Protocol B7981005

A PHASE 2B, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, PARALLEL GROUP, DOSE RANGING STUDY OF ORAL PF-06651600 AND PF-06700841 AS INDUCTION AND CHRONIC THERAPY IN SUBJECTS WITH MODERATE TO SEVERE ULCERATIVE COLITIS

Statistical Analysis Plan
(SAP)

Version: **4.0**

Date: **05 May 2021**

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1. VERSION HISTORY

This SAP for Study B7981005 is based on the protocol Amendment 7 dated 10NOV2020.

Table 1. Summary of Major Changes in SAP Amendments

SAP Version	Change	Rationale
1	Not Applicable	Not Applicable.
2	The endpoints in the chronic and induction periods were separated. Addition of some statistical methods for all variables.	Major updates were required as a result of protocol amendment (version 7, Nov 17, 2020).
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study B7981005. 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.

This study was designed before the estimands terminology was incorporated into the protocols and SAPs. Therefore, discussion of the estimands and intercurrent events is not included into the document.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives and Endpoints During the Induction Period

Table 2. Objectives and Endpoints During the Induction Period

Primary Objective(s):	**Primary Endpoint(s):**
• To evaluate the efficacy of PF-06651600 and PF-06700841 at Week 8 in subjects with moderate to severe UC.	• Total Mayo score at Week 8.
Secondary Objective(s):	**Secondary Endpoint(s):**
• To evaluate the safety and tolerability of PF-06651600 and PF-06700841 in subjects with moderate to severe UC in induction.	• Incidence and severity of laboratory abnormalities, adverse events, serious adverse events and withdrawals due to adverse events, vital signs, 12-lead ECG in the induction period. • Incidence of serious infections (see Section 7.2.8. of Protocol for definition) in the induction period.
• To evaluate the efficacy of PF-06651600 and PF-06700841 in induction of remission at Week 8 in subjects with moderate to severe UC.	• Proportion of subjects achieving remission based on total Mayo score of ≤2 with no individual subscore >1 and a rectal bleeding subscore of 0 at Week 8.
• To evaluate the efficacy of PF-06651600 and PF-06700841 in improvement of endoscopic appearance at Week 8 in subjects with moderate to severe UC.	• Proportion of subjects achieving improvement in endoscopic appearance (defined as a Mayo endoscopic subscore of ≤1) at Week 8.
• To evaluate the effect of PF-06651600 and PF-06700841 in induction of other clinical outcomes in subjects with moderate to severe UC.	• Proportion of subjects achieving clinical response at Week 8. • Proportion of subjects in endoscopic remission at Week 8. • Proportion of subjects in symptomatic remission at Week 8. • Proportion of subjects achieving deep remission at Week 8. • Partial Mayo scores and change from baseline over time at Weeks 2, 4 and 8. • Change from baseline at Week 8 in total Mayo score.
• To evaluate the effect of PF-06651600 and PF-06700841 in induction on patient reported outcomes (PRO) in subjects with moderate to severe UC.	• The scores and change from baseline in Inflammatory Bowel Disease Questionnaire (IBDQ) Total score and domains (Bowel Symptoms, Systemic Symptoms, Emotional Function and Social Function) at Weeks 4 and 8. • The proportion of subjects with IBDQ total score ≥170 at Weeks 4 and 8. • The proportion of subjects with ≥16 point increase in IBDQ total score from baseline at Weeks 4 and 8. • Proportion of subjects with improvement in IBDQ bowel symptom domain at Weeks 4 and 8. The improvement is defined as an increase of at least 1.2 points from baseline in average score among

	IBDQ bowel symptom domain (items 1, 5, 9, 13, 17, 20, 22, 24, 26, 29). • The scores and change from baseline in Short Form 36 version 2, acute (SF-36v2) (physical and mental component summary scores: PCS & MCS, and 8 domain scores) at Weeks 4 and 8. • The scores and change from baseline in EuroQoL 5 Dimensions (EQ-5D-3L & EQ-5D VAS) at Weeks 4 and 8.
CCI	
CCI	• Change from baseline in serum hsCRP levels over time. • Change from baseline in fecal calprotectin. CCI • Change from baseline in hematological values including reticulocytes, hemoglobin, neutrophils, platelets, CCI .
• To explore outcomes based on investigational criteria in induction. CCI	• Proportion of subjects in remission* based on modified Mayo score (Total Mayo score minus PGA). • Proportion of subjects with partial Mayo score ≤2 with no individual subscore >1 in response to treatment over time. • Proportion of subjects with reduction of ≥2 points from baseline in partial Mayo score over time. • Proportion of subjects in endoscopic response at Week 8. Endoscopic response is defined by a decrease from baseline in the endoscopic subscore of 1 point or more. CCI
CCI	

3.2. Objectives and Endpoints During the Chronic Period

Table 3. Objectives and Endpoints During the Chronic Therapy Period

Primary Objective(s):	**Primary Endpoint(s):**
• To evaluate the safety and tolerability of PF-06651600 and PF-06700841 in subjects with moderate to severe UC in the chronic period.	• Incidence and severity of laboratory abnormalities, adverse events, serious adverse events and withdrawals due to adverse events, vital signs, 12-lead ECG in the chronic period. • Incidence of serious infections (see Section 7.2.8 for definition) in the chronic period.
Secondary Objective(s):	**Secondary Endpoint(s):**
• To evaluate the efficacy of PF-06651600 and PF-06700841 at Week 32 in subjects with moderate to severe UC.	• Total Mayo score at Week 32.
• To evaluate the efficacy of PF-06651600 and PF-06700841 for achieving remission at Week 32.	• Proportion of subjects in remission based on total Mayo score of ≤2 with no individual subscore >1 and a rectal bleeding subscore of 0 at Week 32.
• To evaluate the efficacy of PF-06651600 and PF-06700841 in improvement of endoscopic appearance at Week 32 in subjects with moderate to severe UC.	• Proportion of subjects achieving improvement in endoscopic appearance (defined as a Mayo endoscopic subscore of ≤1) at Week 32.
Tertiary/Exploratory Objective(s):	**Tertiary/Exploratory Endpoint(s):**
CCI [redacted]	[redacted]
• To explore the effect of PF-06651600 and PF-06700841 in subjects with moderate to severe UC in the chronic dosing period.	• Proportion of subjects achieving clinical response at Week 32. • Proportion of subjects in endoscopic remission at Week 32. CCI [redacted] • Change from baseline at Week 32 in total Mayo score.
CCI [redacted]	[redacted]

	CCI [redacted]
CCI [redacted]	• Change from baseline in serum high-sensitivity C-reactive protein (hsCRP) levels over time. • Change from baseline in fecal calprotectin. CCI [redacted] • Change from baseline in hematological values including reticulocytes, hemoglobin, neutrophils, platelets, CCI [redacted]
• To explore outcomes based on investigational criteria in the chronic period. CCI [redacted]	• Proportion of subjects in remission* based on modified Mayo score (Total Mayo score minus Physician's global assessment (PGA) at Week 32. CCI [redacted] • Proportion of subjects in endoscopic response at Week 32. Endoscopic response is defined by a decrease from baseline in the endoscopic subscore of 1 point or more. CCI [redacted]
CCI [redacted]	[redacted]

CCI [redacted]	

3.3. Timing of the Efficacy Evaluations and CCI [redacted]

The tables in Section 3.1-3.2 were copied from the most Version 7 (Nov 18, 2020) version of the protocol. Tables 4 and 5 provide an additional insight to the programmer/data analyst. 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 definition of the outcomes is discussed in the Section 5.

The BL characters in the tables denote baseline observations (either day 1 or screening visits) and IND and CHR characters denote observations during the induction and chronic periods of the study respectively.

Table 4. Continuous Outcomes. Scores and Changes from Baseline will be Reported

N	Definition	BL	w2	w4	w8	w12	w16	w20	w24	w32
1	Total Mayo score	BL			IND					CHR
2	Partial Mayo score (PM)	BL	IND	IND	IND	CHR	CHR	CHR	CHR	CHR
3	IBDQ A. Total score B. Bowel symptoms, C. Systemic symptoms D. Emotional function E. Social function	BL		IND	IND					CHR
4	Scores and changes from baseline (based on SF-36v2) A. PCS B. MCS **C.** 8 domain scores	BL		IND	IND					CHR
6	Euro Quality of Life Questionnaire Scores A. EQ-5D-3L B. EQ-5D-VAS	BL		IND	IND					CHR
7	Biomarkers A. hsCRP B. fecal calprotectin	BL BL		IND IND	IND IND		CHR CHR		CHR CHR	CHR CHR
	CCI [redacted]									
	E. hematological values (includes reticulocytes, hemoglobin, neutrophils,platelets, CCI [redacted]	BL								
CCI [redacted]										

BL = Baseline or Screening as per schedule of Activities in the protocol. IND= Induction. CHR= Chronic

Table 5. Binary outcomes. Proportion of Responders will be Reported. Definition of Responder is Given Below

N	Definition	BL	w2	w4	w8	w12	w16	w20	w24	w32
1	**Remission** based on **total** Mayo score	BL			IND					CHR
C C [redacted]		[redacted]			[redacted]					[redacted]
I [redacted]		[redacted]			[redacted]					[redacted]
4	**Endoscopic remission** based on endoscopic subscore of **total** Mayo score	BL			IND					CHR
5	**Clinical response** based on **total** Mayo score	BL			IND					CHR
6	**Endoscopic response** based on endoscopic subscore of **total** Mayo score	BL			IND					CHR

N	Definition	BL	w2	w4	w8	w12	w16	w20	w24	w32
7	**Improvement in endoscopic appearance** based on endoscopic subscore of total Mayo score	BL			IND					CHR
8	**Remission** based on **modified** Mayo score	BL			IND					CHR
[redacted]		[redacted]								
11	**IBDQ total score ≥170**	BL		IND	IND					CHR
12	**≥16 point increase in IBDQ total score from baseline**	BL		IND	IND					CHR
13	**Improvement in IBDQ bowel symptom domain**			IND	IND					CHR
[redacted]		[redacted]								

4. STUDY DESIGN

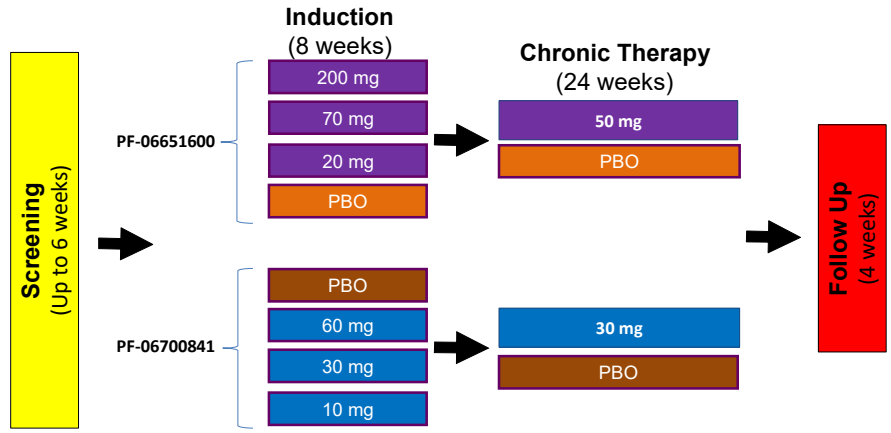
The study design was modified after an enrollment of the initial cohort of subjects. In the initial design (Pre-Amendment 5 protocol) subjects who enrolled into the chronic period of the study were randomized to the active and control treatment arms with the randomization ratio of 2:1. After the modification of the protocol by the Amendment 5 the randomization to placebo in the chronic therapy period was no longer allowed and each subject in the chronic therapy period was assigned to the active arm only. The change in the protocol occurred at the time when approximately 52 subjects were enrolled into the chronic therapy period and therefore limited number of subjects were randomized to the placebo arm during the chronic therapy period.

4.1. Initial (Pre-Amendment 5 Protocol) Study Design

This is a Phase 2b, randomized, double-blind, placebo-controlled, parallel group, multicenter study in subjects with moderate to severe active UC. The first part of the study is a screening period of up to 6 weeks followed by an 8-week duration double-blind induction period. The study will not be blinded across the PF-06651600 and PF-06700841 cohorts but will be placebo-controlled double-blinded within each investigational product. At Week 8, all subjects will be re-randomized within their respective treatment cohort (PF-06651600 or PF-06700841) or placebo into an additional 24 week double blind chronic therapy period

followed by a 4 week follow up period after the last dose of investigational product for a total of 32 weeks.

Figure 1 Study Design Schematic – Pre-Amendment 5 Protocol



Powered for induction only
N = 360 total (55/cohort with total induction placebo = 30)

For analysis, placebo groups will be combined to yield final drug:placebo ratios of 2:2:2:1.

Approximately 360 subjects in total will be randomized into the study. In the induction period, three oral dose levels (20, 70, and 200 mg daily) of PF-06651600 plus matching placebo in a 4:4:4:1 ratio and three oral doses (10, 30, and 60 mg daily) of PF-06700841 plus matching placebo in a 4:4:4:1 ratio will be investigated. For analysis placebo groups will be combined to yield final drug: placebo ratios of 2:2:2:1 for each drug. Following the screening period, subjects who meet the eligibility criteria at the baseline visit will be randomly assigned to receive one of 8 treatments.

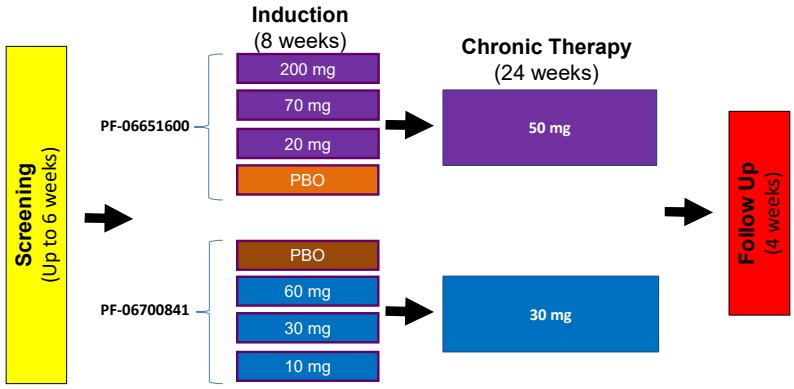
Following the induction period of the study, all subjects, including those on placebo, will be re-randomized within their respective treatment cohort to enter the chronic therapy period. In the chronic therapy period, 50 mg of PF-06651600 and 30 mg of PF-06700841 given daily (or matching placebos) will be investigated. Subjects re-randomized to chronic therapy will be stratified according to their responder status. Responder status will be determined by the use of a decrease from baseline greater than or equal to 2 in the partial Mayo score as a stratification variable. The re-randomization will be conducted using a 2:1 ratio for both PF-06651600 (50 mg):placebo and PF-06700841 (30 mg):placebo.

4.2. Amendment 7 Protocol

This is a Phase 2b, randomized, double-blind, placebo-controlled (in the induction period and not in the chronic dosing period), parallel group, multicenter study in subjects with moderate to severe active UC. The first part of the study is a screening period of up to 6 weeks followed by an 8 week double-blind induction period. The study will not be blinded across

the PF-06651600 and PF-06700841 cohorts, but will be placebo-controlled during the induction phase, and double-blinded within each investigational product. At Week 8, all subjects will be assigned to their respective treatment cohort (either PF-06651600 or PF-06700841 as during the induction phase) into an additional 24 week active chronic dosing period followed by a 4 week follow up period after the last dose of investigational product for a total of 36 weeks. The chronic dosing period is in effect open label; with both subjects and Investigators aware that they have been assigned to PF-06651600 or PF-06700841, and that there is no placebo control.

Figure 2 Study Design Schematic – Amendment 7 Protocol



•Powered for induction period only
•N = 360 total (55/cohort with total induction placebo = 30)
•Randomization into induction period with 4:4:4:1 ratio of actives and a placebo
•For analysis of induction period, placebo groups will be combined to yield 2:2:2:1 ratio of actives and a placebo.

Approximately 360 subjects in total will be randomized into the study. Following the screening period, subjects who meet the eligibility criteria at the baseline visit will be randomly assigned to receive one of 8 treatments. In the induction period, three oral dose levels (20, 70, and 200 mg daily) of PF-06651600 plus matching placebo in a 4:4:4:1 ratio and three oral doses (10, 30, and 60 mg daily) of PF-06700841 plus matching placebo in a 4:4:4:1 ratio will be investigated. For analysis of the induction period, placebo groups will be combined to yield final drug: placebo ratios of 2:2:2:1 for each drug at Week 8.

Following the induction period of the study, all subjects will enter the chronic dosing period in which there will be no placebo arms (Protocol Amendment 5). All subjects (including placebo subjects) from the double-blind PF-06651600 treatment/placebo induction period will receive 50 mg of PF-06651600 for 24 weeks. All subjects (including placebo subjects) from the double-blind PF-06700841/placebo induction period will receive 30 mg of PF-06700841 for 24 weeks.

Any subject who discontinues early from the induction period prior to the Week 8 visit should undergo the procedures for an Early Termination visit on the last day the subject takes the investigational product or as soon as possible thereafter, and will not be permitted to enter the chronic dosing period. For subjects who discontinue early from the chronic dosing period (after the Week 8 visit, but prior to the Week 32 visit), the procedures scheduled for an Early Termination visit will be performed on the last day the subject takes the investigational product or as soon as possible thereafter. After completion of the Early Termination visit subjects will enter the follow-up period.

5. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

5.1. Efficacy and Patient Reported Endpoints

The tables with the listing of the endpoints for induction and chronic periods are presented in Section 3. The details of the calculations for efficacy endpoints are discussed in the Appendices 1-5.

5.2. Baseline Variables

Unless specifically stated otherwise, the baseline value for the induction and chronic periods is defined as the last non-missing measurement collected prior to the first administration of study drug at Day 1. Baseline value will be used as a covariate in statistical models for change from baseline in efficacy endpoints to adjust for baseline disease severity (except for cLDA models).

Baseline data collected/measured at Screening visit are:

- Medical history, prior concomitant medications height, weight, Mayo score (Total), CCI [redacted] and FCP.

Baseline data collected/measured at Baseline (Day 1) are listed below:

a. Complete physical examination, and vital signs & temperature.

b. hsCRP, CCI [redacted] Mayo score (Partial), CCI [redacted] IBDQ, EQ-5D-3L + VAS, and SF-36.

c. Labs (Hematology and serum chemistry (including fasting lipid panel), Cystatin C, GFR, urine analysis, CCI [redacted]).

5.3. Safety Endpoints

Safety will be assessed by the spontaneous reporting of AEs (including rashes and hearing), physical examinations, and clinical laboratory results in all subjects who receive at least one dose of the investigational product. Unscheduled safety assessments may be performed at any time during the study to assess any perceived safety concerns.

5.3.1. Adverse Events

An adverse event is considered treatment-emergent adverse event (TEAE) to a given treatment if the event started during the effective duration of treatment regardless of whether a similar event of equal or greater severity existed in the baseline period.

Safety endpoints will be assessed by the spontaneous reporting of:

- Incidence of TEAEs.
- Incidence of SAEs and AEs leading to discontinuation.
- Incidence of serious infections.

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 subjects.

5.3.2. Laboratory Data

Below is a list of hematology and serum chemistry test parameters.

- **Hematology**: Hemoglobin, hematocrit, red blood cell count, platelet count, white blood cell count, total neutrophils (Abs), eosinophils (Abs), monocytes (Abs), basophils (Abs), lymphocytes (Abs), prothrombin time (PT)/international normalized ratio (INR)/partial thromboplastin time (PTT), and reticulocytes (% and Abs).
- **Serum chemistry**: Blood urea nitrogen, creatinine, cystatin C, glucose, calcium, sodium, potassium, chloride, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, direct bilirubin, alkaline phosphatase, uric acid, albumin, total protein, creatine kinase (CK), CK fractionation, total cholesterol, triglycerides, high-density lipoproteins (HDL), and low-density lipoprotein (LDL).
- CRP.
- [redacted]

5.3.3. Vital Signs, Including Height and Weight and ECG

Vital sign measurements are respiratory rate, oral or tympanic temperature or axillary methods, respiratory rate, pulse rate, and blood pressures.

Height and weight are collected at screening and post-treatment (only weight).

5.3.4. Physical Examinations

Complete physical examination consists of general appearance, skin, head, eyes, ears, nose and throat (HEENT), heart, lungs, breast (optional), abdomen, external genitalia (optional), extremities, neurologic function, back, and lymph nodes. Targeted physical examination consists of skin, heart, lungs, abdomen, and examination of body systems where there are

symptom complaints by the subject. Full and targeted physical examinations must include a full body skin examination. Skin examinations should include visual inspection of the breasts and external genitalia, even if a subject does not wish to have breast and/or external genitalia examined as part of the physical examination.

CCI [redacted]

5.5. PD Endpoints

CCI [redacted]

- High sensitivity C-reactive protein (hsCRP).
- [redacted]
- Fecal calprotectin.

CCI [redacted]

6. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

6.1. Intent-to-Treat Analysis Sets

An intent-to-treat (ITT) analysis set will include all randomized subjects who received at least one dose of PF-06651600, PF-06700841, or placebo. The intent to treat dataset (ITT) will be used for primary efficacy analysis.

As a result of discontinuation in the randomization to placebo during chronic period of the study the number of subjects that are randomized to placebo treatment for each of the treatment arms in induction period will be small. The observations (during both induction and randomization periods for these subjects will not be used in the analysis (see also Section 8.2.3). We will call the corresponding dataset a modified intent-to treat dataset (mITT).

At the time of interim analysis only the incomplete versions of ITT and mITT datasets will be available as the observations for some of the subjects who did not dropped out of the study will be missing. For the continuous outcomes all available data will be used in the corresponding analyses. No imputation of binary outcomes will be done for the binary outcomes and missing values will be excluded from the analyses.

6.2. Safety Analysis Set

The safety (SAF) analysis set is defined as those subjects who received at least one dose of PF-06651600, PF-06700841, or placebo.

CCI [redacted]

7. GENERAL METHODOLOGY AND CONVENTIONS

Final analyses will occur after database lock after Last Subject Last Visit (LSLV).

7.1. Hypotheses and Decision Rules

For any given active arm, the null hypothesis is that the there is no difference between the distributions of the total Mayo score at Week 8 between the pooled placebo group and active arm. This hypothesis is equivalent to the hypothesis that there is no difference between the distributions of the *change from baseline* of total Mayo score at Week 8 between the pooled placebo group and active arm. The equivalence of the two formulation is caused by the equality of the expected values of total Mayo score at the baseline caused by randomization.

The placebo-adjusted treatment effect for a particular group can therefore be defined as the difference between the expected values of total Mayo Scores (ie, expected total Mayo score at Week 8 in the active treatment group minus the expected total Mayo score at Week 8 in the placebo treatment group) or difference between the expected values of *change from baseline* in total Mayo Scores (ie, expected *change from baseline* in total Mayo score at Week 8 in the active treatment group minus the expected *change from baseline* in total Mayo score at Week 8 in the placebo treatment group), A successful treatment should *decrease* total Mayo score and therefore the desired treatment effect is negative. The treatment arm is declared efficacious if an upper limit of 2-sided 90% confidence interval for the treatment effect is below zero.

7.2. Analyses for Continuous Endpoints

- 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 of interest and reference treatment group. There will be no imputation of the missing data. This method will be applied to all continuous endpoints and all visits.

- The constrained Longitudinal Data Analysis (eg, Fitzmaurice, Laird and Ware (2011) and Malincrodt and Lipkovich (2017)) is expected to provide improved estimates in comparison to the ones provided by the descriptive statistics. The modeling approach explicitly uses the equality of the expected baseline values of continuous outcomes at different treatment groups caused by randomization. The model will include baseline and post-baseline values as the response vector and will form fixed effects using treatment andvisit (see SAS code in Appendix 8). An unstructured

variance-covariance matrix will be allowed. If there are convergence issues, a compound-symmetry structure will be used.

- The longitudinal Mixed Model Repeated Measures (MMRM) modeling (eg, Fitzmaurice, Laird and Ware (2011)[6] and Malincrodt and Lipkovich (2017)[7]) will provide an alternative and qualitatively similar estimates to the estimates provided by the cLDA method. The MMRM model uses the change from baseline as an outcome and the baseline value as a covariate. The model includes treatment, baseline, treatment by visit and baseline by visit interactions for post-baseline visits as fixed effects. An unstructured variance-covariance matrix will be allowed. While the MMRM model is similar in spirit to the cLDA the estimates provided by these models may be slightly different and could be viewed as complementary.

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7.3. Analyses for Binary Endpoints

- Chan and Zhang method (1999)[8] provides confidence intervals of proportions of response for each treatment group and difference between the response in the treatment group of interest and reference treatment group. The confidence intervals for one sample proportions will be based on Blyth Still Casella. The analysis will be applied to the ITT dataset without imputation and with non-responder imputation (NRI) of missing data. These analyses will be applied to all binary outcomes at all visits.

- Bayesian e_{max} modeling (as described in the Appendix 6) will be used for the analysis of dose dependence of the probability of remission based on total Mayo score. The analysis will be applied to the ITT dataset of observations at Week 8 with non-responder imputation. Note that this analysis needs to be done separately for two datasets. The first dataset contains observations for pooled placebo data and observations for active treatment groups exposed to the PF-06651600 (JAK3 inhibitor) and the second dataset contains pooled placebo data and PF-06700841 (JAK1-TYK2 inhibitor).

- The stratum-adjusted difference in probabilities of remission based on total Mayo score between the treatment group of interest and reference treatment group will be based on the approach described by Mehrotra and Railkar (2000).[9] The non-responder imputation will be done before the analysis. The analysis will be applied to the ITT dataset of observations at Week 8. The definition of the strata will be given in the Section 8.4.1.

7.4. Analyses for Categorical Endpoints

The frequency and percentage for each category will be presented.

7.5. Analyses for Time-to-Event Endpoints

None.

7.6. Methods to Manage Missing Data

Non-responder imputation (NRI) will be used for the missing binary data. For the continuous outcomes observed data will be used for the analysis. The subjects with the data that have data missing due to COVID 19 will be removed from the analysis (eg, not included into numerator and denominator in the calculation of proportion of responders).

8. ANALYSES AND SUMMARIES

Analyses of efficacy, PRO CCI [redacted] endpoints will be based on the ITT population. Safety analyses will be based on the SAF population.

8.1. Treatment Groups

In the initial design of the trial subjects in the chronic therapy were randomized to the active and placebo group. Table 6 shows the possible sequences of treatment assignments.

Table 6. Treatment Sequences

N	Compound	Dose in the induction period	Dose in the chronic therapy period
1	PF-06651600(JAK3)	200 mg	50 mg
2	PF-06651600(JAK3)	70 mg	50 mg
3	PF-06651600(JAK3)	20 mg	50 mg
4	Placebo	Placebo	50 mg
5	PF-06700841 (JAK1-TYK2)	60 mg	30 mg
6	PF-06700841 (JAK1-TYK2)	30 mg	30 mg
7	PF-06700841 (JAK1-TYK2)	10 mg	30 mg
8	Placebo	Placebo	30 mg
9	PF-06651600(JAK3)	200 mg	Placebo
10	PF-06651600(JAK3)	70 mg	Placebo
11	PF-06651600(JAK3)	20 mg	Placebo
12	Placebo	Placebo	Placebo
13	PF-06700841 (JAK1-TYK2)	60 mg	Placebo
14	PF-06700841 (JAK1-TYK2)	30 mg	Placebo
15	PF-06700841 (JAK1-TYK2)	10 mg	Placebo

The total number of subjects (about 17) who were randomized to placebo in the chronic therapy period (sequences 9-15) is very small.

8.1.1. Induction Period

In the analysis of the data observed up to the end of the induction treatment there are 6 active treatment groups and pooled placebo groups.

Table 7. Treatment Groups in the Induction Period (ITT data set)

N	Compound	Dose in the induction period
1	PF-06651600(JAK3)	200 mg
2	PF-06651600(JAK3)	70 mg
3	PF-06651600(JAK3)	20 mg
4	PF-06700841 (JAK1-TYK2)	60 mg
5	PF-06700841 (JAK1-TYK2)	30 mg
6	PF-06700841 (JAK1-TYK2)	10 mg
7	Placebo (pooled)	Placebo (pooled)

The active treatment groups will be compared to the combined placebo group.

8.1.2. Chronic Dosing Period

The descriptive summaries for all the 15 treatment groups corresponding to the treatment sequences presented in the Table 6 will be provided. A statistical modeling will be used for the analysis of the 8 groups corresponding to the treatment sequences that are assigned into the active treatment group during the chronic therapy period.

8.2. Efficacy, PRO and CCI [redacted] Analyses for the Induction and Chronic Therapy Period

8.2.1. Analyses for Induction Period Observations

The endpoints of interest and time of observations characterization are presented in the Sections 3.1 and 3.3. All the efficacy, PRO CCI [redacted] outcomes will be analyzed based on the ITT data set. The details of approaches are shown in the Tables 8 and 9.

Table 8. Analysis of Continuous Outcomes During Induction Period

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

*The cLDA analysis is not needed for changes from baseline.

Table 9. Analysis of Binary Outcomes During the Induction Period

Method	Imputation	Application
Descriptive Statistics	None	All endpoints and all visits
Chang and Zhang	NRI	All endpoints and all visits
Adjustment for strata	NRI	Remission, modified remission and endoscopic improvement at Week 8 only
Bayesian e_{max} modeling	NRI	Remission based on Total Mayo score at Week 8 only

The goal of the analysis adjusted for strata is to evaluate robustness of the main analysis. The stratification analysis will be performed for remission, modified remission and endoscopic improvement. The stratification analyses will be based on the baseline exposure to the following treatments:

1. Anti-TNF: experienced/naïve.
2. Anti-integrin: experienced/naïve.
3. Anti-IL12/23 experienced/naïve.
4. Biologic: experienced/naïve.
5. Steroid exposure at baseline: y/n.
6. 5-ASA at baseline: y/n.

8.2.2. Primary Efficacy Analysis

Primary efficacy analysis will be conducted based on total Mayo score at Week 8. The Clda-based analysis will provide estimate of the treatment effect. The placebo-adjusted treatment effect for a particular group is defined as the difference between the expected values of total Mayo Scores (ie, expected total Mayo score at Week 8 in the active treatment group minus the expected total Mayo score at Week 8 in the placebo treatment group). A successful treatment should *decrease* total Mayo score and therefore the desired treatment effect is negative. The treatment arm is declared efficacious if an upper limit of 2-sided 90% confidence interval for the treatment effect is below zero.

8.2.3. Analysis of Observations in the Chronic Therapy Period

The endpoints of interest and time of observations characterization are presented in the Sections 3.2 and 3.3. All the efficacy, PRO CCI [redacted] outcomes will be analyzed based on the modified ITT data set.

Table 10. Treatment Groups in the Induction and Chronic Period (mITT data set)

N	Compound	Dose in the induction chronic/periods
1	PF-06651600(JAK3)	200 mg/50 mg
2	PF-06651600(JAK3)	70 mg/50 mg
3	PF-06651600(JAK3)	20 mg/50 mg
4	Placebo	Placebo/50 mg
5	PF-06700841 (JAK1-TYK2)	60 mg/30 mg
6	PF-06700841 (JAK1-TYK2)	30 mg/30 mg
7	PF-06700841 (JAK1-TYK2)	10 mg/30 mg
8	Placebo	Placebo/30 mg

The details of approaches are shown in the Table 11 and Table 12.

Table 11. Analysis of Continuous Outcomes During Chronic Period (main)

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

*The cLDA analysis is not needed for changes from baseline.

Table 12. Analysis of Binary Outcomes During the Chronic Period

Method	Imputation	Application
Descriptive Statistics	None	All endpoints and all visits
Chang and Zhang	NRI	All endpoints and all visits

CCI

CCI

[redacted]

8.5. Baseline and Other Summaries and Analyses

8.5.1. Baseline Summaries

Demographics and medical history will be summarized by treatment group according to Pfizer standards.

8.5.2. Study Conduct and Participant Disposition

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

8.5.3. 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 the total number of days of dosing, and number and percentage of subjects who are compliant with the dosing regimen.

8.5.4. Concomitant Medications and Nondrug Treatments

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

8.6. Safety Summaries and Analyses

Safety analysis will be based on the SAF analysis set.

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 subjects.

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. Categorical outcomes (eg, AEs) will be summarized by subject counts and percentage. Continuous outcome (eg, blood pressure, pulse rate, etc) will be summarized using N, mean, median, standard deviation, etc. Change from baseline in laboratory data, ECGs and vital signs will also be summarized. Subject listings will be produced for these safety endpoints accordingly.

8.6.1. Adverse Events

The safety data will be summarized in accordance with Pfizer Data Standards. All safety data will be summarized descriptively through appropriate data tabulations, descriptive statistics, categorical summaries, and graphical presentations. Safety endpoints for the study include:

- Treatment-emergent AEs and SAEs;
- Withdrawals from active treatment due to AEs;
- Serious infections, defined as any infection (for eg, viral, bacterial, and fungal) requiring hospitalization or parenteral antimicrobials. This definition programmatically should be consistent with 7.2.8 in the protocol.

8.6.2. Laboratory Data

Laboratory data will be summarized, for induction period and chronic dosing period, in accordance with the Pfizer reporting standards.

8.6.3. Vital Signs

Vital signs including will be summarized for each period, in accordance with the Pfizer reporting standards.

8.6.4. Electrocardiograms

ECG data will be summarized for each period, in accordance with the Pfizer reporting standards.

8.6.5. Physical Examination

Physical examination data will be summarized for each period, in accordance with the Pfizer reporting standards.

9. INTERIM ANALYSES

At least one interim analysis (IA) for futility will be performed. The final number and timing of the IA(s) will be defined by the Sponsor, but a preliminarily one will be conducted approximately 6 months after the randomization of the first subject and/or after at least 50% of the planned subjects, ie, approximately 160 subjects, have completed the 8 week induction period.

The interim analysis is based on the remission endpoint. The futility analysis of remission at Week 8 will be utilizing the Bayesian framework outlined in the interim analysis plan. Informative prior distribution model for the placebo arm, will be used for the interim analysis data. The futility might be declared if the posterior probability of the treatment effect of the highest dose for each asset meets a specified criterion as outlined in the Interim analysis plan.

The interim analysis will not have an option to stop the trial early for efficacy.

10. REFERENCES

CCI

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11. APPENDICES

11.1. Appendix 1 Mayo Scoring System for Assessment of Ulcerative Colitis Activity and Outcomes Based on Subscores of Mayo Score

11.1.1. Subscores of Total Mayo Score

The Mayo score ranges from 0 to 12, with higher scores indicating more severe disease. Data are from Schroeder et al.

Stool frequency:

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:

0 = No blood seen
1 = Streaks of blood with stools 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

The scoring denoted by the END incorporates evaluation of friability into the scoring. The END definition is used in all definitions of the outcomes used in the study.

Physician's global assessment:

0 = Normal
1 = Mild disease
2 = Moderate disease
3 = Severe disease
Subscore, 0 to 3

11.1.2. Endpoints Based on the Subscores of Total Mayo Score, Partial Mayo Score and Modified Mayo Scores

Total Set of Subscores of Total Mayo Score consists of four subscores:

- Stool frequency (SFR);
- Rectal bleeding (RBL);
- Finding on endoscopy (END);
- Physician's global assessment (PGA).

Each of the subscores has value within 0-3 range where a higher value indicates a more severe disease symptom. The total 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 MM (t) does not include PGA components 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. **Remission**: total Mayo score of 2 points or lower, with no individual subscore exceeding 1 point and a rectal bleeding subscore of 0. The calculation of the remission status is based on the endoscopy score END (see Appendix 3). The friability status is incorporated into evaluation of END.
2. **Deep remission**: total Mayo score of 2 points or lower, with no individual subscore exceeding 1 point and a 0 on both endoscopic and rectal bleeding subscore.
3. **Symptomatic remission**: total Mayo score of 2 points or lower, with no individual subscore exceeding 1 point, and both rectal bleeding and stool frequency subscores of 0.
4. **Endoscopic remission**: endoscopic subscore of 0.
5. **Clinical response**: decrease from baseline in total Mayo score of at least 3 points and at least 30%, with an accompanying decrease in the subscore for rectal bleeding of at least 1 point or absolute subscore for rectal bleeding of 0 or 1.
6. **Endoscopic response**: a decrease from baseline in the endoscopic subscore of 1 point or more.
7. **Improvement in endoscopic appearance:** Mayo endoscopic subscore of ≤1.

These definitions are summarized in the Table 13.

Table 13. Endpoints Based on the Subscores of Total Mayo Score

N	Outcome at time t	TM	SFR	RBL	END	PGA
1	Remission	TM(t) ≤2	SFR(t) ≤1	RBL(t)=0	END(t) ≤1	PGA (t) ≤1
CCI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	Endoscopic remission	Any	Any	Any	END(t) =0	Any
5	Clinical response	TM(0)-TM(t) ≥3 and 100x(TM(0)-TM(t)/TM(0)≥30%	Any	RBL(0)-RBL(t) ≥1 or RBL(t) ≤1	Any	Any
6	Endoscopic response	Any	Any	Any	END(0)-END(t) ≥1	Any
7	Improvement in endoscopic appearance	Any	Any	Any	END(t) ≤ 1	Any

11.1.3. Endpoints Based on Partial Mayo and Modified Score

CCI [redacted]

[redacted]

3. Remission based on modified Mayo Score: (Total Mayo score minus PGA): endoscopic subscore = 0 or 1 AND stool frequency = 0 or 1 AND rectal bleeding = 0.

4. Response based on modified Mayo Score (Total Mayo score minus PGA): Decrease from baseline in modified total Mayo score of at least 2 points and at least 30%, with an accompanying decrease in the subscore for rectal bleeding of at least 1 point or absolute subscore for rectal bleeding of 0 or 1.

11.2. Appendix 2 Inflammatory Bowel Disease Questionnaire (IBDQ)

This questionnaire is designed to find out how you have been feeling during the last 2 weeks.

You will be asked about symptoms you have been having as a result of your inflammatory bowel disease, the way you have been feeling in general, and how your mood has been.

1. How frequent have your bowel movements been during the last two weeks? Please indicate how frequent your bowel movements have been during the last two weeks by picking one of the options from:

    A. BOWEL MOVEMENTS AS OR MORE FREQUENT THAN THEY HAVE EVER BEEN

    B. EXTREMELY FREQUENT

    C. VERY FREQUENT

    D. MODERATE INCREASE IN FREQUENCY OF BOWEL MOVEMENTS

    E. SOME INCREASE IN FREQUENCY OF BOWEL MOVEMENTS

    F. SLIGHT INCREASE IN FREQUENCY OF BOWEL MOVEMENTS

    G. NORMAL, NO INCREASE IN FREQUENCY OF BOWEL MOVEMENTS

2. How often has the feeling of fatigue or of being tired and worn out been a problem for you during the last 2 weeks? Please indicate how often the feeling of fatigue or tiredness has been a problem for you during the last 2 weeks by picking one of the options from:

    A. ALL OF THE TIME

    B. MOST OF THE TIME

    C. A GOOD BIT OF THE TIME

    D. SOME OF THE TIME

    E. A LITTLE OF THE TIME

    F. HARDLY ANY OF THE TIME

    G. NONE OF THE TIME

3. How often during the last 2 weeks have you felt frustrated, impatient, or restless? Please choose an option from:

    A. ALL OF THE TIME

    B. MOST OF THE TIME

    C. A GOOD BIT OF THE TIME

    D. SOME OF THE TIME

    E. A LITTLE OF THE TIME

    F. HARDLY ANY OF THE TIME

    G. NONE OF THE TIME

4. How often during the last 2 weeks have you been unable to attend school or do your work because of your bowel problem? Please choose an option from:

    A. ALL OF THE TIME

    B. MOST OF THE TIME

    C. A GOOD BIT OF THE TIME

    D. SOME OF THE TIME

    E. A LITTLE OF THE TIME

    F. HARDLY ANY OF THE TIME

    G. NONE OF THE TIME

5. How much of the time during the last 2 weeks have your bowel movements been loose? Please choose an option from:

    A. ALL OF THE TIME

    B. MOST OF THE TIME

    C. A GOOD BIT OF THE TIME

    D. SOME OF THE TIME

    E. A LITTLE OF THE TIME

    F. HARDLY ANY OF THE TIME

    G. NONE OF THE TIME

6. How much energy have you had during the last 2 weeks? Please choose an option from:

    A. NO ENERGY AT ALL

    B. VERY LITTLE ENERGY

    C. A LITTLE ENERGY

    D. SOME ENERGY

    E. A MODERATE AMOUNT OF ENERGY

    F. A LOT OF ENERGY

    G. FULL OF ENERGY

7. How often during the last 2 weeks did you feel worried about the possibility of needing to have surgery because of your bowel problem? Please choose an option from:

    A. ALL OF THE TIME

    B. MOST OF THE TIME

    C. A GOOD BIT OF THE TIME

    D. SOME OF THE TIME

    E. A LITTLE OF THE TIME

    F. HARDLY ANY OF THE TIME

    G. NONE OF THE TIME

8. How often during the last 2 weeks have you had to delay or cancel a social engagement because of your bowel problem? Please choose an option from:

    A. ALL OF THE TIME

    B. MOST OF THE TIME

    C. A GOOD BIT OF THE TIME

    D. SOME OF THE TIME

    E. A LITTLE OF THE TIME

    F. HARDLY ANY OF THE TIME

    G. NONE OF THE TIME

9. How often during the last 2 weeks have you been troubled by cramps in your abdomen? Please choose an option from:

    A. ALL OF THE TIME

    B. MOST OF THE TIME

    C. A GOOD BIT OF THE TIME

    D. SOME OF THE TIME

    E. A LITTLE OF THE TIME

    F. HARDLY ANY OF THE TIME

    G. NONE OF THE TIME

10. How often during the last 2 weeks have you felt generally unwell? Please choose an option from:

    A. ALL OF THE TIME

    B. MOST OF THE TIME

    C. A GOOD BIT OF THE TIME

    D. SOME OF THE TIME

    E. A LITTLE OF THE TIME

    F. HARDLY ANY OF THE TIME

    G. NONE OF THE TIME

11. How often during the last 2 weeks have you been troubled because of fear of not finding a washroom? Please choose an option from:

    A. ALL OF THE TIME

    B. MOST OF THE TIME

    C. A GOOD BIT OF THE TIME

    D. SOME OF THE TIME

    E. A LITTLE OF THE TIME

    F. HARDLY ANY OF THE TIME

    G. NONE OF THE TIME

12. How much difficulty have you had, as a result of your bowel problems, doing leisure or sports activities you would have liked to have done during the last 2 weeks? Please choose an option from:

    A. A GREAT DEAL OF DIFFICULTY; ACTIVITIES MADE IMPOSSIBLE

    B. A LOT OF DIFFICULTY

    C. A FAIR BIT OF DIFFICULTY

    D. SOME DIFFICULTY

    E. A LITTLE DIFFICULTY

    F. HARDLY ANY DIFFICULTY

    G. NO DIFFICULTY; THE BOWEL PROBLEMS DID NOT LIMIT SPORTS OR LEISURE ACTIVITIES

13. How often during the last 2 weeks have you been troubled by pain in the abdomen? Please choose an option from:

    A. ALL OF THE TIME

    B. MOST OF THE TIME

    C. A GOOD BIT OF THE TIME

    D. SOME OF THE TIME

    E. A LITTLE OF THE TIME

    F. HARDLY ANY OF THE TIME

    G. NONE OF THE TIME

14. How often during the last 2 weeks have you had problems getting a good night's sleep, or been troubled by waking up during the night? Please choose an option from:

    A. ALL OF THE TIME

    B. MOST OF THE TIME

    C. A GOOD BIT OF THE TIME

    D. SOME OF THE TIME

    E. A LITTLE OF THE TIME

    F. HARDLY ANY OF THE TIME

    G. NONE OF THE TIME

15. How often during the last 2 weeks have you felt depressed or discouraged? Please choose an option from:

    A. ALL OF THE TIME

    B. MOST OF THE TIME

    C. A GOOD BIT OF THE TIME

    D. SOME OF THE TIME

    E. A LITTLE OF THE TIME

    F. HARDLY ANY OF THE TIME

    G. NONE OF THE TIME

16. How often during the last 2 weeks have you had to avoid attending events where there was no washroom close at hand? Please choose an option from:

    A. ALL OF THE TIME

    B. MOST OF THE TIME

    C. A GOOD BIT OF THE TIME

    D. SOME OF THE TIME

    E. A LITTLE OF THE TIME

    F. HARDLY ANY OF THE TIME

    G. NONE OF THE TIME

17. Overall, in the last 2 weeks, how much of a problem have you had with passing large amounts of gas? Please choose an option from:

    A. A MAJOR PROBLEM

    B. A BIG PROBLEM

    C. A SIGNIFICANT PROBLEM

    D. SOME TROUBLE

    E. A LITTLE TROUBLE

    F. HARDLY ANY TROUBLE

    G. NO TROUBLE

18. Overall, in the last 2 weeks, how much a problem have you had maintaining or getting to, the weight you would like to be at? Please choose an option from:

    A. A MAJOR PROBLEM

    B. A BIG PROBLEM

    C. A SIGNIFICANT PROBLEM

    D. SOME TROUBLE

    E. A LITTLE TROUBLE

    F. HARDLY ANY TROUBLE

    G. NO TROUBLE

19. Many patients with bowel problems often have worries and anxieties related to their illness. These include worries about getting cancer, worries about never feeling any better, and worries about having a relapse. In general, how often during the last 2 weeks have you felt worried or anxious? Please choose an option from:

    A. ALL OF THE TIME

    B. MOST OF THE TIME

    C. A GOOD BIT OF THE TIME

    D. SOME OF THE TIME

    E. A LITTLE OF THE TIME

    F. HARDLY ANY OF THE TIME

    G. NONE OF THE TIME

20. How much of the time during the last 2 weeks have you been troubled by a feeling of abdominal bloating? Please choose an option from:

    A. ALL OF THE TIME

    B. MOST OF THE TIME

    C. A GOOD BIT OF THE TIME

    D. SOME OF THE TIME

    E. A LITTLE OF THE TIME

    F. HARDLY ANY OF THE TIME

    G. NONE OF THE TIME

21. How often during the last 2 weeks have you felt relaxed and free of tension? Please choose an option from:

    A. NONE OF THE TIME

    B. A LITTLE OF THE TIME

    C. SOME OF THE TIME

    D. A GOOD BIT OF THE TIME

    E. MOST OF THE TIME

    F. ALMOST ALL OF THE TIME

    G. ALL OF THE TIME

22. How much of the time during the last 2 weeks have you had a problem with rectal bleeding with your bowel movements? Please choose an option from:

    A. ALL OF THE TIME

    B. MOST OF THE TIME

    C. A GOOD BIT OF THE TIME

    D. SOME OF THE TIME

    E. A LITTLE OF THE TIME

    F. HARDLY ANY OF THE TIME

    G. NONE OF THE TIME

23. How much of the time during the last 2 weeks have you felt embarrassed as a result of your bowel problem? Please choose an option from:

    A. ALL OF THE TIME

    B. MOST OF THE TIME

    C. A GOOD BIT OF THE TIME

    D. SOME OF THE TIME

    E. A LITTLE OF THE TIME

    F. HARDLY ANY OF THE TIME

    G. NONE OF THE TIME

24. How much of the time during the last 2 weeks have you been troubled by a feeling of having to go to the bathroom even though your bowels were empty? Please choose an option from:

    A. ALL OF THE TIME

    B. MOST OF THE TIME

    C. A GOOD BIT OF THE TIME

    D. SOME OF THE TIME

    E. A LITTLE OF THE TIME

    F. HARDLY ANY OF THE TIME

    G. NONE OF THE TIME

25. How much of the time during the last 2 weeks have you felt tearful or upset? Please choose an option from:

    A. ALL OF THE TIME

    B. MOST OF THE TIME

    C. A GOOD BIT OF THE TIME

    D. SOME OF THE TIME

    E. A LITTLE OF THE TIME

    F. HARDLY ANY OF THE TIME

    G. NONE OF THE TIME

26. How much of the time during the last 2 weeks have you been troubled by accidental soiling of your underpants? Please choose an option from:

    A. ALL OF THE TIME

    B. MOST OF THE TIME

    C. A GOOD BIT OF THE TIME

    D. SOME OF THE TIME

    E. A LITTLE OF THE TIME

    F. HARDLY ANY OF THE TIME

    G. NONE OF THE TIME

27. How much of the time during the last 2 weeks have you felt angry as a result of your bowel problem? Please choose an option from:

    A. ALL OF THE TIME

    B. MOST OF THE TIME

    C. A GOOD BIT OF THE TIME

    D. SOME OF THE TIME

    E. A LITTLE OF THE TIME

    F. HARDLY ANY OF THE TIME

    G. NONE OF THE TIME

28. To what extent has your bowel problem limited sexual activity during the last 2 weeks? Please choose an option from:

    A. NO SEX AS A RESULT OF BOWEL DISEASE

    B. MAJOR LIMITATION AS A RESULT OF BOWEL DISEASE

    C. MODERATE LIMITATION AS A RESULT OF BOWEL DISEASE

    D. SOME LIMITATION AS A RESULT OF BOWEL DISEASE

    E. A LITTLE LIMITATION AS A RESULT OF BOWEL DISEASE

    F. HARDLY ANY LIMITATION AS A RESULT OF BOWEL DISEASE

    G. NO LIMITATION AS A RESULT OF BOWEL DISEASE

29. How much of the time during the last 2 weeks have you been troubled by nausea or feeling sick to your stomach? Please choose an option from:

    A. ALL OF THE TIME

    B. MOST OF THE TIME

    C. A GOOD BIT OF THE TIME

    D. SOME OF THE TIME

    E. A LITTLE OF THE TIME

    F. HARDLY ANY OF THE TIME

    G. NONE OF THE TIME

30. How much of the time during the last 2 weeks have you felt irritable? Please choose an option from:

    A. ALL OF THE TIME

    B. MOST OF THE TIME

    C. A GOOD BIT OF THE TIME

    D. SOME OF THE TIME

    E. A LITTLE OF THE TIME

    F. HARDLY ANY OF THE TIME

    G. NONE OF THE TIME

31. How often during the past 2 weeks have you felt a lack of understanding from others? Please choose an option from:

    A. ALL OF THE TIME

    B. MOST OF THE TIME

    C. A GOOD BIT OF THE TIME

    D. SOME OF THE TIME

    E. A LITTLE OF THE TIME

    F. HARDLY ANY OF THE TIME

    G. NONE OF THE TIME

32. How satisfied, happy, or pleased have you been with your personal life during the past 2 weeks? Please choose one of the following options from:

    A. VERY DISSATISFIED, UNHAPPY MOST OF THE TIME

    B. GENERALLY DISSATISFIED, UNHAPPY

    C. SOMEWHAT DISSATISFIED, UNHAPPY

    D. GENERALLY SATISFIED, PLEASED

    E. SATISFIED MOST OF THE TIME, HAPPY

    F. VERY SATISFIED MOST OF THE TIME, HAPPY

    G. EXTREMELY SATISFIED, COULD NOT HAVE BEEN MORE HAPPY OR PLEASED

11.3. Appendix 3 Short Form -36, version 2, acute (SF-36)

Please answer every question. Some questions may look like others, but each one is different. Please take the time to read and answer each question carefully by filling in the bubble that best represents your response.

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.
Thank you for completing this survey!

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. <u>Compared to one week ago</u>, how would you rate your health in general <u>now</u>?

Much better now than one week ago	Somewhat better now than one week ago	About the same as one week ago	Somewhat worse now than one week ago	Much worse now than one week ago
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c. Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d. Climbing several flights of stairs	☐ 1	☐ 2	☐ 3
e. Climbing one flight of stairs	☐ 1	☐ 2	☐ 3
f. Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g. Walking more than a mile	☐ 1	☐ 2	☐ 3
h. Walking several hundred yards	☐ 1	☐ 2	☐ 3
i. Walking one hundred yards	☐ 1	☐ 2	☐ 3
j. Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

[redacted]

4. During the past week, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. Had difficulty performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. During the past week, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

6. **During the past week, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?**

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. **How much bodily pain have you had during the past week?**

None	Very mild	Mild	Moderate	Severe	Very severe
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

8. **During the past week, how much did pain interfere with your normal work (including both work outside the home and housework)?**

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

9. These questions are about how you feel and how things have been with you during the past week. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past week…

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e. Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f. Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g. Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h. Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i. Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10. During the past week, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

11. How TRUE or FALSE is each of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a. I seem to get sick a little easier than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

11.4. Appendix 4. Euro Quality of Life Questionnaire 5 Dimensions 3 Levels and Visual Analog Scale (EQ-5D-3L & VAS)

Please note that the US-based weights will be used for the calculation of EQ-5D-3L & VAS as per the Pfizer data standards.

By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑

I have some problems in walking about ❑

I am confined to bed ❑

Self-Care

I have no problems with self-care ❑

I have some problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

Usual Activities *(eg, work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑

I have some problems with performing my usual activities ❑

I am unable to perform my usual activities ❑

Pain/Discomfort

I have no pain or discomfort ❑

I have moderate pain or discomfort ❑

I have extreme pain or discomfort ❑

Anxiety/Depression

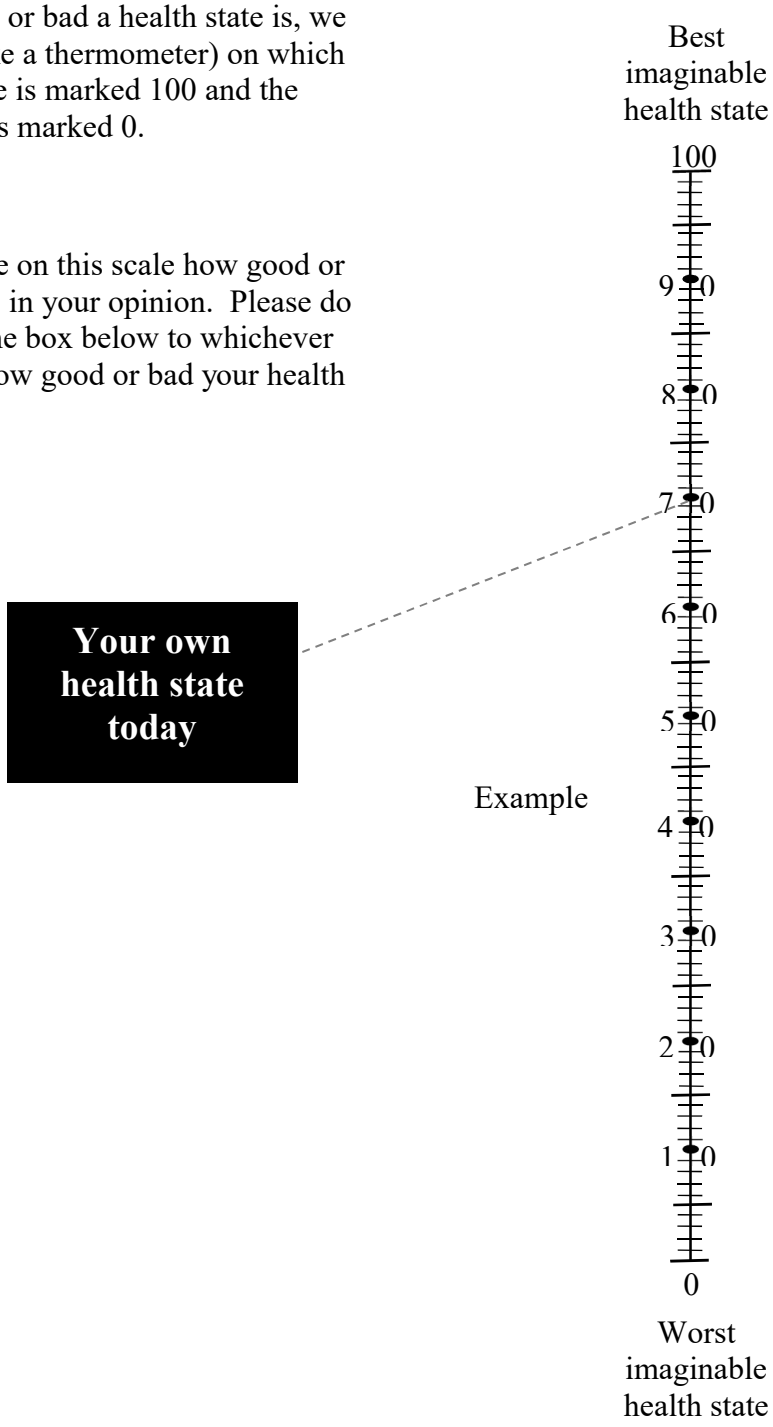
I am not anxious or depressed ❑

I am moderately anxious or depressed ❑

I am extremely anxious or depressed ❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.



CCI

[redacted]

[redacted]

CCI

[redacted]

[redacted]

CCI

[redacted]

[redacted]

11.7. Appendix 7 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 visits if required.

Visit Label	Target Day	Definition [Day window]
Screening		Days -42 to Day 0
Induction Period Weeks 0-8		
Week 0	Day 1, Baseline	Day 1
Week 2	15	Days 2 to 21
Week 4	29	Days 22 to 42
Week 8	57	Days 43 to 70
Chronic Dosing Period Weeks 8-24		
Week 12	85	Day 71 to 98
Week 16	113	Days 99 to 126
Week 20	141	Days 127 to 154
Week 24	169	Days 155 to 196
Week 32/Early Termination	225	Days 197 to 238
Follow-up		
Week 36	253	Day 239 to -

For the lab values, if the calculated study day for the labelled baseline visit is not study Day 1, but falls within 28 days before the start of the study dosing, then that data should be used for the baseline instead of leaving baseline missing.

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 closest to the Target Day. If two visits are equaled distant from the Target Day in absolute value, the later visit should be used.

11.8. Appendix 8 Sample SAS Code for cLDA

Id = subject ID, avisit = visit, trtpn = treatment group, y=response

```
data ds (keep= id avisitn week trtpn y treatment);
set admy;
treatment = trtpn;
if week = 0 then treatment = 1;
run;

proc mixed data = ds;
class id week (ref='0') treatment (ref='1');
model y = week treatment*week / solution cl vciry ddfm = kr outpm=fit3;
repeated week / subject = id type = un R Rcorr;
lsmeans treatment*week /pdiff;
run;
```