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

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Protocol 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

Statistical Analysis Plan
(SAP)

Version: **3**

Date: **14 Dec 2022**

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1. VERSION HISTORY

Table 1. Summary of Major Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1/31 Jan 2020	Original	Not applicable	Not applicable
2/14 Dec 2021	Amendment 2 01Sep 2020 of the protocol		The rationale for this statistical analysis plan amendment was to incorporate non-substantial changes from multiple previously written Protocol Administration Change Letters (PACL). Appropriate detail information was provided on statistical analysis and definition of endpoints; Chan and Zhang method will be used for primary analysis to be comparable to relevant competitor data, MMRM analysis was added for continouse end points, Sensitivity analysis II was updated to include Bayesian emax model for dose response modelling. Relevant endpoints and clarifications have been added: • Clinical remission 2. • PRO summaries. • Histology assessments. • Clarification on Total Mayo and Partial Mayo. • Update on biomarker endpoints. (additional analysis from Baseline till the end of study). • Update on stratification factors. Additional baseline summaries for some of the stratifications factors. • Clarified language was provided around participants who will be treated as non-responders.

			• Additional figures were added to summarize efficacy results. • Update on summaries for immunogenicity endpoints. • Subgroup analysis was updated and subgroups were calrified. • Appendix on windowing was updated. • Appendix summarizing endpoints deriviation was added. • Appendix on Dose Response analysis was added. • Appendix describing summaries of approaches to be used was added. • Appendix in histological scors was added. • [redacted] • Appendix for Samson criteria was added.
3/14 Dec 2022	Amendment 3 15 Mar 2022 of the protocol		The rationale for this statistical analysis plan amendment was to incorporate changes from Protocol Amendment 3. The main changes are associated with updated language on Interim Analysis due to quicker than expected enrollment; 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. Additional analysis for endpoints: Clinical modified response status was added. Clarification on endpoints selected for sensitivity analysis and subgroup analysis was provided.

			Wording around Baseline Summaries was clarified. Typographical and spelling errors as well as cross references corrected throughout the document.

2. INTRODUCTION

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study B7541007. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

Table 2. Study Objectives, Endpoints, and Estimands

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, 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 baseline 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* 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 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. *corrected erroneous protocol language
	• 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 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 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 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.	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	• 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.

UC during 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] over time. • The proportion of participants with [redacted] total score ≥170 over time.	No estimand 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).

	• Change from baseline in [redacted] over time. • Change from baseline in [redacted] over time.	
• [redacted]	[redacted]	
• To collect non-banked samples [redacted] 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]	

2.1. Timing of the Efficacy Evaluation and Evaluation of Biomarkers of Interest (Excludes Safety Outcome and PK)

Table 2 was copied from Version 01Sep 2020 of the protocol. Table 3 and Table 4 provide an additional insight to the programmer/data analysis. They present separately continuous and binary outcomes of interest and show the analysis times based on the observations required by the schedule of activity in the protocol. The definitions of the outcomes are discussed in the following sections and in Appendix 1.2.

Table 3. Binary Outcomes

N	Definition	Study Week Visits
1	Clinical Remisson defined as a total Mayo Score ≤2, with no individual subscore >1)	Induction: BL, w14 Chronic: Follow-up: w56 Endoscopy: BL, w14, w56
2	Clinical Remisson 2 defined as a total Mayo Score ≤2, rectal bleeding subscore=0, endoscopic subscore = 0 or 1, stool frequency subscore=0 or 1, and physician's global assessment=0 or 1)	Induction: BL, w14 Chronic: Follow-up: w56 Endoscopy: BL, w14, w56
3	Remission (def. FDA1, also called modified remission 1)	Induction: BL, w14 Chronic: Follow-up: w56 Endoscopy: BL, w14, w56
4	Remission (def. FDA2, also called modified remission 2)	Induction: BL, w14 Chronic: Follow-up: w56 Endoscopy: BL, w14, w56
5	Endoscopic Improvement	Induction: BL, w14 Chronic: Follow-up: w56 Endoscopy: BL, w14, w56
6	Endoscopic Remission	Induction: BL, w14 Chronic: Follow-up: w56 Endoscopy: BL, w14, w56
7	ADA/NAbs	Induction: BL, w4, w8, w12, w14 Chronic: w16, w20, w24, w28, w32, w36, w40, w44, w48, w52 Follow-up: w56, w60, w64
8	Clinical response	Induction: BL, w14 Chronic: Follow-up: w56 Endoscopy: BL, w14, w56
9	Symptomatic remission	Induction: BL, w14 Chronic: Follow-up: w56 Endoscopy: BL, w14, w56
10	Deep remission	Induction: BL, w14 Chronic: Follow-up: w56 Endoscopy: BL, w14, w56

N	Definition	Study Week Visits
11	Clinical modified response	Induction: BL, w14 Chronic: Follow-up: w56 Endoscopy: BL, w14, w56
12	[redacted]	
13		
14	Histology assessments: • [redacted]	Induction: BL, w14 Chronic: Follow-up: w56

Table 4. Continuous Outcomes

N	Definition	Study Week Visits
1	Total Mayo Score	Induction: BL, w14 Chronic: Follow-up: w56 Endoscopy: BL, w14, w56
2	Partial Mayo Score	Induction: BL, w4, w8, w12, w14 Chronic: w16, w20, w24, w28, w32, w36, w40, w44, w48, w52 Follow-up: w56, w60, w64

N	Definition	Study Week Visits
3	[redacted]	[redacted]
4		
5		
6	Total Mayo sub-scores including diary UC Symptoms • Stool frequency (Subscore 0-3). • Rectal bleeding (Subscore 0-3). • Findings on endoscopy (Subscore 0-3). • Physician's global assessment (Subscore 0-3). • [redacted]	Induction: BL, w4, w8, w12, w14 Chronic: w16, w20, w24, w28, w32, w36, w40, w44, w48, w52 Follow-up: w56, w60, w64 Endoscopy: BL, w14, w56
7	[redacted]	[redacted]
8		
19	[redacted]	Induction: BL, w14 Chronic: Follow-up: w56

2.2. Study 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 2:2:2:2:2:3:1:1:1. The numbers of planned participants for the 9 treatment sequences (A-I) are listed in Table 5. Randomization will be stratified according to whether 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.

Figure 1. Study Design Schema

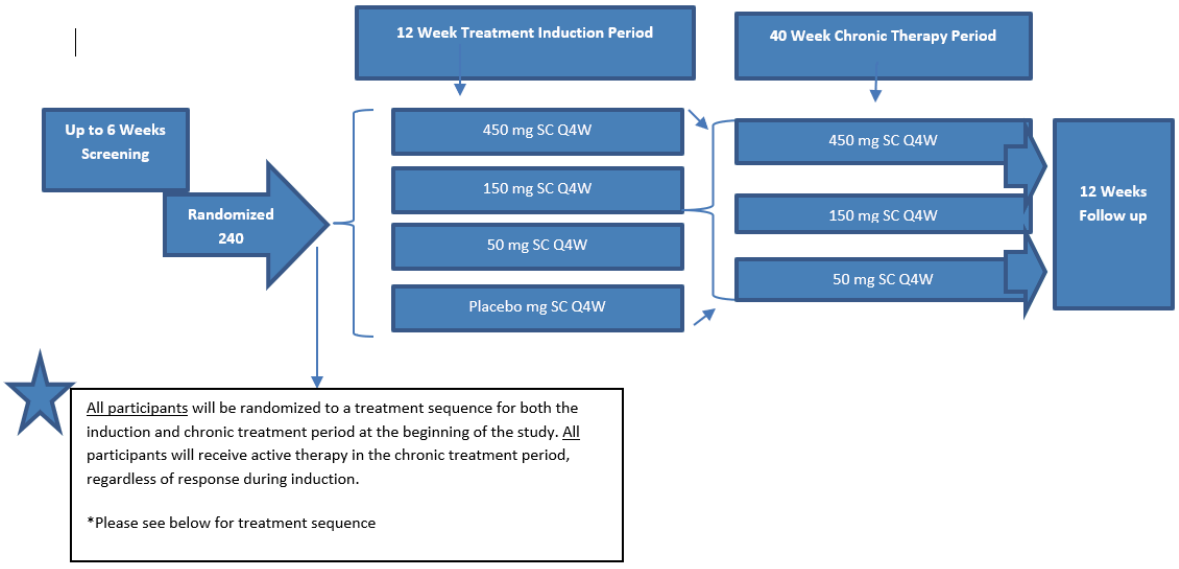


Table 5. Treatment Sequence

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*

[redacted]

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of participants achieving clinical remission (defined as a Total Mayo Score ≤2, with no individual subscore >1) at Week 14. The Total Mayo Score consists of 4 subscores and each graded 0 to 3 with the higher score indicating more severe disease activity:

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

The detailed calculation of Total Mayo Score is included in the Appendix 1.2.

3.2. Secondary Efficacy Endpoints

The secondary endpoints during induction period are:

- 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 will be denoted as modified remission 1 during the reporting.

- 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 will be denoted as modified remission 2 during the reporting.

- Proportion of participants achieving endoscopic improvement (defined as endoscopic subscore = 0 or 1) at Week 14.

- Proportion of participants achieving endoscopic remission (defined as endoscopic subscore = 0) at Week 14.

Additional exploratory analyses for induction period:

- Proportion of participants achieving clinical remission 2 based on total Mayo Score (defined as a total Mayo score ≤2, rectal bleeding subscore=0, endoscopic subscore = 0 or 1, stool frequency subscore=0 or 1, and physician's global assessment=0 or 1 at Week 14).

The secondary endpoints during chronic therapy period are:

- Proportion of participants achieving clinical remission (defined as a Total Mayo Score ≤2, with no individual subscore >1) at Week 56.

- Proportion of participants achieving sustained clinical remission (ie, clinical remission at both Week 14 and Week 56).

- 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).

- Proportion of participants achieving remission FDA definition 2 (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).

- 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).

- Proportion of participants achieving endoscopic remission (defined as endoscopic subscore = 0) at Week 56.

- Proportion of participants achieving sustained endoscopic remission (ie, endoscopic remission at both Week 14 and Week 56).

Additional exploratory analyses for chronic period:

- Among non-responders at Week 14, proportion of participants achieving clinical remission, clinical remission 2, modified remission1, modified remission 2, endoscopic remission and endoscopic improvement at Week 56.

- Proportion of participants achieving clinical remission 2 based on total Mayo Score (defined as a total Mayo score ≤2 rectal bleeding subscore=0, endoscopic subscore = 0 or 1, stool frequency subscore=0 or 1, and physician's global assessment=0 or 1 or 1) at Week 56.

- Proportion of participants achieving sustained clinical remission 2 (ie, clinical remission 2 at both Week 14 and Week 56).

3.3. Tertiary Endpoints

The binary tertiary endpoints are:

- 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, 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, 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, Week 56, and sustained deep remission (ie, deep remission at both Week 14 and Week 56).

The additional exploratory analyses for binary outcomes:

- Proportion of participants achieving clinical modified response (defined as ≥2 point and ≥30% decrease from baseline in modified Mayo Scores, with an accompanying ≥1 point decrease in rectal bleeding subscore or absolute rectal bleeding subscore = 0

or 1) at Week 14, Week 56, and sustained clinical modified response (ie, clinical modified response at both Week 14 and Week 56).

- [redacted]

The continuous tertiary endpoints are:

- Change from baseline in Partial Mayo scores over time. The partial Mayo Score is the Mayo Score without endoscopic subscore, ranging from 0 to 9.
- Change from baseline in subscores of total Mayo score including diary UC Symptoms over time.
- Change from baseline in histopathology scores [redacted] at Week 14, Week 56.

Absolute values of the scores will also be summarized.

The additional exploratory analyses:

- Absolute and change from baseline in Total Mayo scores over time (additional analysis).

The following tertiary endpoints are not within the scope of this SAP and CSR.

- Collection of non-banked exploratory samples 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]
- [redacted]

3.4. Patient Reported Outcome

The following endpoints are the patient reported outcome:

- Change from baseline in [redacted] over time.
- Change from baseline in [redacted] over time.
- Change from baseline in [redacted] over time.
- Change from baseline in [redacted] over time.

The additional exploratory analyses for patients reported outcomes:

- The proportion of subjects with [redacted] total score ≥170 over time.
- The proportion of subjects with ≥16 point increase in [redacted] total score from baseline at over time.
- Number and Percentage of Participants in Each Category of [redacted]
- Additional summary for selected PRO questions may be presented.

[redacted]

3.5. Immunogenicity Endpoint

The secondary endpoints to characterize the immunogenicity are:

- Incidence of development of anti-drug antibodies (ADAs) and neutralizing antibodies (NAbs) during the induction period through Week 14.
- Incidence of development of anti-drug antibodies (ADAs) and neutralizing antibodies (NAbs) from Week 14 through the End of Study Visit.

In addition, for participants with at least one ADA/Nab positive sample, persistent response will be defined as ADA/NAb positive at the last sample.

If sample was tested by mistake for Nab, the results will be presented in listings only and will be excluded from ADA/Nab summaries.

3.6. PK Endpoints

The secondary endpoints to characterize the PK are:

- PF-06480605 concentrations during the induction period through Week 14.
- PF-06480605 concentration from Week 14 through the End of Study Visit.

3.7. Biomarker Endpoints

The secondary endpoints to characterize biomarkers are:

- Change from baseline 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.
- 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.
- Change from Week 14 in 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.

3.8. Safety Endpoints

Safety endpoints will be assessed by the reporting of AE, SAE and TEAE, significant changes in vital signs, clinical laboratory abnormalities, and ECG and clinical laboratory results in all participants who receive at least one dose of the investigational product. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety concerns.

Any abnormal laboratory test results or other safety assessments, 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) are AEs.

An adverse event will be considered a Treatment-Emergent Adverse Event (TEAE) if the event started during the effective duration of treatment. All events that start on or after the first dosing day and time/start time, if collected, but before the last dose plus the lag time will be flagged as TEAEs. The algorithm will not consider any events that started prior to the first dose date. If an AE starts on the same day as the first dose date, it will be considered treatment emergent unless the CRF data indicates otherwise via explicitly recording time for AE onset and treatment dosing.

The safety endpoints include:

- Incidence and severity of treatment emergent adverse events (TEAEs) during the induction period and chronic therapy period.
- Incidence of serious adverse events (SAEs) during the induction period and chronic therapy period.
- Incidence of AEs or SAEs leading to discontinuation during the induction period and chronic therapy period.
- Incidence of clinically significant abnormalities in vital signs, electrocardiograms, (ECGs) and laboratory values during the induction period and chronic therapy period.

All clinical AEs, SAEs, TEAEs withdrawal due to AEs, ECGs, vital signs and safety laboratory data will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of participants.

3.8.1. Laboratory Data

The following safety laboratory tests will be performed at times defined in the Schedule of Activities. 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. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety concerns.

Table 6. 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* (only at screening, Week 12, and Week 52)*	*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,f] *FSH*[e,f] *HBV surface antigen*[f], *HbsAg,*[f] *HBVcore*[f] *antibody, HbcAB*[f], *HBV surface antibody*[f], *HbsAb*[f], *Hepatitis C antibody*[f], *HCV RNA*[f], *HBV DNA testing if applicable*[f]. *HIV* *QFT-G or other IGRA* *Stool Sample to detect enteric Infections and* [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. *Local urine testing will be standard for the protocol unless serum testing is required by local regulation or institutional review board/ethics committee (IRB/EC). 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.*
f. *Screening only unless from Japan.*

3.8.2. Electrocardiogram

The average of the triplicate ECG measurements collected pre dose on Day 1 will serve as each participant's baseline QTc value. Summary of analysis results is described in the Section 6.8.5.

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*

3.8.3. Vital Signs

Vital Signs will be measured including 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.

3.9. Baseline Variables

Baseline of endpoints is defined as the non-missing result (scheduled or unscheduled) closest prior to dosing on Day 1. The definition will be applied to all demographics and baseline characteristics as well.

For Patient Reported Outcomes (PRO), if the questionnaire was not answered prior to dosing on Day 1, but at Day 1, Day 1 questionnaire response will be treated as baseline.

For baseline endoscopy, if there are missing e-diary data, the average will be taken from the 3 most recently available days reported within 7 days prior to the endoscopy preparation. If there are less than 3 available days reported within the 7 days prior to the study visit, the average will be taken from the limited available data, if there are less than 2 valid days available, window time will be extended to 10 days 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.

For ECG measurement, the average of the triplicate ECG measurements collected pre dose on Day 1 will serve as each participant's baseline QTc value.

3.9.1. Covariates

The following baseline variables will be used in calculating the change from baseline endpoints:

- Fecal calprotectin;
- hsCRP;
- serum sTL1A;
- Total Mayo score;
- Partial Mayo score and other eDiary UC Symptoms (including [redacted]);
- [redacted]
- [redacted]

- [redacted]
- Histopathology scores: [redacted] (see Appendix 4);
- Vital signs, ECG parameters QT interval, heart rate, QTc interval, PR interval, and QRS complex.

Absolute score values will be also summarized.

3.9.2. Stratification Factor

The goal of the analysis adjusted for strata is to evaluate robustness of the main analysis (supportive for primary and secondary endpoints). For induction period the stratification analysis will be performed for clinical remission, clinical remission 2, modified remission 1, modified remission 2 and endoscopic improvement. For chronic period the stratification analysis will be performed for clinical remission, clinical remission 2, modified remission 1, modified remission 2, endoscopic improvement and endoscopic remission. The stratification analyses will be based on the baseline exposure to the following treatments (numbers permitting):

- Prior anti-TNF treatment: experienced, naïve.
- Anti-integrin: experienced, naïve.
- Biologic: experienced, naïve.
- Steroid exposure at baseline: yes, no.
- Anti-IL-12/23 Inhibitors: experienced, naïve.

These factors will be incorporated into considerations for statistical analysis described in Section 6.

3.9.3. Other Baseline Variables

The following baseline variables will be summarized for each treatment group and treatment sequence.

Details of summaries are described in Section 6.10.1.

Demographic characteristics:

- Baseline age (<18, 18-44, 45-64, ≥65; and continuous in years);
- Sex (female, male);
- Race (white, black, Asian, other);

- Ethnicity (Hispanic/Latino, non-Hispanic/Latino);
- Baseline body weight (<60, ≥60 to ≤100, >100 kg; and continuous in kg);
- Baseline height (continuous in cm);
- Screening smoking status (never smoked, ex-smoker, smoker).

Baseline disease characteristics:

- Concomitant medication(s) and treatment (s) administered (yes, no);
- Total Mayo score (<9, ≥9; and continuous);
- Partial Mayo Score (<6, ≥6; and continuous);
- Modified Mayo Score;
- Endoscopic subscore (2, 3; and continuous);
- Duration of UC (<10 yrs, ≥10 yrs; and continuous);
- sTL1A concentration;
- Steroid exposure at baseline: yes, no;
- 5-ASA at baseline: yes, no;
- Immunosuppressants: yes, no.

In addition, the presented below baseline variables will be summarized for each treatment group and treatment sequence for:

- Prior anti-TNF treatment: experienced, naïve and by failure reason (inadequate response, loss of response and intolerance);
- Anti-integrin: experienced, naïve and and by failure reason (inadequate response, loss of response and intolerance);
- Anti-IL-12/23 Inhibitors: experienced, naïve and by failure;
- Biologic: experienced, naïve and by failure;
- Steroid exposure at baseline: yes, no.

4. ANALYSIS SETS

Data for all participants will be assessed to determine if participants meet the criteria for inclusion in each analysis population prior to unblinding and releasing the database and classifications will be documented per standard operating procedures.

Defined Population for Analysis	Description
Safety Analysis Population	All participants who take at least 1 dose of investigational product. Participants will be analysed 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 analysed 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 analysed 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.

Following the screening period, participants who meet eligibility criteria at the baseline visit will be allocated to 2 strata according to prior experience in anti-TNFs, ie, prior exposure to anti-TNFs (yes or no). Within each stratum, participants will be randomly assigned to receive 1 of 9 treatment sequences according to randomization schedule.

5. GENERAL METHODOLOGY AND CONVENTIONS

There are analyses planned based on two data snaphots. Final analyses will occur after database lock after Last Subject Last Visit (LSLV).

The primary efficacy analysis will be performed when 100% of participants have completed or have the opportunity to complete the Week 14 visit and 100% of primary endpoint data are available. The second data snapshot analysis will be conducted when approximately all participants have completed or have the opportunity to complete the induction period and up

to 100% of them have completed or have the opportunity to complete at least 6 months of chronic therapy.

The study will be ongoing at the time of both analyses. Selected group of individuals independent from study team will be unblinded to perform these analysis.

The primary analysis may be used to inform on the broader program; no decision directly related to this study will be made from the results of primary analysis. No formal decision rule will be applied.

The primary analysis will be performed by an unblinded statistician. The investigators will remain blinded. The sponsor will review aggregated safety, efficacy and immunogenicity data by treatment group and treatment sequence.

Additional interim snapshots might be taken after the primary efficacy analysis to facilitate further clinical development.

5.1. Hypotheses and Decision Rules

The study is designed to test null hypothesis that the probability of participants achieving clinical remission at Week 14 of each individual PF 06480605 dose group is the same as that for the placebo group. Each individual PF 06480605 dose group will be compared with placebo. An active treatment is considered statistically superior to placebo if the risk difference (treatment vs placebo) estimated using Chan and Zhang method (Section 5.2.1.1) is statistically significant at the 1-sided family-wise type-I error rate of 0.05.

[redacted] *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 without accounting for dropout.*

5.2. General Methods

The participants randomized to the treatment sequences of same treatment dose will be combined in the analysis for induction period.

5.2.1. Analyses for Binary Endpoints

In general, number of participants (N), number (n) and percent (%) of responders will be presented by treatment and visit for binary variables. The confidence intervals for one sample proportions will be based on Blyth Still Casella.

5.2.1.1. Chan and Zhang Method

Chan and Zhang method[5] will be used to provide confidence intervals of difference between the proportions from response in the treatment group of interest and from the placebo group. The confidence intervals for one sample proportions will be based on Blyth Still Casella. The analysis will be applied to the Evaluable Population dataset with non-responder imputation (NRI) of missing data. Change and Zhang method will be applied to all binary outcomes in Induction period.

5.2.1.2. Cochran-Mantel-Haenszel Method

The stratum-adjusted difference in probabilities of clinical remission based on Total Mayo score between the treatment group of interest and placebo group will be based on stratified Cochran-Mantel-Haenszel (CMH) test and the approach described by Mehrotra and Railkar.[1] The treatment differences in proportions will be presented. Their corresponding 2-sided 90% CI will be estimated using the minimum risk weight strategy proposed by Mehrotra and Railkar.[1] The non-responder imputation will be done before the analysis. The analysis will be applied to the Evaluable Population dataset of observations at Week 14. The definitions of the strata are given in Section 3.9.2.

5.2.2. Analyses for Continuous Endpoints

In general, number of participants (N), mean, standard deviation, median, minimum, and maximum will be presented for continuous variables by treatment and visit.

- Descriptive statistics will provide estimates (with confidence intervals based on Wald's method) of expected continuous outcome for each treatment group and difference between the expected values of outcomes in the treatment group and placebo group. There will be no imputation of the missing data. This method will be applied to all continuous endpoints and all visits.

- The longitudinal Mixed Model Repeated Measures (MMRM) modeling (eg, Fitzmaurice, Laird and Ware (2011)[6] and Malincrodt and Lipkovich (2017)[7]) will provide improved estimates in comparison to the ones provided by the descriptive statistics. The MMRM model will include treatment, baseline, treatment by visit and baseline by visit interactions for post-baseline visits as fixed effects. An unstructured variance-covariance matrix will be used. If adaptations are made, eg, excluding baseline from model or alternative covariance structure, this will be noted in the CSR.

5.2.3. Analyses for Categorical Endpoints

Frequency and percentage for each category will be presented using observed data.

5.3. Methods to Manage Missing Data

In general, for descriptive statistics missing values will not be imputed. In addition, for safety endpoints missing values will not be imputed. Other methods for handling missing values are discussed below.

Participant who had a data missing due to COVID19 will be removed from analysis for this specific 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 COVID19).

5.3.1. Binary Data

5.3.1.1. Induction Period

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 efficacy endpoint at Week 14; otherwise, data collected from the early withdrawal visit will be used for analysis (except for COVID related reasons; see Section 5.3). Similar approach will be taken with other binary endpoints.

If study participant missed Week 14 visit, but continued on the study, the participant will be treated as a non-responder for the binary endpoints at Week 14.

5.3.1.2. Chronic Therapy Period

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 efficacy endpoint at Week 56; otherwise, data collected from the early withdrawal visit will be used for analysis analysis (except for COVID related reasons; see Section 5.3). Similar approach will be taken with other binary endpoints.

Study participants who discontinued prior or at Week 52 or missed final endoscopy visit will be treated as a non-responder at the Week 56 visit.

5.3.2. Continuous Data

The missing continuous data are assumed missing at random and will not be imputed in the statistical analysis.

5.3.3. PK and Biomarker Data

If a concentration value is not collected or cannot be analyzed due to sample quality issues, it will be considered as missing data and will not be imputed. If actual sampling time is missing, the protocol-stated nominal time will be used.

5.3.4. Missing Dates

In compliance with Pfizer standards, if the day of the month is missing for any date used in a calculation, the 1st of the month will be used to replace the missing date unless the calculation results in a negative time duration (eg, date of resolution cannot be prior to date of onset; if replacing resolution date with the 1st of the month results in a negative duration, the resolution date will be set to the onset date). Pfizer standards are similarly used if both month and day are missing (January 1 unless negative time duration).

If the start date is missing for an AE, the AE is considered to be treatment emergent unless the collection date is prior to the treatment start date.

6. ANALYSES AND SUMMARIES

6.1. Primary Efficacy Endpoint Analysis

- Endpoint: Proportion of participants achieving clinical remission (defined as a Total Mayo Score ≤2, with no individual subscore >1) at Week 14. The calculation for Total Mayo score is described in the Appendix 1.2.

6.1.1. Main Analysis

- Estimand strategy: Composite (Section 2).
- Analysis set: Evaluable population ITT(Section 4).
- Analysis methodology: The response comparing each dose (450 mg, 150 mg and 50 mg) of active treatment against placebo will be analyzed using Chan and Zhang method (Section 5.2.1.1) for the difference between two proportions. The observed risk difference and corresponding 2-sided 90% exact CI of comparing each treatment dose versus placebo will be presented. P-values will be presented for each comparison.
- Intercurrent events and missing data: handling of missing data is described in Section 5.3.1.1.
- The number and percent of response will be presented for each treatment group over time.
- The number and percent of response will be presented for each treatment group by stratification factors (Section 3.9.2).
- Plot of risk difference for each comparison with 2-sided 90% CI will be presented.

- Additional summary plots may be generated.

6.1.2. Sensitivity Analyses (I)

The stratified Cochran-Mantel-Haenszel (CMH) test of a difference in proportions will be carried out (supportive for primary and selected secondary endpoints, Section 5.2.1.2). The primary analysis will be adjusted by the stratification factors (Section 3.9.2).

- The observed risk difference of comparing each treatment dose versus placebo will be presented. Their corresponding 2-sided 90% CIs will be estimated using the minimum risk weight method.

- Plot of risk difference for each comparison with 2-sided 90% CI will be presented.

- Handling of missing data is described in Section 5.3.

6.1.3. Sensitivity Analyses (II)

[redacted]

6.2. Secondary Efficacy Endpoints Analyses

6.2.1. Induction Period

The following endpoints will be analyzed by using the same methodology.

- Proportion of participants achieving remission Food and Drug Administration (called modified remission 1), (FDA) definition 1 - defined as endoscopic subscore = 0 or 1, stool frequency subscore = 0, and rectal bleeding subscore = 0) at Week 14.

- Proportion of participants achieving remission (called modified remission 2, 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.

- Proportion of participants achieving endoscopic improvement (defined as endoscopic subscore = 0 or 1) at Week 14.

- Proportion of participants achieving endoscopic remission (defined as endoscopic subscore = 0) at Week 14.

Following the same methodology, additional exploratory analysis will be performed for:

- Proportion of paticipants achieving clinical remission 2 (defined as a total Mayo Score ≤2, rectal bleeding subscore=0, endoscopic subscore = 0 or 1, stool frequency subscore=0 or 1, and physician's global assessment=0 or 1) at Week 14.

6.2.1.1. Main Analysis

- Estimand strategy: Composite.
- Analysis set: Evaluable population ITT.
- Analysis methodology: The response comparing each dose level (450 mg, 150 mg and 50 mg) of active treatment against placebo will be analyzed using Chan and Zhang method (Section 5.2.1.1) for the difference between two proportions. The observed risk difference and corresponding 2-sided 90% exact CI of comparing each treatment dose versus placebo will be presented.
- Intercurrent events and missing data: handling of missing data during induction period is described in Section 5.3.1.1.
- The number and percent of response will be presented for 450 mg, 150 mg, 50 mg and placebo group by time.
- The number and percent of response will be presented for 450 mg, 150 mg, 50 mg and placebo group by stratification factors (Section 3.9.2).
- Plot of risk difference for each comparison with 2-sided 90% CI will be presented. For selected secondary endpoints additional summary plots may be generated.

Of note, forest plots and/or bar plots may be created to summarize all types of binary outcomes (including primary endpoints, secondary endpoints, selected tertiary endpoints, and endpoints summarized by strata).

6.2.1.2. Sensitivity Analysis (I)

The stratified Cochran-Mantel-Haenszel (CMH) test of a difference in proportions will be carried out (supportive for primary and selected secondary endpoints, Section 5.2.1.2). The analysis will be adjusted by the stratification factors (Section 3.9.2).

- The observed risk difference of comparing each treatment dose versus placebo will be presented. Their corresponding 2-sided 90% CIs will be estimated using the minimum risk weight method.
- Plot of risk difference for each comparison with 2-sided 90% CI will be presented.

Summary of approaches to be used for primary and secondary outcomes in Induction Period is presented in Appendix 3.

6.2.1.3. Sensitivity Analysis (II)

A 4-parameter Bayesian emax model may be fitted to the data to characterize the dose response relationship. Details are provided in Appendix 2.

6.2.2. Chronic Therapy Period

For all efficacy and PD endpoints mITT population wil be used for analysis.

6.2.2.1. Remission Endpoints

The following endpoints will be analyzed using the same methodology.

- Proportion of participants achieving clinical remission (defined as a Total Mayo Score ≤2, with no individual subscore >1) at Week 56.
- Proportion of participants achieving remission (called modified remission 1, based on 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 remission (called modified remission 2, based on 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 endoscopic improvement (defined as endoscopic subscore = 0 or 1) at Week 56.
- Proportion of participants achieving endoscopic remission (defined as endoscopic subscore = 0) at Week 56.

Additional exploratory analyses for remission:

- Proportion of participants achieving clinical remission 2 (defined as a total Mayo Score ≤2, rectal bleeding subscore=0, endoscopic subscore = 0 or 1, stool frequency subscore=0 or 1, and physician's global assessment=0 or 1) at Week 56.
- Among non-responders at Week 14, proportion of participants achieving clinical remission, clinical remission 2, modified remission 1, modified remission 2, endoscopic improvement and endoscopic remission at Week 56.

6.2.2.1.1. Main Analysis

- Estimand strategy: Composite.

- Analysis set: Evaluable population.
- Analysis methodology: The response at Week 56 comparing each treatment sequence will be analyzed descriptively. The confidence intervals for one sample proportions will be based on Blyth Still Casella.
- Intercurrent events and missing data: handling of missing data is described in Section 5.3.1.2.
- The number and percent of response will be presented for each treatment sequence at Week 14 and Week 56.
- The number and percent of response will be presented for each treatment sequence at Week 14 and Week 56 by stratification factors (numbers permitting, Section 3.9.2).

6.2.2.2. Sustained Remission Endpoints

The following endpoints will be analyzed using the same methodology.

- Proportion of participants achieving sustained clinical remission (ie, clinical remission at both Week 14 and Week 56).
- Proportion of participants achieving sustained remission FDA definition 1 (ie, remission FDA definition 1 at both Week 14 and Week 56).
- Proportion of participants achieving sustained remission FDA definition 2 (ie, remission FDA definition 2 at both Week 14 and Week 56).
- Proportion of participants achieving sustained endoscopic improvement (ie, endoscopic improvement at both Week 14 and Week 56).
- Proportion of participants achieving sustained endoscopic remission (ie, endoscopic remission at both Week 14 and Week 56).

Additional exploratory analyses for sustained remission endpoints:

- Proportion of participants achieving sustained clinical remission 2 (ie, clinical remission 2 at both Week 14 and Week 56).

6.2.2.2.1. Main Analysis

- Estimand strategy: Composite.
- Analysis set: Evaluable population (modified Intention-To-Treat) who achieved the corresponding remission or improvement to the endpoints at Week 14.

- Analysis methodology: The response at Week 56 comparing each treatment sequence will be analyzed descriptively. The confidence intervals for one sample proportions will be based on Blyth Still Casella.

- Intercurrent events and missing data: handling of missing data is described in Section 5.3.1.2.

- The number and percent of response will be presented for each treatment sequence at Week 56.

- The number and percent of response will be presented for each treatment sequence at Week 56 by selected stratification factors (numbers permitting, Section 3.9.2).

6.3. Tertiary Endpoints Analyses

6.3.1. Binary Data

For the following binary endpoints, the numbers and percent of participants achieving the response will be presented for 4 treatment groups at Week 14 (induction period) and for 9 treatment sequences at Week 56 (chronic period). The numbers and percent of participants achieving the sustained clinical response or remission will be summarized for 9 treatment sequences at Week 56. The confidence intervals for one sample proportions will be based on Blyth Still Casella. For analysis at Week 14, the response comparing each dose (450 mg, 150 mg and 50 mg) of active treatment against placebo will be analyzed using Chan and Zhang method (Section 5.2.1.1) for the difference between two proportions.

- 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, 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, 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, Week 56, and sustained deep remission (ie, deep remission at both Week 14 and Week 56).

The additional exploratory analyses for binary outcomes:

- Proportion of participants achieving clinical modified response (defined as ≥2 point and ≥30% decrease from baseline in modified Mayo Scores, with an accompanying ≥1 point decrease in rectal bleeding subscore or absolute rectal bleeding subscore = 0 or 1) at Week 14, Week 56, and sustained clinical modified response (ie, clinical modified response at both Week 14 and Week 56).
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

6.3.2. Continuous Data

For the following continuous endpoints, the summary statistics of N, mean, 90% confidence interval, median, standard deviation, minimum and maximum will be presented.

- Absolute and Change from baseline in Partial Mayo scores over time. The derivation of partial Mayo Score is described in the Appendix 1.2.
- Absolute and Change from baseline in Total Mayo scores over time. The derivation of Total Mayo Score is described in the Appendix 1.2.
- Absolute and Change from baseline in diary UC Symptoms over time.
- Absolute and Change from baseline in histopathology scores at Week 14 and Week 56.

Analysis plan will follow similar methodology presented for Patient Reported Outcome.

6.4. Analysis of Patient Reported Outcome Data

The following continues endpoints are analyzed by using the same methodology.

- Absolute and Change from baseline in [redacted] over time.
- Absolute and Change from baseline in [redacted] over time.
- Absolute and Change from baseline in [redacted] over time.
- Absolute and Change from baseline in [redacted] over time.

Absolute values of the scores will be also summarized for these endpoints.The analysis plan is the following:

- Analysis set: Evaluable population.
- Descriptive statistics for actual, change from baseline and percent change from baseline during induction period will be presented by treatment group for nominal time points specified in the SoA. Treatment sequences with the same induction treatment will be combined in this summary analysis.
- Descriptive statistics for actual, change from baseline and percent change from baseline throughout the study will be presented by treatment sequence for nominal time points specified in the SoA.
- Missing data will not be imputed.
- Statistical analysis of total scores and domain scores by treatment group as well as treatment sequence using MMRM will be performed for selected PROs
- Plot of mean and 90% confidence interval (LS means plot) of the actual and percent change from baseline will be presented for four treatment groups of induction period. Same plot will be generated for each treatment sequence that includes both induction period and chronic therapy period.

Additional exploratory analyses for patients reported outcomes will present the numbers and percent of participants meeting the conditions listed below for 4 treatment groups at Week 14 (induction period: 0-14 week) and for 9 treatment sequences at Week 56 (chronic period 0-56 week). For analysis up to Week 14, the response comparing each dose (450 mg, 150 mg and 50 mg) of active treatment against placebo will be analyzed using Chan and Zhang method (Section 5.2.1.1) for the difference between two proportions.

- The proportion of subjects with [redacted] total score ≥170 over time.
- The proportion of subjects with ≥16 point increase in [redacted] total score from baseline over time.

- Additional summary for selected PRO items may be presented.

[redacted]

6.5. Analysis of Immunogenicity Data

The immunogenicity endpoints are:

- Incidence of development of anti-drug antibodies (ADAs) and neutralizing antibodies (NAbs) during the induction period through Week 14.
- Incidence of development of anti-drug antibodies (ADAs) and neutralizing antibodies (NAbs) from Week 14 through the End of Study Visit.

The statistical analysis is as follows:

- Analysis Set: Immunogenicity analysis population.
- Intercurrent events and missing data: the missing data will not be imputed.
- Analysis methodology: Incidences of ADAs and NAbs, both continuous and categorical (ie, positive or negative or not done), will be summarized descriptively by treatment group by visit for induction period and by treatment sequence by visit for all visits.
- Table may be produced summarizing the total number of samples analyzed by treatment group and by treatment sequence for ADAs, NAbs, positive ADA at baseline, positive ADA Post Dose, positive NAb at Baseline and positive NAb Post Dose.
- The incidence, cumulative incidence (numbers and percentage) of participants deemed Post Dose positive for ADA and NAb will be summarized over time, overall for study drug (regardless of dose) and by treatment group for induction period and by treatment sequence.
- The descriptive statistics of PK concentration will be summarized by visit and by ADA status (positive, negative, not done) in each treatment group for the induction period and in each treatment sequence. Same analysis will be carried out for NAbs.
- The descriptive statistics of total sTL1A concentration will be summarized by visit and by ADA status (positive, negative, not done) in each treatment group for the induction period and in each treatment sequence. Same analysis will be carried out for NAbs.

- The descriptive statistics of partial Mayo will be summarized by visit and by ADA status (positive, negative, not done) in each treatment group and treatment sequence. Same analysis will be carried out for NAbs.

- The number and percentage of participants achieving clinical remission, clinical remission 2, modifed remission 1,modified remission 2, endoscopic improvement at Week 14 will be summarized by ADA status (positive, negative, not done) in each treatment group. Same analysis will be carried out for NAbs.

- The number and percentage of participants achieving clinical remission, clinical remission 2, modifed remission 1, modified remission 2, endoscopic improvement, endoscopic remission at Week 56 will be summarized by ADA status (positive, negative, not done) for each treatment sequence. Same analysis will be carried out for NAbs.

- The summary of time to first ADA/NAbs onset Post Baseline, overall and by treatment group and by treatment sequence.

- The summary of time to first ADA/NAbs onset Post Baseline by Visit, by treatment group and by treatment sequence.

- The summary statistics of ADA/NAb titers over time for each treatment group for induction period and treatment sequence will be presented.

- The summary of ADA and NAb status at the end of study to characterized the participants response as persistent or not.

- Listing of individual level ADA and NAb response.

Summaries for samples for which testing was not done may also be included in selected summaries. Additional summaries by grouped treatment sequences might be provided.

In addition, data permitting the following analysis may be provided:

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

- Impact of ADA and NAb status on biomarkers (ie, serum TL1A, fecal calprotectin, hsCRP).

- Impact of ADA and NAb status on modified remission 1, modified remission 2, and endoscopic improvement 2 endpoints.

6.6. Analysis of PK Data

- Endpoints:

  a. PF-06480605 concentrations during the induction period through Week 14.

  b. PF-06480605 concentration from Week 14 through the End of Study Visit.

- Analysis set: PK Concentration Population.

- Analysis methodology: PK concentrations will be summarized and presented with descriptive statistics. Population PK modeling may be performed with the concentration data from this study alone or combined with data from other studies. In addition, a relationship between exposures and efficacy/safety endpoints may be evaluated using population PK/PD approach. Any population analyses conducted will not be part of the clinical study report (CSR) and may be reported separately.

- Intercurrent events and missing data: the missing data will not be imputed. The values below limit of quantification are discussed in Section 5.3.3.

- A listing of all concentrations by participant, treatment sequence, and nominal time post-dose. The concentration listing will also include the actual times. Deviations from the nominal time will be given in a separate listing.

- A summary of concentrations by nominal time post-dose in each treatment group for induction period and in each treatment sequence for induction and chronic period, where the set of statistics will include n, mean, median, standard deviation, coefficient of variation (CV), minimum, maximum and the number of concentrations above the lower limit of quantification.

- Median concentrations time plots (on both linear and semi-log scales) against nominal time post-dose in each treatment group and treatment sequence.

- Mean (SE) concentrations time plots (on both linear and semi-log scales) against nominal time post-dose in each treatment group and treatment sequence.

- Individual concentration time plots by participant (on both linear and semi-log scales) against actual time post-dose (there may be separate plots for each participant per scale).

Note: The length of time used for the x-axes of these plots will be decided on review of the data and will depend on how long PF-06480605 concentration is quantifiable in the matrix. For summary statistics, median and mean plots by sampling time, the nominal PK sampling time will be used, for individual participant plots by time, the actual PK sampling time will be used.

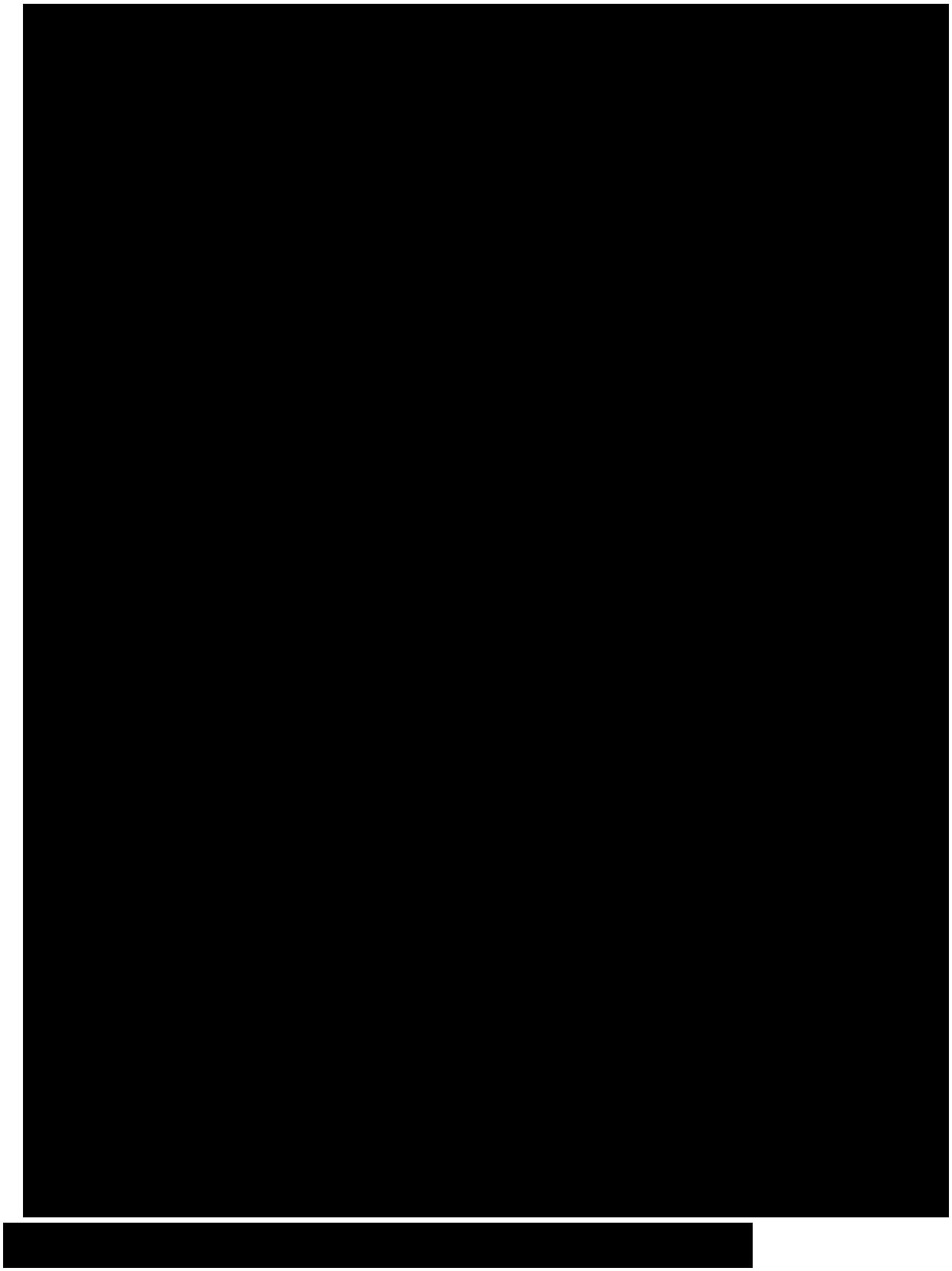
- If data permits, non-compartmental PK parameters may be derived from the PF-06480605 serum concentrations.

- PK parameters will be summarized by visit or dosing visit.

Additional summaries by grouped treatment sequences might be provided.

[redacted]

[redacted]



6.8. Safety Summaries and Analyses

All safety analyses will be performed on the safety population. For chronic period summaries, safety population will include all participants who took at least 1 dose of investigational product in the chronic period. The safety analysis results will be summarized descriptively. All clinical AEs, SAEs, TEAEs, withdrawal due to AEs, ECGs, vital signs and safety laboratory data will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of participants.

Safety endpoints (Section 3.8) will be summarized descriptively through appropriate data tabulations by participant counts and percentage. Participant listings will be produced for the safety endpoints accordingly. Other statistical analysis for safety data are described in the following.

6.8.1. Adverse Events

Adverse events reported throughout the study will be analyzed by treatment group, treatment sequence, and applicable period according to Pfizer reporting standard. Summaries will be presented for induction period, chronic period up to Week 56 visit, and Follow-up period (post Week 56 visit).

All safety analyses will be performed on the safety population. The safety analysis results will be summarized descriptively. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate. All safety endpoints will be listed and summarized in accordance with Pfizer Standards.

Additional safety analysis may be done as needed based on the safety data.

[redacted]

a. [redacted]

[redacted]

b. [redacted]

[redacted]

a. [redacted]

b. [redacted]

c. [redacted]

d. [redacted]

[redacted]

a. [redacted]

b. [redacted]

c. [redacted]

[redacted]

[redacted]

[redacted]

6.8.4. Laboratory Data

Unscheduled clinical labs may be obtained at any time during the study to assess any perceived safety concerns at the investigator's discretion. Laboratory data will be listed and summarized in accordance with the Pfizer reporting standards.

6.8.5. Electrocardiograms

ECG data will be summarized according to Pfizer reporting standard. The value and 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, using N, mean, 90% confidence interval, standard deviation, median, minimum and maximum.

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.

6.8.6. Vital Signs

Vital signs (systolic blood pressure, diastolic blood pressure pulse, pulse rates and temperature) will be measured after 5 minutes of rest as indicated in the Schedule of Activities. The outcome will be summarized using N, mean, 90% confidence interval, median, standard deviation, minimum and maximum in accordance with the Pfizer reporting standards.

6.9. Subgroup Analyses

The number and proportion of participants achieving clinical remission, clinical remission 2, modified remission 1, modified remission 2 and endoscopic improvement at Week 14; and the number and proportion of participants achieving clinical remission, clinical remission 2, modified remission 1, modified remission 2, endoscopic improvement and endoscopic remission at Week 14 and by Week 56 by treatment group will be summarized for the subgroups below (numbers permitting):

- Prior anti-TNF treatment: experienced, naïve;
- Anti-integrin: experienced, naïve;
- Anti-IL-12/23 Inhibitors: experienced, naïve;
- Biologic: experienced, naïve;
- Steroid exposure at baseline: yes, no.

Biologics include all participants who had exposure to at least one category: anti-TNF or anti-Integrin or anti-IL-12/23 Inhibitors.

6.10. Baseline and Other Summaries and Analyses

6.10.1. Baseline Summaries

The baseline variables described in Section 3.9.3 will be summarized for each of 4 treatment groups of induction period and for each treatment sequence.

6.10.2. Study Conduct and Participant Disposition

Participant's evaluation, disposition, discontinuation will be summarized, separately for induction and chronic dosing periods by treatment, according to Pfizer standards.

6.10.3. Study Treatment Exposure

A summary of compliance and the number of doses received as well as the median total dose by visit and treatment group will be provided for each period.

The exposure to study drug will be summarized by total number of applications, the total number of days of dosing, the number and the proportion of participants who are compliant with the dosing regimen.

6.10.4. Concomitant Medications and Nondrug Treatments

Prior drug and non-drug treatment, concomitant drug and non-drug treatment will be summarized according to Pfizer standard.

In addition, summaries for steroids at baseline and change in doses over time in Induction and Chronic period will be presented.

Individual plots/listings may be generated to present the behavior of subjects on steroids.

7. 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 plans.

7.1. Interim Analyses and Summaries

The focus of the first IA analyses will be to assess the primary efficacy endpoint by comparing each active treatment dose (450 mg, 150 mg and 50 mg) versus placebo at Week 14. The key analysis strategy is described in details in the following:

- Estimand strategy: Composite (Section 2).
- Analysis set: Evaluable population (Section 4).
- Analysis methodology: The response comparing each dose (450 mg, 150mg and 50 mg) of active treatment against placebo will be analyzed using Chang and Zhang method (Section 5.2.1.1) and CMH method (Section 5.2.1.2).
- Intercurrent events and missing data: handling of missing data is same as described in Section 5.3.1.1.
- The number and percent of response will be presented for completers by each treatment group over time.
- The number and percent of response will be presented for completers by each treatment group and selected stratification factor
- The CMH estimate of risk difference of comparing each treatment dose versus placebo will be presented. Their corresponding 2-sided 90% CIs will be estimated using the minimum risk weight method.

The focus of the second IA will be to characterize long term immunogenicity and safety. The key analysis strategy is described in Sections 6.5, 6.7 and 6.8.

8. REFERENCES

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9. APPENDICES

Appendix 1. Data Derivation Details

Appendix 1.1. Definition and Use of Visit Windows in Reporting

Visit windows will be used for efficacy variables, and for any safety data that display/summarize by study visit.

For other endpoints (eg, ECG, vital signs), visit windows will be applied for summary statistics by study visit if required.

For the lab values, if the calculated study day for the labelled baseline visit is not study Day 1, but falls within 42 days before the start of the study dosing, then that data should be used for the baseline instead of leaving baseline missing.

For Week 14 visit, if participant missed the visit window, but came for that visit before medical product administration at week 16 visit, the participant results will be included in Week 14 analysis.

For Week 56 visit, if participant missed the visit window or endoscopy, but came for endoscopy visit within 8 weeks from the last dose administration visit at Week 52, the participant data will be included in Week 56 analysis. If applicable, components of the score should be pulled from that endoscopy visit when reporting for endoscopy and histology related endpoints.

The use of visit windows in reporting are listed below:

Visit Label	Target Day	Start Day	End Day
Screening	NA	Day -42	Day -1
Week 0	Day 1	Day 1	Day 1
Week 4	Day 29	Day 2	Day 43
Week 8	Day 57	Day 44	Day 71
Week 12	Day 85	Day 72	Day 90
Week 14	Day 99	Day 91	Day 106
Week 16	Day 113	Day 107	Day 127
Week 20	Day 141	Day 128	Day 155

Visit Label	Target Day	Start Day	End Day
Week 24	Day 169	Day 156	Day 183
Week 28	Day 197	Day 184	Day 211
Week 32	Day 225	Day 212	Day 239
Week 36	Day 253	Day 240	Day 267
Week 40	Day 281	Day 268	Day 295
Week 44	Day 309	Day 296	Day 323
Week 48	Day 337	Day 324	Day 351
Week 52	Day 365	Day 352	Day 379
Week 56	Day 393	Day 380	Day 407
Week 60	Day 421	Day 408	Day 435
Week 64	Day 449	Day 436	NA

For the other values, if the calculated study day for the labelled baseline visit is not study Day 1, but falls before the start of the study dosing, then that data should be used for the baseline instead of leaving baseline missing.

If two or more visits fall into the same window, keep the one closer to the Target Day. If two visits are equaled distant from the Target Day in absolute value, the larger visit should be used.

If applicable, early withdrawal visit will be mapped to visit week using windowing and summarize together with subjects remaining on the study.

Follow up visits after early withdrawal visit may be summarized separately due to potential for confounding caused by allowance to start rescue medication after early withdrawal visit (early withdrawal visit Follow up visit 1, early withdrawal visit Follow up visit 2, early withdrawal visit Follow up visit 3) and they will be presented together (information will be included in listings).

For subjects who are on the study, visits summaries for follow up will be presented by Week 56, Week 60 and Week 64.

Appendix 1.2. Endpoint Derivations

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

The Total Mayo score ranges from 0 to 12, with higher scores indicating more severe disease.

Data are from Schroeder et al.

Stool frequency (SFR)[†]:

0 = Normal no. of stools for this subject

1 = 1 to 2 stools more than normal

2 = 3 to 4 stools more than normal

3 = 5 or more stools more than normal

Subscore: 0 to 3

Rectal bleeding (RBL)[‡]:

0 = No blood seen

1 = Streaks of blood with stool less than half the time

2 = Obvious blood with stool most of the time

3 = Blood alone passes

Subscore: 0 to 3

Findings on endoscopy (END):

0 = Normal or inactive disease

1 = Mild disease (erythema, decreased vascular pattern, mild friability)

2 = Moderate disease (marked erythema, lack of vascular pattern, friability, erosions)

3 = Severe disease (spontaneous bleeding, ulceration)

Subscore: 0 to 3

Physician's global assessment (PGA)[§]:

0 = Normal

1 = Mild disease

2 = Moderate disease

3 = Severe disease

Subscore: 0 to 3

† Each subject serves as his or her own control to establish the degree of abnormality of the stool frequency.

‡ The daily bleeding score represents the most severe bleeding of the day.

§ The physician's global assessment acknowledges the three other criteria, the subject's daily recollection of abdominal discomfort and general sense of wellbeing, and other observations, such as physical findings and the subject's performance status.

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] 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.

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.

Each of the Mayo subscores has value within 0-3 range where a higher value indicated a more severe disease symptoms. The Total Mayo Score TM(t) at each time is calculated as the sum of the subscores so that

- TM(t)=SFR(t)+RBL(t)+END(t)+PGA(t)

The Partial Mayo Score PM(t) does not incorporate the endoscopy score so that:

- PM(t)=SFR(t)+RBL(t)+ PGA(t)

The modified Mayo Score PM(t) does not incorporate the endoscopy Physician's global assessment score so that:

- MM(t)= SFR(t)+RBL(t)+END(t)

The following definitions of binary outcomes are based on the subscores of the Total Mayo Score:

1. **Clinical Remission**: Total Mayo Score ≤2, with no individual subscore >1.
2. **Clinical Remission 2**: Total Mayo Score ≤2, rectal bleeding subscore = 0 and with all other subscore scores = 0 or 1.
3. **Remission FDA definition 1 (Remission FDA1, also called Modified remission 1)**: endoscopic subscore = 0 or 1, stool frequency subscore = 0, and rectal bleeding subscore = 0.
4. **Remission FDA definition 2 (Remission FDA2, also called Modified remission 2)**: endoscopic subscore = 0 or 1, ≥1-point decrease from baseline to achieve a stool frequency subscore = 0 or 1, and rectal bleeding subscore = 0.
5. **Endoscopic Improvement**: endoscopic subscore = 0 or 1.

6. **Endoscopic Remission**: endoscopic subscore = 0.

7. **Clinical Response**: ≥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.

8. **Symptomatic Remission:** a Total Mayo Score ≤2 with no individual subscore >1 and both rectal bleeding and stool frequency subscores of 0.

9. **Deep Remission:** a Total Mayo Score ≤2 with no individual subscore >1 and both endoscopic and rectal bleeding subscores of 0.

10. **Clinical modified response:** decrease from baseline in the modified Mayo score of ≥2 points and ≥30% from baseline, plus a decrease in rectal bleeding subscores of ≥1 or an absolute rectal bleeding subscores of ≤1

These definitions are summarized in the Table 7.

Table 7. Endpoints Based on the Subscores of Total Mayo Score

N	Outcome at time t	Mayo Score	SFR	RBL	END	PGA
1	**Clinical Remission**	TM(t) ≤2	SFR(t) ≤1	RBL(t) ≤1	END(t) ≤1	PGA(t) ≤1
2	**Clinical Remission 2**	TM(t) ≤2	SFR(t) ≤1	RBL(t) = 0	END(t) ≤1	PGA(t) ≤1
3	**Remission FDA1 (modified remission 1)**	Any	SFR(t) =0	RBL(t) = 0	END(t) ≤1	Any
4	**Remission FDA2 (modified remission 2)**	Any	SFR(0) – SFR(t) ≥1 and SFR(t) ≤1	RBL(t) = 0	END(t) ≤1	Any
5	**Endoscopic Improvement**	Any	Any	Any	END(t) ≤1	Any
6	**Endoscopic Remission**	Any	Any	Any	END(t) =0	Any
7	**Clinical Response**	TM(0)-TM(t) ≥3 and $100 \times \frac{TM(0)-TM(t)}{TM(0)} \geq 30\%$	Any	RBL(0) – RBL(t) ≥1 or RBL (t) ≤1	Any	Any
8	**Symptomatic Remission**	TM(t) ≤2	SFR(t) =0	RBL(t) = 0	END(t) ≤1	PGA(t) ≤1

N	**Outcome at time t**	**Mayo Score**	**SFR**	**RBL**	**END**	**PGA**
9	**Deep Remission**	TM(t) ≤2	SFR(t) ≤1	RBL(t) = 0	END(t) =0	PGA(t) ≤1
10	**Clinical modified response**	MM(0)-MM(t) ≥2 and $100 \times \frac{MM(0)-MM(t)}{MM(0)} \geq 30\%$	Any	RBL(0) – RBL(t) ≥1 or RBL (t) ≤1	Any	Any

Appendix 3. Summary of Approaches to be Used for Primary and Secondary Outcomes in Induction Period (Efficacy, PRO, and Biomarkers)

Analysis of Binary Outcomes During the Induction Period

Method	Imputation	Application
Descriptive Statistics	None	All endpoints and all visits specified in the protocol
Chan and Zhang	NRI	All endpoints and all visits specified in the protocol
Adjustment for strata (supportive for primary and selected secondary endpoints)	NRI	clinical remission, clinical remission 2, modified remission 1, modified remission 2 and endoscopic improvement at Week 14
Bayesian e_{max} modeling (supportive for primary endpoint)	NRI	clinical remission at Week 14
CMH test (supportive for primary and selected secondary enspoints)	NRI	clinical remission, clinical remission 2, modified remission 1, modified remission 2 and endoscopic improvement at Week 14

Analysis of Continuous Outcomes During Induction Period

Method	Imputation	Application
Descriptive Statistics	None	All endpoints and all visits
MMRM	None	All endpoints and all visits

Summary of Approaches to be Used for Outcomes in Chronic Period (Efficacy, PRO, and Biomarkers)

Analysis of Binary Outcomes during the Chronic Period

Method	Imputation	Application
Descriptive Statistics	None	All endpoints and all visits specified in the protocol
Blyth-Still-Casella (one-sample proportions)	NRI	All endpoints and all visits specified in the protocol

Analysis of Continouse Outcomes during the Chronic Period

Method	Imputation	Application
Descriptive Statistics	None	All endpoints and all visits specified in the protocol
MMRM	None	All endpoints and all visits specified in the protocol

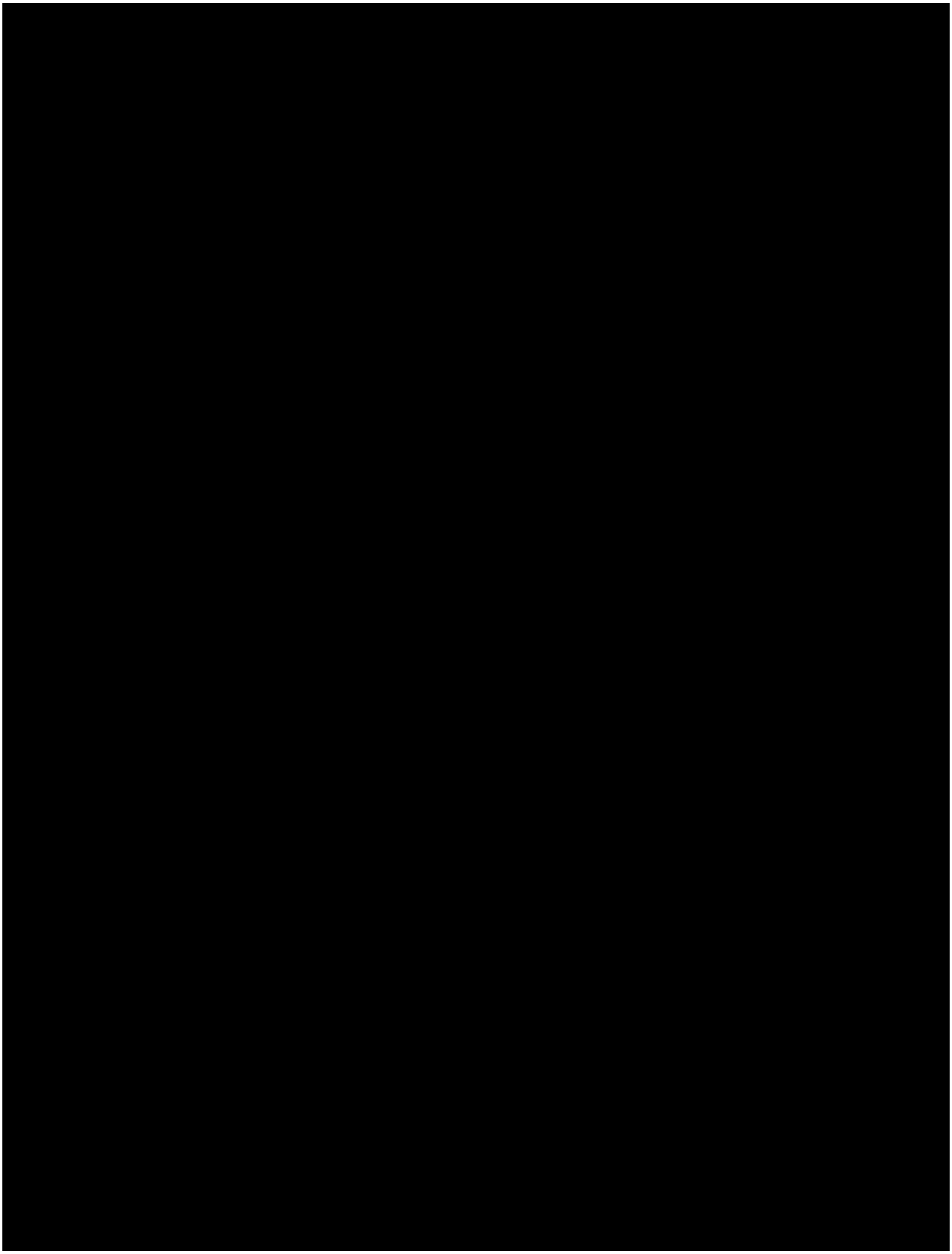
Appendix 4. Histological Scores

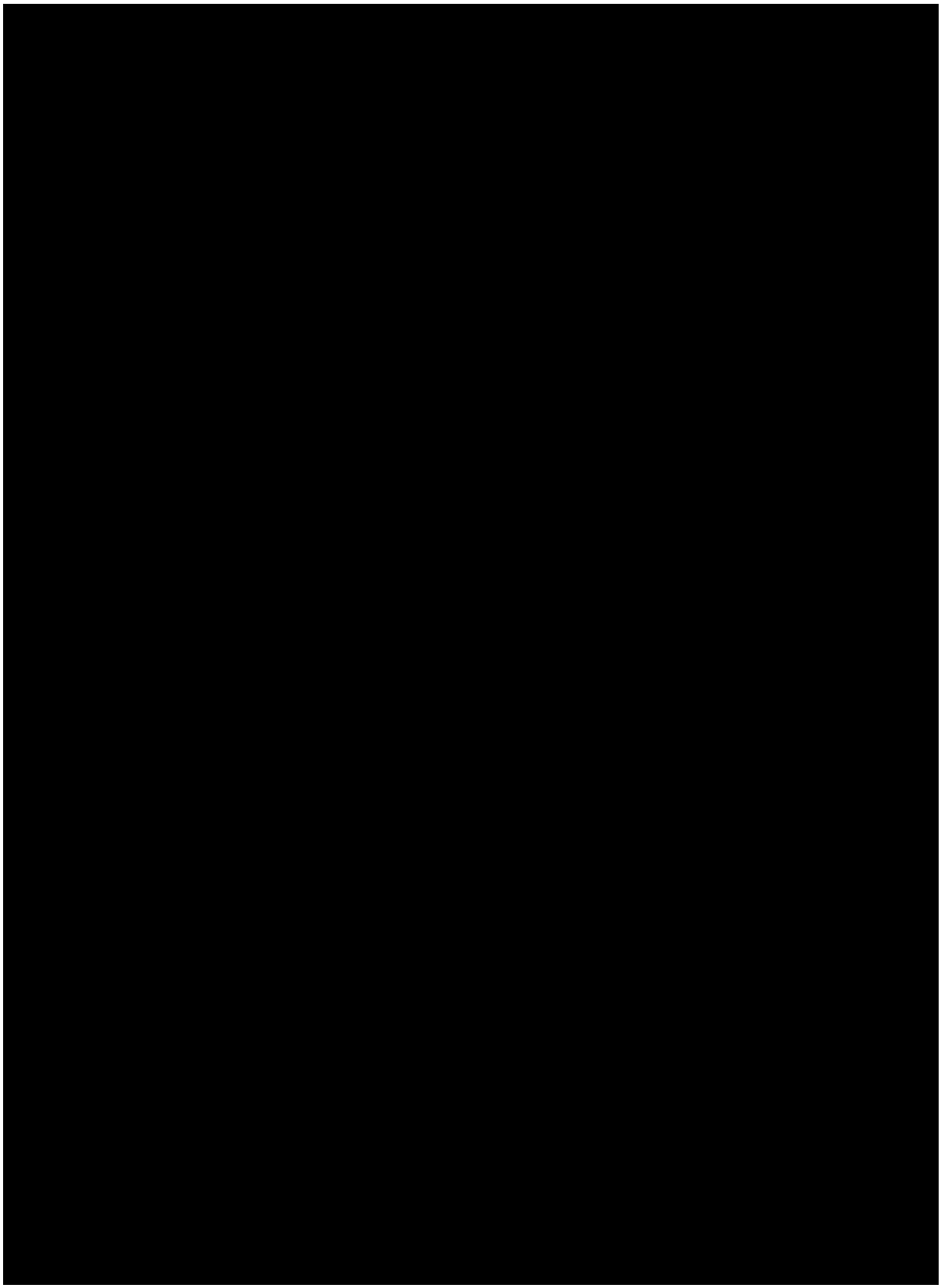
[redacted]

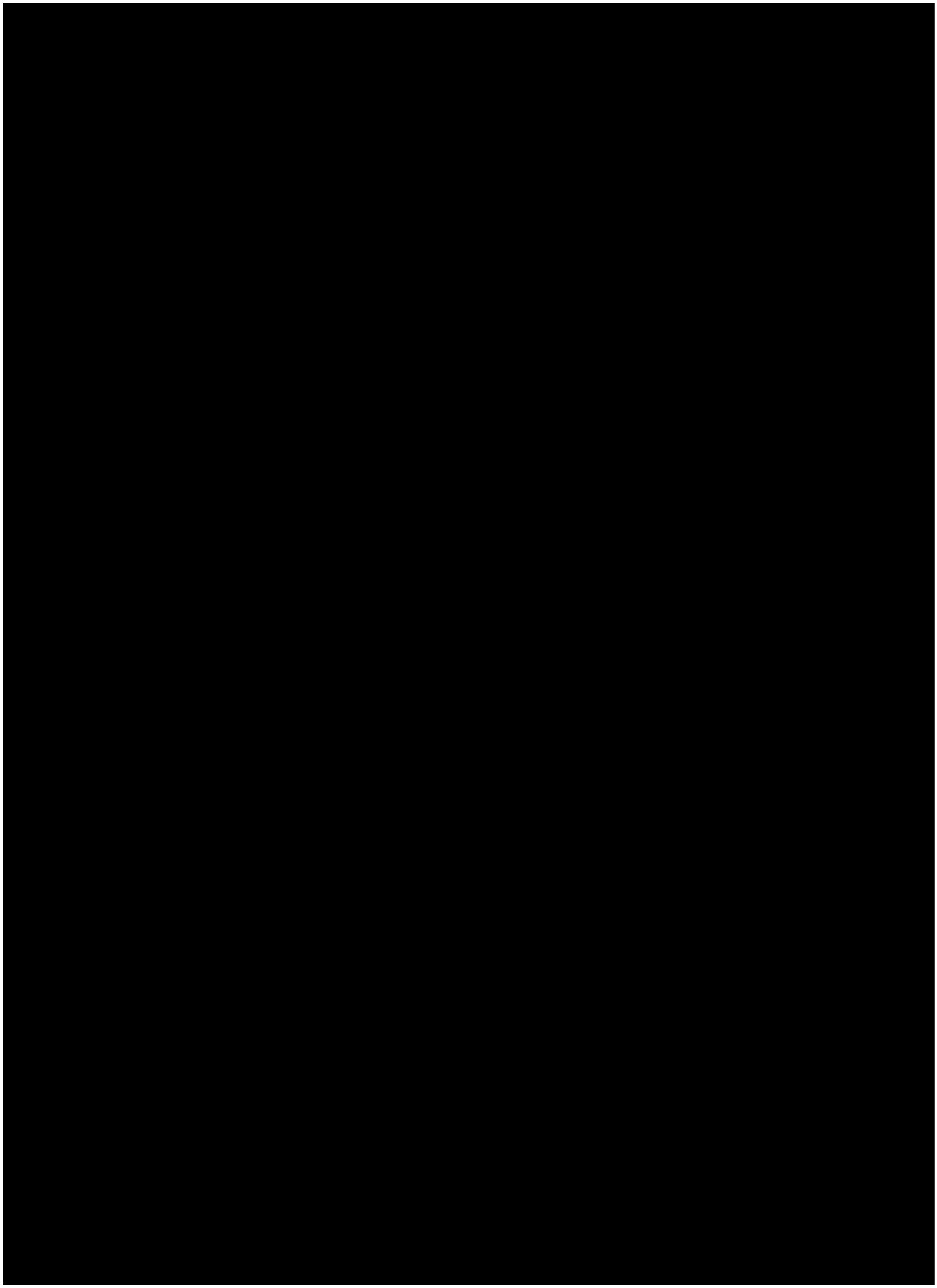
[redacted]

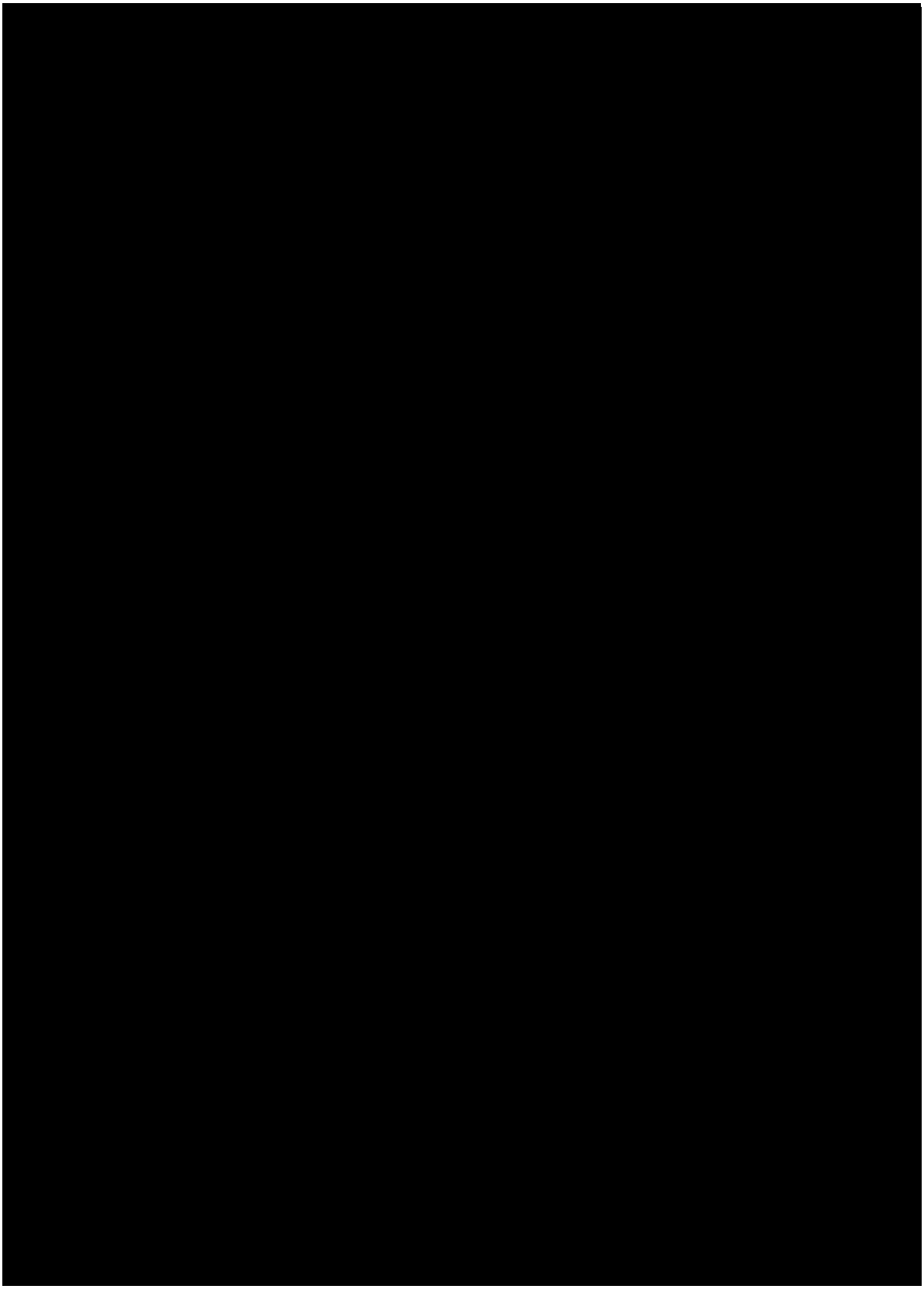
[redacted]

[redacted]









Appendix 7. List of Abbreviations

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 time
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
C_{max}	maximum observed concentration
CM	centimeter
CONSORT	Consolidated Standards of Reporting Trials
CPK	Creatine Phosphokinase
CRA	Cytokine Release Assay
CRF	case report form
CRO	contract research organization
CRU	clinical research unit
CSF	cerebrospinal fluid
CSR	clinical study report
CT	clinical trial

Abbreviation	Term
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
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
eDiary	Electronic diary
EDP	exposure during pregnancy
EFD	embryo fetal development
EMA	European Medicines Agency
END	Findings on endoscopy
EoT	End of Treatment
[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
HbA_{1c}	hemoglobin A_{1c}
HBcAb	hepatitis B core antibody
HBsAb	Hepatitis surface antibody
HBsAg	hepatitis B surface antigen
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
hsCRP	high sensitivity C-reactive protein
IB	investigator's brochure
IBD	Inflammatory bowel disease

Abbreviation	Term
[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
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
MCS	Mental component summary
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model Repeated Measures
mg	milligram
6-MP	Mercaptopurine
msec	millisecond
MTX	methotrexate
N/A	not applicable
Nab	neutralizing antibodies
NIMP	noninvestigational medicinal product
NK	Natural killer cells
NOAEL	no-observed-adverse-effect level
PBMC	peripheral blood mononuclear cell
PCD	primary completion date

Abbreviation	Term
PCS	physical component summary
PD	pharmacodynamic(s)
PGA	Physician global assessment
[redacted]	
PI	principal investigator
PK	pharmacokinetic(s)
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
Q4W	every 4 weeks
R_{ac}	Accumulation ratios
RBC	red blood cell
RBL	Rectal bleeding
[redacted]	
RNA	ribonucleic acid
SAD	Single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
[redacted]	
SFR	Stool frequency
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
$t_{1/2}$	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