each vial and carton will be labeled as required per country requirement. All vials will be provided in cartons and both will be labeled in a blinded fashion according to local regulatory requirements.	Study intervention will be provided in vials packaged in individual cartons. Each vial and carton will be labeled as required per country requirement. All vials will be provided in cartons and both will be labeled in a blinded fashion according to local regulatory requirements.
Current/Former Name(s) or Alias(es)]	N/A	N/A

PF-06480605 is a sterile solution for subcutaneous injection. Each vial contains 200 mg of PF-06480605 in [redacted]mL of solution. PF-06480605 will be provided in dosage strength of 100 mg/mL in single-use, sterile vials. Placebo for PF-06480605 will also be provided by Pfizer as a sterile liquid solution in single-use, sterile vials.

Doses of 50 mg, 150 mg, and 450 mg PF-06480605 or Placebo will be administered through 4 treatment arms in a 12-week induction phase. After the induction phase, doses of 50 mg, 150 mg, and 450 mg PF-06480605 will be administered through 3 treatment arms in a 40-week chronic therapy phase.

PF-06480605 and placebo are supplied in a [redacted]mL glass vial and a [redacted]mL extractable volume with a stopper and aluminum overseal. All vials will be provided in cartons and both will be labeled in a blinded fashion according to local regulatory requirements.

6.1.1. Administration

Investigational product withdraw and dilution will be completed by an unblinded pharmacist at the investigational site. Administration to the study participant will be completed by blinded site personnel at the investigative site. All participants will be administered [redacted] SC injections every 4 weeks to maintain the blind.

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 Investigational Product Manual, (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 investigational product manual (IP manual), package insert, or equivalent for storage conditions of the study intervention once reconstituted and diluted.

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

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

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

6.2.1. Preparation and Dispensing

Once eligibility has been confirmed through the screening period process, each participant will be randomized (See Table 4). The investigational product will be dispensed using an interactive response technology, (IRT) drug management system at each visit from Visit 1 to Visit 15, with the exception of visit 5, as no drug is dispensed at this visit. A qualified staff member will dispense the investigational product via unique container numbers on the label provided, in quantities appropriate for the study visit schedule.

See the IP manual for instructions on how to prepare the investigational product for administration. Investigational product should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance.

PF-06480605 and placebo will be prepared by qualified unblinded site personnel according to the IP manual. The investigational product will be administered in a blinded manner to participants.

6.3. Measures to Minimize Bias: Randomization and Blinding

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, randomization number, and dispensable unit (DU) or container number when investigational product is being supplied via the IRT system. The IRT system will provide a confirmation report containing the participant number, randomization number, and DU or container number assigned. The confirmation report must be stored in the site's files.

Investigational product will be dispensed at the study visits summarized in the SoA.

Returned investigational product must not be redispensed to the participants.

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

Blinded study with unblinded site pharmacist/site staff who are dispensing drug: Participants will be assigned to receive investigational product according to randomization scheme. Investigators will remain blinded to each participant's assigned investigational product throughout the course of the study. In order to maintain this blind, an otherwise uninvolved third party will be responsible for the preparation and dispensing of all investigational product and will endeavor to ensure that there are no differences in time taken to dispense or visual presentation following randomization.

In the event of a Quality Assurance audit, the auditor(s) will be allowed access to unblinded investigational product records at the site(s) to verify that randomization/dispensing has been done accurately.

6.3.2. Breaking the Blind

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's treatment assignment unless this could delay further management of the participant. If a participant's treatment assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and case report form (CRF).

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

6.4. Study Intervention Compliance

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

6.5. Concomitant Therapy

Any prior history (any time prior to the signing of the ICD with no limitations of time) of corticosteroids, immunosuppressives (AZA, 6-MP, and MTX), anti-TNFs, anti-integrins, anti- IL-12/23 and JAK inihitors will be recorded on the CRF. Any prior UC medications taken during the 30 days prior to screening and biologic therapies within 90 days prior to screening must be recorded on the CRF. Medications taken within 42 days before the first dose of IP will be documented as prior medications. Please see Appendix 8 and 9.

Medication(s) administered/taken following the first dose of IP will be documented as concomitant medication.

6.5.1. Permitted Medications

Participants will be allowed to use the following medications as detailed below:

1. [redacted]
2. [redacted]
3. [redacted]
4. [redacted]

All concomitant medication(s) and treatment (s) administered/taken during the study must be recorded with indication, daily dose, start and stop dates of administration. All participants will be questioned about concomitant medication at each site visit.

Hormonal contraceptives that meet the requirements of this study are allowed to be used in participants who are women of childbearing potential (WOCBP) (See Appendix 4).

6.5.2. Prohibited Medications

See Appendix 8 for details regarding prohibited concomitant medications. Sites are encouraged to contact the sponsor should there be questions as to whether a medication is permitted or prohibited.

[redacted]

6.5.3. Rescue Medication

Rescue medication, defined as anything listed under prohibited medications is not permitted per the protocol. Participants are free to withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor. If a participant requires initiation of a new therapy for ulcerative colitis, or medication that is on the prohibited list of medication (Appendix 8) the participant should be withdrawn from the study and appropriate treatment should be administered at the discretion of the investigator.

6.6. Dose Modification

Not Applicable.

6.7. Intervention After the End of the Study

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

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue IP. Per the study estimands, if investigational product is permanently discontinued, the participant will remain in the study for follow up. Note that discontinuation of investigational product does not represent withdrawal from the study.

If a safety or tolerability concern arises, in particular if not responsive to symptomatic management, dosing with double-blinded IP may be stopped in an individual participant at investigator discretion.

Any participant who prematurely withdraws from the treatment period (after being randomized and during active study intervention) should be followed for 3 study visits (one being the Early Withdrawal Visit) for a total of 12 weeks from the last dose of interventional product.

- Early Withdrawal Visit (replaces Visit 16, follow-up visit 1) to be performed and completed. This includes colonoscopy or sigmoidoscopy.
- Visit 17 (follow-up 2) is completed 8 weeks after the last dose of investigational product.
- Visit 18 (follow-up 3) is completed 12 weeks after the last dose of investigational product. This is the End of Study Visit.

See the SoA for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

7.1.1. Criteria for Discontinuation

Discontinuation of IP must occur for a participant meeting any of the following conditions:

- Criteria for a potential Hy's law case are met (See Appendix 6).
- Liver Injury (See Appendix 6).
- Intent to become pregnant or pregnancy confirmed by serum beta human chorionic gonadotropin (β-hCG) testing. (See Appendix 4).
- ECG changes (See Appendix 7).
- Progressive/Unstable Disease State where the participant would benefit from medication currently prohibited during the treatment period.

See the SoA for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

7.2. Participant Discontinuation/Withdrawal From the Study

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

At the time of discontinuing from the study, if possible, an early discontinuation/withdrawal visit 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/withdrawal visit applies only to participants who are randomized and then are prematurely withdrawn from the study. Participants should be questioned regarding their reason for withdrawal. Any participant who prematurely withdraws from the treatment period (after being randomized and during active study intervention) should be followed for 3 study visits (one being the Early Withdrawal Visit) for a total of 12 weeks from the last dose of interventional product.

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

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

When a participant withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported on the Clinical Trial (CT) SAE Report. In addition, following an SAE, lack of completion of all or any of the early discontinuation/withdrawal procedures will not be viewed as protocol deviations due to reasons of safety of the participant.

Withdrawal of Consent:

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

7.3. Lost to Follow-up

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

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

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

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

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

Study procedures and their timing are summarized in the 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.

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.

8.1. Efficacy Assessments

Efficacy assessments for this study will include Mayo Scores, and endoscopic subscores. The following procedures and assessments are required to achieve the scores.

8.1.1. Colonoscopy/Sigmoidoscopy

A screening endoscopy (ie, colonoscopy or flexible sigmoidoscopy) should be performed preferably [redacted] (Day 1) to allow Total Mayo Score calculation. The endoscopic subscore, read by the Central Reader must be available at the baseline visit. The assessment by the Central Reader will be used to derive the Total Mayo Score for study eligibility. The endoscopic report and pathology report must be available in the source documents.

Two additional colonoscopies or sigmoidoscopies, with biopsies will be performed at Week 14 (Visit 5), and Week 56, (Visit 16).

When the participant comes in at the scheduled Visit 5(Week 14) or Visit 16 (Week 56) and has their endoscopy procedure the site can either wait until they receive the results of the centrally read endoscopy score to activate Visit 5 (Week 14), or Visit 16 (Week 56) in the trialweb, OR they can activate Visit 5 (Week 14) or Visit 16 (Week 56) in trialweb on the day of the visit. The visit window will not close after the calendar day so they can leave the visit activated until they receive the central reader results of the endoscopy. The centrally read endoscopy score must be used for the total mayo score.

If the participant discontinues the IP early before completing study treatment period, a colonoscopy or sigmoidoscopy should be performed along with other protocol required early discontinuation/withdrawal procedures (see SoA and Section 7.1). Bowel preparation should be conducted as per local standard routine. The position of the endoscope will be based on the length of the instrument at various levels of insertion as well as the morphological features of the intestine as seen during the screening endoscopy (ie, colonoscopy or sigmoidoscopy). The report and any photographs and/or video recordings taken during the procedure per local regulations should be filed in the participant's chart. The findings of the endoscopy (ie, colonoscopy or sigmoidoscopy) component should be completed at the end of the procedure to document the endoscopic subscore. Intestinal Biopsy Collection [redacted]

Intestinal tissue biopsies will be collected at screening, Week 14 and Week 56. If the participant withdraws early from treatment, a colonoscopy or sigmoidoscopy should be completed at that time. Jumbo forceps should be used to obtain biopsies during each colonoscopy procedure. Biopsies should be taken one at a time, and each should be immediately placed into a separate sample collection tube, as specified in the central vendor procedure manual. During each endoscopy procedure, [redacted] should be taken from abnormally inflamed colonic mucosa and [redacted] should be taken from normal appearing colonic mucosa, resulting in a total of [redacted] biopsies from each participant, if possible. All inflamed pre-treatment biopsies should be obtained in a targeted manner from the most affected area, 15-30 cm from the anal verge, extremely ulcerated areas should be avoided. During post-treatment endoscopies, samples should be obtained from approximately the same anatomic location as the baseline assessment. For all biopsies collected, the colonic segment and approximate distance from the anal verge for each sample should be recorded in the source documents. If [redacted] biopsies cannot be collected during the endoscopy, then samples from inflamed tissues should be prioritized in the following order: [redacted] During the baseline assessment, if increased inflammation is identified further than 15-30 cm, the location should be noted in the source documents (ie, colonic segment and approximate distance from anal verge) and an additional [redacted] biopsies should be taken for histology both before and after treatment, if possible. If these

[redacted]additional inflamed biopsies are collected for histology, then the total biopsy samples collected during pre and post treatment endoscopies will be [redacted]

During treatment endoscopies, samples should be obtained from approximately the same anatomic location as the baseline, pre-treatment biopsy collection. For all biopsies collected, record the colonic segment and approximate distance from the anal verge for each sample in the source documents. Exploratory biomarkers may be analyzed.

8.1.2. Total Mayo Score

Total Mayo Score will be based on the centrally-read endoscopic subscore, stool frequency, rectal bleeding and physician's global assessment.

The Mayo Score is a tool designed to measure disease activity for UC. The Mayo scoring system ranges from 0 to 12 points and consists of 4 subscores, each graded 0 to 3 with the higher score indicating more severe disease activity (See Appendix 10).

- Stool frequency (Subscore 0-3).
- Rectal bleeding (Subscore 0-3).
- Findings on endoscopy (Subscore 0-3).
- Physician's global assessment (Subscore 0-3).

Calculation of the Mayo Score requires an assessment of the participant's stool frequency and any amount of blood in the stool. The Mayo scores will be calculated based on the participant's stool electronic diary, (e-diary) data recorded over the [redacted]days prior to the endoscopy bowel preparation procedure. Investigator sites will be trained on the electronic diary usage and will train participants on use of the e-diary. Electronic diary data entered by the participant will be reviewed by the site at each visit.

For baseline endoscopy and post-baseline endoscopies, if there are missing e-diary data, the average will be taken from the [redacted]days reported within 7 days prior to the endoscopy preparation.

Note: that if there is 1 day of e-diary data or no e-diary data recorded prior to the baseline endoscopy preparation, then the patient cannot be randomized into the study.

If there are less than [redacted]days reported within the 7 days prior to the study visit, the average will be taken from the limited available data unless there is no e-diary data reported within 7 days. In this case, stool frequency and rectal bleeding subscores will be considered as missing.

The endoscopic imaging appearance will be read by the Central Reader.

The physician's global assessment (PGA) acknowledges the other 3 criteria, the subscores, the [redacted] record of abdominal discomfort and functional assessment and other observations such as physical findings, and the patient's performance status. It is preferred that the same medically qualified clinician performs all such assessments for a given participant throughout the study.

The Mayo Score must be ≥6 and ≤12 with an endoscopic subscore of at least 2 and meet all other eligibility criteria to be randomized into the study. The duration of the time between the Mayo endoscopic subscore assessment and baseline should not exceed approximately 10 days.

8.1.3. Participant Stool Diary

Participants will use an e-diary to record [redacted] stool counts, and rectal bleeding. This information is needed to calculate the partial mayo scores collected during the study.

- E-diary: Questions:
  - [redacted]

Diary data will be assessed at each study visit from screening until the end of the follow up period (Week 64). The information extracted will be used for calculation of Mayo score considering the data recorded over the [redacted] days prior to each study visit. [redacted] day patient e-diary data must be completed and assessed prior to any bowel preparations. If there are missing e-diary data, the average will be taken from the [redacted] most recently available days reported within 7 days prior to the endoscopy preparation. If there are less than [redacted] available days reported within the 7 days prior to the study visit, the average will be taken from the limited available data unless there is no e-diary data reported within 7 days. In this case, stool frequency and rectal bleeding subscores will be considered as missing. Note: that if there is 1 day of e-diary data or no e-diary data recorded prior to the baseline endoscopy preparation, then the patient cannot be randomized into the study.

In order to encourage consistent e-diary recording, participants should enter e-diary data continuously throughout the study. Instructions for completing the e-diary will be provided to participants at screening and reviewed at subsequent visits.

8.1.4. Partial Mayo Score

The partial Mayo Score (Mayo Score without endoscopic subscore, ranging from 0 to 9) will be calculated from the participant's stool diary that is collected [redacted] on the e-diary. The score will be reviewed at all scheduled visits, prior to administration of IP.

8.1.5. UC Medical History (Screening)

A diagnosis of UC for ≥3 months. A medical report documenting disease duration and extent of disease (eg, proctosigmoiditis, left-sided colitis, and pancolitis) based upon prior colonoscopy/flexible sigmoidoscopy must be available in source documentation. A biopsy report must be available to confirm the histological diagnosis in the participant's source documentation.

8.1.6. Medical History (Screening)

Investigators should make all reasonable efforts to obtain an accurate and complete medical history and history of prior medication use when evaluating whether a participant is eligible for the study. The following will be collected at screening: complete medical history, UC disease history (including disease duration and prior treatments) and tobacco use history. If the status of a participant's medical history is in doubt or information pertaining to a critical variable is conflicting, every reasonable step to secure proper documentation of correct medical status should be attempted. Documentation of the medical and medication histories over the protocol defined time periods should be available for sponsor review during the source data verification process. Questions about prior medications or eligibility should be directed to the Sponsor Clinician or Sponsor Medical Monitor.

8.1.7. Prior Medications (Screening)

Any prior history (any time prior to signing the ICD with no limitations of time) of corticosteroids, immunosuppressives, (AZA, 6-MP, and MTX) anti-TNFs, anti-integrins, anti-IL-12/23 and JAK inhibitors will be recorded on the CRF.

8.1.8. Patient Reported Outcomes

In addition to the [redacted] stool diary, there are 4 patient reported outcomes in this study, that will be collected at specific scheduled visits (See the SoA). [redacted] When a participant arrives at the site for a scheduled visit, the patient reported outcome, (PRO) should be completed as the first assessment or closest to the first assessment as possible, according to the SoA. The site must also provide to the participants patient reported outcome assessments in the following order, [redacted] and prior to any other clinical assessments.

8.1.9. Rater Qualifications

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

8.1.10. Imaging Assessments

Management of Incidental Findings

An incidental finding is one unknown to the participant that has potential health or reproductive importance, which is discovered unexpectedly in the course of a research study but is unrelated to the purpose and beyond the aims of the study.

- Endoscopy, (Colonoscopy or flexible sigmoidoscopy) images will be reviewed by a central review facility. The purpose of this review is to evaluate images for disease activity in the colon. Central image review is not a complete medical review of the participant. If, during the central review process, an unexpected observation is identified, and this finding could, in the opinion of the central reviewer, have a significant health or reproductive consequence, this finding may be shared with the study sponsor for disclosure to the principal investigator (PI). All follow-up testing and final diagnosis will be left to the discretion of the medical professionals at the site or those with an existing physician-participant relationship. The PI will be responsible for reporting any AEs identified from incidental findings as described in the AE reporting section. Identification of such incidental findings during the central review process should not be expected, and the site maintains responsibility for performing a general safety review of all images as per site protocols.

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 concerns.

8.2.1. Physical Examinations, Height and Weight

Complete and targeted physical examinations are performed as indicated according to the SoA.

It is recommended that weight be measured in kilograms (kg) and that height be measured in centimeters (cm), however pounds (lbs) and inches may be used, (in). Height and weight will be measured to 1 decimal place. Height and weight measured without shoes, and multiple layers of clothing.

For measuring weight, a scale with appropriate range and resolution should be used and must be placed on a stable, flat surface. (see the SoA).

8.2.1.1. Complete Physical Examinations

Physical examinations may be conducted by a physician, trained physician's assistant or nurse practitioner as acceptable and according to local regulation. A complete physical examination will include, at a minimum, assessments of general appearance; skin, head, eyes, ears, nose, and throat (HEENT), heart, lungs, breast (optional), abdomen, and external genitalia (optional), extremities, neurologic function, back, and lymph nodes.

8.2.1.2. Targeted Physical Examinations

Targeted physical examinations must be performed by a physician, trained physician's assistant or nurse practitioner as acceptable and according to local regulation and should include skin, heart, lungs, abdomen and examination of body systems where there are symptom complaints by the participant.

8.2.2. Vital Signs

Vital Signs will be measured with the participant in a sitting position after 5 minutes of rest and will include temperature, (oral tympanic, or axillary C°or F°) systolic blood pressure, (BP), diastolic BP, and pulse rate (PR), and will be measured at the nominal time points specified in the SoA per the following specifications:

BP and pulse rate measurements will be assessed with a completely automated device in a sitting position. Manual techniques will be used only if an automated device is not available. It is preferred that the same arm (preferably the dominant arm) be used throughout the study.

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

8.2.3. Chest X-Ray or Chest Computerized Tomography, (CT)(Screening only)

The study will accept a Chest x-ray examination (or chest CT) performed up to 12 weeks prior to screening if available. If no previous exam has been completed, a Chest X-ray (posterior-anterior and lateral views) or a CT scan may be performed at the discretion of the investigator however local guidelines should be followed. There should be no evidence of tuberculosis (TB), general infections, heart failure or malignancy if taken at screening or within the 12 weeks prior to screening and must be read by a qualified radiologist, or an expert of lung disease. Documentation of the official reading must be available in the source documentation.

8.2.4. Interferon Gamma Release Assay Tuberculin Test (Screening only)

Participants will be screened for infection with TB using a Interferon Gamma Release Assay (IGRA) test. The following are acceptable IGRA assays: QuantiFERON®-TB Gold test (QFT-G), QuantiFERON®-TB Gold In-Tube test (QFT-GIT) and T-SPOT® TB test. Site personnel should follow the processing and analyses steps based on the assay chosen.

Documentation of IGRA product used and the test result must be in the participant's source documentation

If the results of the IGRA are indeterminate, the test may be repeated, and if a negative result is obtained, enrollment may proceed. A positive test on repeat is exclusionary.

Participants with repeat indeterminate IGRA results may be enrolled after consultation with pulmonary or infectious disease specialist that determines low risk of infection (ie, participant would be acceptable for immunosuppressant (eg, anti-TNF) treatment without additional action).

Participants adequately treated (in the opinion of the appropriately qualified personnel - which may include a pulmonary or infectious disease specialist, or locally acceptable expert as defined by local guidelines) for latent and/or active tuberculosis infection may be enrolled regardless of IGRA results provided the treatment is well documented in the subject's medical records and/or source documentation prior to enrollment in the study. See Appendix 2.

8.2.5. HIV (Screening only)

All participants will be screened for human immunodeficiency virus, (HIV), tested at the site's local lab, or central lab if necessary. Note: a documented negative HIV test within 12 months of screening is acceptable and does not need to be repeated. See Appendix 2.

8.2.6. Hepatitis

All participants will be tested for Hepatitis B and C.

Participants must undergo testing for HBV surface antigen (HBsAg), HBV core antibody (HBcAb), and HBV surface antibody (HBsAb). This will be performed in CLIA (Clinical Laboratory Improvement Amendments) certified laboratory.

- Participants who are negative for all three serology tests may be eligible.
- Participants who are HBsAg positive will be excluded.
- HbsAg negative, HBcAb positive, and HBsAb negative participants are to be excluded from the study.
- Participants who are HBsAg negative, HBcAb negative and HBsAb positive may be eligible for the study. Partipants enrolling from Japan or other countries that require HBV DNA testing, the following is to be implemented:
    - Participants who are HBsAg negative, HBcAb negative and HBsAb positive and provide documentation of prior HBV vaccination, may be eligible for the study and will not require HBV DNA.
    - Participants who are HBsAg negative, HBcAb negative and HBsAb positive without documentation of prior HBV vaccination AND participants who are HBsAg negative, HBcAb positive, and HBsAb positive, will have HBV DNA assessed at screening. If HBV DNA is detectable, participants will be excluded. If HBV DNA is not detectable, participants may be eligible. If enrolled, HBV DNA will also be assessed at Week 12 and repeated every 12 Weeks and if detected during the study, participant will be discontinued from study participation.

For hepatitis C, all participants will undergo testing for hepatitis C antibody (HCVAb) during Screening. Participants with positive HCVAb tests will be reflex tested for HCV ribonucleic acid (hepatitis C virus, (HCV) RNA). Only participants with negative HCVAb or HCV RNA will be allowed to enroll in the study. See Appendix 2.

Hepatitis testing (HBsAg, HBcAb, HBsAb, HCV Ab, and HCV RNA) will be performed by the central laboratory. HBV DNA testing will be performed locally as per country requirement. Note: if needed, this testing can be done by the central lab.

8.2.7. Active Enteric Infections (Positive Stool culture and sensitivity) (Screening only)

All participants will be tested for the presence of known pathogenic bacterial, parasitic, fungal infections, including [redacted] Participants with clinically significant underlying disease will be screen-failed, so as not to predispose participants to infections. However, participants may be treated and re-tested or re-screened at the discretion of the investigator. See Appendix 2.

8.2.8. Electrocardiograms

12-Lead ECGs 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. All scheduled ECGs should be performed after the participant has rested quietly for at least 10 minutes in a supine position.

- Baseline ECG:

  For the pre-dose, DAY 1 ECG assessment, triplicate 12-lead ECGs will be obtained approximately 2-4 minutes apart; the average of the triplicate ECG measurements collected pre-dose on Day 1 will serve as each participant's baseline QTc value.

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

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

8.2.9. Injection Site Reactions

Each participant will be monitored for 60 minutes after their first dose of IP. After 60 minutes the injection site will be monitored for redness, swelling, or any type of inflammation and this should be recorded as an injection site reaction, if applicable on the appropriate CRF.

If the participant has a delayed reaction, (after they leave the investigative site) this should also be captured as an injection site reaction, on the adverse event CRF page. At the next dosing visits, (if there were no injection site reactions) the participant may be monitored for 30 minutes after dosing for the remaining visits per the investigator discretion.

8.2.10. Contraception Checks

For women of child bearing status, contraception will be discussed at every scheduled visit to ensure compliance.

8.2.11. 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.

Screening laboratory tests with abnormal results (if considered by the investigator to be transient and inconsistent with the participant's clinical condition) may be repeated within the screening window to confirm abnormal results. If results return to protocol acceptable limits within the screening period, the participant may enter the study.

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

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within the 3 month follow up period 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.

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

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

8.2.12. 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 the participant's receiving the investigational product. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) and at the end of the study. Pregnancy tests may also be repeated if requested by institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations. If a urine test cannot be confirmed as negative (eg, an

ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded if the serum pregnancy result is positive.

8.3. Adverse Events and Serious Adverse Events

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

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

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

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 participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving investigational product), through and including a minimum of 3 months after the last administration of the investigational product.

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

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving investigational product), through and including Visit 18.

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 AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be

reasonably related to the study intervention or study participation, the investigator must promptly report the SAE to Pfizer using the CT SAE Report Form.

8.3.1.1. Reporting SAEs to Pfizer Safety

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

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

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in Section 8.3.1, 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 7.3).

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

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

8.3.4. 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, institutional review boards (IRBs)/ethics committees (ECs), and investigators.

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

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

8.3.5. 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

Details of all pregnancies in female participants will be collected after the start of study intervention and until 3 months after the last dose of investigational product. If the participant completes the study up through Visit 18, the IP will be sufficiently washed out of the participant as the average half-life of the drug is approximately 20 days.

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

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

8.3.5.2. Exposure During Breastfeeding

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

8.3.5.3. 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.

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

8.3.6. 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.

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;
- The administration of an incorrect dosage;
- The administration of investigational product that has undergone temperature excursion from the specified storage range, unless it is determined by the sponsor that the investigational product under question is acceptable for use;
- The administration of expired investigational product.

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.**

8.3.7. Lack of Efficacy

Lack of efficacy is reportable to Pfizer Safety only if associated with an SAE.

8.4. Treatment of Overdose

For this study, when IP >450 mg is administered SC, within less than 2 weeks (between dosing) will be considered an overdose.

The Sponsor does not recommend specific treatment for an overdose. In the event of an overdose, the investigator/treating physician should:

1. Contact the medical monitor immediately.
2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities.
3. Obtain a blood sample for pharmacokinetic (PK) analysis as scheduled at the next scheduled visit 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 l, evaluation of the participant.

8.5. Pharmacokinetics

8.5.1. Serum for Analysis of PF-06480605

Blood samples ([redacted]) to provide approximately [redacted] serum for PK analysis will be collected into appropriately labeled tubes 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 PK samples at the exact nominal time relative to dosing.

- Any *scheduled* pre-dose collection (ie, C_{trough}) obtained post dose **or** not collected, will be captured as a protocol deviation even if results are deemed evaluable.

Details regarding the collection, processing, storage and shipping of the blood samples will be provided in the lab manual. The samples must be processed and shipped as indicated to maintain sample integrity. Any deviations from the processing steps (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.

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

As part of understanding the PK of the IP, samples may be used for further characterization and/or evaluation of the bioanalytical method. These data will be used for internal exploratory purposes and will not be included in the clinical report. Samples collected for this purpose will be retained in accordance with local regulations and, if not used within this timeframe, will be destroyed.

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

8.5.2. Analysis of Anti-PF-06480605 Antibodies and Neutralizing Anti-PF-06480605 Antibodies

Blood samples ([redacted]) to provide [redacted] aliquots of approximately [redacted] of serum each for ADA and NAb analyses will be collected into appropriately labeled tubes with no preservative (no anticoagulant and no serum separator gel may be used) at times specified in the SoA.

Details regarding the collection, processing, storage and shipping of the blood samples will be provided in the lab manual. The samples must be processed and shipped as indicated to maintain sample integrity. Any deviations from the processing steps (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.

Samples will be analyzed using validated analytical methods in compliance with Pfizer SOPs. Samples determined to be positive for ADA may be further characterized for NAb.

As part of understanding the immunogenicity of PF-06480605, samples may be used for additional characterization of an observed immunogenicity response and/or evaluation of the bioanalytical method. These data will be used for internal exploratory purposes and will not be included in the clinical study report (CSR). Samples collected for this purpose will be retained in accordance to local regulations and if not used within this timeframe will be destroyed.

8.5.3. Exploratory Immunogenicity Peripheral Blood Mononuclear Cell (PBMC) Samples

Blood samples (approximately [redacted] will be collected in sodium heparin tubes and will be transferred into appropriate labeled and prepared Accuspin tubes for preparation of cells for exploratory [redacted] immunogenicity analyses at the times specified in the SoA.

Detailed collection, processing, storage, and shipment instructions are provided in the lab manual.

8.5.4. Exploratory Analysis of ADA Epitopes/Affinities

Blood samples ([redacted]) to provide approximately [redacted] serum for exploratory immunogenicity characterization will be collected into appropriate labeled plastic silica clot activator tubes with no preservative (no anticoagulant and no serum separator gel may be used) at the times specified in the SoA.

Detailed collection, processing, storage, and shipment instructions are provided in the lab manual.

Samples will be analyzed using an exploratory analytical method.

Samples collected for this purpose will be retained in accordance to local regulations and if not used within this timeframe, will be destroyed.

8.6. Pharmacodynamics

Please see (Section 8.8).

8.7. Genetics

8.7.1. Specified Genetics

Genetics (specified analyses) are not evaluated in this study.

8.7.2. Banked Biospecimens for Genetics

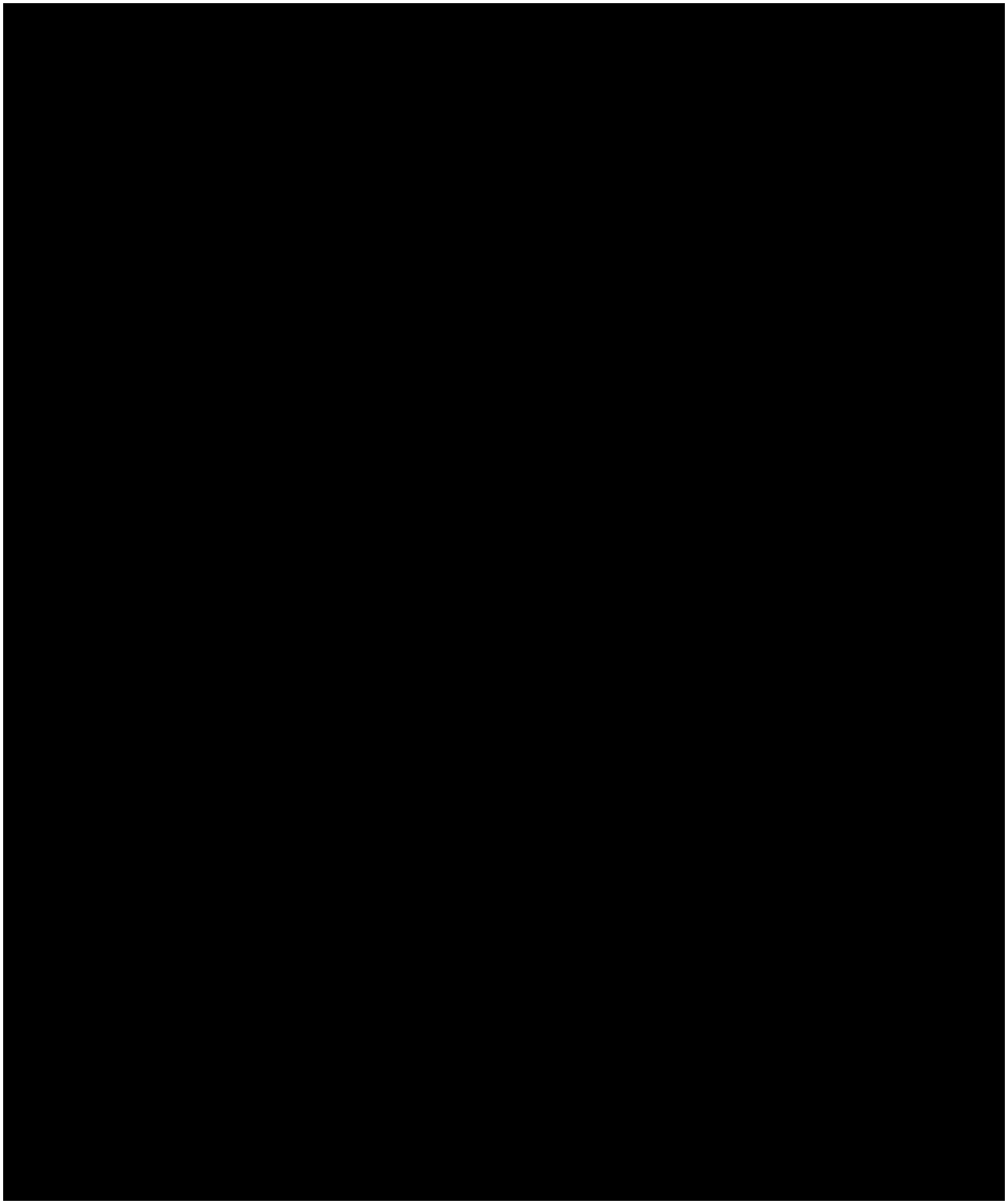
[redacted]

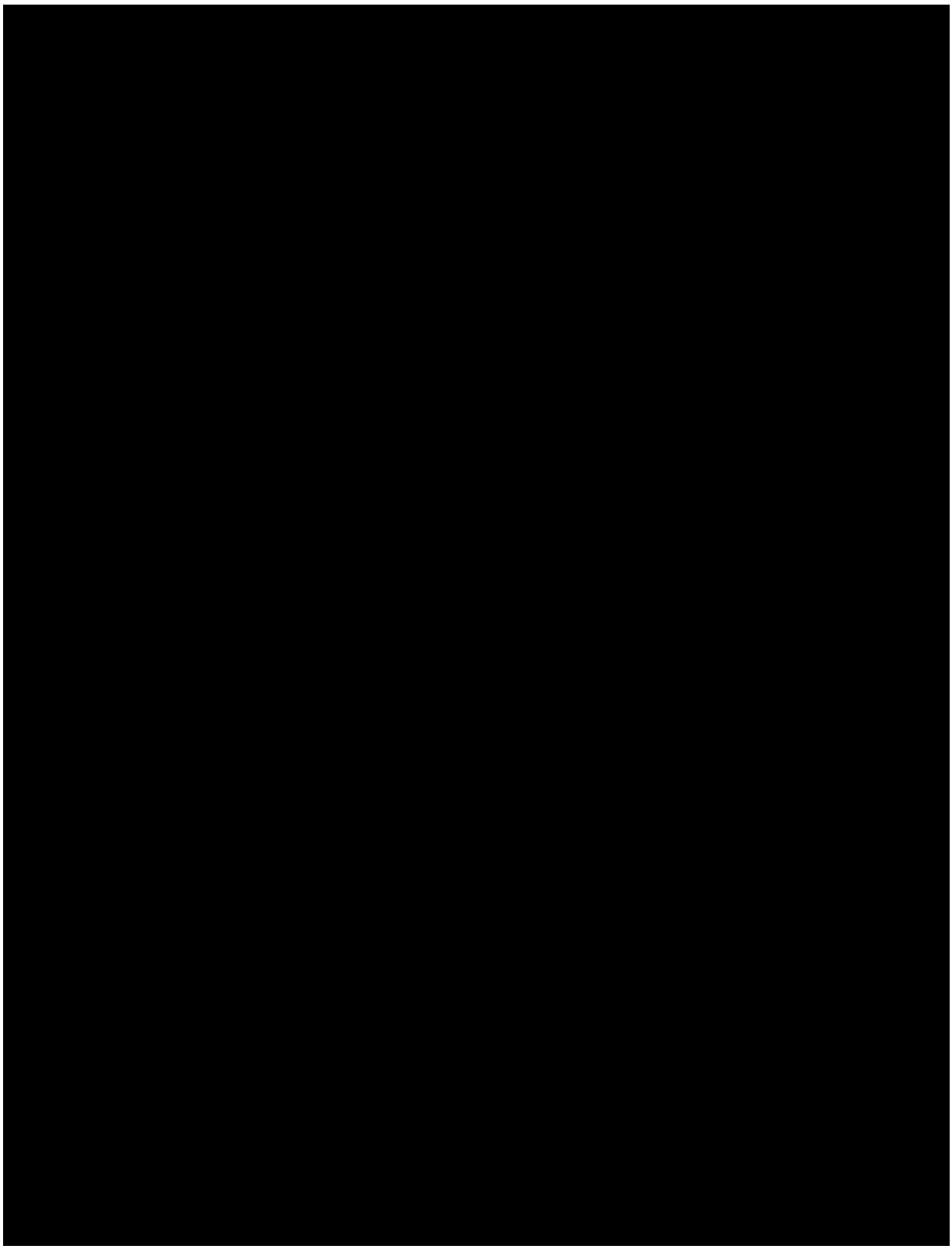
[redacted]

Unless prohibited by local regulations or IRB/EC decision, participants will be asked to indicate on the consent document whether they will allow their banked biospecimens to also be used to design and conduct research in order to gain a further understanding of other diseases and to advance science, including development of other medicines for patients. This component of the sampling banking is optional for participants; they may still participate in the study even if they do not agree to the additional research on their banked biospecimens. The optional additional research does not require the collection of any further samples.

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

8.8. Biomarkers





[redacted]

8.9. Health Economics

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

9. STATISTICAL CONSIDERATIONS

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

9.1. Estimands and Statistical Hypotheses

9.1.1. Estimands

The primary estimand for the primary endpoint of clinical remission at Week 14 will be the population average treatment difference between PF-06480605 and placebo in the proportion of participants with moderate to severe ulcerative colitis who achieve the binary remission endpoint without discontinuing treatment prior to the Week 12 Visit. If a study participant discontinues treatment prior to Week 12 Visit but did not attend the early study

withdrawal visit, then the participant will be considered as a non-responder for the primary analysis.

Specifically, if a study participant experienced any event leading to early withdrawal and did not attend the early withdrawal visit or missed the visit for reasons not associated with COVID-19, the missing data will be imputed with non–responder for the binary endpoints.

Estimands for other binary endpoints are similarly defined as for the primary endpoint. The intercurrent events will be handled in the similar way to the primary estimand (Section 3). No estimands are defined for PK, biomarkers, immunogenicity, safety endpoints and tertiary endpoints.

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

9.2. Sample Size Determination

Assuming a placebo remission rate of 6%, at least 80% power, a one-sided type-I error α=0.05, the true effect of PF-06480605 with a remission rate of 28% (ie, a placebo-adjusted effect of 22%) at the highest dose, and a 6:4:3:3 allocation ratio in the order of PF-06480605 450 mg, 150 mg, 50 mg, and placebo, a total of approximate 216 participants will need to complete the induction period. Assuming an approximately 10% dropout rate in the induction period, approximately a total of 240 participants (ie, ~90 in the 450 mg dose group, ~60 in the 150 mg dose group, ~45 in both the 50 mg dose group and the placebo group) will be enrolled in this study. This sample size plan will also provide at least 80% power to detect a placebo-adjusted treatment effect of 16% without multiplicity adjustment for the high dose (450 mg) group.

9.3. Populations for Analysis

For purposes of analysis, the following populations are defined:

Defined Population for Analysis	Description
Safety Analysis Population	All participants who take at least 1 dose of investigational product. Participants will be analyzed according to the product they received.
Evaluable Population Intention-To-Treat (ITT)	All participants randomly assigned to investigational product and who take at least 1 dose of investigational product in Induction Period. Participants will be analyzed according to the product they were randomized.
Evaluable Population modified Intention-To-Treat (mITT)	All participants randomly assigned to investigational product and who take at least 1 dose of investigational product in the Chronic Period. Participants will be analyzed according to the treatment sequence they were randomized.
PK Concentration Population	All participants randomly assigned to investigational product and who take at least 1 dose of PF-06480605 and in whom at least 1 concentration value is reported.
Biomarker Analysis Population	All participants randomly assigned to investigational product and who take at least 1 dose of PF-06480605 and in whom at least 1 measurement of biomarker of interest is reported.
Immunogenicity Analysis Population	All participants randomly assigned to investigational product and who take at least 1 dose of PF-06480605 and in whom at least 1 post-treatment anti-drug (PF-06480605) antibody determination is reported.

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

Endpoint	Statistical Analysis Methods
Primary	• The proportions responding and the risk difference between the treatment arms and the placebo arm will be analyzed using an unconditional exact method: risk differences and corresponding 2 sided unconditional exact 90% confidence intervals will be computed using the Chan and Zhang[24] method. The confidence intervals for one sample proportions will be based on Blyth Still Casella. Details will be documented in the SAP. If a study participant discontinued treatment prior to Week 12 Visit and didn't attend the early withdrawal visit, the participant will be considered as a non-responder for the binary remission endpoint at Week 14 for the primary analysis unless reason for missed visit was due to COVID-19.
Secondary	• Secondary binary endpoints will be analyzed in the similar way as the primary endpoint. Secondary continuous endpoints will be analyzed descriptively and/or using longitudinal mixed models. Details will be documented in the SAP.
Tertiary	• Analysis methods for tertiary will be described in the SAP finalized before database lock.

9.4.2. Safety Analyses

All safety analyses will be performed on the safety population.

Endpoint	Statistical Analysis Methods
Primary	• Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate. All safety endpoints will be listed and summarized according to Pfizer Data Standards. • Categorical outcomes (eg, AEs) will be summarized by participant counts and percentages. • Continuous outcome (eg, BP, heart rate, ECG intervals, etc.) will be summarized using N, mean, median, standard deviation, etc. • Laboratory data, ECG intervals, and vital signs crossing the thresholds of clinical concern will be tabulated according to Pfizer Data Standards.

9.4.2.1. Adverse Events

All safety endpoints (including AEs, SAEs, withdrawals due to AEs or SAEs) will be listed and summarized according to Pfizer Data Standards.

9.4.2.2. Electrocardiogram Analyses

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

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

Safety QTc Assessment

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

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

9.4.3. Other Analyses

9.4.3.1. Pharmacokinetic Analysis

PK concentrations will be summarized and presented with summary statistics. A population PK model may be developed for the purpose of estimating PK parameters. Any population PK model developed to characterize the PK data will be reported separately. Data permitting, the relationship between exposure and clinical responses (efficacy and safety) during 12 weeks of treatment in participants with moderate to severe active UC may be explored using either observed or modeled exposures. Any population analyses conducted will not be part of the clinical study report (CSR) and may be reported separately.

[redacted]

9.4.3.3. PK/PD Unblinding Plan

A PK/PD unblinding plan approved by the clinical lead, clinical pharmacology lead, and statistical lead will be in place to describe the procedures to be employed in safeguarding the study blind for members of the study team. These procedures will be in accordance with applicable Pfizer standard operating procedures (SOPs) for releasing randomization codes and breaking the study blind. Under this plan a group of statisticians, PK/PD data provider, PK/PD analyst and PK/PD support would be unblinded in order to initiate the building of

statistical models of the PK, dose/response as well as exposure/response analysis models and conduct associated simulations. The aim of this work would be to facilitate a fuller interpretation of the study upon completion (or at appropriate interim milestone if any). This group will not serve on the study team during the period of early unblinding. The unblinding may occur after the last participant has been randomized. The details of the procedures will be described in the PK/PD Unblinding Plan for Modeling and Simulation for Study B7541007 which will be finalized prior to the start of the PK/PD unblinding.

9.4.3.4. Immunogenicity Analysis

Overall incidence of development of ADA and of NAb will be reported along with relationships of incidence with respect to time. Both continuous endpoints and categorical endpoints (ie, positive and negative) will be reported for the ADA and NAb assays by time points samples were collected. Data permitting, the impact of ADA and NAb on PK, PD, safety and efficacy profiles may be explored.

Additional immunogenicity assessments, including ADA epitopes and affinities are exploratory in nature and may not be conducted or reported.

9.5. Interim Analyses

Two interim analyses may be conducted for the study. Both interim analyses will be conducted by an unblinded team independent of the study team and results from these analyses may be reviewed by an internal review committee (IRC). No members of the study team will be part of the unblinded team or IRC.

The first analysis will be conducted when 100% of participants have completed or have the opportunity to complete the Week 14 Visit. Each SC induction dose group of PF-06480605 (450 mg, 150 mg and 50 mg) will be compared with the placebo group in the primary endpoint of Week 14 remission. Interim analysis results may be used for internal business decisions regarding future study planning.

The second interim analysis may be conducted when all participants have completed or have the opportunity to complete the induction period and approximately 100% of them have completed or have the opportunity to complete at least 6 months of chronic therapy. Interim analysis results may be used for internal decisions regarding future study planning.

9.5.1. Data Monitoring Committee

This study will use an internal review committee (IRC). An external data monitoring committee will not be utilized. An IRC charter will be developed to govern the details of any IRC operations.

The IRC will be responsible for ongoing monitoring of safety of participants in the study according to the IRC charter. Members of the IRC will be qualified and experienced in reviewing and interpreting clinical study data. The IRC members will be independent of the study team, and unblinded to treatment. Recommendations may be made to alter the current study. The recommendations made by the IRC will be forwarded to the appropriate

authorized Pfizer personnel for review and final decision. Pfizer will communicate such decisions, which may include summaries of aggregate analyses of safety data, to regulatory authorities, investigators, as appropriate. Details of the IRC are described in the IRC charter.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

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

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

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

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

The investigator will be responsible for the following:

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

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

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

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

10.1.3. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant 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 participant's personal data.

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

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

The investigator further must ensure that each study participant 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. Participants who are rescreened are required to sign a new ICD and will receive a new screening number.

The ICD will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorized designee will explain to each participant the objectives of the exploratory research. 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. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate in this optional research will not provide this separate signature.

10.1.4. Data Protection

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

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

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

10.1.5. Dissemination of Clinical Study Data

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

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

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in 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.

10.1.6. Data Quality Assurance

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

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

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

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

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

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

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

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

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

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

10.1.7. Source Documents

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

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

Definition of what constitutes source data can be found in the monitoring plan.

10.1.8. Study and Site Closure

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

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

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

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

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

10.1.9. Publication Policy

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

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

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

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

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

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

10.1.10. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the in the 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 participant's participation in the study. The contact number can also be used by investigator

staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the participant directly, and if a participant calls that number, he or she will be directed back to the investigator site.

10.2. Appendix 2: Clinical Laboratory Tests

The following safety laboratory tests will be performed at times defined in the 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 5. Protocol Required Safety Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs) PT/INR/PTT	BUN/urea and creatinine Glucose Calcium Sodium Potassium Chloride AST, ALT Total bilirubin Direct Bilirubin[a] Alkaline phosphatase Uric acid Albumin Total protein Creatine Kinase (CK) CK fractionation[b]	pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Microscopy[c] Urine Pregnancy	Serum or urine pregnancy test (β-hCG)[d] Urine drug screen[d] FSH[e] HBV: HBsAg,HBV surface antigen, HBcAB, HBVcore antibody, HBV surface antibody, HBsAb, HBV DNA, HCV RNA Hepatitis C antibody, HCVAb HIV QFT-G or other IGRA Stool Sample to detect enteric pathogens, [redacted]

Abbreviations: Abs = absolute; ALT = alanine aminotransferase; AST = aspartate aminotransferase; β-hCG = beta-human chorionic gonadotropin; BUN = blood urea nitrogen; FSH = follicle-stimulating hormone; IGRA=interferon gamma release assay; qual = qualitative; RBC = red blood cell; PT=prothrombin time; PTT=partial prothrombin time; QFT-G=quantiferon gold; WBC = white blood cell.

a. Only if total bilirubin is elevated.
b. Only if CK is elevated.
c. Only if urine dipstick is positive for blood, protein, nitrites, or leukocyte esterase.
d. Serum or urine β-hCG for female participants of childbearing potential, according to the SoA. Urine Drug Screen, please see lab manual for details.
e. For confirmation of postmenopausal status only in female participants who have been amenorrheic for at least 12 consecutive months.

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.

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

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

10.3.2. Definition of SAE

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

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

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

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

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.
- 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) Serious Adverse Event (SAE) Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious adverse events (AEs); and (3) exposure to the

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). Note: Include all SAEs associated with exposure during pregnancy or breastfeeding. Include all AEs/SAEs associated with occupational exposure.

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

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

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

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

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

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the investigator's brochure (IB) and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the 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.
- 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

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

10.4.2. Female Participant Reproductive Inclusion Criteria

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

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

  OR

- Is a WOCBP and using an acceptable contraceptive method as described below during the intervention period and (for a minimum of 3 months after the last dose of investigational product). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

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

10.4.3. Woman of Childbearing Potential (WOCBP)

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

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

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:

   - Documented hysterectomy;
   - Documented bilateral salpingectomy;
   - Documented bilateral oophorectomy.

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

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

2. Postmenopausal female:

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

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

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

10.4.4. Contraception Methods

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

2. Intrauterine device (IUD).

3. Intrauterine hormone-releasing system (IUS).

4. Bilateral tubal occlusion.

5. Vasectomized partner:

   - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the 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;

- Injectable.

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.

9. Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.

10. Male or female condom with or without spermicide.

11. Cervical cap, diaphragm, or sponge with spermicide.

12. 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 exposure during pregnancy (EDP) occurs if:

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

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

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

If a participant or participant's partner becomes or is found to be pregnant during the participant's treatment with the investigational product, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a 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).

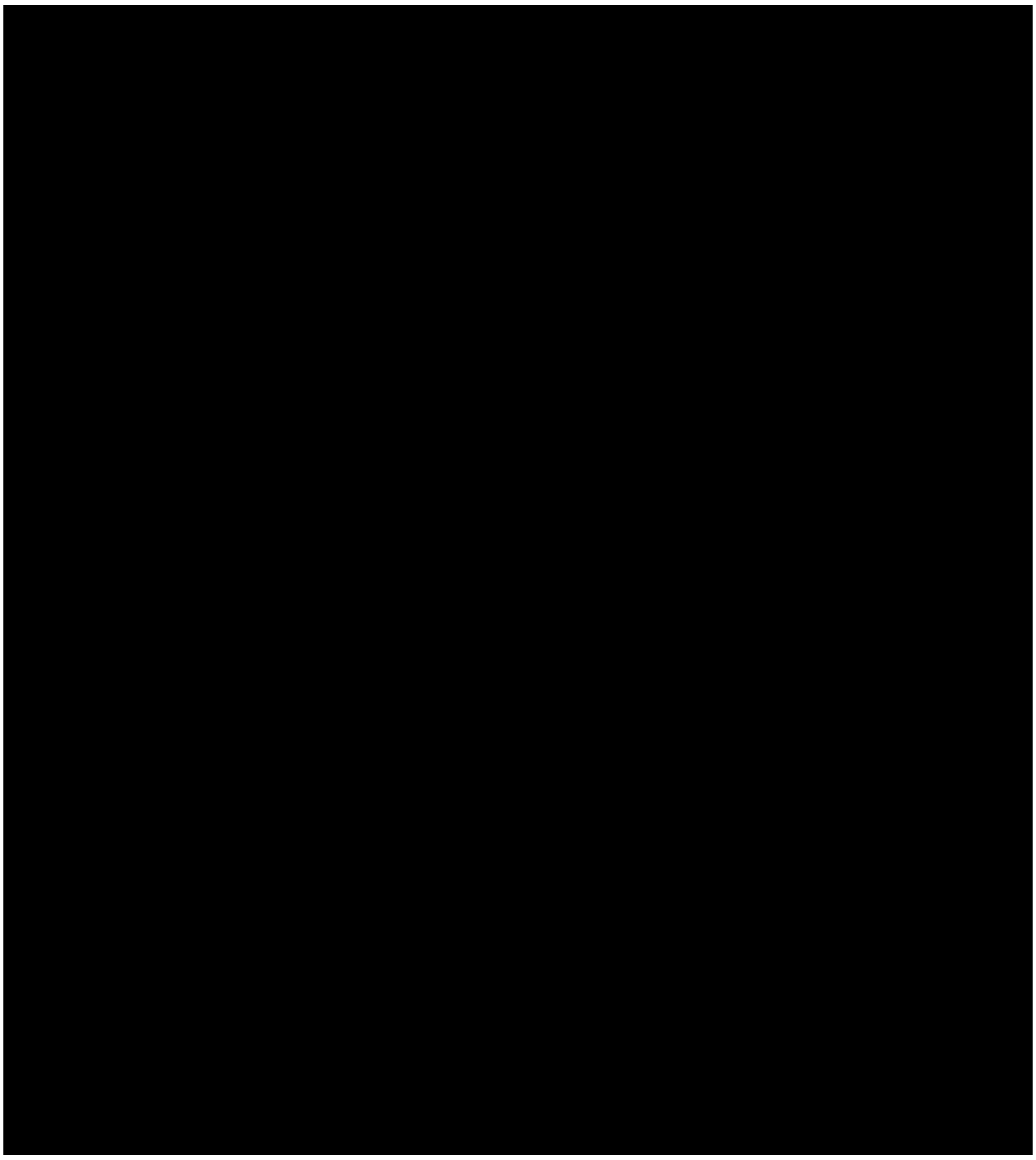
Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP supplemental 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 preprocedural 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.



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

Potential Cases of Drug-Induced Liver Injury

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

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

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

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

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

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

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

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor. The participant should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

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

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

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

10.7. Appendix 7: ECG Findings of Potential Clinical Concern

ECG Findings That May Qualify as Adverse Events (AEs)
• 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. • New-onset atrial flutter or fibrillation, with controlled ventricular response rate: ie, rate <120 bpm. • New-onset type I second-degree (Wenckebach) AV block of >30 seconds' duration. • Frequent premature ventricular complexes (PVCs), triplets, or short intervals (<30 seconds) of consecutive ventricular complexes.
ECG Findings That May Qualify as Serious Adverse Events (SAEs)

• 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 patients in sinus rhythm, with documented periods of asystole ≥3.0 seconds or any escape rate <40 bpm, or with an escape rhythm that is below the AV node;
  • In awake, symptom-free patients with atrial fibrillation and bradycardia with 1 or more pauses of at least 5 seconds or longer;
  • Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120 bpm.
• Sustained supraventricular tachycardia (rate >120 bpm) ("sustained" = short duration with relevant symptoms or lasting >1 minute).

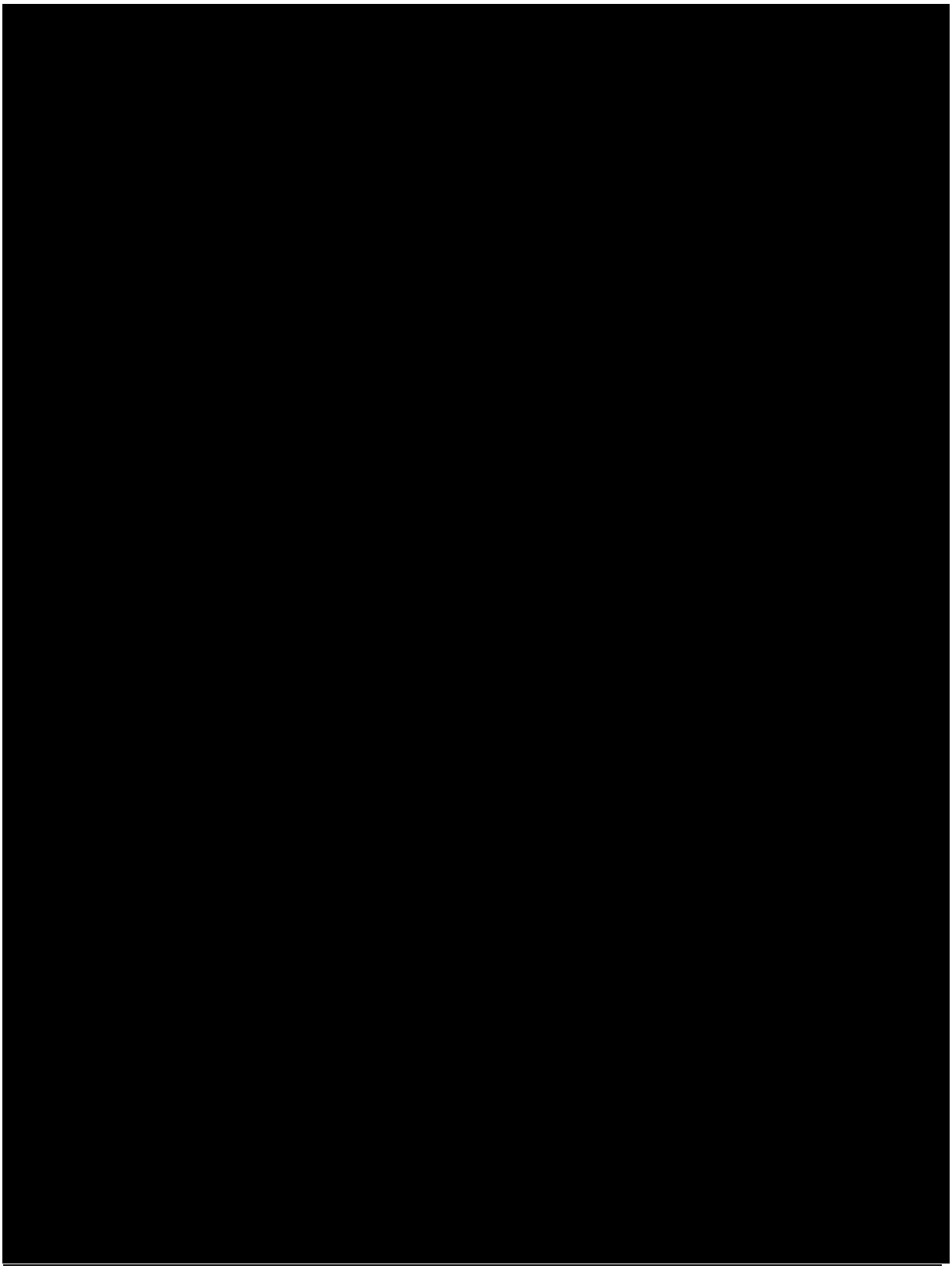
- Ventricular rhythms >30 seconds' duration, including idioventricular rhythm (rate <40 bpm), accelerated idioventricular rhythm (40< x <100), and monomorphic/polymorphic ventricular tachycardia >100 bpm (such as torsades de pointes).
- Type II second-degree (Mobitz II) AV block.
- Complete (third-degree) heart block.

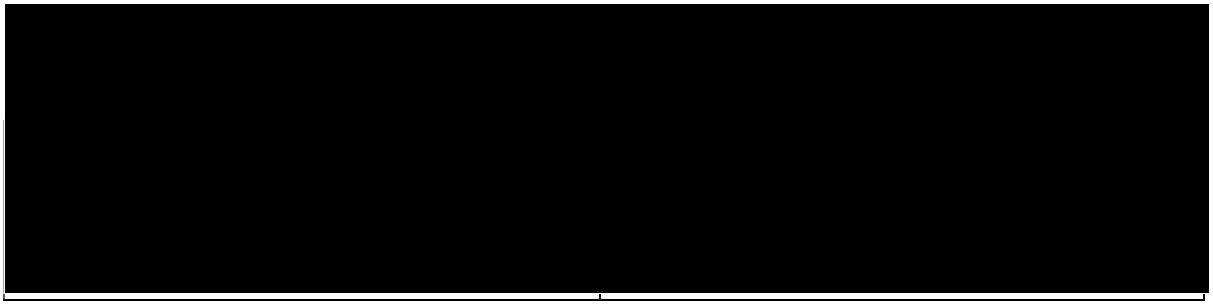
ECG Findings That Qualify as Serious Adverse Events

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

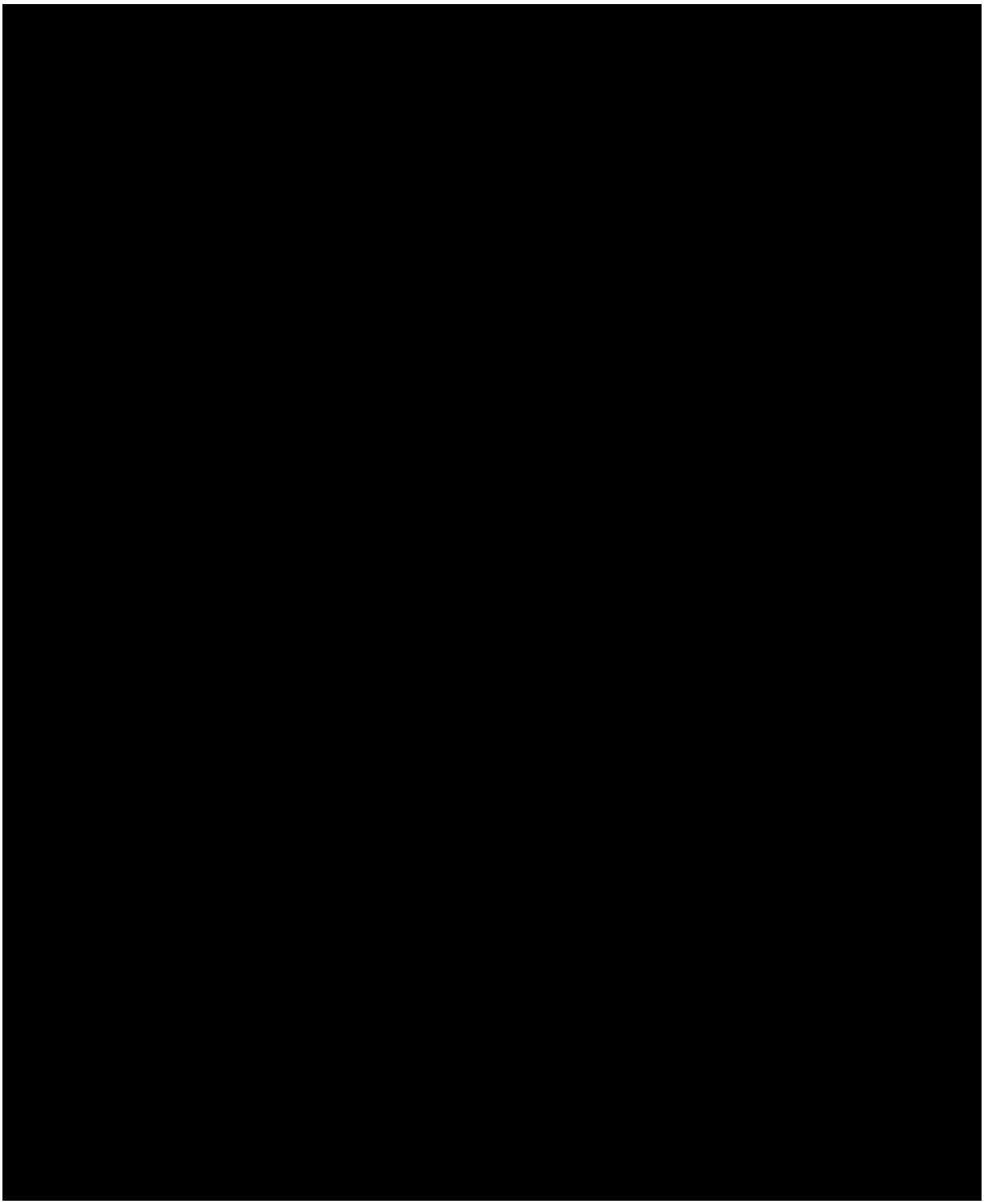
The enumerated list of major events of potential clinical concern are recommended as "alerts" or notifications from the core ECG laboratory to the investigator and Pfizer study team, and not to be considered as all inclusive of what to be reported as AEs/SAEs.

10.8. Appendix 8: Prohibited Concomitant Medications





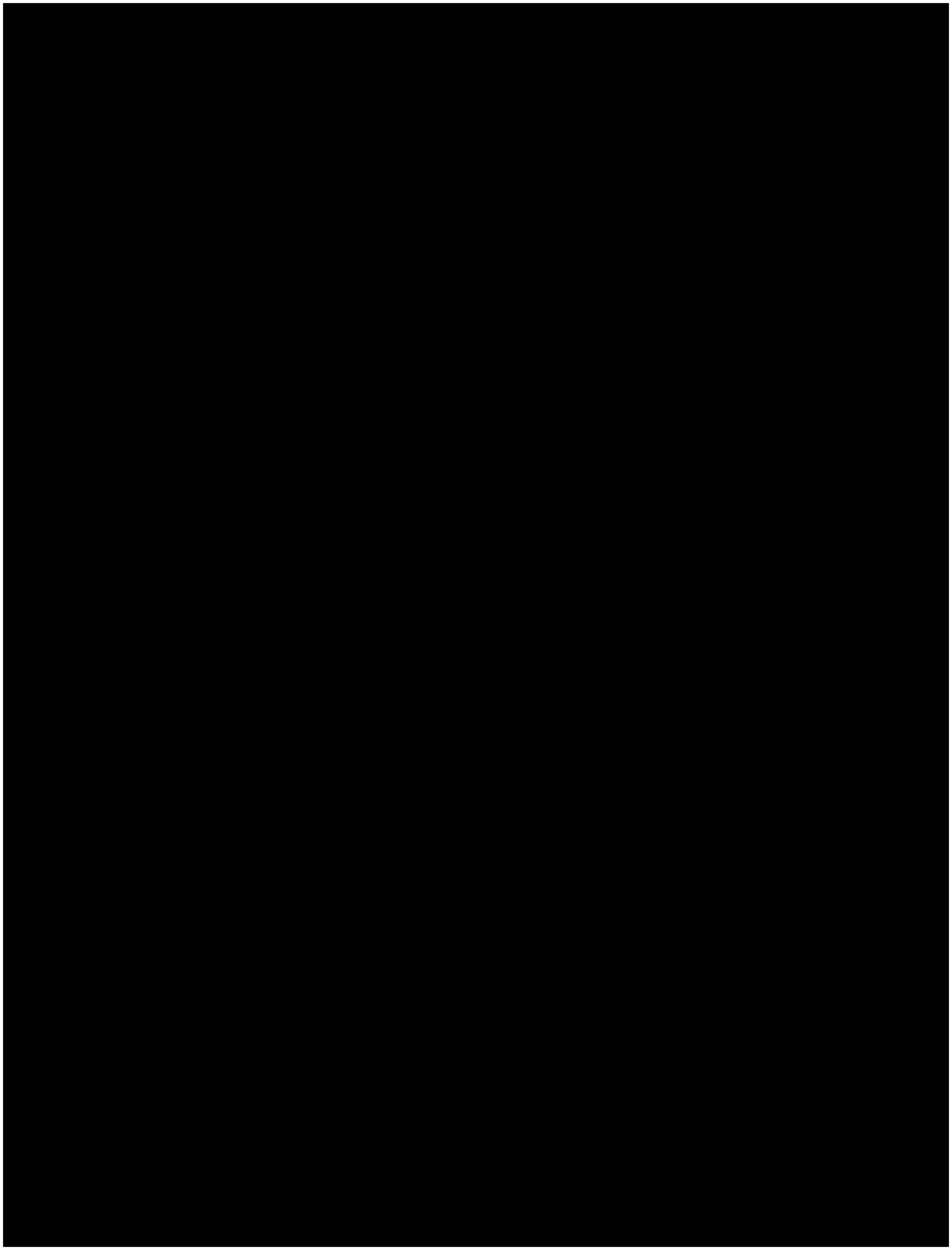
10.9. Appendix 9: Permitted Concomitant Medications for UC

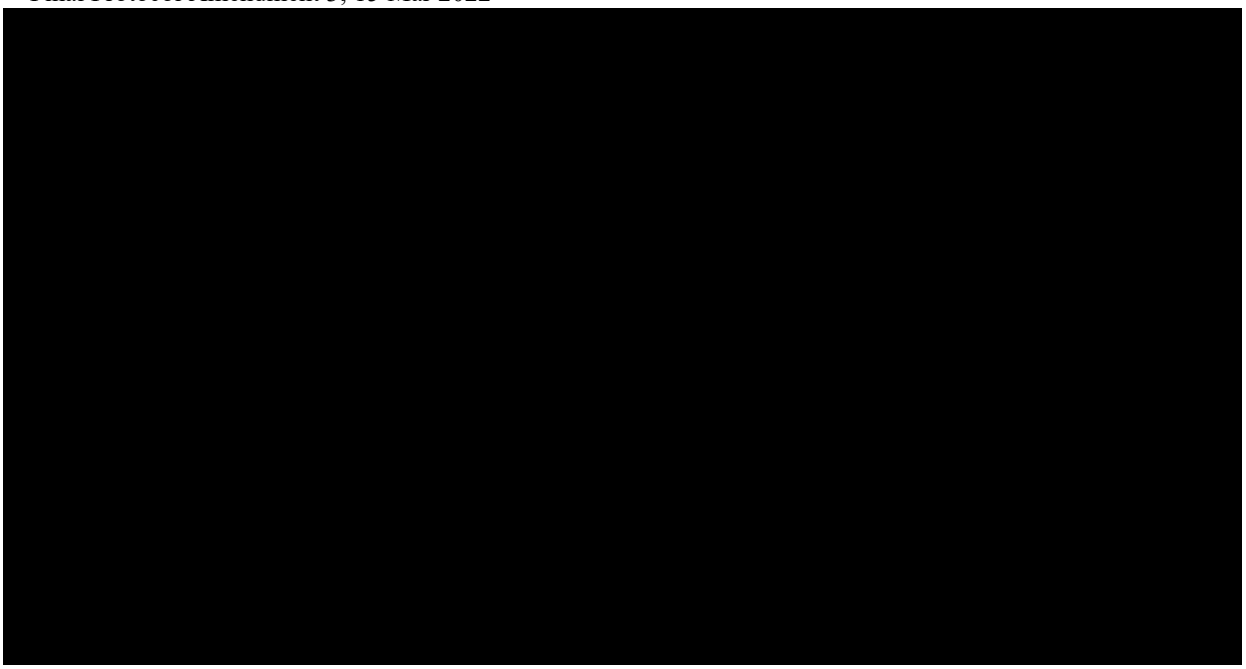


10.10. Appendix 10: Mayo Scoring System for Assessment of Ulcerative Colitis

Grade	Bowel Frequency	Rectal Bleeding	Physician's Global Assessment	Endoscopy/Sigmoidoscopy Finding
0	Normal number of stools per day for this patient	No blood seen	Normal	Normal or inactive disease
1	1 or 2 more stools than normal	Streaks of blood with stool less than half the time	Mild disease	Mild disease (erythema, decreased vascular pattern)
2	3 or 4 more stools than normal	Obvious blood with stool most of the time	Moderate disease	Moderate disease (marked erythema, absent vascular pattern, friability, erosions)
3	5 or more stools than normal	Blood alone passed	Severe disease	Severe disease (spontaneous bleeding, ulceration)

Note: The Modified Mayo Disease Activity Index (MMDAI) was modified by the deletion of "friability" from an endoscopy score equal to 1. Presence or absence of friability will also be assessed.





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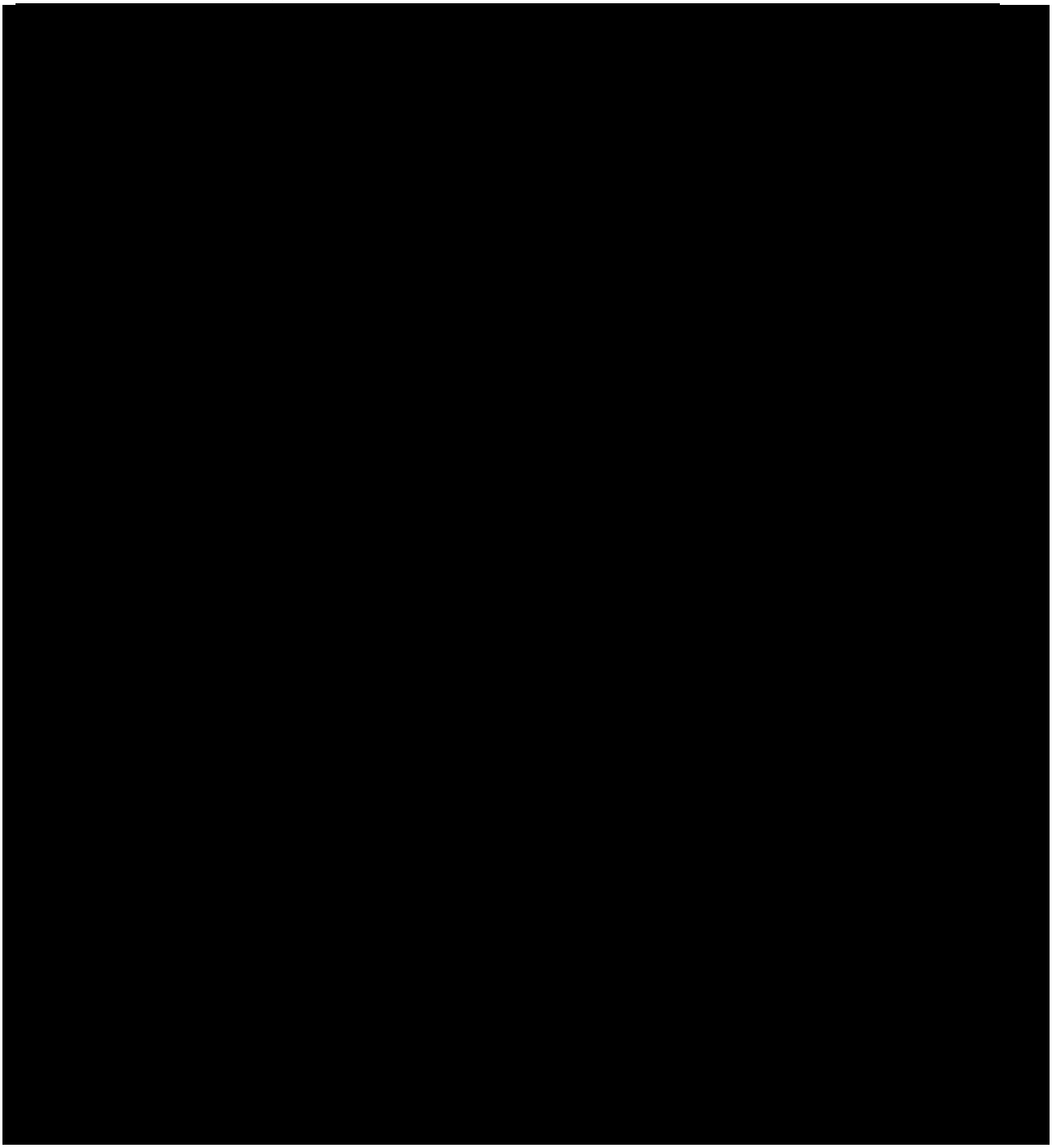

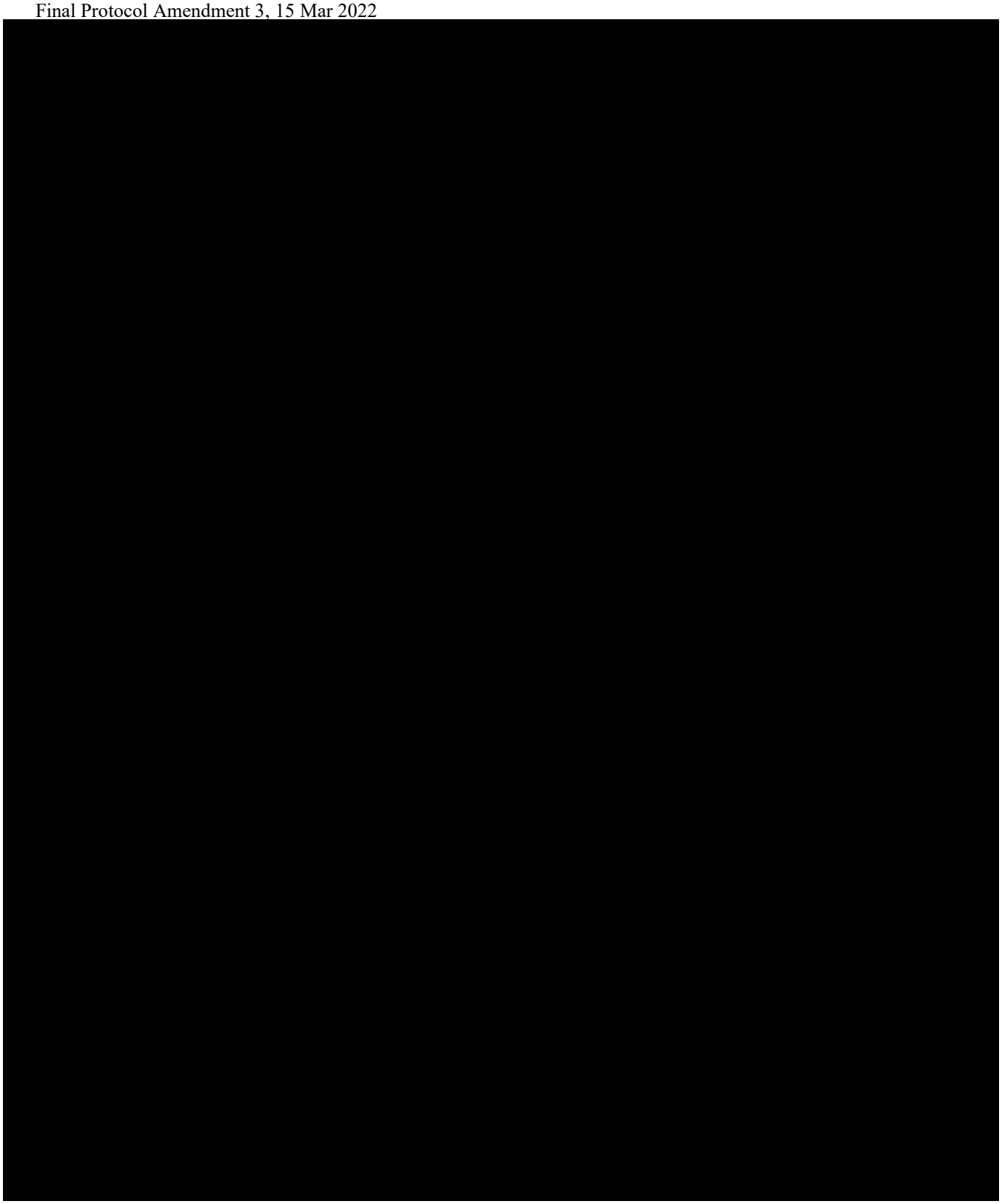

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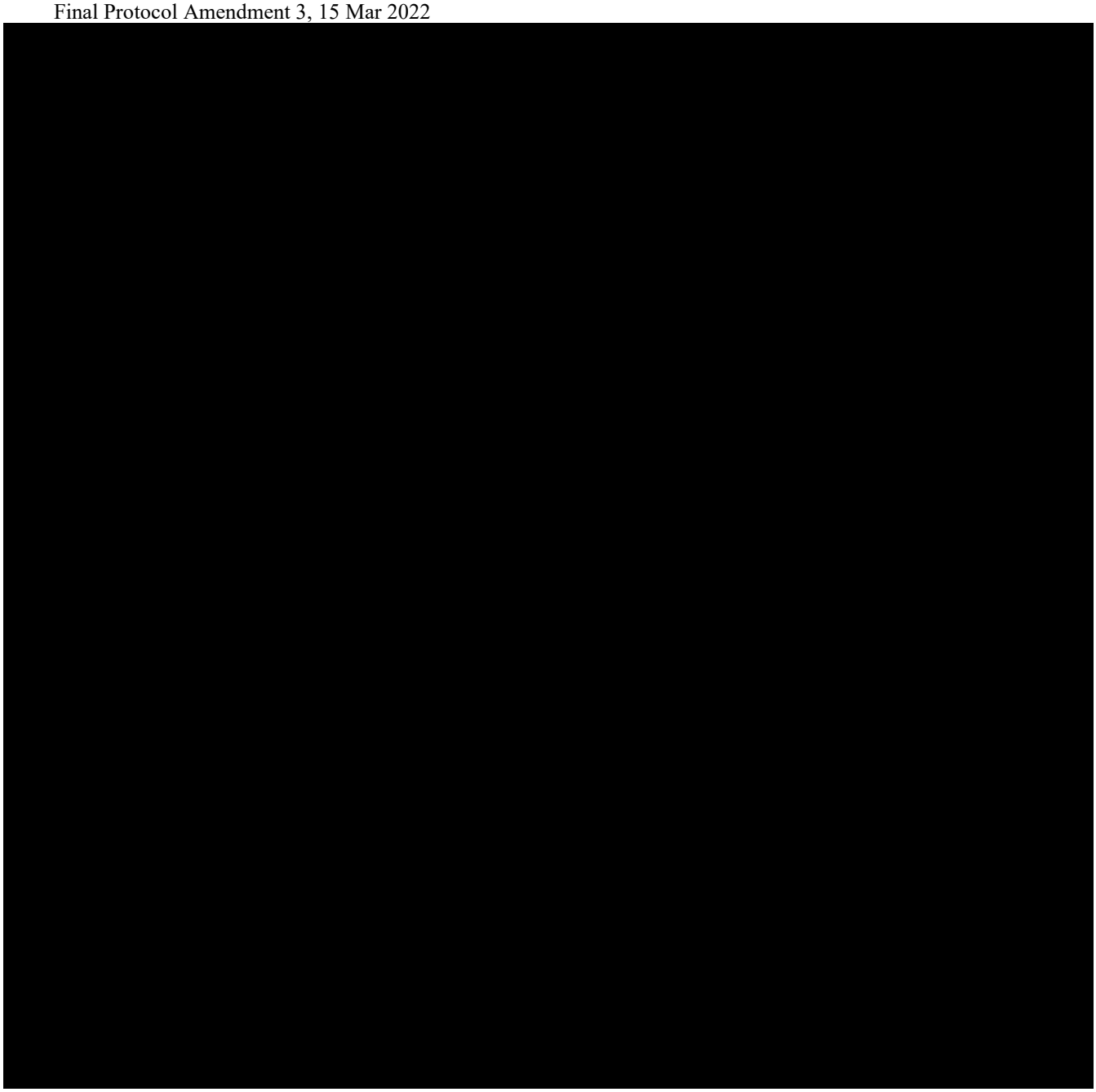

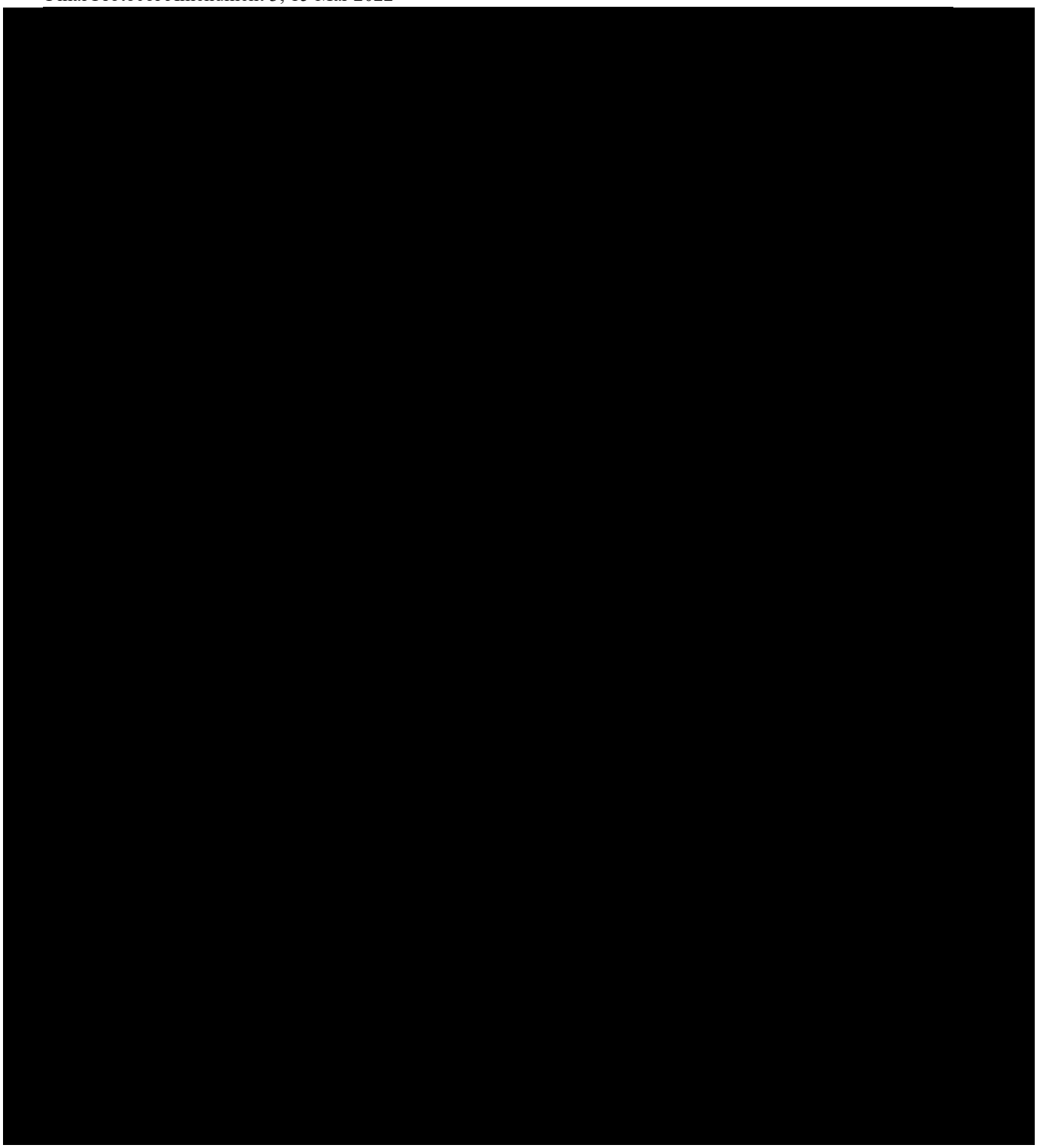

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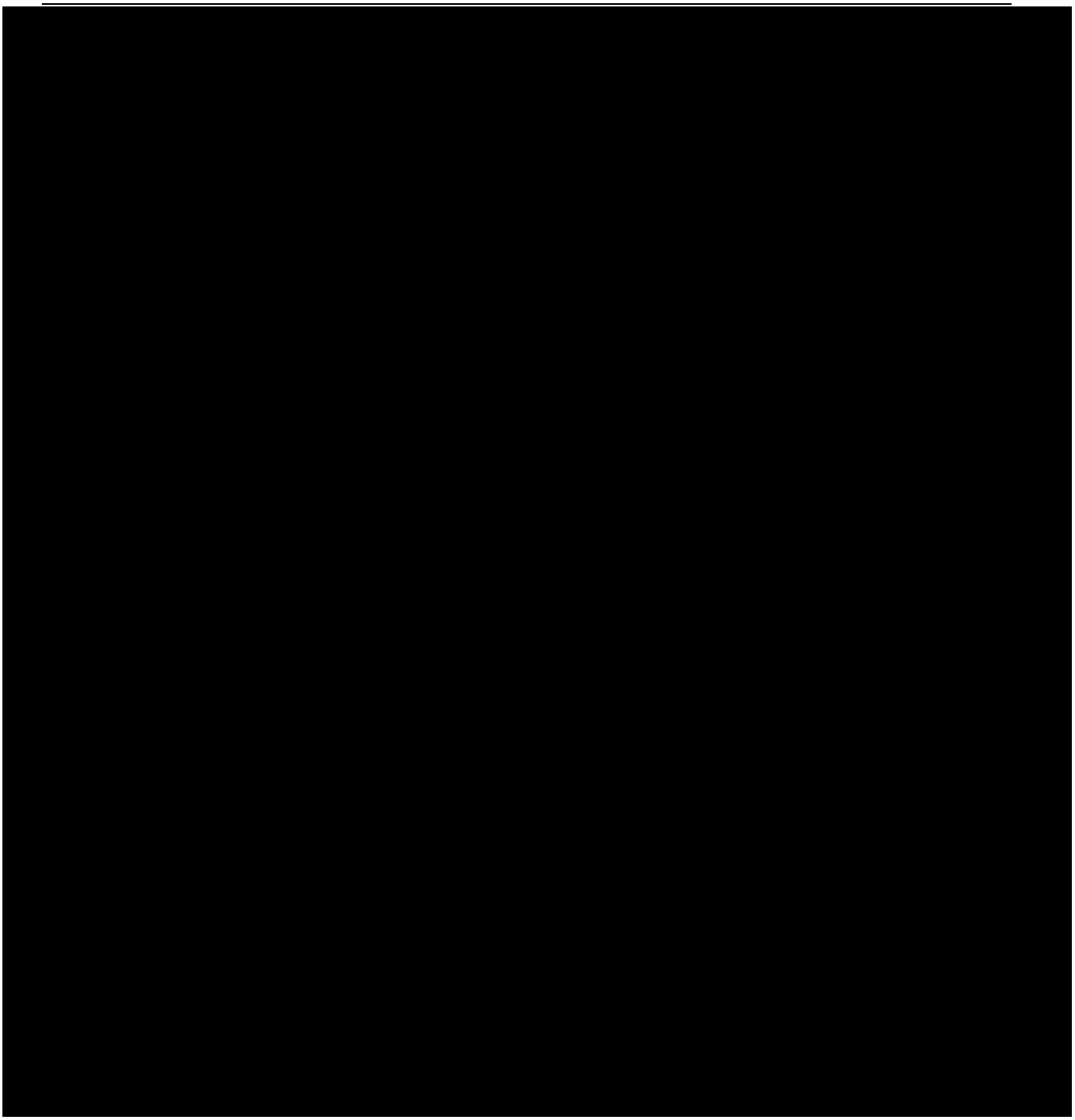

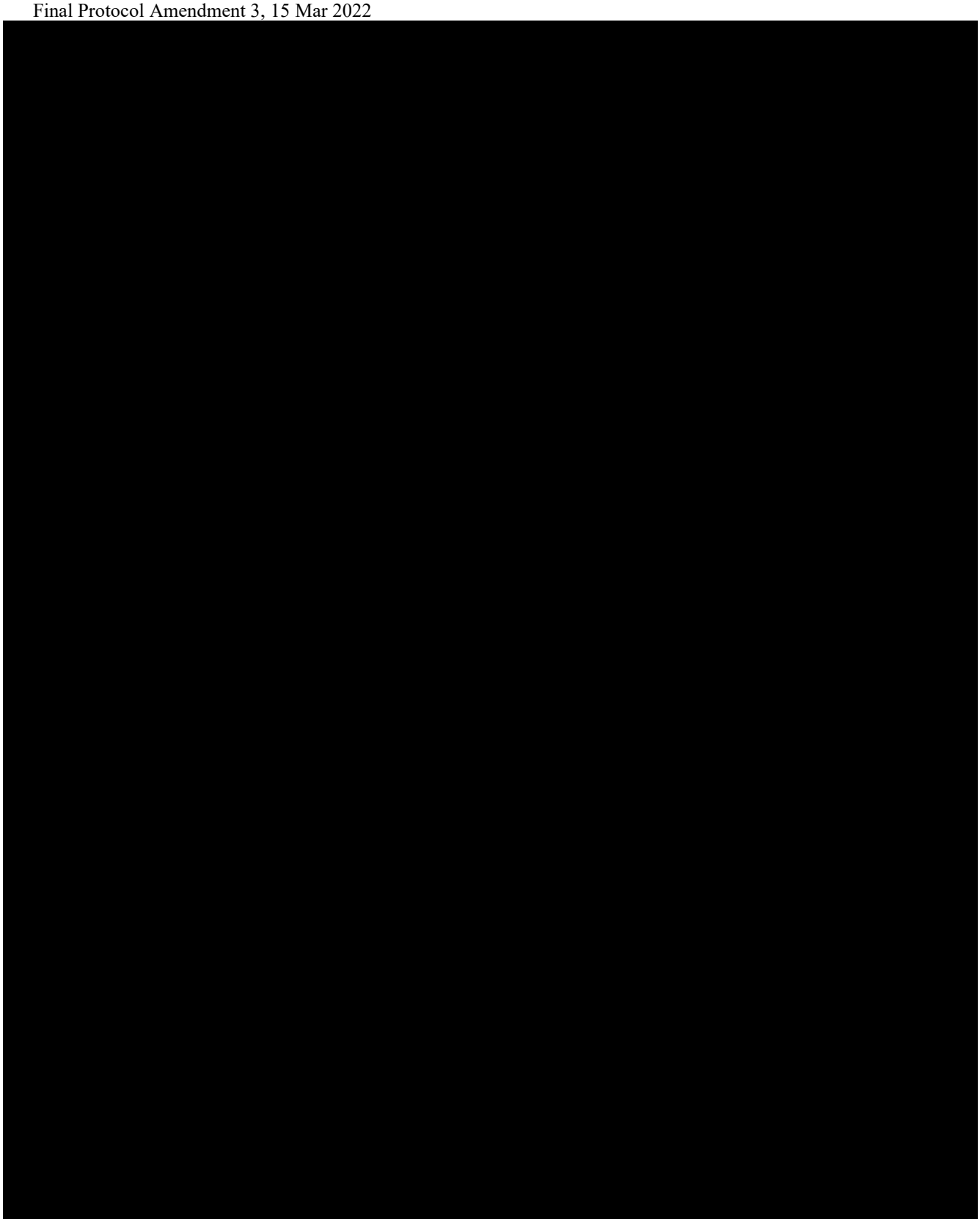

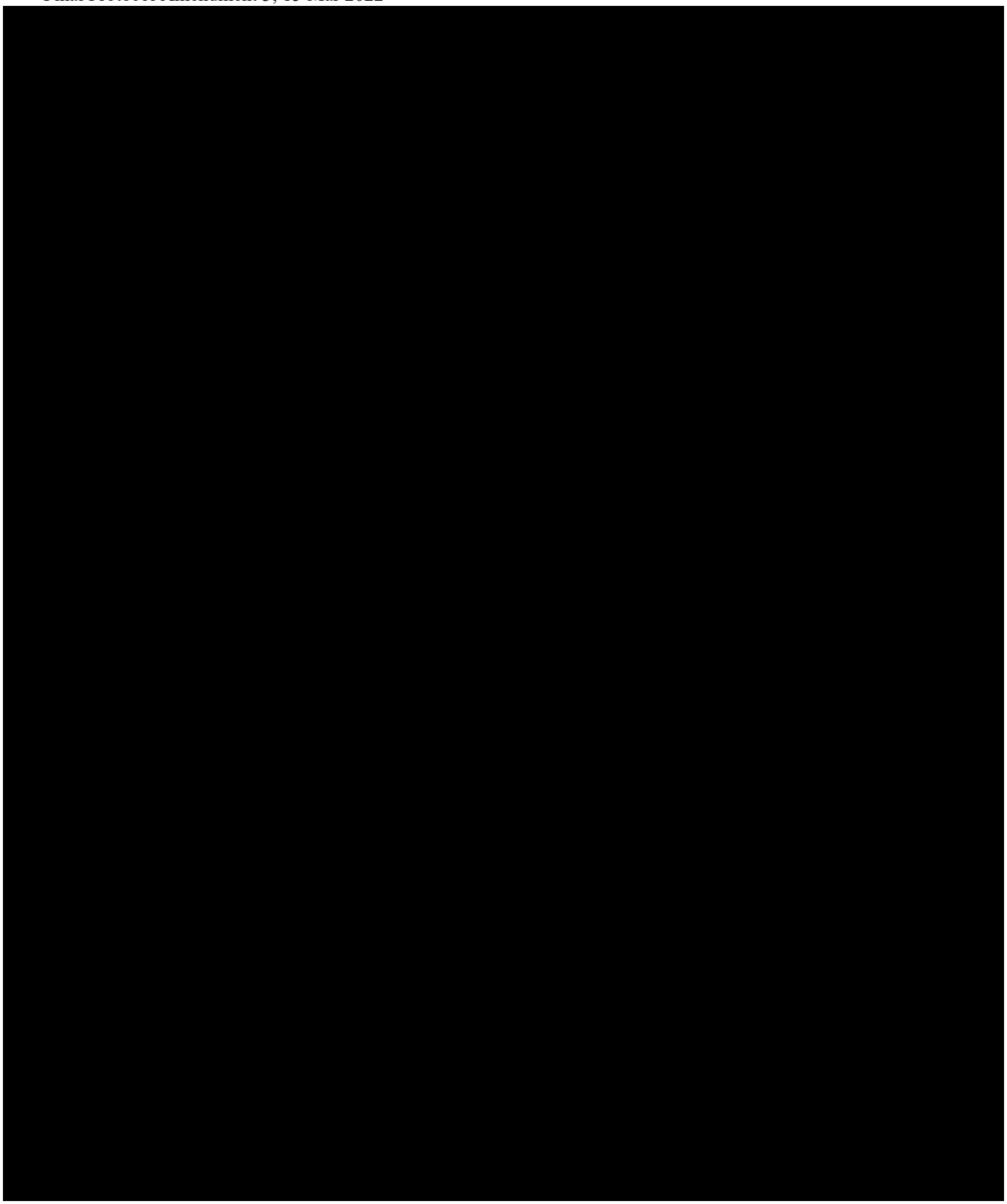

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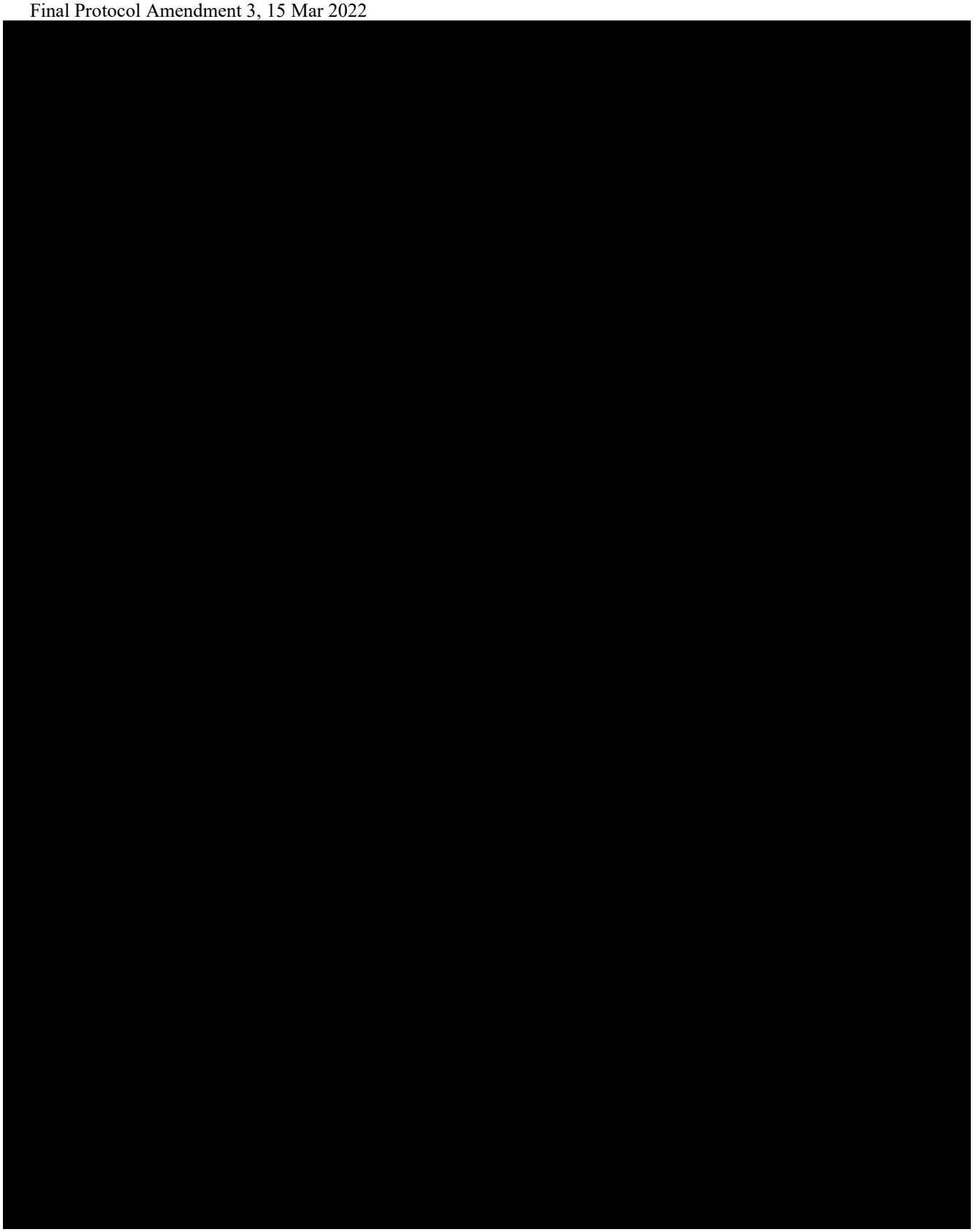

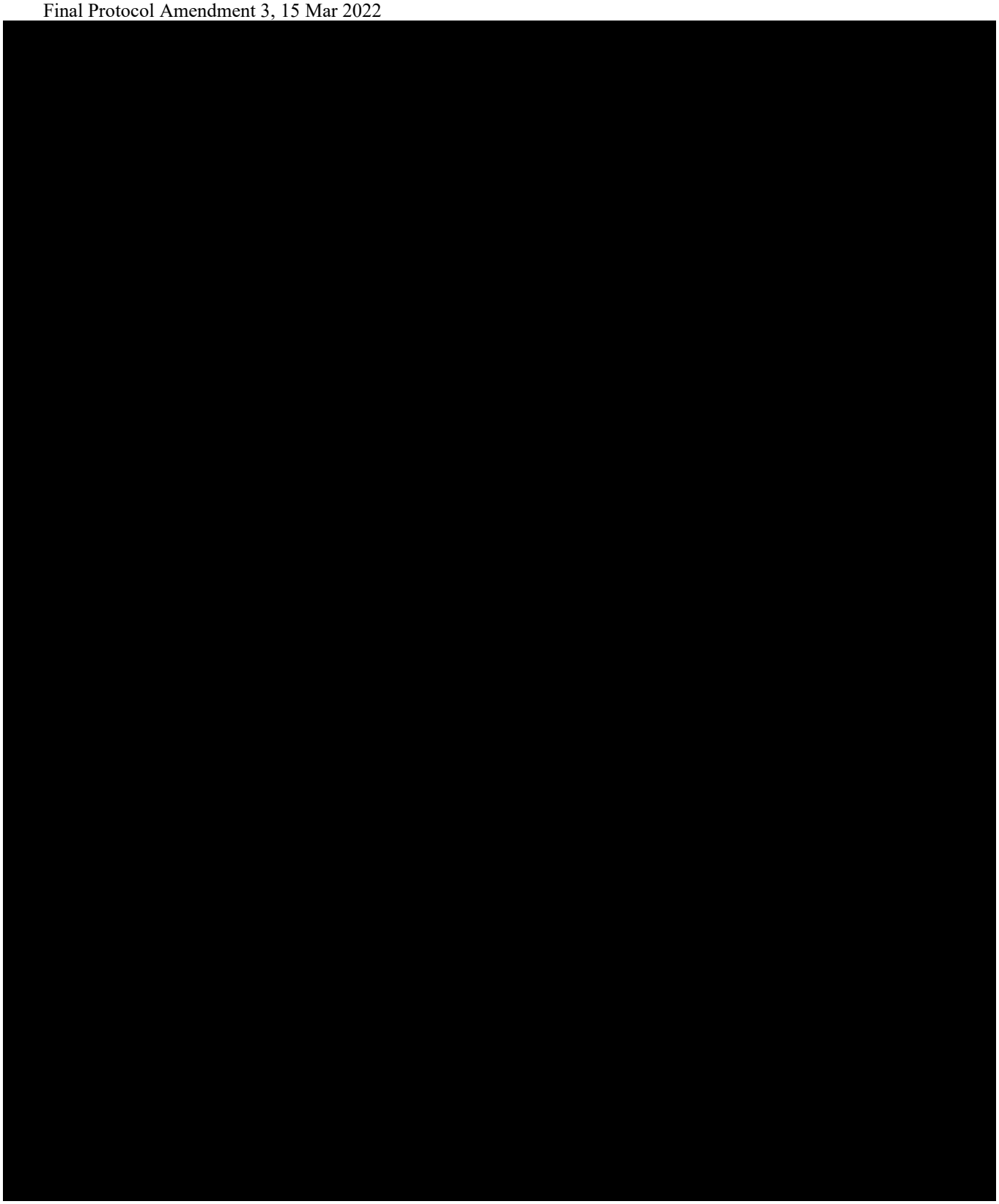

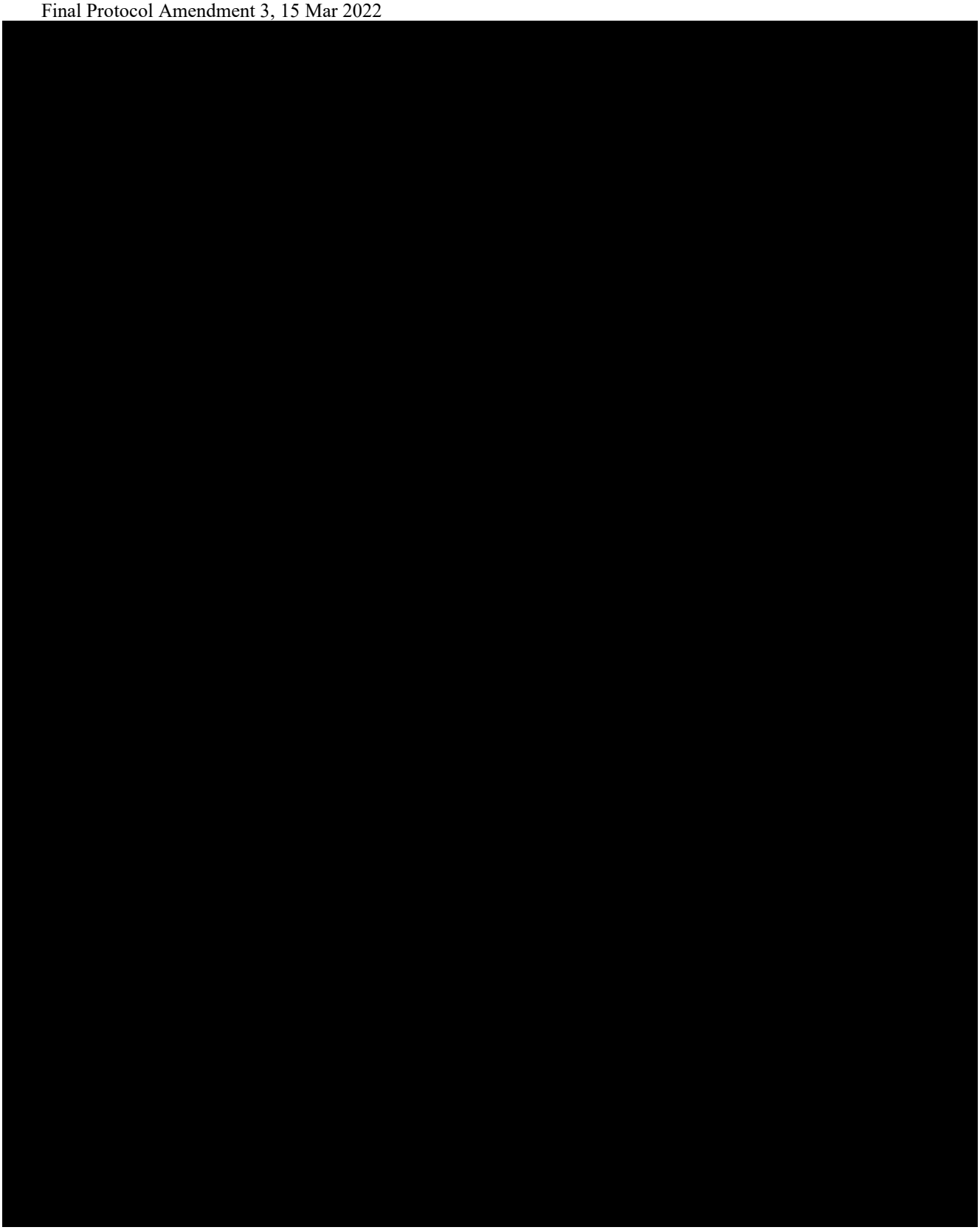

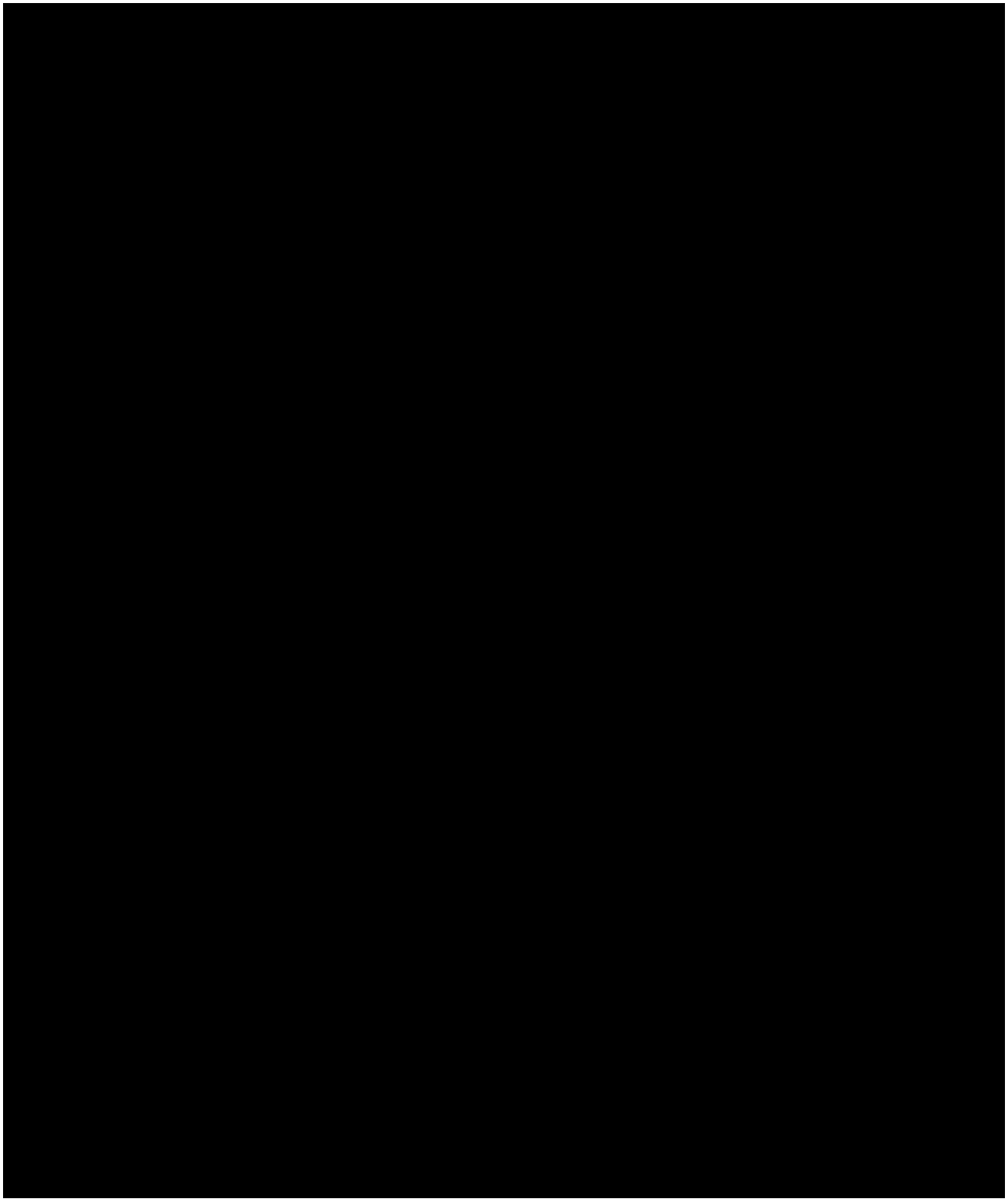

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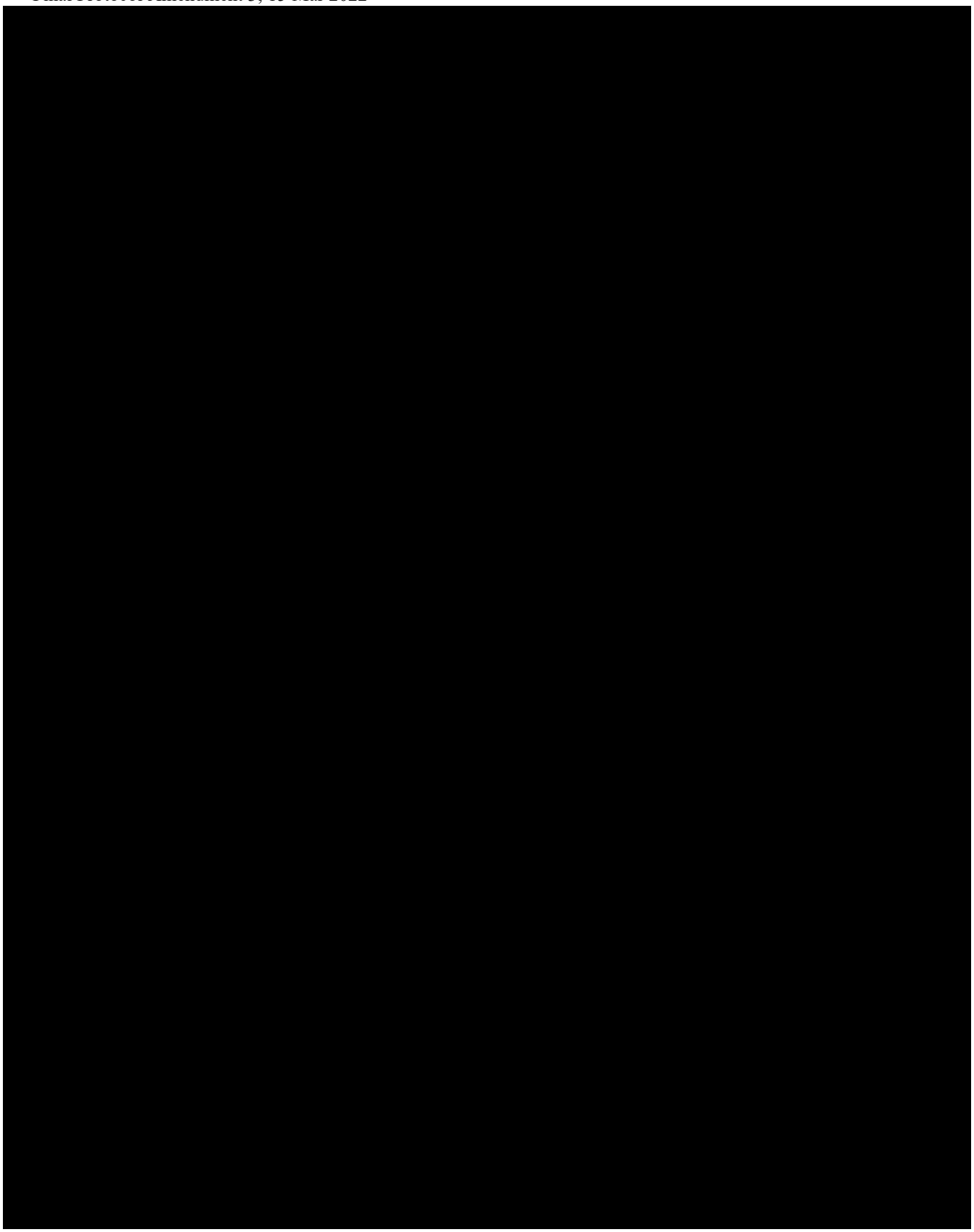

10.15. Appendix 15 Alternative Measures During Public Emergencies

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 globally 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).

10.15.1. Telehealth Visits (if applicable)

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 Schedule of Activities 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 may be performed during a telehealth visit:

- Review and record any AEs and SAEs since the last contact. Refer to Section 8.3 and Appendix 3.
- Review and record any new concomitant medications or changes in concomitant medications since the last contact.
- Review and record contraceptive method. Confirm that the participant is adhering to the contraception method(s) required in the protocol. Refer to Appendix 4 (if applicable).
- Patient Reported Outcomes (if applicable).

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

10.15.2. Home Health Visits (If applicable)

A home health care service will be utilized to facilitate scheduled visits per the Schedule of Activities. Home health visits include a healthcare provider conducting an in-person study visit at the participant's location, rather than an in-person study visit at the site. The following may be performed during a home health visit:

- Lab Collection;
- Physical exam;

- Vital Signs;
- ECG; (if applicable).

Germany: alternative practices will be considered and implemented to ensure safety monitoring of participants. Sites will not utilize home health visits in accordance with Medicinal Products Act of Germany § 4 para.25.

Japan: sites will contact their participants by phone to assess and confirm their safety status. If warranted, the investigator will request the participant to visit the site for an emergency medical assessment that includes protocol defined assessments, home health visits will not occur.

10.15.3. Laboratory Testing: (If applicable)

- 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:

  Please refer to Appendix 2, under Table 5: Protocol Required Safety Laboratory Assessments. Not all laboratory collections may be possible.

  - Hematology;
  - Chemistry;
  - Urinalysis;
  - Viral Surveillance (if applicable);
  - Pregnancy testing (if applicable);
  - PK (if applicable).

- 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.

- 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.

10.15.4. Electrocardiograms (If applicable)

- 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.

10.15.5. Adverse Events and Serious Adverse Events

- If a participant has COVID-19 during the study, this should be reported as an adverse event (AE) or serious adverse events (SAE) and appropriate medical intervention provided.

  There are no known drug class effects of anti-TL1A, however it is per the investigator's judgement on whether or not the participant should discontinue study invervention. It is recommended that the investigator discuss temporary or permanent discontinuation of study intervention with the study medical monitor.

10.16. Appendix 16: Abbreviations

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

Abbreviation	Term
Abs	absolute
ADA	antidrug antibodies
AE	adverse event
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASA	acetylsalicylic acid
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{inf}	area uder the curve infinity
AUC_t	area under the curve over the dosing interval
AV	atrioventricular
AZA	azathioprine
BBS	Biospecimen Banking System
β-hCG	beta-human chorionic gonadotropin
BMI	body mass index
BP	blood pressure
bpm	beats per minute
bSAP	biomarker statistical analysis plan
BSI	back-scattering interferometry
BUN	blood urea nitrogen
C°	Celsius
CD	Crohn's disease
[redacted]	
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CL	clearance
CLIA	Clincal Laboratory Improvements Amendment
C_{max}	maximum observed concentration
cm	centimeter
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Corona Virus Disease 2019
CPK	creatine phosphokinase
CRA	Cytokine Release Assay
CRF	case report form
CRO	contract research organization
CSF	cerebrospinal fluid

Abbreviation	Term
CSR	clinical study report
CT	clinical trial
CT	Computed tomography
DAI	disease activity index
DCs	dendritic cells
DcR3	decoy receptor 3
DSS	extran sulphate sodium
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
DR3	death receptor 3
DU	dispensable unit
E1	Estimands 1
E2	Estimands 2
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
eDiary/e-/Diary	electronic diary
EDP	exposure during pregnancy
EFD	embryo fetal development
EMA	European Medicines Agency
[redacted]	
EU	European Union
EudraCT	European Clinical Trials Database
F	bioavailability
F°	farenheight
FIH	first in human
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GM-CSF	granulocyte-macrophage colony-stimulating factor
GWAS	genome wide association study
HBcAb	hepatitis B core antibody
HBsAb	hepatitis surface antibody
HBsAg	hepatitis B surface antigen
HBV DNA	hepatitis B deoxyribonucleic acid
HCVAb	hepatitis C antibody
HCV RNA	hepatitis C ribonucleic acid
HEENT	head, eyes, ears, nose, throat
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HRT	hormone replacement therapy

Abbreviation	Term
hsCRP	high sensitivity C-reactive protein
IB	investigator's brochure
IBD	inflammatory bowel disease
[redacted]	
ICD	informed consent document
ICH	International Council for Harmonisation
ID	identification
IGRA	Interferon Gamma Release Assay
IL	inter-Leuken
ILCs	innate lymphoid cells
IM	intra muscular
IMP	investigational medicinal product
IN	inches
IND	investigational new drug
INF γ	interferon gamma
INR	international normalized ratio
IP	investigational product
IP manual	investigational product manual
IRB	institutional review board
IRC	internal review committee
IRT	interactive response technology
ITT	Intention-To-Treat
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
IWR	interactive Web-based response
JAK	janus kinase inhibitors
kg	kilogram
lbs	pounds
LBBB	left bundle branch block
LFT	liver function test
MAD	Multiple ascending dose
mg	milligram
mITT	modified Intention-To-Treat
MMDAI	Modified Mayo Disease Activity Index
6-MP	mercaptopurine
msec	millisecond
MTX	methotrexate
N/A	not applicable
NAb	neutralizing antibodies
NIMP	noninvestigational medicinal product
NK	natural killer cells

Abbreviation	Term
NOAEL	no-observed-adverse-effect level
PACL	Protocol administration change letter
PBMC	peripheral blood mononuclear cell
PCD	primary completion date
PD	pharmacodynamic(s)
PGA	Physician Global Assessment
[redacted]	
PI	principal investigator
PK	pharmacokinetic(s)
PMDA	Pharmaceutical and Medical Device Agency
PPD	purified protein derivative
PR	pulse rate
PRO	patient reported outcomes
PTR	peak to trough ratio
PT	prothrombin time
PTT	partial thromboplastin time
PVC	premature ventricular contraction/complex
Q2W	every 2 weeks
QFT-GIT	Quantiferon gold TB test in a tube
QFT-G	Quantiferon gold TB test
Q4W	every 4 weeks
QTc	corrected QT
QTcF	corrected QT (Fridericia method)
qual	qualitative
R_{ac}	accumulation ratios
RBC	red blood cell
RNA	ribonucleic acid
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
[redacted]	
SNPs	single nucleotide polymorphisms
SoA	schedule of activities
SOP	standard operating procedure
SRSD	single reference safety document
SSID	study specific participant identification number
SToD	study team on demand
sTL1A	soluable TL1A
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis

Abbreviation	Term
TBili	total bilirubin
TEAE	treatment emergent adverse event
TL1A	TNF-like factor 1A
TNF	tumor necrosis factor
$t_{1/2}$	terminal half-life
UA	urine analysis
UC	ulcerative colitis
UK	United Kingdom
ULN	upper limit of normal
US	United States
Vss	volume of distribution at steady state
WBC	white blood cell
WOCBP	woman of childbearing potential
WONCBP	woman of non child bearing potential

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