A PHASE 2B, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL GROUP, DOSE-RANGING STUDY TO EVALUATE THE EFFICACY AND SAFETY OF PF-06882961 ADMINISTRATION IN ADULTS WITH OBESITY

Study Intervention Number:	PF-06882961
Study Intervention Name:	Danuglipron
US IND Number:	148671
EudraCT Number:	2020-001312-19
Protocol Number:	C3421019
Phase:	2b

Short Title: A Phase 2b Study to Evaluate the Efficacy and Safety of PF-06882961 in Adults With Obesity

Document History

Document	Version Date
Amendment 2	16 September 2022
Amendment 1	16 December 2021
Original protocol	14 September 2020

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

Protocol Amendment Summary of Changes Table

Amendment 2 (16 September 2022)

Overall Rationale for the Amendment: The protocol was amended to add Cohort 3 to randomize approximately 112 participants across 4 additional study arms, including placebo and 3 PF-06882961 arms with 4-week dose titration steps to target doses of 80 mg BID, 140 mg BID and 200 mg BID. This cohort was added to characterize the tolerability and efficacy profile of 4-week dose titration steps. A separate visit schedule for Cohort 3 was added to the protocol to correspond to the 4-week dose titration intervals and extension of the treatment phase to 32 weeks for this cohort, to allow sufficient treatment duration at steady state dosing given the longer titration steps, and to generate additional efficacy data over a longer treatment period.

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Title page	Removed “26-Week” and “2-Part” from full title and short title.	Revised title to remove treatment duration and 2-part design as these aspects are not applicable to all cohorts in the study with the addition of Cohort 3.	Substantial
1.1 Synopsis	Revised wording in relevant sections to reflect the addition of Cohort 3.	Changed the synopsis to be consistent with corresponding sections of the main protocol to include Cohort 3.	Substantial
1.2 Schema	Inserted Figures 2 & 4 to show Cohort 3 Overall Study Schema & Titration Schema.	Added diagram representations of the study schema and titration schema for Cohort 3.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
1.3 Schedule of Activities (SoA)	Added a SoA table specific to Cohort 3, with in-clinic visits at 4-week intervals and interim telephone contacts between visits.	A separate SoA was developed to reflect the different visit schedule and treatment phase duration for Cohort 3.	Substantial
3 Objectives, Estimands, and Endpoints	Revised the table and footnotes, to define End of Treatment for Cohort 3 as Week 32 and specified weeks for Cohort 3 in endpoints as applicable.	The different treatment phase duration and visit schedule for Cohort 3 required revisions to specify timepoints where different weeks will be used in the endpoints from what is applicable for Cohorts 1 and 2.	Substantial
2.1 Study Rationale 4.1 Overall Design 4.2 Scientific Rationale for Study Design 4.3 Justification for Dose	Added details to describe Cohort 3 as applicable in sections, including randomization to double-blinded study intervention in 1 of 4 arms (placebo: 3 PF-06882961 arms with 4-week titration steps), the 32 week double-blind treatment phase, the rationale for adding Cohort 3 to characterize the tolerability and efficacy profile of 4-week dose titration steps, with placebo included to maintain the double-blind aspect, and the dose levels of 80 mg BID, 140 mg BID and 200 mg BID.	Revised sections as applicable to add information to reflect the study design with the addition of Cohort 3.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
6.1. Study Intervention(s) Administered 6.1.1 Administration 6.3.1 Allocation to Study Intervention	Revised the study intervention table to include Cohort 3 details, and inserted separate tables to show titration schemes and target doses for randomized regimens for Cohort 3.	Added information on study intervention, dosing and titration for Cohort 3 where it differs from Cohorts 1 and 2.	Substantial
8.1.3. Tertiary Efficacy Parameters: Patient Centered Outcome Assessments (PCOAs)	Revised the PCOA table to specify timepoints applicable for Cohort 3.	Some timepoints for administration of PCOAs for Cohort 3 differ from Cohorts 1 and 2 due to the different visit schedule, and treatment phase duration.	Substantial
8.4 Treatment of Overdose	Added that Cohort 3 overdose is defined as more than [redacted] tablets in 24 hours.	The definition of overdose for Cohort 3 is different from Cohorts 1 and 2, given the different tablet configuration for dosing.	Substantial
8.5 Pharmacokinetics	Added the specific visits with post-dose PK sampling for Cohort 3.	Visits with PK sampling for Cohort 3 differ from Cohorts 1 and 2 due to the different visit schedule and treatment phase duration.	Substantial
9 Statistical Considerations 9.1. Estimands and Statistical Hypotheses 9.2. Sample Size Determination 9.3 Analysis Sets 9.4 Statistical Analyses	Added details regarding statistical considerations and analyses for Cohort 3, including that data from participants in Cohort 3 will be analyzed separately from combined Cohorts 1 and 2, as well as End of Treatment definition and sample size.	Revised subsections as applicable to describe statistical aspects for Cohort 3.	Substantial
Throughout protocol	Revised wording to make references to visit numbers and SoA	Changed language where necessary to allow for	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
	applicable for Cohort 3.	differences between Cohort 3 and Cohorts 1 and 2.	
4.2 Scientific Rationale for Study Design 10.8 Appendix 8: Prohibited Prior/Concomitant Medications	Revised to allow CCI at dose of CCI mg, but prohibited at doses CCI mg.	CCI was previously prohibited at any dose, but is now allowed at the CCI mg dose based on current clinical DDI data.	Substantial
5 Study Population	Added wording to Exclusion # 16 to specify the washout for investigational products which are CCI	Revised based on current DDI information.	Substantial
10.8 Appendix 8: Prohibited Prior/Concomitant Medications	Changed timeframe for restriction for CCI to have a washout prior to first dose of study intervention rather than only post-randomization. Revised format to present as 2 tables: 1 for medications that may interact at the PK level, and 1 for other prohibited medications. Included more examples of medications in specific categories.	Updated to be consistent with current DDI information.	Substantial
6.6.1 Dose Titration	Added language to reflect that guidance will be provided separately for	Clarified that although dose modification is not allowed, guidance will be provided separately by the sponsor	Nonsubstantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
	approaches to manage mechanism of action based gastrointestinal-related AEs.	regarding approaches to manage gastrointestinal AEs.	
2.2.1 Nonclinical Overview 2.2.2 Clinical Overview 2.3.1 Risk Assessment	Revised wording to reflect updated information based on the most recent IB.	Revised to be consistent with the most recent IB.	Nonsubstantial
1.1 Synopsis 1.3 Schedule of Activities (SoA) 2.1 Study Rationale 3 Objectives, Estimands, and Endpoints 4 Study Design Throughout protocol	Clarified that the initial study design with a 2-part double-blinded treatment phase was applicable to Cohorts 1 and 2 and that Part B was approved before any participant reached the end of Part A. Removed wording referring to approaches for study conduct and data analyses if Part B was not approved.	The original protocol included a 2-part double-blind treatment phase with Part B dosing Weeks 17-26 contingent on supportive data from a nonclinical toxicology study ongoing at the time of original protocol finalization. Part B was approved and all participants in Cohorts 1 and 2 were able to continue into Part B, so removed wording for alternative approaches if Part B was not conducted.	Nonsubstantial
Throughout protocol	Replaced “standard” with “1-week” and “slow” with “2-week” when referring to titration schemes for study arms in Cohorts 1 and 2.	Revised terminology for description of titration schemes for Cohorts 1 and 2 to denote number of weeks rather than “standard” and “slow” (ie, 1-week and 2-week, respectively) for consistency in how titration is described across all 3 cohorts in the study.	Nonsubstantial
4.1.1. Assessment of Safety and Tolerability While Study is Ongoing	Added wording to clarify safety reviews performed, including specifying the frequency for unblinded IA by the	Clarified wording regarding safety reviews.	Nonsubstantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
4.2 Scientific Rationale for Study Design 9.5 Interim Analyses	IRC is at least once annually during study conduct.		
9.5.1. PK/PD Unblinding Plan	Deleted sentence describing estimated timing of PK/PD data cuts.	Removed statement as not accurate at the time of the amendment and not needed to be in the protocol.	Nonsubstantial
1.1 Synopsis	Deleted cross-references to other sections in the protocol, removed table numbering and deleted tertiary endpoints from the Objectives, Estimands, and Endpoints table.	Revised to be consistent with current protocol template for synopsis content.	Nonsubstantial
2.2.2.1 Clinical Safety 4.2 Scientific Rationale for Study Design 4.3 Justification for Dose 11 References	Renumbered references due to deleting a reference in Section 2 that was no longer referred to due to rewording, reordering of sentences in Section 4.2, and inserting a new reference in Section 4.3 for longer dose titration for Cohort 3.	Revised references.	Nonsubstantial
10.10 Appendix 10: Protocol Amendment History	Moved the Summary of Changes for Amendment 1 to appear in an added appendix (Appendix 10) and renumbered the Appendix for Abbreviations to be Appendix 11.	Added an appendix for Protocol Amendment History for placement of the Summary of Changes for the previous amendment to be consistent with the current protocol template.	Nonsubstantial

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. PROTOCOL SUMMARY

1.1. Synopsis

Short Title: A Phase 2b Study to Evaluate the Efficacy and Safety of PF-06882961 in Adults With Obesity

Rationale

This multicenter, Phase 2b, randomized, double-blind, placebo-controlled, parallel group, dose-ranging study is being conducted in adults with obesity. This study will assess the efficacy, safety, tolerability and PK of PF-06882961 in adults with obesity and is intended to enable selection of efficacious doses for future clinical development of PF-06882961 for weight loss in adults with obesity.

Objectives, Estimands, and Endpoints

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
• To compare the effect of multiple dose levels of PF-06882961 versus placebo on body weight in participants with obesity.	• Estimand 1: This estimand is intended to provide a population level estimate of the mean treatment effect (PF-06882961 versus placebo) on a continuous endpoint in all evaluable participants while on treatment.	• Percent CFB in body weight at End of Treatment.[a]
Secondary:	**Secondary:**	**Secondary:**
• To characterize the safety and tolerability of multiple dose levels of PF-06882961 administered to participants with obesity.	• There are no defined estimands for these endpoints and they will be analyzed using Pfizer data standards as applicable.	• Incidence of treatment emergent AEs [AEs and SAEs], and clinically significant abnormal laboratory, vital signs and ECG parameters. • Assessment of mental health as determined by C-SSRS and PHQ-9.
• To compare the effect of multiple dose levels of PF-06882961 versus placebo on additional parameters of body weight in participants with obesity.	• Estimand 2: This estimand is intended to provide a population level estimate of the odds ratio treatment effect (PF-06882961 versus placebo) on a binary endpoint in all evaluable	• Response as defined by a body weight loss of ≥5% from baseline at End of Treatment.[a]

Objectives	Estimands	Endpoints
	participants while on treatment.	
	• Estimand 1 as above.	• **Cohorts 1 and 2**: Percent CFB in body weight at Weeks 2, 4, 6, 8, 10, 12, 16, 18 and 22. • **Cohort 3**: Percent CFB in body weight at Weeks 4, 8, 12, 16, 20, 24 and 28.
	• Estimand 3: This estimand is intended to provide a population level estimate of the mean treatment effect (PF-06882961 versus placebo) on a continuous endpoint in all evaluable participants while on treatment.	• Absolute CFB in waist circumference at End of Treatment.[a]
	• Estimand 4: This estimand will be similar to 3 above.	• Absolute CFB in waist-to-hip ratio at End of Treatment.[a]
• To compare the effect of multiple dose levels of PF-06882961 versus placebo on glycemic parameters in participants with obesity.	• Estimand 5: This estimand will be similar to 3 above.	• **Cohorts 1 and 2**: Absolute CFB in HbA1c at Weeks 16 and 26. • **Cohort 3**: Absolute CFB in HbA1c at Weeks 16, 24 and 32.
	• Estimand 6: This estimand will be similar to 3 above.	• Absolute CFB in FPG at each planned in-clinic study visit up through the End of Treatment visit.[b]

Note: For all endpoints, baseline is defined as the result closest prior to dosing at V3 (Day 1).

a. End of Treatment defined as Week 26 for Cohorts 1 and 2, and as Week 32 for Cohort 3.

b. For Cohorts 1 and 2, this includes Weeks 2, 4, 6, 8, 10, 12, 16, 18, 22 and 26; for Cohort 3, this includes Weeks 4, 8, 12, 16, 20, 24, 28 and 32.

Overall Design

This is a Phase 2b, multicenter, randomized, double-blind, placebo-controlled, parallel group, study to assess the efficacy, safety, tolerability and PK of twice daily oral administration of PF-06882961 in adult participants with obesity. There are 3 Cohorts included in the study: Cohort 1 under the original protocol, Cohort 2 added under Amendment 1, and Cohort 3 added under Amendment 2.

Eligible participants who maintain acceptable compliance during a 2-week placebo run-in period are randomized on Day 1 to double-blinded study intervention. For Cohort 1, participants were randomized into 1 of 9 study arms (placebo: 5 PF-06882961 arms with 1-week titration steps: 3 PF-06882961 arms with 2-week titration steps). Additional participants were enrolled into the placebo and 3 2-week titration arms as part of Cohort 2, which was added to better characterize the tolerability and efficacy profile of the 2-week titration schemes, relative to the 1-week titration schemes, with placebo included to maintain the double-blind study design. For Cohort 2, all SoA activities are the same as for the original cohort (Cohort 1) of randomized participants. In Cohort 3, participants will be randomized to 1 of 4 additional study arms (placebo: 3 PF-06882961 arms with 4-week titration steps) to characterize the tolerability and efficacy profile of 4-week dose titration steps, with placebo included to maintain the double-blind aspect.

Randomization is stratified according to biological gender (female versus male), as both tolerability and efficacy may be different between men and women. This stratification is intended to balance the numbers of participants of either gender across treatment arms. In addition, no more than approximately 70% of the trial population will consist of 1 gender, in order to permit adequate representation of both men and women in the trial population.

Number of Participants

There will be total of approximately 581 participants across all 3 cohorts of this study.

Combining Cohorts 1 and 2, there were a total of approximately 469 participants randomized (approximately 67 in the placebo, approximately 60 in each of the 5 PF-06882961 arms with 1-week titration steps and approximately 34 in each of the 3 PF-06882961 arms with 2-week titration steps). In Cohort 3, approximately 112 participants will be randomized to 4 additional study arms (approximately 16 in the placebo and approximately 32 in each of 3 PF-06882961 arms with 4-week titration steps).

Intervention Groups and Duration

For the purposes of this protocol, study intervention refers to PF-06882961 and matching placebo. Blinded study intervention will be provided as tablets for oral administration, with the placebo run-in being single blinded (participant only) and the randomized treatment period being double-blinded. Participants in Cohorts 1 and 2 are instructed to take 4 tablets of study intervention in the morning with food and 4 tablets of study intervention in the evening with food, for a total of 8 tablets daily. Participants in Cohort 3 are instructed to take 2 tablets of study intervention in the morning with food and 2 tablets of study intervention in the evening with food, for a total of 4 tablets daily. The morning and evening doses should be taken approximately 10-12 hours apart and at approximately the same time each day.

All dosing regimens for all cohorts include dose titration to enhance tolerability of PF-06882961, where the dose level is increased at set intervals of 1, 2 or 4 weeks until a target dose is achieved. For Cohort 1, participants were randomized into 9 arms in a 3:3:3:3:3:3:1:1:1 ratio (placebo: 5 PF-06882961 arms with 1-week titration steps:

3 PF-06882961 arms with 2-week titration steps). In Cohort 2, additional participants were randomized to the placebo and the 3 PF-06882961 arms with 2-week titration steps in a 1:2:2:2 ratio . For the 5 1-week titration PF-06882961 groups in Cohort 1, the target dose levels for each of the arms are 40 mg BID, 80 mg BID, 120 mg BID, 160 mg BID, and 200 mg BID, with titration from a starting dose of CCI mg BID. For the 3 2-week titration PF-06882961 groups in Cohorts 1 and 2, target dose levels for each of the arms are 120 mg BID, 160 mg BID, and 200 mg BID, with titration from a starting dose of CCI mg BID (see table below for Cohorts 1 and 2). For Cohort 3, participants will be randomized in a 1:2:2:2 ratio to 4 arms (placebo: 3 PF-06882961 arms with 4-week titration steps), and the target dose levels are 80 mg BID, 140 mg BID, and 200 mg BID, with titration from a starting dose of CCI mg BID (see table below for Cohort 3).

Following the initial screening period to confirm eligibility (up to 4 weeks), screening continues with a 2-week placebo run-in period. Eligible participants who maintain acceptable compliance during the run-in period are randomized on Day 1 to double-blinded study intervention. For Cohorts 1 and 2, the total dosing duration in the double-blind treatment phase is approximately 26 weeks, followed by an approximate 4-week follow-up. The total duration of participation in this study for the participants in Cohorts 1 and 2 is approximately 32 weeks, including the 2-week single-blind run-in period, but excluding the initial screening period. For the 1-week titration arms in Cohort 1, up to CCI weeks of the dosing duration are used for titration. For the 2-week titration arms in Cohorts 1 and 2, up to CCI weeks are used for dose titration. For Cohort 3, the double-blind treatment phase is 32 weeks, followed by an approximate 4-week follow-up. The total duration of study participation for participants in Cohort 3 is approximately 38 weeks, including the 2-week single-blind run-in period, but excluding the initial screening period. For Cohort 3, up to CCI weeks of the dosing duration are used for titration.

Target Doses for Randomized Regimens for Cohorts 1 and 2

Regimen Description (dosed twice daily)	**Cohort 1**	**Cohort 2**	CCI	**Total Number of Tablets per dose**
Placebo	x	x		CCI
PF-06882961 – 40 mg (1-week titration steps)	x			
PF-06882961 – 80 mg (1-week titration steps)	x			
PF-06882961 – 120 mg (1-week titration steps)	x			
PF-06882961 – 160 mg (1-week titration steps)	x			
PF-06882961 – 200 mg (1-week titration steps)	x			
PF-06882961 – 120 mg (2-week titration steps)	x	x		
PF-06882961 – 160 mg (2-week titration steps)	x	x		
PF-06882961 – 200 mg (2-week titration steps)	x	x		

Target Doses for Randomized Regimens for Cohort 3

Regimen Description (dosed twice daily)	CCI	**Total Number of Tablets per dose**
Placebo		CCI
PF-06882961 – 80 mg (4-week titration steps)		
PF-06882961 – 140 mg (4-week titration steps)		
PF-06882961 – 200 mg (4-week titration steps)		

Data Monitoring Committee or Other Independent Oversight Committee: Yes

This study will use an IRC, an external DMC will not be utilized. The IRC is independent of the study team and includes only internal (ie, Pfizer colleague) members. The IRC charter describes the role of the IRC in more detail.

Statistical Methods

Detailed methodology for summary and statistical analyses of the data collected in this study is further detailed in a SAP, which will be maintained by the sponsor. Data from participants enrolled into the original cohort (Cohort 1) and Cohort 2 will be combined for reporting, where data from the placebo and 2-week titration arms will be combined from the 2 cohorts and analyzed together. Data from participants enrolled into Cohort 3 will be analyzed separately unless otherwise specified.

The primary estimand (Estimand 1) will be the population average treatment effect on the percent CFB in body weight at End of Treatment of PF-06882961 compared to placebo in all evaluable participants while on treatment.

For Cohorts 1 and 2, End of Treatment is defined as Week 26. For Cohort 3, End of Treatment is defined as Week 32. Measurements after discontinuation of study intervention will be censored and treated as missing data. Missing data due to censoring, study withdrawal or other reasons will have data imputed based on a MAR assumption. The population-based treatment effect will be percent CFB in each PF-06882961 arm compared to placebo.

A secondary estimand will be the population odds ratio of the treatment effect of achieving a body weight loss ≥5% from baseline at End of Treatment of PF-06882961 compared to placebo in all evaluable participants while on treatment. All other key secondary continuous clinical endpoints will be analyzed using a similar estimand to the primary estimand described above.

The primary analysis of the primary endpoint will be conducted using a MMRM analysis of the CFB in body weight through End of Treatment, and Cohorts 1 and 2 will be analyzed separately to Cohort 3. MMRM models will be fitted to the CFB of $\log_e$-transformed values. The model for Cohorts 1 and 2 will include Weeks 2, 4, 6, 8, 10, 12, 16, 18, 22 and 26. The model for Cohort 3 will include Weeks 4, 8, 12, 16, 20, 24, 28 and 32.

The primary analysis will include all participants randomly assigned to study intervention and who take at least 1 dose of randomized study intervention. The MMRM models will include treatment, time, strata (females versus males) and treatment-by-time interaction as fixed effects, baseline as a covariate and the baseline-by-time interaction with time fitted as a repeated effect and participant as a random effect. Baseline body weight will be included on the $\log_e$ scale. An unstructured correlation matrix will be used, and the Kenward-Roger approximation will be used for estimating degrees of freedom for the model parameters. Missing values will be imputed as part of the MMRM model assumptions and no adjustments will be made for multiplicity. The modelled mean $\log_e$-differences and 90% CIs for the $\log_e$-differences at End of Treatment will be extracted from the model and exponentiated to provide estimates of the relative difference in each PF-06882961 treatment arm reported separately, compared to placebo.

1.2. Schema

Figure 1. Overall Study Schema for Cohorts 1 and 2

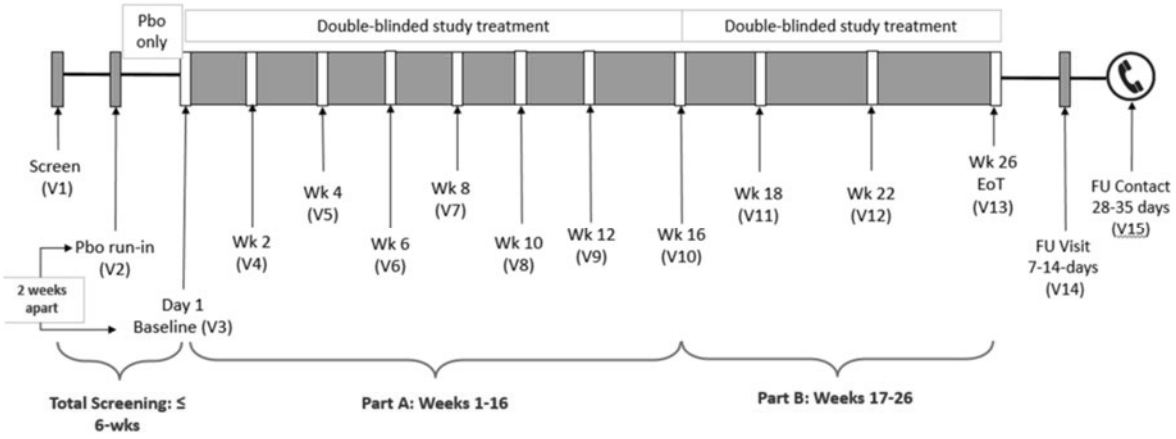


Figure 2. Overall Study Schema for Cohort 3

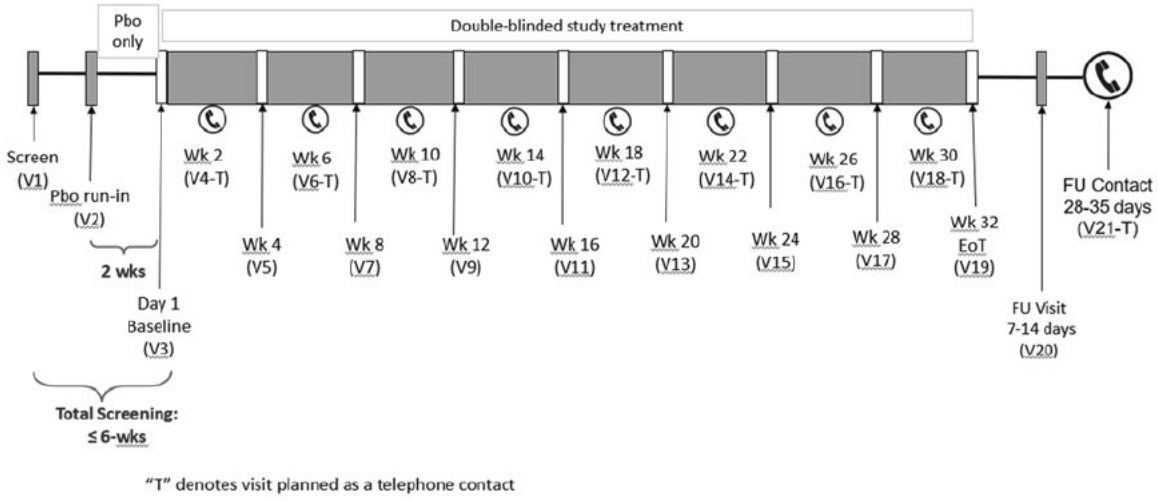
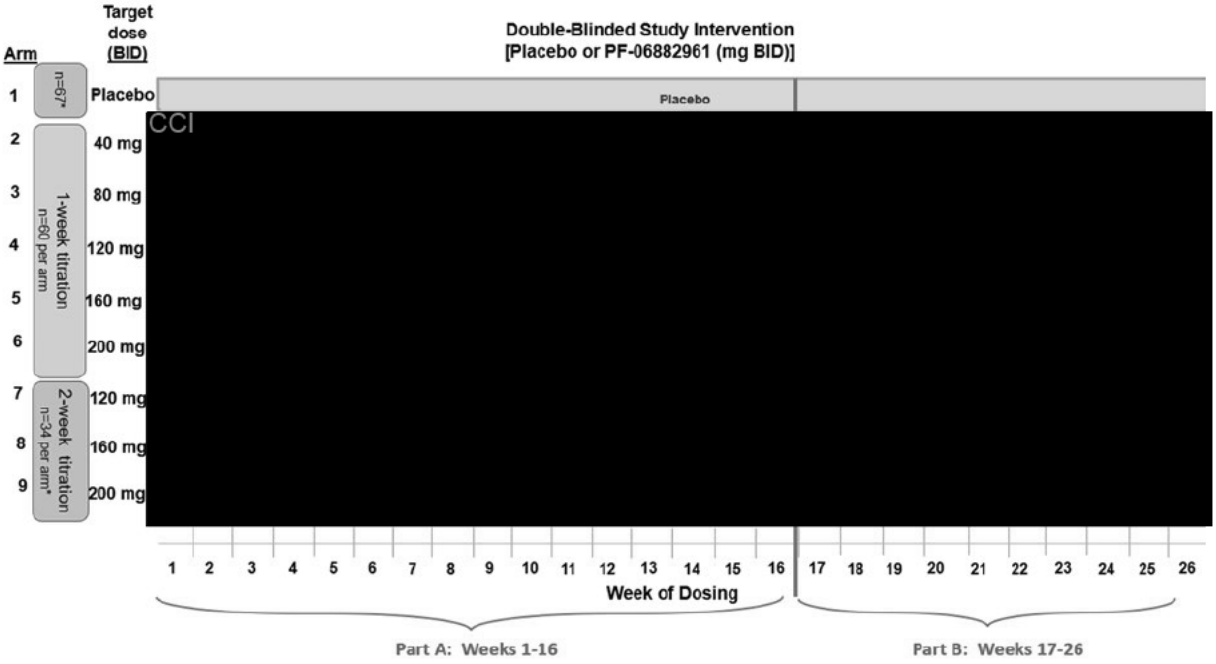
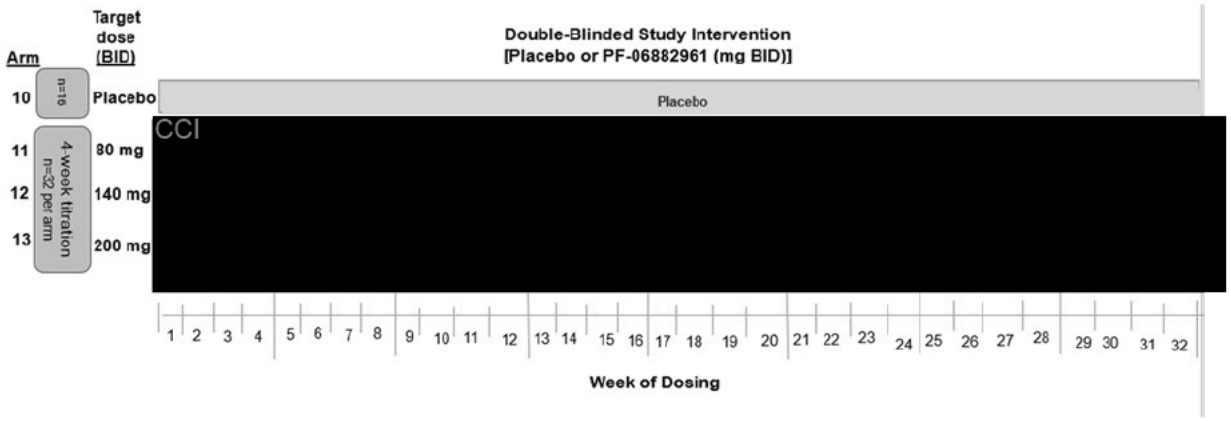


Figure 3. Titration Schema for Cohorts 1 and 2



* Placebo (Arm 1) n=67 which includes Cohort 1 (n=60) and Cohort 2 (n=7). The 2-week titration arms (Arms 7, 8 and 9) n=34 per arm which includes Cohort 1 (n=20) and Cohort 2 (n=14).

Figure 4. Titration Schema for Cohort 3



1.3. Schedule of Activities (SoA)

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

1.3.1. SoA for Cohorts 1 and 2

Protocol Activity (See Appendix 11 for abbreviations)	Screening Phase		Treatment Phase										End of Treatment[a]	Follow-up[b]		Early Term/ Discontinuation[c]
	Screen	Pbo run-in														
Study Part[b]			Part A								Part B					
Weeks Relative to Dosing on Day 1			0	2	4	6	8	10	12	16[a]	18	22	26	27-28	30-31	ET
Days Relative to Dosing on Day 1[d]	-42 to -15	-14±3	1	14±3	28±3	42±3	56±3	70±3	84±3	112±3	126±3	154±3	182±3	189-196	210-217	
Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15[e]	
Informed consent & demography	x															
Review of eligibility criteria	x	x	x													
Medical history	x															
SF-36v2® (all sites)[f]		x	x							x			x			
PGI-S (US only)[f]		x	x	x	x	x	x	x	x	x	x	x	x			
PROMIS®, IWQOL-Lite-CT© (US only)[f]		x	x							x			x			
PGI-C (US only)[f]					x					x			x			
Open-ended inquiry for AEs	x	→	→	→	→	→	→	→	→	→	→	→	→	→	x	x
Review prior/concomitant treatments	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Review drug, alcohol, tobacco use	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Review contraception use (females only)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Mental health questionnaires (C-SSRS, PHQ-9)	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x
Physical examination[g]	x		x							x			x	x		x
Body weight (in duplicate)[h]	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x
Waist and hip circumference (in triplicate)	x		x	x	x	x	x	x	x	x	x	x	x	x		x
Supine 12-lead ECG (pre-dose)	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x
Supine vital signs (in triplicate) (pre-dose unless noted)	x	x	x[i]	x	x	x	x[i]	x	x	x[i]	x	x	x[i]	x		x

Protocol Activity (See Appendix 11 for abbreviations)	Screening Phase		Treatment Phase										End of Treatment[a]	Follow-up[b]		Early Term/ Discontinuation[c]
	Screen	Pbo run-in														
Study Part[b]			Part A								Part B					
Weeks Relative to Dosing on Day 1			0	2	4	6	8	10	12	16[a]	18	22	26	27-28	30-31	ET
Days Relative to Dosing on Day 1[d]	-42 to -15	-14±3	1	14±3	28±3	42±3	56±3	70±3	84±3	112±3	126±3	154±3	182±3	189-196	210-217	
Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15[e]	
Registration in trial (via IRT)	x															
Eating-Related Factors Daily Diary (US only)[j]		x	→	→	→	→	→	→	→	→	→	→	x			
Dietary & physical activity counseling		x	x		x		x		x	x	x	x	x			
Review dosing diary		x	x	x	x	x	x	x	x	x	x	x	x			x
Randomization in trial (via IRT)			x													
Dispensation of study intervention supply & dosing diary		x[k]	x	x	x	x	x	x	x	x[l]	x[l]	x[l]				
Dose study intervention on site (with food)		x	x	x	x	x	x	x	x	x	x	x	x			
Compliance check of returned study intervention			x	x	x	x	x	x	x	x	x	x	x			x
Blood sampling for:																
Hematology, Chemistry (including FPG and eGFR)	x		x	x	x	x	x	x	x	x	x	x	x	x		x
FSH (females only); C-peptide	x															
Pregnancy test (all females)[o]	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x
HbA1c	x		x							x			x			x
Lipids, TSH, free T4, calcitonin, amylase, lipase, TBA, PT/INR/aPTT, FPI	x		x		x		x		x	x		x	x	x		x
PF-06882961 PK (pre-dose unless noted)			x[m]		x		x[m]	x		x[m]			x[m]			x
Banked biospecimen: Prep B1 & B2			x							x			x			x
Banked biospecimen: Prep D1 (only Day 1)[n]			x													
Urine Sampling for:																
Urine drug screen	x															
Urinalysis (and microscopy, reflexive)	x		x		x		x		x	x		x	x	x		x
On-site urine pregnancy test (all females)[o]		x	x	x	x	x	x	x	x	x	x	x	x	x		x

a. **End of Treatment:** Defined as Week 26.

b. **Study part and Follow-up:** In Part A (Weeks 1-16) participants will be randomized and dosed with double-blinded study intervention on Day 1 and dosing will continue through 16 weeks. In Part B (Weeks 17-26) participants in Part A will continue dosing, according to randomization from Part A.

c. **Early termination/discontinuation**: This visit applies only to participants who are enrolled/randomized and then are prematurely withdrawn from the study, ie, permanently discontinued *both from the study intervention and from the study*. ***Note***: discontinuation of study intervention does not represent withdrawal from the study. If only study intervention is discontinued, the participant will remain in the study and continue with all visits and assessments (except for dosing activities and assessment of PK). See Section 7 for further details.

d. **Days relative to Dosing on Day 1:** Dosing occurs on Day 1 and timing of subsequent visits is determined by adding the number of days noted to Day 1. For example, V4 is Day 1+14 days (±3 days), V5 is Day 1+28 days (±3 days), etc.

e. **Follow-up V15:** Visit may be a phone call.

f. **Site based PROs**: Completed at the site on an electronic tablet. Participants at ex-US sites will only complete the SF-36v2®. Participants at US sites will complete all PRO assessments (SF-36v2®, PGI-S, PGI-C, PROMIS® Fatigue, PROMIS® Physical Function, IWQOL-Lite-CT©). See Section 8.1.3 for more details.

g. **Physical examination:** Complete physical examination performed according to the SoA, with height measured at V1 only. A limited physical examination is performed at follow-up V14 and may be performed at non-specified visits if there are findings during the previous exam or new/open AEs, if appropriate and at investigator discretion.

h. **Body weight:** The second weight measurement should be obtained at least 1-2 minutes apart from the first weight measurement.

i. **Supine vital signs** (BP and pulse rate)**:** At V3, V7, V10 and V13, triplicate vital signs will be measured pre-dose *and* triplicate vital signs will be measured 1 time within the window of approximately 2-6 hours *post-dose* (around the same time as post-dose PK samples are collected and according to the chronology in Appendix 9)**.**

j. **Eating-Related Factors Daily Diary**: Only participants at selected US sites will complete this PRO diary, which will be done daily at home on a handheld device.

k. **Study intervention**: For V2 only, study intervention reflects single blinded placebo. For V3 through V12, study intervention is dispensed via IRT and reflects double-blinded randomized PF-06882961 or placebo.

l. **Dispensation of study intervention at V10-V12 (Weeks 16-22)**: For V10-12 only, study intervention dispensation via IRT will be permitted only after formal agreement with regulatory authorities and IRBs/ECs as described in "b" above.

m. **PK sampling:** At V3, V7, V10 and V13, PK samples will be collected pre-dose *and* one time within the window of approximately 2-6 hours *post-dose* (around the same time as post-dose vital sign measurements and according to the chronology in Appendix 9).

n. **Banked biospecimen Prep D1:** If not collected on the designated collection day, collect at the next available time point when biospecimens are being collected in conjunction with a participant visit.

o. **Pregnancy tests:** Serum and urine pregnancy tests are required for all females regardless of childbearing potential. For the on-site urine pregnancy tests performed at each visit V2 through V14, the test result must be negative in order to continue participation in the study.

1.3.2. SoA for Cohort 3

Protocol Activity (See Appendix 11 for abbreviations)	Screening Phase		Treatment Phase																End of Treatment[a]	Follow-up		Early Term/ Discontinuation[b]
	Screen	Pbo run-in																				
Weeks Relative to Dosing on Day 1			0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	33-34	36-37	ET
Days Relative to Dosing on Day 1[c]	-42 to -15	-14±3	1	14±3	28±3	42±3	56±3	70±3	84±3	98±3	112±3	126±3	140±3	154±3	168±3	182±3	196±3	210±3	224±3	231-238	252-259	
Visit ("T" denotes telephone contact)[d]	V1	V2	V3	V4-T	V5	V6-T	V7	V8-T	V9	V10-T	V11	V12-T	V13	V14-T	V15	V16-T	V17	V18-T	V19	V20	V21-T	
Informed consent & demography	x																					
Review of eligibility criteria	x	x	x																			
Medical history	x																					
SF-36v2® (all sites)[e]		x	x								x				x				x			
PGI-S (US only)[e]		x	x		x		x		x		x		x		x		x		x			
PROMIS®, IWQOL-Lite-CT© (US only)[e]		x	x								x				x				x			
PGI-C (US only)[e]					x						x				x				x			
Open-ended inquiry for AEs	x	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	x	x
Review prior/concomitant treatments	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Review drug, alcohol, tobacco use	x	x	x		x		x		x		x		x		x		x		x	x	x	x
Review contraception use (females only)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Mental health questionnaires (C-SSRS, PHQ-9)	x	x	x		x		x		x		x		x		x		x		x	x		x
Physical examination[f]	x		x								x								x	x		x
Body weight (in duplicate)[g]	x	x	x		x		x		x		x		x		x		x		x	x		x
Waist and hip circumference (in triplicate)	x		x		x		x		x		x		x		x		x		x	x		x
Supine 12-lead ECG (pre-dose)	x	x	x		x		x		x		x		x		x		x		x	x		x
Supine vital signs (in triplicate) (pre-dose unless noted)	x	x	x[h]		x		x[h]		x		x[h]		x		x[h]		x		x[h]	x		x
Registration in trial (via IRT)	x																					
Eating-Related Factors Daily Diary (US only)[i]		x	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	x			

Protocol Activity (See Appendix 11 for abbreviations)	Screening Phase		Treatment Phase																End of Treat-ment[a]	Follow-up		Early Term/ Dis-cont-inua-tion[b]
	Screen	Pbo run-in																				
Weeks Relative to Dosing on Day 1			0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	33-34	36-37	ET
Days Relative to Dosing on Day 1[c]	-42 to -15	-14±3	1	14±3	28±3	42±3	56±3	70±3	84±3	98±3	112±3	126±3	140±3	154±3	168±3	182±3	196±3	210±3	224±3	231-238	252-259	
Visit ("T" denotes telephone contact)[d]	V1	V2	V3	V4-T	V5	V6-T	V7	V8-T	V9	V10-T	V11	V12-T	V13	V14-T	V15	V16-T	V17	V18-T	V19	V20	V21-T	
Dietary & physical activity counseling		x	x		x		x		x		x		x		x		x		x			
Review dosing diary[j]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			x
Randomization in trial (via IRT)			x																			
Dispense study intervention supply & dosing diary		x[k]	x		x		x		x		x		x		x		x					
Dose study intervention on site (with food)		x	x		x		x		x		x		x		x		x		x			
Compliance check of returned study intervention			x		x		x		x		x		x		x		x		x			x
Blood sampling for:																						
Hematology, Chemistry (including FPG and eGFR)	x		x		x		x		x		x		x		x		x		x	x		x
FSH (females only); C-peptide	x																					
Pregnancy test (all females)[l]	x	x	x		x		x		x		x		x		x		x		x	x		x
HbA1c	x		x								x				x				x			x
Lipids, TSH, free T4, calcitonin, amylase, lipase, TBA, PT/INR/aPTT, FPI	x		x		x		x		x		x		x		x		x		x	x		x
PF-06882961 PK (pre-dose unless noted)			x[m]		x		x[m]		x		x[m]		x		x[m]		x		x[m]			x
Banked biospecimen: Prep B1 & B2			x								x								x			x
Banked biospecimen: Prep D1 (only Day 1)[n]			x																			
Urine Sampling for:																						
Urine drug screen	x																					
Urinalysis (and microscopy, reflexive)	x		x		x		x		x		x		x		x		x		x	x		x

Protocol Activity (See Appendix 11 for abbreviations)	Screening Phase		Treatment Phase																End of Treatment[a]	Follow-up		Early Term/ Discontinuation[b]
	Screen	Pbo run-in																				
Weeks Relative to Dosing on Day 1			0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	33-34	36-37	ET
Days Relative to Dosing on Day 1[c]	-42 to -15	-14±3	1	14±3	28±3	42±3	56±3	70±3	84±3	98±3	112±3	126±3	140±3	154±3	168±3	182±3	196±3	210±3	224±3	231-238	252-259	
Visit ("T" denotes telephone contact)[d]	V1	V2	V3	V4-T	V5	V6-T	V7	V8-T	V9	V10-T	V11	V12-T	V13	V14-T	V15	V16-T	V17	V18-T	V19	V20	V21-T	
On-site urine pregnancy test (all females)[l]		x	x		x		x		x		x		x		x		x		x	x		x

a. **End of Treatment:** Defined as Week 32.

b. **Early termination/discontinuation**: This visit applies only to participants who are enrolled/randomized and then are prematurely withdrawn from the study, ie, permanently discontinued ***both from the study intervention and from the study***. ***Note***: discontinuation of study intervention does not represent withdrawal from the study. If only study intervention is discontinued, the participant will remain in the study and continue with all visits and assessments (except for dosing activities and assessment of PK). See Section 7 for further details.

c. **Days relative to Dosing on Day 1:** Dosing occurs on Day 1 and timing of subsequent visits is determined by adding the number of days noted to Day 1. For example, V4-T is a telephone contact at Day 1+14 days (±3 days), V5 is an in-clinic visit at Day 1+28 days (±3 days), etc.

d. **Visit**: Visits with a "T" are planned as telephone contacts, while other visits are planned as in-clinic study visits.

e. **Site based PROs**: Completed at the site on an electronic tablet. Participants at ex-US sites will only complete the SF-36v2®. Participants at US sites will complete all PRO assessments (SF-36v2®, PGI-S, PGI-C, PROMIS® Fatigue, PROMIS® Physical Function, IWQOL-Lite-CT©). See Section 8.1.3 for more details.

f. **Physical examination:** Complete physical examination performed according to the SoA, with height measured at V1 only. A limited physical examination is performed at follow-up V20 and may be performed at non-specified visits if there are findings during the previous exam or new/open AEs, if appropriate and at investigator discretion.

g. **Body weight:** The second weight measurement should be obtained at least 1-2 minutes apart from the first weight measurement.

h. **Supine vital signs** (BP and pulse rate)**:** At V3, V7, V11, V15 and V19, triplicate vital signs will be measured pre-dose ***and*** triplicate vital signs will be measured 1 time within the window of approximately 2-6 hours ***post-dose*** (around the same time as post-dose PK samples are collected and according to the chronology in Appendix 9)**.**

i. **Eating-Related Factors Daily Diary**: Only participants at selected US sites will complete this PRO diary, which will be done daily at home on a handheld device.

j. **Dosing diary review**: For telephone visits, this review consists of site staff reminding participants to record doses taken as well as any missed doses in their dosing diary and to bring the diary to in-clinic study visits. For onsite visits, site staff should review the returned dosing diary entries with participants.

k. **Study intervention**: For V2 only, study intervention reflects single blinded placebo. For V3, V5, V7, V9, V11, V13, V15 and V17, study intervention is dispensed via IRT and reflects double-blinded randomized PF-06882961 or placebo.

l. **Pregnancy tests:** Serum and urine pregnancy tests are required for all females regardless of childbearing potential. For the on-site urine pregnancy tests performed at each planned in-clinic visit V2 through V20, the test result must be negative in order to continue participation in the study.

m. **PK sampling:** At V3, V7, V11, V15 and V19, PK samples will be collected pre-dose ***and*** 1 time within the window of approximately 2-6 hours ***post-dose*** (around the same time as post-dose vital sign measurements and according to the chronology in Appendix 9).

n. **Banked biospecimen Prep D1:** If not collected on the designated collection day, collect at the next available time point when biospecimens are being collected in conjunction with a participant visit.

2. INTRODUCTION

GLP-1 is a neuroendocrine hormone that is predominantly released from the small intestine in response to food intake.[1] GLP-1 activation of the GLP-1R stimulates insulin release, inhibits glucagon secretion in a glucose-dependent manner, and delays gastric emptying.[2,3] In addition, GLP-1 has been shown to increase satiety and suppress food intake.[4] PF-06882961 is an orally administered, small molecule GLP-1R agonist that has been demonstrated, in nonclinical models, to stimulate glucose-dependent insulin release and suppress food intake with equivalent efficacy to an injectable peptide GLP-1R agonist approved for the treatment of T2DM.

PF-06882961 is an oral, small molecule GLP-1R agonist that is currently being investigated for the treatment of T2DM, and also as an adjunct to diet and exercise for weight loss in adult participants with obesity.

2.1. Study Rationale

This multicenter, Phase 2b, randomized, double-blind, placebo-controlled, parallel group, dose-ranging study is being conducted in adults with obesity. There are 3 Cohorts included in the study: Cohort 1 under the original protocol, Cohort 2 added under Amendment 1, and Cohort 3 added under Amendment 2, as described in Section 4.

This study will assess the efficacy, safety, tolerability and PK of PF-06882961 in adults with obesity and is intended to enable selection of efficacious doses for future clinical development of PF-06882961 for weight loss in adults with obesity.

2.2. Background

Obesity is a chronic disease that is associated with serious co-morbidities, including T2DM, dyslipidemia, hypertension, atherosclerosis, obstructive sleep apnea and certain cancers,[5] and is also associated with increased all-cause mortality.[6] The global burden of obesity is high with more than 600 million adults estimated to have obesity worldwide. In addition, the prevalence of obesity has doubled in more than 70 countries since 1980 and poses a major public health challenge.[7,8] First line treatment for obesity is lifestyle intervention including diet, exercise and behavioral therapy. While effective in many patients, lifestyle intervention is often not sustainable, and many patients regain weight after initial weight loss.[9] Pharmacotherapy has been approved for the long-term treatment of obesity and can be a useful adjunct to lifestyle intervention to augment and maintain weight loss.

Marketed injectable GLP-1R agonists have demonstrated robust glycemic efficacy, weight loss, and cardiovascular safety, with more than one marketed agent demonstrating cardiovascular benefit.[10] Based on the clinical history of injectable GLP-1R agonists, an oral, small molecule GLP-1R agonist is expected to decrease appetite and food intake, resulting in weight loss in patients with obesity, while avoiding the subcutaneous injection required by currently available peptidic GLP-1R agonists.

2.2.1. Nonclinical Overview

2.2.1.1. Nonclinical Pharmacokinetics and Metabolism

In all species evaluated, PF-06882961 was highly bound to plasma proteins with unbound fraction CCI . The in vitro and in vivo metabolic profile of PF-06882961 in toxicology species and human was similar with no evidence of human-specific metabolites. CCI

Refer to the IB for more details on the nonclinical PK and metabolism of PF-06882961.

2.2.1.2. Nonclinical Safety

The nonclinical safety profile of PF-06882961 has been adequately characterized to support progression into long term clinical trials.

PF-06882961 was administered to Wistar-Han rats and cynomolgus monkeys in repeat-dose toxicity studies up to 6 months with a 1-month recovery and 9 months with a 3-week lead-in and 1-month recovery, respectively. The NOAEL in the 6-month toxicity study in rats with a 1-month recovery phase was CCI mg/kg/day with a mean combined-sex unbound C_{max} of CCI ng/mL and unbound AUC_{24} of CCI ng•h/mL. No adverse findings were observed in the 9-month cynomolgus monkey study at doses up to CCI mg/kg/day. The primary effects were consistent with the expected pharmacology of the test article, and the NOAEL in this pivotal 9-month toxicity study in cynomolgus monkeys with a 3-week lead-in (39 weeks total exposure) and 1-month recovery phase was CCI mg/kg/day once daily with a mean unbound combined sex C_{max} of CCI ng/mL and an unbound AUC_{24} of CCI ng•h/mL.

Studies were conducted to evaluate the effects on fertility, reproduction, and early embryonic development in male and female rats, and embryo-fetal developmental studies were conducted in rats and rabbits. In rats, there was no PF-06882961-related maternal toxicity and no adverse effects on embryo-fetal development. The NOAEL for maternal and developmental toxicity in rats was the highest dose tested, and this led to exposures that were higher than the NOAELs identified in the 6 and 9-month toxicity studies in rats and monkeys. In rabbits, while maternal toxicity and adverse lower fetal body weight were observed at the highest dose tested, the NOAEL of CCI mg/kg/day led to exposures that were higher than the NOAELs identified in the 6 and 9-month toxicity studies in rats and monkeys.

Additional details on the nonclinical safety of PF-06882961 are provided in the IB.

2.2.2. Clinical Overview

As of the protocol finalization date, the safety of PF-06882961 has been assessed in 9 completed studies. A total of 788 participants were enrolled in these studies; of these, 665 participants were exposed to at least one dose of PF-06882961. There are 3 completed Phase 1 single dose clinical studies in healthy participants and 1 completed single dose study in otherwise healthy participants with obesity. There are 3 completed Phase 1 multiple dose clinical studies in participants with T2DM, Japanese participants with T2DM, and otherwise healthy participants with obesity. PF-06882961 has been further evaluated in 2 completed Phase 2 studies over a dose range of 2.5 mg to 200 mg BID. Across these 2 Phase 2 studies, a total of 562 participants (534 participants with T2DM and 28 non-diabetic participants with obesity) were randomized, of whom 474 were exposed to at least 1 dose of PF-06882961.

Refer to the IB for more details on these studies and the known drug class effects of marketed injectable GLP-1R agonists.

2.2.2.1. Clinical Safety

PF-06882961 at single doses up to 300 mg and multiple doses up to 200 mg BID has been considered safe with a tolerability profile in line with the mechanism of action.

Across the 2 completed Phase 2 clinical studies, 58% of the 562 participants dosed with PF-06882961 or placebo reported all-causality TEAEs. The majority of these events were mild (68%) to moderate (29%) in intensity, did not lead to serious sequelae, and resolved upon discontinuation. CCI [redacted] The most commonly reported treatment-related TEAEs reported included nausea (CCI% of participants) and vomiting (CCI% of participants). Hypoglycemic adverse events were reported in <5% of randomized participants. Severe hypoglycemia was reported in 1 participant with T2DM; this event was not a SAE.

In the two Phase 2 trials, there were no apparent dose-related trends in the proportion of participants meeting categorical thresholds of potential clinical concern for clinical laboratory values, vital signs, or ECG parameters.

Additional details on clinical experience with PF-06882961 are provided in the IB.

2.2.2.2. Clinical Pharmacokinetics

Following multiple oral dose administration of PF-06882961 to participants with T2DM, median T_{max} ranged from CCI hours post dose and mean $t_{1/2}$ values ranged from CCI to CCI hours. CCI [redacted]

CCI [redacted]

A complete review of the clinical pharmacokinetics and clinical pharmacology profile of PF-06882961 CCI [redacted] can be found in the IB.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of PF-06882961 may be found in the IB, which is SRSD for this study.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s) PF-06882961		
Thyroid C-cell tumors	The potential risks are based on product labeling for peptidic marketed GLP-1R agonists (ie, semaglutide, liraglutide, dulaglutide, and exenatide) due to dose-dependent and treatment duration-dependent thyroid C-cell tumors in nonclinical studies in rats and mice at clinically relevant exposures. Thyroid C-cell tumors have not been observed with PF-06882961 in clinical or nonclinical studies.	Potential participants with a personal or family history of medullary thyroid carcinoma or Multiple Endocrine Neoplasia syndrome type 2 are excluded from the clinical development program. Thyroid function tests are included in the clinical trial protocols to monitor participants' thyroid function.
Pancreatitis	The potential risks are based on product labeling for peptidic GLP-1R agonists (ie, semaglutide, liraglutide, exenatide and dulaglutide). Pancreatitis has not been observed in the PF-06882961 clinical trial program.	Per exclusion criteria, potential participants with acute pancreatitis or a history of pancreatitis are not eligible for study entry. Serum amylase and lipase are monitored during the clinical studies.
Hypoglycemia	Clinical trials with peptidic GLP-1R agonists have not demonstrated an increased risk for hypoglycemia. However, when administered in combination with anti-diabetic agents that are known to have an increased risk of hypoglycemia (such as insulin or sulfonylureas), an increased risk for hypoglycemia was observed. Participants with obesity who do not have co-existing T2DM would not be taking anti-diabetic agents and therefore would not be expected to have an increased risk for hypoglycemia. A low overall incidence of generally mild hypoglycemia has been reported in the PF-06882961 clinical development program to date.	Anti-diabetic medications are prohibited in this study, and blood glucose is monitored via central lab assessments at every clinical visit in this study. Participants are informed about the signs and symptoms of hypoglycemia, and are monitoring for these symptoms at clinical study visits.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Impairment in renal function	The potential risks are based on product labeling for peptidic marketed GLP-1R agonists, and predominantly occur in patients with significant nausea, vomiting, and dehydration. Data from the completed clinical studies with PF-06882961 do not suggest an increased risk to renal function. CCI [redacted]	Per exclusion criteria, potential participants with significant renal impairment (<60 mL/min/1.73 m^2) are not eligible for study entry. Renal function is monitored at each study visit by the central lab assessments of serum BUN, creatinine and eGFR.
Gastrointestinal adverse reactions	The potential risks are based on product labeling for peptidic marketed GLP-1R agonists (ie, semaglutide, liraglutide, exenatide and dulaglutide). Gastrointestinal AEs, the majority of which were mild in severity, have been observed in the clinical program with PF-06882961. In nonclinical studies with PF-06882961, gastrointestinal adverse effects have been seen in rats and monkeys.	Participants are monitored during the clinical study visits, via body weight, vital signs and laboratory assessments, to prevent potential sequelae of any severe gastrointestinal reactions, eg, dehydration.
Diabetic retinopathy complications	The potential risk is based on the product labeling for the peptidic GLP-1R agonists semaglutide and dulaglutide where patients with T2DM and diabetic retinopathy who are taking these agents should be monitored for progression of diabetic retinopathy, as rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy. This risk has not been listed in the prescribing information for other marketed GLP-1R agonists. There are no nonclinical or clinical data involving PF-06882961 to suggest an increased risk of diabetic retinopathy complications.	Potential participants with diabetes mellitus are excluded from this clinical study.
Suicidal ideation and behavior	The potential risk is based on the product labeling for the injectable GLP-1R agonists liraglutide and semaglutide for obesity. This risk has not been listed in the prescribing information for other marketed GLP-1R agonists for T2DM. There are no nonclinical or clinical data involving PF-06882961 to suggest an increased risk of suicidal ideation and behavior.	Suicidal ideation and behavior, along with symptoms of depression, will be monitored at every clinic visit after randomization using the C-SSRS and PHQ-9 questionnaires, with referral to a MHP for further evaluation if needed.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Increase in HR	The potential risk is based on the product labeling for the injectable GLP 1R agonists liraglutide and semaglutide for T2DM and for obesity. Increases in HR have been noted in the clinical program with PF-06882961 with most values within the normal range. While there have been isolated vital sign values outside the reference ranges observed, in these cases the values were not considered clinically significant and there were no clinically significant adverse trends observed across dose levels, to date.	Vital signs, including HR and BP, and ECGs are assessed at all onsite study visits in all participants.
Acute gallbladder disease	Substantial or rapid weight loss can increase the risk of cholelithiasis. The potential risk is based on the product labeling for the injectable GLP 1R agonist liraglutide for obesity and also exenatide. In the completed clinical studies with PF-06882961, no treatment-emergent events of cholelithiasis have been observed.	Participants with symptomatic gallbladder disease are excluded from this clinical study. Participants are monitored at clinical visits for AEs and laboratory tests that may suggest development of acute gallbladder disease.
Study Procedures		
Use of a placebo arm	Participants randomized to placebo may not experience weight loss efficacy.	A majority of the randomized study population will receive PF-06882961, and all participants will receive lifestyle counseling, which is standard of care for management of obesity.

2.3.2. Benefit Assessment

Based on the clinical history of injectable GLP-1R agonists, participants with obesity randomized to PF-06882961 may have diminished food intake and decreased body weight. Other potential benefits for all participants in this study may include receiving lifestyle counseling, receiving medical evaluations/assessments associated with clinical study visits (eg, physical examinations, ECGs, labs), and contributing to the process of developing a potential new therapy for weight loss.

2.3.3. Overall Benefit/Risk Conclusion

Considering all available clinical and nonclinical data, the benefit-risk profile of PF-06882961 supports continued clinical development in participants with obesity.

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
• To compare the effect of multiple dose levels of PF-06882961 versus placebo on body weight in participants with obesity	• Estimand 1: This estimand is intended to provide a population level estimate of the mean treatment effect (PF-06882961 versus placebo) on a continuous endpoint in all evaluable participants while on treatment.	• Percent CFB in body weight at End of Treatment.[a]
Secondary:	**Secondary:**	**Secondary:**
• To characterize the safety and tolerability of multiple dose levels of PF-06882961 administered to participants with obesity.	• There are no defined estimands for these endpoints and they will be analyzed using Pfizer data standards as applicable.	• Incidence of treatment emergent AEs [AEs and SAEs], and clinically significant abnormal laboratory, vital signs and ECG parameters. • Assessment of mental health as determined by C-SSRS and PHQ-9.
• To compare the effect of multiple dose levels of PF-06882961 versus placebo on additional parameters of body weight in participants with obesity.	• Estimand 2: This estimand is intended to provide a population level estimate of the odds ratio treatment effect (PF-06882961 versus placebo) on a binary endpoint in all evaluable participants while on treatment.	• Response as defined by a body weight loss of ≥5% from baseline at End of Treatment.[a]
	• Estimand 1 as above.	• **Cohorts 1 and 2**: Percent CFB in body weight at Weeks 2, 4, 6, 8, 10, 12, 16, 18 and 22. • **Cohort 3**: Percent CFB in body weight at Weeks 4, 8, 12, 16, 20, 24 and 28.
	• Estimand 3: This estimand is intended to provide a population level estimate of the mean treatment effect (PF-06882961 versus placebo) on a continuous	• Absolute CFB in waist circumference at End of Treatment.[a]

Objectives	Estimands	Endpoints
	endpoint in all evaluable participants while on treatment.	
	• Estimand 4: This estimand will be similar to 3 above.	• Absolute CFB in waist-to-hip ratio at End of Treatment.[a]
• To compare the effect of multiple dose levels of PF-06882961 versus placebo on glycemic parameters in participants with obesity.	• Estimand 5: This estimand will be similar to 3 above.	• **Cohorts 1 and 2**: Absolute CFB in HbA1c at Weeks 16 and 26. • **Cohort 3**: Absolute CFB in HbA1c at Weeks 16, 24 and 32.
	• Estimand 6: This estimand will be similar to 3 above.	• Absolute CFB in FPG at each planned in-clinic study visit up through the End of Treatment visit.[b]
Tertiary/Exploratory:	**Tertiary/Exploratory:**	**Tertiary/Exploratory:**
• To compare the effect of multiple dose levels of PF-06882961 versus placebo on body weight in participants with obesity who do not have major protocol deviations.	• Estimand 7: This estimand is intended to provide a population level estimate of the mean treatment effect (PF-06882961 versus placebo) on a continuous endpoint in evaluable participants with no major protocol deviations and while on treatment.	• Percent CFB in body weight at each planned in-clinic study visit up through the End of Treatment visit.[b]
• To characterize the PK of PF-06882961 in participants with obesity.	• There is no defined estimand for this endpoint and this will be analyzed using Pfizer data standards as applicable.	• Trough plasma concentrations of PF-06882961 at time points specified in the SoA for the applicable cohort (see SoA for Cohorts 1 and 2, and SoA for Cohort 3).
• To compare the effect of multiple dose levels of PF-06882961 versus placebo on markers of insulin resistance in participants with obesity.	• There are no defined estimands for these endpoints and they will be analyzed using Pfizer data standards as applicable.	• **Cohorts 1 and 2**: CFB in fasting plasma insulin, HOMA-IR and HOMA-B at Weeks 4, 8, 12, 16, 22 and 26. • **Cohort 3**: CFB in fasting plasma insulin, HOMA-IR and HOMA-B at Weeks 4, 8, 12, 16, 20, 24, 28 and 32.
• To compare the effect of multiple dose levels of PF-06882961 versus placebo on additional parameters of body weight in participants with obesity.	• Estimand 3: This estimand is defined above.	• **Cohorts 1 and 2**: Absolute CFB in waist circumference at Weeks 2, 4, 6, 8, 10, 12, 16, 18 and 22. • **Cohort 3**: Percent CFB in body weight at Weeks 4, 8, 12, 16, 20, 24 and 28.
	• Estimand 4: This estimand will be similar to 3 above.	• **Cohorts 1 and 2**: Absolute CFB in waist-to-hip ratio at Weeks 2, 4, 6, 8, 10, 12, 16, 18 and 22. • **Cohort 3**: Percent CFB in body weight at Weeks 4, 8, 12, 16, 20, 24 and 28.

Objectives	Estimands	Endpoints
• To compare the effect of multiple dose levels of PF-06882961 versus placebo on glycemic category in participants with obesity.	• There are no defined estimands for these endpoints and they will be analyzed using Pfizer data standards as applicable.	• Shift from baseline in glycemic category (normoglycemia, pre-diabetes, or T2DM) at End of Treatment.[a]
• To compare the effect of multiple dose levels of PF-06882961 versus placebo on BP and lipid levels in participants with obesity.	• There are no defined estimands for these endpoints and they will be analyzed using Pfizer data standards as applicable.	• CFB in systolic and diastolic BP at each planned in-clinic study visit up through the End of Treatment visit. • **Cohorts 1 and 2**: CFB in lipid parameters at Weeks 4, 8, 12, 16, 22 and 26. • **Cohort 3**: CFB in lipid parameters at Weeks 4, 8, 12, 16, 20, 24, 28 and 32.
• To compare the effect of multiple dose levels of PF-06882961 versus placebo on PCOAs in participants with obesity.	• There are no defined estimands for these endpoints and they will be analyzed using Pfizer data standards as applicable.	• **Cohorts 1 and 2:** CFB in SF-36v2® subscales and summary scores at Weeks 16 and 26. • **Cohort 3**: CFB in SF-36v2® subscales and summary scores at Weeks 16, 24 and 32.
• To compare the effect of multiple dose levels of PF-06882961 versus placebo on PCOAs in participants with obesity (US sites only).	• There are no defined estimands for these endpoints and they will be analyzed using Pfizer data standards as applicable.	• **Cohorts 1 and 2**: CFB in Eating-Related Factors Daily Diary at Weeks 4, 8, 12, 16, 22 and 26. • **Cohort 3**: CFB in Eating-Related Factors Daily Diary at Weeks 4, 8, 12, 16, 20, 24, 28 and 32. • CFB in PGI-S at each planned in-clinic study visit up through the End of Treatment visit.[b] • **Cohorts 1 and 2**: CFB in PROMIS® Fatigue at Weeks 16 and 26. • **Cohort 3:** CFB in PROMIS® Fatigue at Weeks 16, 24 and 32. • **Cohorts 1 and 2**: CFB in PROMIS® Physical Function at Weeks 16 and 26. • **Cohort 3**: CFB in PROMIS® Physical Function at Weeks 16, 24 and 32. • **Cohorts 1 and 2**: CFB in IWQOL-Lite-CT© at Weeks 16 and 26. • **Cohort 3**: CFB in IWQOL Lite-CT© at Weeks 16, 24 and 32. • **Cohorts 1 and 2**: PGI-C at Weeks 4, 16 and 26. • **Cohort 3**: PGI-C at Weeks 4, 16, 24 and 32.
Note: For all endpoints, baseline is defined as the result closest prior to dosing at V3 (Day 1). See Section 9.1 for additional details regarding Estimands.		

Objectives	Estimands	Endpoints
a. End of Treatment defined as Week 26 for Cohorts 1 and 2, and as Week 32 for Cohort 3. b. For Cohorts 1 and 2, this includes Weeks 2, 4, 6, 8, 10, 12, 16, 18, 22 and 26; for Cohort 3, this includes Weeks 4, 8, 12, 16, 20, 24, 28 and 32.		

4. STUDY DESIGN

4.1. Overall Design

This Phase 2b, multicenter, randomized, double-blind, placebo-controlled, parallel group, study will assess efficacy, safety, tolerability and PK of twice daily oral administration of PF-06882961 in adult participants with obesity. There are 3 Cohorts included in the study: Cohort 1 under the original protocol, Cohort 2 added under Amendment 1, and Cohort 3 added under Amendment 2, as described below.

For all cohorts, following the initial screening period to confirm eligibility (up to 4 weeks), screening continues with a 2-week placebo run-in period which will be single-blinded (participant). Eligible participants who maintain acceptable compliance during the run-in period are randomized on Day 1 to double-blinded study intervention.

This study was initially designed with a 2-part double-blinded treatment phase, as the 16-week dosing duration of Part A was supported by the nonclinical toxicology data available at the time of the original protocol finalization, and dosing in Part B over Weeks 17-26 was contingent on availability of supportive nonclinical data from a 9-month toxicology study in monkeys (Study CCI) that was ongoing at that time, and is now completed. For Cohort 1, participants were randomized into 9 arms: a placebo arm, 5 arms with 1-week titration steps (also referred to as standard titration in previous protocol versions), and 3 arms with 2-week titration steps (also referred to as slow titration in previous protocol versions). Protocol Amendment 1 added Cohort 2 where additional participants were randomized to the placebo and the 3 arms with 2-week titration steps. All SoA activities are the same for Cohort 2 as for the original cohort (Cohort 1) of randomized participants. Part B was approved before any participant reached the end of Part A, and participants in both Cohorts 1 and 2 were able to proceed directly from Part A to Part B. Accordingly, the primary endpoint for Cohorts 1 and 2 is based on End of Treatment defined as Week 26. For participants in Cohorts 1 and 2, the total duration of dosing with double-blinded study intervention is 26 weeks, followed by an approximate 4-week follow-up. The total duration of participation in this study for the participants in Cohorts 1 and 2 is approximately 32 weeks, including the 2-week single-blind run-in period, but excluding the initial screening period.

For Cohort 3, added under protocol Amendment 2, participants will be randomized to placebo or 1 of 3 PF-06882961 arms with 4-week dose titration steps. The overall approach to study procedures is similar to the previous cohorts, however, the double-blinded treatment phase is not presented as 2-parts (as there is now supportive data for the full dosing duration as described above) and the visit schedule for Cohort 3 is adjusted to correspond to the 4-week dose titration intervals. The double-blinded treatment phase for Cohort 3 is extended to 32 weeks compared to 26 weeks for Cohorts 1 and 2 in order to allow for sufficient steady

state dosing given the longer titration intervals, and to generate additional efficacy data over a longer treatment period. Accordingly, the primary endpoint for Cohort 3 is based on End of Treatment defined as Week 32. For Cohort 3, the total duration of dosing with double-blinded study intervention is 32 weeks, followed by an approximate 4-week follow-up. The total duration of study participation for participants in Cohort 3 is approximately 38 weeks, including the 2-week single-blind run-in period, but excluding the initial screening period.

All dosing regimens for all cohorts include dose titration to enhance tolerability of PF-06882961, where the dose level is increased at set intervals of 1, 2 or 4 weeks until a target dose is achieved (see Table 1 for Cohorts 1 and 2, and Table 2 for Cohort 3). For all cohorts, dosing is to occur with food twice daily. For the 5 1-week titration PF-06882961 groups in Cohort 1, the target dose levels for each of the arms are 40 mg BID, 80 mg BID, 120 mg BID, 160 mg BID, and 200 mg BID, with titration from a starting dose of [redacted] mg BID, and up to [redacted] weeks of the dosing duration used for titration. For the 3 2-week titration PF-06882961 groups in Cohorts 1 and 2, target dose levels for each of the arms are 120 mg BID, 160 mg BID, and 200 mg BID, with titration from a starting dose of [redacted] mg BID, and up to [redacted] weeks used for titration. Both Cohorts 1 and 2 also include a placebo arm. For Cohort 3, participants will be enrolled into 4 study arms, and target dose levels are placebo and PF-06882961 doses of 80 mg BID, 140 mg BID, and 200 mg BID. For Cohort 3, titration will occur at 4-week intervals from a starting dose of [redacted] mg BID, and up to [redacted] weeks will be used for titration to reach the target dose. Additional details regarding dose titration are provided in Section 6.1 and in the IP Manual.

There will be total of approximately 581 participants across all 3 cohorts of this study. In Cohort 1, approximately 420 participants (approximately 60 in each of the placebo and 5 1-week titration PF-06882961 arms and approximately 20 in each of the 3 2-week titration PF-06882961 arms) were randomized. All dosing arms, including placebo, were enrolled simultaneously in Cohort 1. Subsequently, in Cohort 2, approximately 49 additional participants were randomized to the placebo and 2-week titration arms (approximately 7 in the placebo and approximately 14 in each of the 3 2-week titration arms.). Combining Cohorts 1 and 2, there were a total of approximately 469 participants randomized (approximately 67 in the placebo, approximately 60 in each of the 5 1-week titration arms and approximately 34 in each of the 3 2-week titration arms). In Cohort 3, approximately 112 participants will be randomized to 4 additional study arms (approximately 16 in the placebo and approximately 32 in each of 3 PF-06882961 arms with 4-week titration steps).

Randomization is stratified according to biological gender (female versus male), as both tolerability and efficacy may be different between men and women.[11] This stratification is intended to balance the numbers of participants of either gender across treatment arms. In addition, no more than approximately 70% of the trial population will consist of 1 gender, in order to permit adequate representation of both men and women in the trial population.

4.1.1. Assessment of Safety and Tolerability While Study is Ongoing

In accordance with the sponsor's standard practices, emerging safety data are reviewed periodically in a blinded manner by the sponsor's clinical team on an ongoing basis during study conduct. An interim analysis of the unblinded safety data by the IRC will occur at least once annually while the study is ongoing, as described in Section 9.5. In addition, during study conduct for Cohorts 1 and 2, there were 3 blinded safety reviews performed by selected members of the sponsor's study team; each of these blinded safety reviews was separated by at least 1 month from the previous review.

4.2. Scientific Rationale for Study Design

This study is designed to assess the efficacy and safety of PF-06882961 in adult participants with obesity. After completing initial screening activities in V1, a placebo run-in period (ie, V2 to V3) is included in this study to familiarize participants with the study treatment regimens and to exclude those who are not compliant with single-blinded placebo dosing prior to randomization. Clinical laboratory tests, assessments of vital signs and 12-lead ECGs, physical examinations, measurement of body weight, waist and hip circumference, AE monitoring, and collection of blood for PK samples will provide data to evaluate the efficacy, safety, tolerability and PK of PF-06882961. In order to reduce variability in the assessment of the primary endpoint, body weight, all body weight measurements will be collected in duplicate. Waist and hip circumference[12,13] will be measured in triplicate, as additional parameters of body weight. Similarly, in an effort to reduce variability and better quantitate potential changes in BP and pulse rate during the study, all measurements of BP and pulse rate will be collected in triplicate and the mean systolic and diastolic BP and mean pulse rate will be reported at each time point.

As part of the clinical safety laboratory tests, calcitonin, amylase, and lipase will be assessed, as these laboratory parameters have been shown to increase with marketed GLP-1R agonists.[14-17] In addition, TSH, FT4, lipids, coagulation profile and TBA will be assessed, based on non-adverse findings in the nonclinical studies with PF-06882961. Assessment of suicidal ideation and behavior by the C-SSRS[18] and PHQ-9[19] will also be performed based on the potential risk related to the product labeling for the injectable GLP-1R agonist liraglutide for obesity.[17] The collection of blood samples, specifically HbA1c, FPG, and FPI will be used to assess changes in glycemic parameters and insulin resistance in this study population. FPG and FPI levels will be used to calculate HOMA-IR and HOMA-B.[20]

There are 3 cohorts included in this study: Cohort 1 under the original protocol, Cohort 2 added under Amendment 1 and Cohort 3 added under Amendment 2. Cohort 1 included placebo, 5 PF-06882961 arms with 1-week titration steps, and 3 PF-06882961 arms with 2-week titration steps. For Cohort 2, additional participants were randomized to the placebo and 3 arms with 2-week titration steps. This cohort was added to better characterize the tolerability and efficacy profile of the 2-week titration schemes, relative to the 1-week titration schemes, with placebo included to maintain the double-blind study design. The study design for Cohorts 1 and 2 was chosen to permit sufficient efficacy[21] and tolerability assessment of both arms with 1-week titration steps and arms with 2-week steps. The target

doses and titration schemes initially utilized in this study were informed by the doses administered and tolerability data from the C3421002 study. Cohort 3 is being added under Amendment 2, and includes 4 arms, which are placebo and 3 PF-06882961 arms with 4-week dose titration steps. This cohort is added to characterize the tolerability and efficacy profile of 4-week titration steps, with placebo included to maintain the double-blind aspect. In this study, the total duration of dosing with randomized double-blinded study intervention is 26 weeks for participants in Cohorts 1 and 2, and 32 weeks for participants in Cohort 3. The duration of double-blinded treatment for Cohort 3 is extended to 32 weeks in order to allow for sufficient steady state dosing given the longer titration intervals, and to generate additional efficacy data over a longer treatment period. Downward titration of dosing is not permitted during the study; participants who do not tolerate the titration scheme and/or assigned dose may be required to discontinue dosing of study intervention.

In accordance with guidelines for the management for obesity,[22] all participants will receive dietary and physical activity counseling.

GLP-1R agonists typically are not associated with hypoglycemia unless co-administered with anti-diabetic agents that can cause hypoglycemia (such as insulin or sulfonylureas), which are prohibited in this study. Blood glucose concentrations will be monitored throughout the study as part of the safety laboratory measurements. In addition, all participants will be instructed at placebo run-in and randomization regarding the symptoms associated with, and management of, hypoglycemia, which will permit the monitoring of symptomatic HAEs.

PCOAs have been included to understand how the study intervention affects eating-related factors such as appetite, hunger and food-cravings. Recognizing the wider impact of obesity on patients, additional PRO measures for fatigue, physical function and health-related quality of life have also been included.[23,24]

An interim analysis of the unblinded safety data by the IRC will be performed at least once annually while the study is ongoing, and dose level(s) may be dropped if deemed necessary. See Section 4.1.1 and Section 9.5 for additional information regarding the interim analysis.

Females of childbearing potential may be enrolled into this study given the availability of embryo fetal developmental toxicity studies with PF-06882961. However, as marketed GLP-1R agonists are listed as contraindicated in pregnancy, the use of a highly effective method of contraception is required and measures will be taken to limit the risk of pregnancy in the female population enrolled [see SoA for the applicable cohort (SoA for Cohorts 1 and 2, and SoA for Cohort 3) and Appendix 4].

The potential risk of exposure to PF-06882961 in a sexual partner of a male participant in this study via ejaculate is low, and therefore no contraception (condom) use in male participants is warranted. The calculated safety margin is CCI between the estimated partner exposure due to seminal transfer and the NOAEL for serious manifestations of developmental toxicity in nonclinical studies. The safety margin of CCI is based on applying a 10-fold safety factor for interspecies extrapolation and a 10-fold safety factor for susceptible populations.[25]

CCI [redacted]

Banked Biospecimens will be collected and stored for further analyses which may, for example, provide greater understanding of the study intervention.

4.3. Justification for Dose

The PF-06882961 doses selected for this study are based on observed safety, tolerability, PK, and PD data to date, as well as the anticipated effect on body weight and exposure margins relative to the completed toxicology studies. As the tolerability profile of multiple doses of PF-06882961 has been assessed primarily in the setting of a BID dosing regimen, the proposed dosing regimen for the current study is BID.

This study is designed to evaluate the dose response of PF-06882961 from lower doses, predicted to have sub-maximal effects on body weight loss up to doses expected to have greater weight loss efficacy in the participant population, while still having an adequate tolerability profile. Body weight loss projections based on preliminary modeling of Phase 1 data from C3421002 had indicated that the proposed target dose levels assessed in Cohorts 1 and 2 of 40 mg BID, 80 mg BID, 120 mg BID, 160 mg BID and 200 mg BID are expected to result in body weight loss that is approximately CCI [redacted] of the projected body weight loss at the highest dose in this study (200 mg BID). The 200 mg BID dose was projected to result in CCI [redacted]. Selection of higher doses for assessment of efficacy in obesity, compared with glycemic efficacy in T2DM, is consistent with the observation that higher doses of GLP-1R agonists are generally needed for treatment of obesity. In Cohort 3, 3 dose levels (80 mg BID, 140 mg BID and 200 mg BID) will be evaluated with the aim to generate additional efficacy and tolerability data using 4-week titration steps. In line with what has been observed with other marketed GLP-1R agonists,[27] 4-week titration steps may further improve tolerability and mitigate gastrointestinal side effects compared to the shorter titration steps implemented in Cohorts 1 and 2.

The dose range selected for PF-06882961 across all cohorts of this study has been demonstrated to be safe with no clinically relevant dose-related adverse trends identified in previous clinical studies and a tolerability profile in line with the mechanism of action (Section 2.2.2.1). The expected PF-06882961 exposure at the highest 200 mg BID dose is approximately [CCI]-fold and [CCI]-fold lower (for C_{max} and AUC_{24}, respectively) than the exposure observed at the NOAEL in the pivotal 9-month toxicology study in monkeys, after accounting for differences in plasma protein binding between species. Based on the above, PF-06882961 doses up to 200 mg BID are viewed as appropriate for assessment in this study with an expected acceptable safety and tolerability profile.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study, including the last follow-up visit, approximately 28 to 35 days post last dose of study intervention.

The end of the study is defined as the date of the last visit of the last participant in the study across all sites globally.

5. STUDY POPULATION

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

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

5.1. Inclusion Criteria

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

Age and Sex:

1. Male or female participants between the ages of 18 (or the minimum country-specific age of consent if >18) and 75 years, inclusive, at V1.

    - Women can be of child-bearing potential, however, cannot be pregnant, breastfeeding, or planning to become pregnant while participating in the study.

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

Type of Participant and Disease Characteristics:

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

Body Mass Index (BMI) and Weight:

3. Participants with obesity, defined as a BMI ≥30.0 kg/m^2 at V1.

4. Stable body weight, defined as <5 kg change (per participant report) for 90 days before V1.

Informed Consent:

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

5.2. Exclusion Criteria

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

Medical Conditions:

1. Known intolerance or hypersensitivity to GLP-1R agonists.

2. Any condition possibly affecting drug absorption (eg, prior bariatric surgery, gastrectomy, or any area of intestinal resection, active inflammatory bowel disease or pancreatic insufficiency).

3. Current or prior diagnosis of T1DM or T2DM or secondary forms of diabetes. ***Note:*** women with medical history of gestational diabetes that resolved upon delivery are eligible if they meet the other eligibility criteria.

4. History of myocardial infarction, unstable angina, arterial revascularization, stroke, New York Heart Association Functional Class II-IV heart failure, or transient ischemic attack within 6 months prior to V1.

5. Any malignancy not considered cured (except focal, treated basal cell carcinoma and squamous cell carcinoma of the skin); a participant is considered cured if there has been no evidence of cancer recurrence in the previous 5 years.

6. Personal or family history of medullary thyroid carcinoma or Multiple Endocrine Neoplasia syndrome type 2, or participants with suspected medullary thyroid carcinoma per the investigator's judgment.

7. History of acute pancreatitis within 180 days (6 months) prior to V1 or any history of chronic pancreatitis.

8. Symptomatic gallbladder disease.

9. Medical history or characteristics suggestive of genetic or syndromic obesity or obesity induced by other endocrinological disorders (eg, Cushing Syndrome).

10. History of major depressive disorder or history of other severe psychiatric disorders (eg, schizophrenia or bipolar disorder) within the last 2 years.

11. Any lifetime history of a suicide attempt.

12. Known medical history of active liver disease (other than non-alcoholic hepatic steatosis), including chronic active hepatitis B or C, or primary biliary cirrhosis.

13. Known history of HIV.

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

Prior/Concomitant Therapy:

15. See Appendix 8 for details regarding prohibited prior/concomitant medications.

Prior/Concurrent Clinical Study Experience:

16. Previous administration with an investigational product (eg, drug or vaccine) within 30 days (or as determined by the local requirement) or 5 half-lives before the first dose of study intervention used in this study, whichever is longer. CCI [redacted]

17. Known prior participation in a trial involving PF-06882961.

Diagnostic Assessments:

18. A PHQ-9 score ≥15 obtained at V1, V2 or V3.

19. Response of "yes" to question 4 or 5, or on any behavioral question on the C-SSRS at V1, V2 or V3.

20. At V1, V2 or V3 prior to randomization, supine BP ≥160 mmHg (systolic) or ≥100 mmHg (diastolic), following at least 5 minutes of supine rest. BP should be measured in triplicate and the average of the 3 BP values should be used to determine the participant's eligibility.

21. At V1, V2 or V3 prior to randomization, 12-lead ECG that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results (eg, QTcF interval >450 msec, complete LBBB, signs of an acute or indeterminate-age myocardial infarction, ST-T interval changes suggestive of myocardial ischemia, second- or third-degree AV block, or serious bradyarrhythmias or tachyarrhythmias). If the QTcF exceeds 450 msec, or QRS exceeds 120 msec, the ECG should be repeated 2 more times and the average of the 3 QTcF or QRS values should be used to determine the participant's eligibility. Computer-interpreted ECGs should be overread by a physician experienced in reading ECGs before excluding participants.

22. A positive urine drug screen at V1 that is consistent with illicit drug use. ***Note:*** Participants who have been medically prescribed medications including but not limited to, opiates/opioids or benzodiazepines and report the use of these drugs to the investigator at V1 may be allowed to participate with notification to the sponsor.

23. Participants with ANY of the following abnormalities in clinical laboratory tests at V1, as assessed by the study specific laboratory and confirmed by a single repeat test, if deemed necessary:

    - HbA1c ≥6.5%;
    - AST or ALT level ≥2 times ULN;
    - TBili level ≥1.5 times ULN;
    - Fasting C-peptide <0.8 ng/mL;
    - TSH >1.5 times ULN or < LLN;
    - Serum calcitonin > ULN;
    - Amylase or lipase > ULN;
    - FPG ≥126 mg/dL (7 mmol/L);
    - eGFR <60 mL/min/1.73 m^2 as calculated by the CKD-EPI equation.

Other Exclusions:

24. Compliance of <89% (based on tablet count) during the 2-week placebo run-in period, as assessed prior to randomization on Day 1 (see Section 6.4).

25. Participation in a formal weight reduction program (eg, Weight Watchers) within 90 days prior to V1.

26. History of regular alcohol consumption exceeding 7 drinks/week for female participants or 14 drinks/week for male participants (1 drink = 5 ounces [150 mL] of wine or 12 ounces [360 mL] of beer or 1.5 ounces [45 mL] of hard liquor) within 6 months prior to V1.

27. Known or suspected illicit drug use.

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

29. Unwilling or unable to comply with the Lifestyle Considerations section of the protocol (see Section 5.3).

30. Living in the same household as a participant who is currently in screening or in the randomized treatment phase of the study. Note: participants can be enrolled in the study if another member of their household has already screen failed or is in the follow-up phase of the study.

31. Body weight exceeds the maximum capacity of the site's scale, preventing accurate assessment of body weight.

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

5.3. Lifestyle Considerations

The following sections describe guidelines for diet, physical activity, alcohol, caffeine and tobacco use and contraception requirements that are to be followed throughout the study.

5.3.1. Dietary Restrictions

- Participants must abstain from all food and drink (except water) for at least 8 (preferably 10) hours prior to any body weight, waist and hip measurements, and blood sample collections, except for post-dose PK collections.

- Water may be consumed as desired (ad libitum).

- Study intervention must be administered BID in the morning and evening with food, approximately 10-12 hours apart.

- On scheduled visits to the site, ***in the morning,*** from start of run-in (V2) through the last visit in the treatment phase for the respective cohort (see SoA for Cohorts 1 and 2, and SoA for Cohort 3), participants should be instructed to arrive fasting for at least 8 hours (***without*** having food/breakfast) and ***without*** self-administration of study intervention. ***Note***: Participants may take their morning dose of antihypertensive medication and/or lipid modifying medication before their visit per their usual routine, if applicable.

- On the mornings of the above visits, the study intervention will be administered at the site with food.

- Participants will be counseled on appropriate dietary and physical activity guidelines, as described in Section 5.3.2 and Section 5.3.3, for obesity at the times listed in the SoA for the applicable cohort (see SoA for Cohorts 1 and 2, and SoA for Cohort 3) and asked to maintain these guidelines throughout participation in the study. ***Note***: Participation in formal weight loss programs should be avoided during participation in this study.

5.3.2. Dietary Counseling

At times listed in the SoA for the applicable cohort (see SoA for Cohorts 1 and 2, and SoA for Cohort 3), participants will receive dietary counseling by appropriate site staff with instruction to induce an energy deficit of ≥500 kcal/day from the participant's estimated total energy expenditure (TEE), in accordance with guidelines,[22] using the formula below:

- TEE = Resting energy expenditure (REE) x activity factor.

For all participants, an activity factor of 1.3 (to match a sedentary activity level) will be used. The REE for each participant will be calculated with the Harris Benedict formula for men and women, using the participant's body weight, height, and age obtained at V1, as listed below:[28]

- For women: REE (kcal/d) = 655 + 9.5 (weight in kg) + 1.9 (height in cm) – 4.7 (age in years).

- For men: REE (kcal/d) = 66 + 13.8 (weight in kg) + 5.0 (height in cm) – 6.8 (age in years).

5.3.3. Physical Activity Counseling

At times listed in the SoA for the applicable cohort (see SoA for Cohorts 1 and 2, and SoA for Cohort 3), participants will be instructed to maintain physical activity for ≥150 minutes per week (≥30 minutes per day most days of the week) in accordance with guidelines.[22]

Prior to clinical study visits, participants will be instructed not to perform physically strenuous exercise (for example: heavy lifting, weight training, calisthenics and aerobics) within 48 hours prior to blood sample collections; walking at a normal pace is permitted.

5.3.4. Alcohol, Caffeine, and Tobacco

- Intake of alcohol is permitted in moderation (see exclusion criterion 26 for acceptable amount of alcohol consumption).

- Caffeine containing products will be permitted during the study with the following restrictions: caffeine containing products may not be consumed within 1 hour prior to measuring vital signs and ECGs.

- Use of nicotine-containing products is permitted in this study with the following restrictions: nicotine-containing products may not be used within 1 hour prior to measuring vital signs and ECGs.

5.3.5. Contraception

The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual participant from the permitted list of contraception methods (see Appendix 4 Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the SoA for the applicable cohort (see SoA for Cohorts 1 and 2, and SoA for Cohort 3), the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

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

6. STUDY INTERVENTION

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

For the purposes of this protocol, study intervention refers to PF-06882961 and matching placebo tablets. All tablets (across unit dose strengths and placebo) are identical in appearance and are to be taken orally.

6.1. Study Intervention(s) Administered

Intervention Name	PF-06882961	Placebo for PF-06882961
ARM Name (group of patients receiving a specific treatment or no treatment)	Active	Placebo
Type	Drug	Drug
Dose Formulation	Tablet	Tablet
Unit Dose Strength(s)	[redacted]	Not applicable
Target Dosage Level(s) (achieved upon titration)	Cohort 1 and Cohort 2: 40 mg BID, 80 mg BID, 120 mg BID, 160 mg BID, 200 mg BID Cohort 3: 80 mg BID, 140 mg BID, 200 mg BID	0 mg BID
Route of Administration	Oral	Oral
Use	Experimental	Placebo
IMP or NIMP	IMP	IMP
Sourcing	Provided centrally by the sponsor. Refer to the IP Manual.	Provided centrally by the sponsor. Refer to the IP Manual.
Packaging and Labeling	Cohort 1 and Cohort 2: Study intervention will be provided in blister packs. Each blister pack will be labeled as required per country requirement. Cohort 3: Study intervention will be provided in bottles. Blinded labels will be utilized for placebo run-in, titration and stable dosing blister packs, and bottles.	Cohort 1 and Cohort 2: Study intervention will be provided in blister packs. Each blister pack will be labeled as required per country requirement. Cohort 3: Study intervention will be provided in bottles. Blinded labels will be utilized for placebo run-in, titration and stable dosing blister packs, and bottles.

6.1.1. Administration

Participants will be provided with blinded study intervention, consisting of identical tablets, packaged in blister packs for Cohorts 1 and 2, and in bottles for Cohort 3. The same dosing paradigm will be used for the single-blind placebo run-in and the randomized double-blind study intervention administered in the study.

Participants in Cohorts 1 and 2 are instructed to take 4 tablets of study intervention (PF-06882961 or matching placebo) in the morning with food and 4 tablets of study intervention in the evening with food, for a total of 8 tablets of study intervention daily. Participants in Cohort 3 are instructed to take 2 tablets of study intervention (PF-06882961 or matching placebo) in the morning with food and 2 tablets of study intervention in the evening with food, for a total of 4 tablets of study intervention daily. All participants are instructed to swallow the study intervention whole, and not crush, chew, break or dissolve the study intervention prior to swallowing.

The morning and evening doses should be taken approximately 10-12 hours apart and at approximately the same time each day. Participants should be instructed that if they forget to take a dose at their usual time, they should take that dose as soon as possible (with food), ensuring that there is ***at least an 8 hour interval between that dose and the next dose***. If the interval to the next dose is less than 8 hours, then the forgotten dose should not be administered.

Dosing and administration instructions along with a dosing diary, will be provided to participants to support at home dosing of the study intervention. When participants self-administer the study intervention at home, they will record each dose in the diary.

Morning dosing will occur at the site with food at V2-V13 for Cohorts 1 and 2 (see SoA for Cohorts 1 and 2), and at scheduled in-clinic study visits for Cohort 3 (see SoA for Cohort 3). Participants will be instructed to arrive at the site in the fasted state for each of these visits. Participants will be instructed to bring their study intervention supply and dosing diary with them, and to delay self-administration of study intervention until directed to dose during their visit. When participants dose at the site, they will self-administer the study intervention under supervision by site staff. Onsite dosing will be administered from newly dispensed study intervention, with the exception of the End of Treatment visit (ie, the last dose), which will be administered from study intervention supply brought back to the site by the participant, as no new study intervention is dispensed at the End of Treatment visit. The date and time of each dose administered at the site will be recorded in the site source documents, in the diary and in the CRF. Additionally, the date and time of the previous 2 doses of double-blinded study intervention prior to each of the pre-dose PK blood collections (ie, the 2 most recent doses prior to the visit as noted in the diary) will be entered in the CRF.

The actual titration schemes for PF-06882961 to be used in this study are provided in Table 1 for Cohorts 1 and 2, and Table 2 for Cohort 3. Details regarding dose titration are provided in the IP Manual.

Table 1. Titration and Dosing Schemes for Cohorts 1 and 2

		Arm 1	Arm 2	Arm 3	Arm 4	Arm 5	Arm 6	Arm 7	Arm 8	Arm 9
	Cohort 1	x	x	x	x	x	x	x	x	x
	Cohort 2	x						x	x	x
	Target Dose[a]	Placebo	40 mg BID	80 mg BID	120 mg BID	160 mg BID	200 mg BID	120 mg BID	160 mg BID	200 mg BID
Study Part	Study Week		PF-06882961 (mg BID) 1-week Titration Steps					PF-06882961 (mg BID) 2-week Titration Steps		
Part A: Weeks 1-16	1	0	[redacted]							
	2	0								
	3	0								
	4	0								
	5	0								
	6	0								
	7	0								
	8	0								
	9	0								
	10	0								
	11	0								
	12	0								
	13	0								
	14	0								
	15	0								
	16	0								
Part B: Weeks 17-26	17	0								
	18	0								
	19	0								
	20	0								
	21	0								
	22	0								
	23	0								
	24	0								
	25	0								
	26	0								

a. Target dose achieved after titration from starting dose.

Table 2. Titration and Dosing Schemes for Cohorts 3

	Arm 10	Arm 11	Arm 12	Arm 13
Target Dose[a]	Placebo	80 mg BID	140 mg BID	200 mg BID
Study Week		PF-06882961 (mg BID) 4-week Titration Steps		
1	0	[redacted]		
2	0			
3	0			
4	0			
5	0			
6	0			
7	0			
8	0			
9	0			
10	0			
11	0			
12	0			
13	0			
14	0			
15	0			
16	0			
17	0			
18	0			
19	0			
20	0			
21	0			
22	0			
23	0			
24	0			
25	0			
26	0			
27	0			
28	0			
29	0			
30	0			
31	0			
32	0			

a. Target dose achieved after titration from starting dose.

6.2. Preparation/Handling/Storage/Accountability

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

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

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

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

5. Study interventions should be stored in their original containers.

6. Site staff will instruct participants on the proper storage requirements for take-home study intervention.

7. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the IPAL or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record. All study intervention that is taken home by the participant, both used and unused, must be returned to the investigator by the participant. Returned study intervention must not be redispensed to the participants.

8. Further guidance and information for the final disposition of unused study interventions are provided in the IP manual. All destruction must be adequately documented. If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer.

Upon identification of a product complaint, notify the sponsor within 1 business day of discovery as described in the IP Manual.

6.2.1. Preparation and Dispensing

A qualified staff member will dispense the study intervention using the IRT system via unique container numbers on the blister cards or bottles provided, in quantities appropriate according to the SoA for the applicable cohort (see SoA for Cohorts 1 and 2, and SoA for Cohort 3). The participant should be instructed to maintain the product in the original containers provided throughout the course of dosing and bring the original containers to the site at the next study visit.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Study Intervention

Assignment of placebo in the run-in period and allocation of participants to treatment groups for the double-blind treatment period will proceed through the use of an IRT system (IWR). The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's ID and password, the protocol number, and the participant number. For the placebo run-in, the site personnel will then be provided with a DU or container number; for the double-blind treatment period, the site personnel will then be provided with a randomization number, and DU or container number(s). The IRT system will provide a confirmation report containing the participant number, randomization number, and DU or container number(s) assigned. The confirmation report must be stored in the site's files.

For Cohort 1, a randomization code using the method of random permuted blocks will be utilized to randomize eligible participants in 3:3:3:3:3:3:1:1:1 (placebo: 5 1-week titration PF-06882961 arms: 3 2-week titration PF-06882961 arms) prior to the first dose of double-blinded study intervention. For the additional participants enrolled as part of Cohort 2, a randomization code using the method of random permuted blocks will be utilized to randomize eligible participants in 1:2:2:2 (placebo: 3 2-week titration PF-06882961 arms) prior to the first dose of double-blinded study intervention. For Cohort 3, a randomization code using the method of random permuted blocks will be utilized to randomize eligible participants in 1:2:2:2 (placebo: 3 4-week titration PF-06882961 arms) prior to the first dose of double blinded study intervention. Participants will be randomized to 1 of the blinded study intervention regimens described in Table 3 for Cohorts 1 and 2, and Table 4 for Cohort 3.

Table 3. Target Doses for Randomized Regimens for Cohorts 1 and 2

Regimen Description (dosed twice daily)	Cohort 1	Cohort 2	CCI	Total Number of Tablets per dose
Placebo	x	x		
PF-06882961 – 40 mg (1-week titration steps)	x			
PF-06882961 – 80 mg (1-week titration steps)	x			
PF-06882961 – 120 mg (1-week titration steps)	x			
PF-06882961 – 160 mg (1-week titration steps)	x			
PF-06882961 – 200 mg (1-week titration steps)	x			
PF-06882961 – 120 mg (2-week titration steps)	x	x		
PF-06882961 – 160 mg (2-week titration steps)	x	x		
PF-06882961 – 200 mg (2-week titration steps)	x	x		

Table 4. Target Doses for Randomized Regimens for Cohort 3

Regimen Description (dosed twice daily)	CCI	Total Number of Tablets per dose
Placebo		
PF-06882961 – 80 mg (4-week titration steps)		
PF-06882961 – 140 mg (4-week titration steps)		
PF-06882961 – 200 mg (4-week titration steps)		

For Cohorts 1 and 2, all doses will appear identical, will be packaged in blister packs with blinded labels and the same dosing paradigm will be used for the single-blind placebo run-in and the 26-week double-blind dosing period. The same randomized treatment assignment in Part A will be continued in Part B. For Cohort 3, all doses will appear identical, will be packaged in bottles with blinded labels and the same dosing paradigm will be used for the single-blind placebo run-in and the 32-week double-blind dosing period.

Study intervention will be dispensed at the study visits summarized in the SoA for the applicable cohort (see SoA for Cohorts 1 and 2, and SoA for Cohort 3).

Returned study intervention must not be redispensed to the participants.

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

6.3.2. Breaking the Blind

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

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

6.4. Study Intervention Compliance

Compliance with study intervention will be assessed at each site visit by counting returned tablets and this will be documented in the source documents and CRF. Deviation(s) from the prescribed dosage regimen should be recorded in the CRF.

A record of the number of study intervention tablets dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records.

Compliance (as assessed by tablet count) will be defined as self-administration, by the participants, of:

- ≥89% of the study-supplied placebo administered during the placebo run-in period. Based on the visit window, for a run-in that is 11-13 days, 2 missed doses (or fewer) are allowed, and for a run-in that is 14-17 days, 3 missed doses (or fewer) are allowed. Participants who do not meet this compliance threshold are not eligible to be randomized into the study (see Section 5.2).

- ≥80% of the study supplied from Day 1 through End of Treatment, inclusive. Investigators must closely follow non-compliant, randomized, participants in order to enhance their adherence to treatment. Any participant who fails to meet the criterion of ≥80% compliance will be re-educated by the site staff on the importance of compliance with study intervention.

6.5. Concomitant Therapy

Participants in this study will be allowed to be on certain concomitant medications that have been prescribed. Attempts should be made not to alter the doses and regimens of the background medications after randomization and for the duration of participation in this study, except in circumstances where a change in dose is deemed medically necessary. Any changes must be captured in the CRF. Additionally, many over-the-counter medications are

also permitted during this study unless specified as prohibited in Appendix 8, eg, appetite suppressants.

Treatments taken within 28 days before the first dose of randomized study intervention on Day 1 will be documented as prior treatment. Treatments taken after the first dose of randomized study treatment will be documented as concomitant treatment.

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

See Appendix 8 for details regarding prohibited concomitant medications, as well as medications with timeframes for restriction prior to V1 or prior to first dose of study intervention. Sites are encouraged to contact the sponsor should there be questions as to whether a medication is permitted or prohibited.

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

6.5.1. Antihypertensive Medications

The use of background antihypertensive agent(s) is permitted unless otherwise noted in Appendix 8. Doses of antihypertensive agent(s) must be stable for at least 4 weeks prior to screening and throughout the study, ***except*** in circumstances where a change in dose is deemed medically necessary. Any changes in doses of these medications must be captured in the CRF.

6.5.2. Lipid Modifying Medications

The use of background lipid modifying agents is permitted unless otherwise noted in Appendix 8. Doses of such lipid modifying agents must be stable for at least 4 weeks prior to screening and throughout the study, ***except*** in circumstances where a change in dose is deemed medically necessary. Any changes in doses of these medications must be captured in the CRF.

6.5.3. Rescue Medicine

There is no rescue therapy to reverse the AEs observed with PF-06882961; standard medical supportive care should be provided to manage the AEs.

6.6. Dose Modification

6.6.1. Dose Titration

Dose titration schemes are utilized for each study intervention dosing arm in this study as described in Section 6.1.1. Dose adjustment, either during dose titration or steady state dosing, will not be permitted per protocol. Separate materials on participant education and approaches to manage temporary mechanism of action based gastrointestinal-related AEs will be provided by the sponsor prior to initiation of dosing for Cohort 3.

6.6.2. Considerations for Pausing or Stopping Active Dose(s) Based on Observed Safety

The decision to stop dosing for 1 or more active dose(s) of PF-06882961 may be considered based on recommendations from the IRC according to their review of unblinded, study-level emerging, observed safety data (see Section 9.5), for reasons such as the following:

- More than 50% of participants develop a moderate or severe AE in the gastrointestinal SOC not responsive to symptomatic management.

6.7. Intervention After the End of the Study

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

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

It may be necessary for a participant to permanently discontinue study intervention. Reasons for permanent discontinuation of study intervention include the following:

- Criteria for a potential Hy's law case are met (see Appendix 6);
- Intent to become pregnant or pregnancy confirmed by β-hCG testing;
- Safety or tolerability concern arises, in particular if not responsive to symptomatic management, dosing with double-blind study intervention may be stopped in an individual participant at the discretion of the investigator;
- Based on mental health assessment as outlined in Section 8.2.6, should be discontinued from dosing at the discretion of the investigator.

If the criteria for permanent discontinuation are met, the site should notify the sponsor Medical Monitor or sponsor Clinician.

Note that discontinuation of study intervention does not represent withdrawal from the study. If study intervention is definitively discontinued, the participant will remain in the study to be evaluated for obesity, and will be expected to continue with all study visits and assessments as outlined in the SoA for the applicable cohort (see SoA for Cohorts 1 and 2, and SoA for Cohort 3), with the exception of dosing activities and assessment of PK. See the SoA for the applicable cohort (see SoA for Cohorts 1 and 2, and SoA for Cohort 3) for data to be collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed.

In the event of discontinuation of study intervention, it must be documented on the appropriate CRF/in the medical records whether the participant is discontinuing further receipt of study intervention or also from study procedures, posttreatment study follow-up, and/or future collection of additional information.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request. Reasons for discontinuation from the study include the following:

- Refused further follow-up;
- Lost to follow-up;
- Death;
- Study terminated by sponsor;
- Safety or behavioral reasons at the discretion of the investigator, including reasons related to mental health assessments as described in Section 8.2.6.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted. See the SoA for the applicable cohort (see SoA for Cohorts 1 and 2, and SoA for Cohort 3) for assessments to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

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

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

If the participant withdraws from the study and also withdraws consent (see Section 7.2.1) for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

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

7.2.1. Withdrawal of Consent

Participants who request to discontinue receipt of study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him or her or persons previously authorized by the participant to provide this information. Participants should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the

withdrawal is only from further receipt of study intervention or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

7.3. Lost to Follow-up

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

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

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

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

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

Study procedures and their timing are summarized in the SoA for the applicable cohort (see SoA for Cohorts 1 and 2, and SoA for Cohort 3). Protocol waivers or exemptions are not allowed.

Safety issues should be discussed with the sponsor immediately upon occurrence or awareness to determine whether the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA for the applicable cohort (see SoA for Cohorts 1 and 2, and SoA for Cohort 3), is essential and required for study conduct.

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

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

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

The total blood sampling volume for individual participants who complete the study is approximately 280 mL. The actual collection times of blood sampling may change. Additional blood samples may be taken for safety assessments at times specified by the sponsor, provided the total volume taken during the study does not exceed 550 mL during any period of 60 consecutive days.

8.1. Efficacy Assessments

Efficacy assessments for this study include measurements of body weight, waist circumference, and waist-to-hip ratio (calculated from waist and hip circumference measurements). In addition, PCOAs will be completed to assess how the participants feel and function.

8.1.1. Primary Efficacy Parameter: Body Weight

Body weight is the primary efficacy assessment for this study. Body weight will be measured in duplicate as indicated in the SoA for the applicable cohort (see SoA for Cohorts 1 and 2, and SoA for Cohort 3). The second weight measurement should be obtained at least 1-2 minutes apart from the first weight measurement.

Weight will be recorded using a calibrated scale (with the same scale used as much as practically possible for the duration of the study) reporting weight in either pounds (lb) or kilograms (kg), and accuracy to the nearest 0.2 lb (or 0.1 kg); ie, the device must be able to distinguish a difference between 150.4 lb (68.4 kg) versus 150.2 lb (68.3 kg). Calibration of the scale must occur within 3 months prior to study initiation at the site and at least every 6 months during study conduct. The scale must be placed on a stable, flat surface.

Weight measurement should be taken under the following conditions:

- Participant is in a fasted state (see Section 5.3.1);
- After the participant has been asked to void of urine (ie, forced void);
- After the participant has removed shoes and bulky layers of clothing and jackets so that only light clothing (with empty pockets) or a hospital gown remains;
- With the participant standing still while on the scale.

8.1.2. Secondary Efficacy Parameters: Waist and Hip Circumference

Waist and hip circumference will be measured at the times specified in the SoA for the applicable cohort (see SoA for Cohorts 1 and 2, and SoA for Cohort 3) and will be used to calculate the waist-to-hip ratio. The waist circumference is defined as the abdominal circumference located at the approximate midpoint between the lower margin of the last palpable rib and the top of the iliac crest. The hip circumference is defined as the circumference around the widest portion of the buttocks.[12,13]

Waist and hip measurements should be taken under the following conditions:

- Participant is in a fasted state (see Section 5.3.1);
- After the participant has been asked to void of urine (ie, forced void);
- With the participant wearing light clothing or a hospital gown that allows access for the measurements to be taken with the tape touching the skin (not clothing) for waist measurements, and the tape touching the skin if possible for hip measurements;
- While the participant is standing with their feet close together, their weight equally distributed to each leg, and arms at their side but with waist and hips accessible;
- After the participant has been asked to breathe normally; the reading of the measurement should be taken at the end of a normal exhalation.

These measurements will be obtained using an anthropometric tape (stretch-resistant). The tape should be snug around the body, but not pulled so tight that it is constricting. The tape should be in the horizontal all around the body, parallel to the floor at the level at which the measurement is made and avoiding twists in the tape. The waist and hip circumference will be measured in triplicate,[12] with a brief interval (at least 1-2 minutes) between successive measurements. All 3 measurements will be recorded in inches or cm, rounded to the nearest $1/16^{th}$ inch or 0.1 cm.

8.1.3. Tertiary Efficacy Parameters: Patient Centered Outcome Assessments (PCOAs)

The PCOAs consist of PRO assessments which will be implemented using sponsor-provided ePRO devices. Participants will complete specific PRO assessments based on their site country location as described in the SoA for the applicable cohort (see SoA for Cohorts 1 and 2, and SoA for Cohort 3) and Table 5.

Table 5. Patient Reported Outcome Measures

Measure	Frequency	Number of Questions	*Estimated* Completion Time	US Sites Only[a]	Ex-US Sites[b]
Eating-Related Factors Daily Diary[c]	**Cohorts 1, 2 and 3:** Daily, starting at V2 (Pbo run-in) to End of Treatment	5	2 minutes	At home, (handheld device)	N/A
PGI-S	**Cohorts 1, 2 and 3:** At each planned in-clinic study visit, starting at V2 (Pbo run-in) to End of Treatment	4	1 minute	At the clinic (electronic tablet)	
PGI-C	**Cohorts 1 and 2:** V5 (Week 4) V10 (Week 16) V13 (Week 26) **Cohort 3:** V5 (Week 4) V11 (Week 16) V15 (Week 24) V19 (Week 32)	4	1 minute		
PROMIS® Fatigue Custom 9-item	**Cohorts 1 and 2:** V2 (Pbo run-in) V3 (Day 1) V10 (Week 16) V13 (Week 26) **Cohort 3:** V2 (Pbo run-in) V3 (Day 1) V11 (Week 16) V15 (Week 24) V19 (Week 32)	9	11 minutes		
PROMIS® Physical Function Custom 13-item	**Cohorts 1 and 2:** V2 (Pbo run-in) V3 (Day 1) V10 (Week 16) V13 (Week 26) **Cohort 3:** V2 (Pbo run-in) V3 (Day 1) V11 (Week 16) V15 (Week 24) V19 (Week 32)	13			

Measure	Frequency	Number of Questions	*Estimated* Completion Time	US Sites Only[a]	Ex-US Sites[b]
IWQOL-Lite-CT©	**Cohorts 1 and 2:** V2 (Pbo run-in) V3 (Day 1) V10 (Week 16) V13 (Week 26) **Cohort 3:** V2 (Pbo run-in) V3 (Day 1) V11 (Week 16) V15 (Week 24) V19 (Week 32)	20			
SF-36v2®	**Cohorts 1 and 2:** V2 (Pbo run-in) V3 (Day 1) V10 (Week 16) V13 (Week 26) **Cohort 3:** V2 (Pbo run-in) V3 (Day 1) V11 (Week 16) V15 (Week 24) V19 (Week 32)	36	9 minutes	At the clinic (electronic tablet)	At the clinic (electronic tablet)

a. Participants from US sites will complete all PRO assessments.

b. Participants from ex-US sites will complete only the SF-36v2®.

c. Participants from selected US sites will complete the Eating-Related Factors Daily Diary.

Every effort should be made to have the participant complete all PRO assessments as per the SoA for the applicable cohort (see SoA for Cohorts 1 and 2, and SoA for Cohort 3). Site-based PRO assessments should be completed by the participant at the beginning of the visit before any medical procedures or interactions with the medical staff (as much as practically possible) take place.

Additional details regarding the process of administration of the PROs will be provided in a study-specific user manual supplied by the sponsor.

8.1.3.1. Eating-Related Factors Daily Diary

The Eating-Related Factors Daily Diary is a daily, self-administered questionnaire that measures eating-related factors. The diary consists of 5 items that ask participants to evaluate their hunger, appetite, fullness, and cravings in the past 24 hours.

8.1.3.2. Patient's Global Impression of Severity (PGI-S)

The PGI-S is a supportive item recommended by FDA for use as an anchor measure to generate an appropriate threshold that represents meaningful within-patient change in the target patient population. There are 4 PGI-S items that ask participants to evaluate the severity of their hunger, appetite, fullness, and cravings in the past 7 days.

8.1.3.3. Patient's Global Impression of Change (PGI-C)

The PGI-C is a supportive item recommended by FDA for use as an anchor measure to generate an appropriate threshold that represents meaningful within-patient change in the target patient population. There are 4 PGI-C items that ask participants to rate the overall change in their hunger, appetite, fullness, and cravings since they started taking the study medication.

8.1.3.4. PROMIS® Fatigue Custom 9-item Version

The PROMIS® Fatigue[29] Custom 9-item Version is a self-reported measure that assesses a range of symptoms in the past 7 days from mild subjective feelings of tiredness to an overwhelming, debilitating, and sustained sense of exhaustion that likely decreases one's ability to execute daily activities and function normally in family or social roles. A global raw score ranging from 9 to 45 is calculated and can be translated into a T-score (Mean=50, SD=10) using the applicable score conversion table or online HealthMeasures Scoring Service,[30] where full derivation details will be provided in the SAP.

8.1.3.5. PROMIS® Physical Function Custom 13-item Version

The PROMIS® Physical Function[31] Custom 13-item Version is a self-reported measure that assesses capability rather than actual performance of physical activities. It includes assessment of one's ability to walk, climb stairs, run/jog, exercise as well as instrumental activities of daily living. A global raw score ranging from 13 to 65 is calculated and can be translated into a T-score (Mean=50, SD=10) using the applicable score conversion table or online HealthMeasures Scoring Service,[30] where full derivation details will be provided in the SAP.

8.1.3.6. Impact of Weight on Quality of Life–Lite (IWQOL-Lite) Clinical Trials Version

The IWQOL-Lite-CT©[32] was developed for use in the context of clinical trials for obesity, with 20 items addressing concerns that are specifically relevant to the study population.

8.1.3.7. SF-36v2® Health Survey

The SF-36v2®[33] is a 36-item questionnaire that measures functional health and well-being from a patient's perspective. It is a generic questionnaire and can be used across age (adults), disease, and treatment groups. The questionnaire consists of 8 health domain scales: physical functioning (10 items), role-physical (4 items), bodily pain (2 items), general health (5 items), vitality (4 items), social functioning (2 items), role-emotional (3 items), mental health (5 items), reported health transition (1 item) and 2, physical and mental component summary scores. Each health domain scale raw score is transformed to 0-100 scale which can then be converted to norm-based T-scores (Mean=50, SD=10) using scoring software provided by the developer, where full derivation details will be provided in the SAP.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA for the applicable cohort (see SoA for Cohorts 1 and 2, and SoA for Cohort 3). Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

8.2.1. Physical Examinations

Physical examinations are performed as indicated in the SoA for the applicable cohort (see SoA for Cohorts 1 and 2, and SoA for Cohort 3).

Physical examinations may be conducted by a physician, trained physician's assistant or nurse practitioner as acceptable and according to local regulation. A complete physical examination will include, at a minimum, assessments of the participant's general appearance, head, ears, eyes, nose, mouth, throat, neck (including thyroid examination), skin, heart and lung examinations, lymph nodes, as well as gastrointestinal, musculoskeletal and neurological systems.

Height will be measured after the participant has removed their shoes and will be collected at V1 only.

A limited physical examination is performed at the in-clinic follow-up visit and may be performed at non-specified visits if there are findings during the previous physical examination or new/open AEs, if appropriate and at investigator discretion. The limited physical examination will be focused on general appearance, lungs, heart, and participant reported symptoms.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2. Vital Signs

8.2.2.1. Blood Pressure and Pulse Rate

In this study, assessment of vital signs (systolic BP, diastolic BP, and pulse rate) will occur at the nominal time points specified in the SoA for the applicable cohort (see SoA for Cohorts 1 and 2, and SoA for Cohort 3) per the following specifications:

- At V1, the participant's arm circumference should be measured (eg, using an anthropometric tape) at the midpoint of the length of the upper arm and the appropriate cuff selected and used throughout the study.

- BP and pulse rate will be measured via an automated device using an oscillometric method (not auscultation).

  - Assessment of BP and pulse rate can be manual (rather than using an automated device), only if an automated device is not available; however, when done manually pulse rate must be measured in the brachial/radial artery for at least 30 seconds.

- Supine BP and pulse rate will be measured with the participant's arm supported at the level of the heart, following a rest of at least 5 minutes and BP will be recorded to the nearest mm Hg. Triplicate assessments will be measured, with an interval of at least 1-2 minutes between each measurement, and these will be performed pre-dose (as applicable) at each planned in-clinic study visit. For visits with post-dose PK collections as specified in the SoA for the applicable cohort (see SoA for Cohorts 1 and 2, and SoA for Cohort 3), these triplicate assessments will also be performed 1 time within the window of approximately 2-6 hours post-dose (around the same time as post-dose PK samples are collected and according to the chronology in Appendix 9). Each triplicate reading will be recorded, and the average of the 3 measurements at V3 (Day 1) will serve as the participant's baseline.

- Same arm (preferably the dominant arm) will be used for BP and pulse rate assessments throughout the study, whenever possible.

- Participants should be instructed not to speak during BP and pulse rate measurements.

- See Appendix 9 for proposed chronology of procedures for nominal time points when vital sign assessments coincide with other procedures.

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

8.2.3. Electrocardiograms

Standard 12-lead ECGs should be collected at times specified in the SoA section of this protocol for the applicable cohort (see SoA for Cohorts 1 and 2, and SoA for Cohort 3) using an ECG machine that automatically calculates the HR and measures PR, QT, and QTcF intervals and QRS complex. All scheduled ECGs should be performed after the participant has rested quietly for at least 10 minutes in a supine position, and prior to dosing (as applicable), according to the chronology in Appendix 9.

If a) a post-dose QTcF interval remains ≥30 msec from the baseline **and** is >450 msec; or b) an absolute QTcF value is ≥500 msec for any scheduled ECG for greater than 4 hours (or sooner, at the discretion of the investigator); or c) QTcF intervals get progressively longer, the participant should undergo continuous ECG monitoring (eg, cardiac telemetry or frequent ECG ascertainment as per investigator's medical judgment). A cardiologist should be consulted if QTcF intervals do not return to less than the criteria listed above after 8 hours of monitoring (or sooner, at the discretion of the investigator).

In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads be placed in the same positions each time in order to achieve precise ECG recordings. If a machine-read QTcF value is prolonged, as defined above, repeat measurements may not be necessary if a qualified medical provider's interpretation determines that the QTcF values are in the acceptable range.

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

8.2.4. Clinical Safety Laboratory Assessments

See Appendix 2 for the list of clinical safety laboratory tests to be performed and the SoA for the applicable cohort (see SoA for Cohorts 1 and 2, and SoA for Cohort 3) for the timing and frequency. All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA for the applicable cohort (see SoA for Cohorts 1 and 2, and SoA for Cohort 3). Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

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

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 to 35 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

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

See Appendix 6 for suggested actions and follow-up assessments in the event of potential DILI.

8.2.5. Management of Hypoglycemia

While hypoglycemia is not expected in the study participants, FPG will be measured at each clinic visit via the central lab. In addition, as a precaution, participants will be instructed to recognize the signs and symptoms associated with hypoglycemia.

Any episode of hypoglycemia must be captured on the AE CRF with specific details captured on the HAE Form CRF. For the definition of a hypoglycemic episode and severity categorization see Section 8.2.5.1 below.

8.2.5.1. Definition and Severity of Hypoglycemic Adverse Event (HAE)

The investigator must assess the glucose values reported by the central laboratory, as well as any signs or symptoms reported by the study participant.

HAE is defined as one of the following:[34]

a. Asymptomatic hypoglycemia: An event not accompanied by typical symptoms of HAE but a glucose value of <70 mg/dL (3.9 mmol/L) using either glucometer (fingerstick blood glucose) at the study site or sponsor-identified central laboratory (plasma glucose).

b. Documented symptomatic hypoglycemia: An event during which typical symptoms of HAE are accompanied with a glucose value of <70 mg/dL (3.9 mmol/L), using glucometer at the study site or sponsor identified central laboratory, and the clinical picture includes prompt resolution with food intake, subcutaneous glucagon, or IV glucose.

c. Probable symptomatic hypoglycemia: An event during which symptoms of HAE are not accompanied by a glucose determination but was presumably caused by a glucose concentration of <70 mg/dL (3.9 mmol/L), and the clinical picture includes prompt resolution with food intake, subcutaneous glucagon, or IV glucose.

Each episode of HAE must be categorized with respect to severity. In order to characterize the event as severe, all 3 criteria below must be met:

1. The participant was unable to treat him/herself. Neurologic impairment, and not the age of the participant, is the explanation for why the participant could not treat him/herself and required the assistance of another person.

2. The participant exhibited at least 1 of the following neurological symptoms:

   - Memory loss;
   - Confusion;
   - Uncontrolled behavior;
   - Irrational behavior;
   - Unusual difficulty in awakening;
   - Suspected seizure;
   - Seizure;
   - Loss of consciousness.

3. Either:

    - If blood glucose was measured and was ≤54 mg/dL (2.7 mmol/L) using glucometer (or central laboratory); or

    - If blood glucose was not measured, the clinical manifestations were reversed by oral carbohydrates, subcutaneous glucagon, or IV glucose.

Events that do not meet all the criteria above for severe HAE are characterized as mild or moderate in severity.

8.2.6. Mental Health Questionnaires

8.2.6.1. Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is an interview-based rating scale to systematically assess suicidal ideation and suicidal behavior.[18] The "baseline/screening" version of the C-SSRS will be administered at V1. The "since last visit" version of the C-SSRS will be administered at the other visits specified in the SoA for the applicable cohort (see SoA for Cohorts 1 and 2, and SoA for Cohort 3). The C-SSRS will be administered by study site staff who have completed training in its administration. Participants who respond "yes" to questions 4 or 5 (indicating suicidal ideation), or to any suicidal behavioral question on the C-SSRS at V1, V2 or V3 will not be permitted in the study (see Section 5.2).

8.2.6.1.1. Rater Qualifications

For specific rating assessments, only qualified raters will be allowed to evaluate and/or rate participants in this study. The minimum qualifications a rater must meet will be outlined in a guidance document provided to each participating site. The level of experience with the target population (or equivalent), specific scale experience (or equivalent), and certification required (if applicable) will be listed and used to determine whether a rater is approved for a given assessment. The rater must become certified to perform selected study assessments before he or she can participate in the conduct of the study. For specifically defined assessments, rater training and standardization exercises may be conducted, and written and signed documentation will be provided by the site for each rater's certification. In return, each site will be provided written and signed documentation outlining each rater's certification for specific study assessments. Recertification may be required at periodic intervals during the study. The raters who administer specific study assessments will be documented in a centralized location and all site staff who administer ratings will be verified in the site study documentation during the conduct of the study.

8.2.6.2. Patient Health Questionnaire-9 (PHQ-9)

The PHQ-9 is a 9 item self-report scale for the assessment of depressive symptoms.[19] The PHQ-9 will be completed by participants and reviewed by site staff at the pre-defined time points outlined in the SoA for the applicable cohort (see SoA for Cohorts 1 and 2, and SoA for Cohort 3). A PHQ-9 score of ≥15 at V1, V2 or V3 indicates clinically significant depression and serves as an exclusion criterion for this study (see Section 5.2).

8.2.6.3. Referral to a Mental Health Professional

A participant should be referred to a MHP for any of the following reasons:

- Response of "yes" to question 4 or 5, or on any behavioral question on the C-SSRS;
- A score of ≥15 on the PHQ-9;
- In the investigator's judgment a risk assessment or exclusion is required.

A clinically-qualified MHP is a MHP with appropriate training in the assessment of suicide risk, according to local clinical practice standards and regulations, who would normally evaluate the risk for suicidal ideation and behavior in a patient.

Participants who have recurrent suicidal ideation or behavior during the study should be discontinued from the study and treated appropriately. If a study participant endorses a 4 or 5 on the ideation subscale or any behavioral item of the C-SSRS on 2 or more occasions and is confirmed to have active suicidal ideation or behavior on both occasions by a risk assessment conducted by a qualified MHP, then the participant should be discontinued from the study and treated appropriately.

Participants who meet criteria for referral to a MHP, but refuse evaluation and/or treatment by a MHP, must be assessed by the investigator to determine if the participant should be discontinued from dosing or from the study.

8.2.7. Pregnancy Testing

Pregnancy tests will be both urine and serum, and must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in all females at the times listed in the SoA for the applicable cohort (see SoA for Cohorts 1 and 2, and SoA for Cohort 3). Following a negative pregnancy test result at screening, appropriate contraception must be commenced and a second negative pregnancy test result will be required at the baseline visit prior the participant's receiving the study intervention. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) and at the end of the study. Pregnancy tests may also be repeated if requested by IRBs/ECs or if required by local regulations.

8.3. Adverse Events and Serious Adverse Events

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

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

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether the

event meets the criteria for classification as an SAE or caused the participant to discontinue the study intervention (see Section 7.1).

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

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

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

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

Follow-up by the investigator continues throughout and after the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator.

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

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

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

Investigators are not obligated to actively seek AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and he/she considers the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the CT SAE Report Form.

8.3.1.1. Reporting SAEs to Pfizer Safety

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

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

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

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

8.3.2. Method of Detecting AEs and SAEs

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

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

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

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

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

8.3.4. Regulatory Reporting Requirements for SAEs

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

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

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

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

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

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

8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

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

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

- If EDP occurs in a participant or a participant's partner, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until 28 calendar days after the last administration of IP.
- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the CT SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

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

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

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

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

8.3.5.2. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

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

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

An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the exposure during breastfeeding.

8.3.5.3. Occupational Exposure

An occupational exposure occurs when a person receives unplanned direct contact with the study intervention, which may or may not lead to the occurrence of an AE. Such persons may include healthcare providers, family members, and other roles that are involved in the trial participant's care.

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

8.3.6. Cardiovascular and Death Events

Not applicable.

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

Not applicable.

8.3.8. Adverse Events of Special Interest

Not applicable.

8.3.8.1. Lack of Efficacy

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

8.3.9. Medical Device Deficiencies

Not applicable.

8.3.10. Medication Errors

Medication errors may result from the administration or consumption of the study intervention by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Exposures to the study intervention under study may occur in clinical trial settings, such as medication errors.

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

Medication errors include:

- Medication errors involving participant exposure to the study intervention;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant.

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

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

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

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

8.4. Treatment of Overdose

For this study, any dose of study intervention greater than CCI tablets for Cohorts 1 and 2, or CCI tablets for Cohort 3, within a 24-hour time period will be considered an overdose.

There is no specific antidote for overdose with PF-06882961. Treatment of overdose should consist of general supportive measures.

In the event of an overdose, the investigator/treating physician should:

1. Contact the medical monitor within 24 hours.

2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities for at least 5 half-lives or 28 calendar days after the overdose of PF-06882961 (whichever is longer).

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

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

5. Obtain a blood sample for PK analysis within 2 days from the date of the last dose of study intervention if requested by the medical monitor (determined on a case-by-case basis).

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

8.5. Pharmacokinetics

Blood samples of approximately 3 mL each, to provide sufficient ***plasma*** for PK analysis, will be collected into appropriately labeled tubes containing K_2EDTA, at times defined in the SoA for the applicable cohort (see SoA for Cohorts 1 and 2, and SoA for Cohort 3) and according to the chronology in Appendix 9, with collections occurring prior to dosing with study intervention on the given scheduled visit, and also 1 time within the window of approximately 2 to 6 hours post-dose at specific visits noted in the SoA (ie, also collected post-dose for Cohorts 1 and 2 at V3, V7, V10 and V13, and for Cohort 3 at V3, V7, V11, V15 and V19). The date/time of the blood collections related to PK (both pre- and post-dose samples) should be noted in source documents and captured in the CRF.

Instructions for the collection and handling of biological samples will be provided in the laboratory manual. To maintain sample integrity:

- Any deviations from the PK sample handling procedures (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised. Any deviation from the specified sample handling procedure resulting in compromised sample integrity will be considered a protocol deviation;

- Any scheduled pre-dose collection (ie, trough concentration) obtained post dose or any post dose samples not collected within the approximately 2-6 hours post dose interval, will be captured as a protocol deviation even if results are deemed evaluable.

As part of understanding the PK of the study intervention, samples may be used for metabolite identification and/or evaluation of the bioanalytical method, as well as for other internal exploratory purposes. These data will not be included in the clinical report.

Samples will be analyzed using a validated analytical method in compliance with Pfizer SOPs.

8.6. Pharmacodynamics

PD parameters evaluated in this study include HbA1c, FPG, FPI, HOMA-IR, and HOMA-B, and will be collected according to the SoA for the applicable cohort (see SoA for Cohorts 1 and 2, and SoA for Cohort 3). The PD parameters will be assessed by the Central Laboratory as part of the clinical laboratory assessments (see Appendix 2).

8.7. Genetics

8.7.1. Specified Genetics

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

8.7.2. Banked Biospecimens for Genetics

A 4-mL blood sample optimized for DNA isolation Prep D1 will be collected as local regulations and IRBs/ECs allow.

Banked Biospecimens may be used for research related to the study intervention(s) and adults with obesity. Genes and other analytes (eg, proteins, RNA, nondrug metabolites) may be studied using the banked samples.

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

8.8. Biomarkers

8.8.1. Specified Gene Expression (RNA) Research

Specified gene expression (RNA) research is not included in this study.

8.8.2. Specified Protein Research

Specified protein research is not included in this study.

8.8.3. Specified Metabolomic Research

Specified metabolomic research is not included in this study.

8.8.4. Banked Biospecimens for Biomarkers

Additional Banked Biospecimens in this study are as follows and will be collected at the timepoints outlined in the SoA for the applicable cohort (see SoA for Cohorts 1 and 2, and SoA for Cohort 3):

- 10-mL whole blood (Prep B2 optimized for serum);
- 10-mL whole blood (Prep B1 optimized for plasma).

Banked Biospecimens will be collected as local regulations and IRB/ECs allow.

Banked Biospecimens may be used for research related to the study intervention(s) and adults with obesity. Genes and other analytes (eg, proteins, RNA, nondrug metabolites) may be studied using the banked samples.

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

8.9. Immunogenicity Assessments

Immunogenicity assessments are not included in this study.

8.10. Health Economics

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

9. STATISTICAL CONSIDERATIONS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in a SAP, which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment. Data from participants enrolled into the original cohort (Cohort 1) and Cohort 2 will be combined for reporting, where data from the placebo and 2-week titration arms will be combined from the 2 cohorts and analyzed together. Data from participants enrolled into Cohort 3 will be analyzed separately unless otherwise specified.

9.1. Estimands and Statistical Hypotheses

Estimands related to percent CFB in body weight:

The primary estimand (Estimand 1) will be the population average treatment effect on the percent CFB in body weight at End of Treatment of PF-06882961 compared to placebo in all evaluable participants while on treatment. For Cohorts 1 and 2, End of Treatment is defined as Week 26. For Cohort 3, End of Treatment is defined as Week 32. This reflects a combination of the 'Hypothetical' and 'While on treatment' strategies as outlined in the ICH-E9 (R1) guidance.[35]

Measurements after discontinuation of study intervention will be censored and treated as missing data. Missing data due to censoring, study withdrawal or other reasons will have data imputed based on a MAR assumption. The population-based treatment effect will be the mean percent CFB in each PF-06882961 arm compared to placebo. This estimand will similarly be applied to the percent changes from baseline in body weight at all time points through to End of Treatment. For all cohorts, all randomized participants who take at least 1 dose of study intervention will be included.

An additional exploratory estimand (Estimand 7) will be analyzed, which will be the population average treatment effect on the percent CFB in body weight at End of Treatment of PF-06882961 compared to placebo in evaluable participants with no major protocol deviations and while on treatment. This reflects a combination of the 'Hypothetical', 'While on treatment' and 'Principal stratum' strategies as outlined in the ICH-E9 (R1) guidance.[35]

This is the same as Estimand 1 except that participants with major protocol deviations (eg, inadequate study intervention compliance, use of prohibited medication, etc.) will be excluded from this analysis. Major protocol deviations will be reviewed prior to database lock to identify such participants, with further details included in the SAP.

Estimands related to achieving body weight loss ≥5% at End of Treatment:

A secondary estimand (Estimand 2) will be the population odds ratio of the treatment effect of achieving a body weight loss ≥5% from baseline at End of Treatment of PF-06882961 compared to placebo in all evaluable participants while on treatment. This reflects a combination of the 'Hypothetical' and 'While on treatment' strategies as outlined in the ICH-E9 (R1) guidance.[35]

Measurements after discontinuation of study intervention will be censored and treated as missing data. Missing data due to censoring, study withdrawal, or other reasons (eg, laboratory failure) may be imputed as outlined in the SAP. The population-based treatment effect will be the odds of achieving a body weight loss ≥5% from baseline at End of Treatment on PF-06882961 compared to the odds of achieving this on placebo (ie, odds ratio).

Estimands related to other endpoints:

Estimand 3 is similar to Estimand 1, except the population average treatment effect is on the absolute CFB in waist circumference at End of Treatment. The population based treatment effect will be the mean CFB in each PF-06882961 arm compared to placebo.

Estimands 4, 5 and 6 will utilize the same approach as Estimand 3 for the associated endpoint(s).

Tertiary endpoints may be analyzed using similar estimands or analyzed in a descriptive manner without reference to an estimand. Other supporting estimands may be used for some of the primary and secondary endpoints as a means to examine the robustness of results, compare to available literature and/or be used for future study planning as needed. Details of these estimands and analyses will be presented in the SAP.

9.2. Sample Size Determination

For Cohort 1, the sample size was based on the need to have an adequately sized safety database of participants on PF-06882961 in an obese population up to 26 weeks of dosing following Phase 2 clinical development. Approximately 420 participants (approximately 60 in each of the placebo and 5 PF-06882961 arms with 1-week titration steps and

approximately 20 in each of the 3 PF-06882961 arms with 2-week titration steps) were to be randomized in the original cohort (Cohort 1). The sample size of Cohort 1 also provided acceptable operating characteristics for decision making based on the primary endpoint, the percent CFB at End of Treatment in body weight.

For Cohort 1, assuming a 25% drop-out rate there would be expected to be approximately 315 completed participants, with approximately 45 completed participants per arm for each of the placebo and 1-week titration PF-06882961 arms. For End of Treatment defined as Week 26, this yields 80% power to detect a placebo-adjusted reduction in body weight of CCI% (comparing PF-06882961 to placebo), using a 1-sided t-test at a 5% level and assuming a conservative SD on the loge-scale of CCI for body weight change at Week 26, based on historical internal studies.

For Cohort 2, approximately 49 additional participants were to be randomized to the placebo and 2-week titration PF-06882961 arms (approximately 7 in the placebo and approximately 14 in each of the 3 2-week titration arms). This sample size was selected to provide additional tolerability data on the 2-week titration arms and provide improved operating characteristics of the primary endpoint.

Assuming a 25% drop-out rate, with the combination of placebo and the 2-week titration arms from both Cohorts 1 and 2 (approximately 67 participants randomized to placebo and approximately 34 participants in each of the 2-week titration arms in total) there would be expected to be approximately 50 completed placebo participants and approximately 25 completed participants in each of the 2-week titration arms. For End of Treatment defined as Week 26, this yields 80% power to detect a placebo-adjusted reduction in body weight of CCI% (comparing a 2-week titration arm of PF-06882961 to placebo), using a 1-sided t-test at a 5% level, and assuming a conservative SD on the $\log_e$-scale of CCI for body weight change at Week 26, based on historical internal studies.

For Cohort 3, approximately 112 additional participants will be randomized (approximately 16 in the placebo and approximately 32 in each of the 3 PF-06882961 arms with 4-week titration steps). This sample size was selected to provide additional tolerability data using 4-week titration steps and provide acceptable operating characteristics for the primary endpoint. Assuming a discontinuation rate of 25%, it is expected that approximately 84 of these participants will complete the study, with approximately 12 completing the placebo arm and approximately 24 completing each of the PF-06882961 arms. For End of Treatment defined as Week 32, this yields 80% power to detect a placebo-adjusted reduction in body weight of CCI% (comparing PF-06882961 to placebo) at Week 32, using a 1-sided t-test at a 5% level and assuming a conservative SD on the $\log_e$-scale of CCI for body weight change at Week 32, based on historical internal studies. If judged necessary by the sponsor to meet study objectives (for example, if the rate of discontinuation or rate of non-compliance is higher than anticipated), then up to approximately 140 participants may be randomized into Cohort 3, to ensure a sufficient number of completing participants.

Participants who withdraw from the study will not be replaced. Evaluable participants are defined as in Section 9.3.

9.3. Analysis Sets

For purposes of analysis, the following analysis sets are defined for the combined Cohorts 1 and 2, and separately for Cohort 3:

Participant Analysis Set	Description
Enrolled	"Enrolled" means a participant's agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.
Randomly assigned to study intervention	All participants randomly assigned to study intervention regardless of whether or not study intervention was administered.
Evaluable	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the randomized study intervention.
Safety	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the study intervention they actually received.

Defined Analysis Set	Description
Estimand Set 1 (related to estimands 1, 2, 3, 4, 5 and 6)	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. For participants who discontinue study intervention, all subsequent values will be censored.
Estimand Set 2 (related to estimand 7)	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention and do not have major protocol deviations. Major protocol deviations will be reviewed prior to database lock to identify such participants, with further details included in the SAP. For participants who discontinue study intervention, all subsequent values will be censored.

PK Concentration Set	All participants randomly assigned to study intervention and who take at least 1 dose of PF-06882961 and in whom at least 1 concentration value is reported.

9.4. Statistical Analyses

The SAP will be developed and finalized before any analyses are performed and will describe the analyses and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.4.1. General Considerations

Cohorts 1 and 2 will generally be analyzed separately from Cohort 3, with all treatment arms of PF-06882961 and placebo analyzed separately. For Cohorts 1 and 2, reporting of the placebo and the 2-week titration PF-06882961 arms will be based on the combined set of participants from both cohorts, ie, the original cohort (Cohort 1) and Cohort 2.

For Cohorts 1 and 2, End of Treatment is defined as Week 26. For Cohort 3, End of Treatment is defined as Week 32.

9.4.1.1. Analyses for Continuous Endpoints

The MMRM model(s) will include treatment, time, strata (females versus males) and treatment-by-time interaction as fixed effects, baseline as a covariate and the baseline-by-time interaction with time fitted as a repeated effect and participant as a random effect. An unstructured correlation matrix will be used, and the Kenward-Roger approximation will be used for estimating degrees of freedom for the model parameters.

Missing values will be imputed as part of the MMRM model assumptions.

9.4.1.2. Analyses for Categorical Endpoints

The logistic regression model(s) will include a term for treatment, strata (females versus males), and baseline will be included as a covariate.

Missing values will be imputed using multiple imputation where the model will include treatment, baseline and strata (females vs. males) and will include all time course data up to Week 26 or Week 32, depending on the cohort. The logistic regression model will be applied to each imputed dataset and the parameter estimates will be combined using standard multiple imputation techniques. Further details will be described in the SAP.

9.4.2. Primary Endpoint(s)

A MMRM analysis (as per Section 9.4.1) of the percent CFB in body weight through End of Treatment will be used to estimate the treatment effect related to the primary Estimand 1. MMRM models will be fitted to the combined Cohorts 1 and 2 data and separately to the Cohort 3 data. Baseline body weight will be included on the $\log_e$-scale. The MMRM models

will be fitted to the CFB of $\log_e$-transformed values to Weeks 2, 4, 6, 8, 10, 12, 16, 18, 22 and 26 for Cohorts 1 and 2 or Weeks 4, 8, 12, 16, 20, 24, 28 and 32 for Cohort 3 from the Estimand Set 1. The modelled mean $\log_e$-differences and 90% CIs for the $\log_e$-differences at the End of Treatment timepoint will be extracted from the model and exponentiated to provide estimates of the relative difference in each PF-06882961 treatment arm reported separately, compared to placebo.

No adjustments will be made for multiplicity.

9.4.3. Secondary Endpoint(s)

For the secondary endpoints described below in the table, models will be fitted to the combined Cohorts 1 and 2 data, and separately to the Cohort 3 data.

Endpoint	Statistical Analysis Methods
Secondary: Response as defined by a body weight loss ≥5% at End of Treatment.	A logistic regression analysis utilizing multiple imputation for missing values (as per Section 9.4.1.2) of participants who achieved a body weight loss ≥5% at the End of Treatment timepoint and those that didn't will be used to estimate the treatment effect related to the secondary estimand 2. Baseline body weight will be included in the logistic regression and multiple imputation analyses. The logistic regression model will be fitted to the End of Treatment timepoint only after multiple imputation has been applied to Estimand Set 1. No adjustments will be made for multiplicity.
Secondary: Percent CFB in body weight at Weeks 2, 4, 6, 8, 10, 12, 16, 18 and 22 for Cohorts 1 and 2, and at Weeks 4, 8, 12, 16, 20, 24 and 28 for Cohort 3	Results related to this endpoint will be obtained from the Primary Analysis model. No adjustments will be made for multiplicity. This analysis will estimate the treatment effect related to Estimand 1.
Secondary: Absolute CFB in waist circumference at End of Treatment	Absolute CFB in waist circumference at each planned in-clinic study visit up through the End of Visit Treatment visit will be analyzed using an MMRM model (as per Section 9.4.1.1). Baseline waist circumference will be included as a covariate in the model. No adjustments will be made for multiplicity. Results at the End of Treatment timepoint will be extracted from the model. This analysis will be applied to Estimand Set 1 to estimate the treatment effect related to Estimand 3.

Endpoint	Statistical Analysis Methods
Secondary: Absolute CFB in waist-to-hip ratio at End of Treatment	Absolute CFB in waist-to-hip ratio at each planned in-clinic study visit up through the End of Visit Treatment visit will be analyzed using an MMRM model (as per Section 9.4.1.1). Baseline waist-to-hip ratio will be included as a covariate in the model. No adjustments will be made for multiplicity. Results at the End of Treatment timepoint will be extracted from the model. This analysis will be applied to Estimand Set 1 to estimate the treatment effect related to Estimand 4.
Secondary: CFB in HbA1c at Weeks 16 and 26 for Cohorts 1 and 2, and Weeks 16, 24 and 32 for Cohort 3	CFB in HbA1c at Weeks 16 and 26 for Cohorts 1 and 2, and Weeks 16, 24 and 32 for Cohort 3, will be analyzed using an MMRM model (as per Section 9.4.1.1). Baseline HbA1c will be included as a covariate in the selected model. No adjustments will be made for multiplicity. This analysis will be applied to Estimand Set 1 to estimate the treatment effect related to Estimand 5.
Secondary: CFB in FPG at each planned in-clinic study visit up through the End of Treatment	CFB in FPG at each planned in-clinic study visit up through the End of Treatment will be analyzed using an MMRM model (as per Section 9.4.1.1). Baseline FPG will be included as a covariate in the model. No adjustments will be made for multiplicity. This analysis will be applied to Estimand Set 1 to estimate the treatment effect related to Estimand 6.

9.4.4. Tertiary/Exploratory Endpoint(s)

For the purposes of reporting the shift in glycemic categories,[34] the following definitions will be used:

- Normoglycemia: FPG <100 mg/dL and HbA1c <5.7%;
- Pre-diabetes: FPG 100-125 mg/dL (both inclusive) or HbA1c 5.7-6.4% (both inclusive);
- T2DM: FPG ≥126 mg/dL or HbA1c ≥6.5%.

For discordant results between FPG and HbA1c with respect to the glycemic category criteria, the higher category will be used (eg, a participant with FPG of 124 mg/dL and HbA1c of 6.6% would be classified as T2DM).

Further details on the definitions and analyses of this and other Tertiary/Exploratory endpoints will be described in the SAP.

9.4.5. Other Safety Analyses

The safety data will be summarized in accordance with Pfizer Data Standards. All participants who receive study intervention (safety population) will be included in the safety analyses. All safety data will be summarized descriptively through appropriate data tabulation, descriptive statistics, categorical summaries, and graphical presentations. Safety endpoints for the study are referenced in Section 8.2.

Results may also be reported by strata (females versus males), where details will be described in the SAP.

9.4.5.1. Electrocardiogram Interval Analyses

CFB for the ECG parameters QT interval, HR, QTcF interval, PR interval, and QRS complex will be summarized by treatment and time.

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

Safety QTcF Assessment

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

9.4.6. Other Analyse(s)

Tertiary/Exploratory analyses not included in the efficacy or safety analyses outlined above will be documented in the SAP and may not be reported in the CSR.

Pharmacogenomic or biomarker data from Banked Biospecimens may be collected during or after the trial and retained for future analyses; the results of such analyses are not planned to be included in the CSR.

9.5. Interim Analyses

An interim analysis will be performed at least once annually while the study is ongoing, after at least 25% of participants (ie, approximately 105) are randomized, with further details provided in the IRC charter. This interim analysis will assess, at a minimum, unblinded safety of the randomized participants. Additional interim analyses for safety and/or efficacy may be performed if needed. Further details will be provided in the IRC charter.

Interim analysis results may be used for internal business decisions including, but not limited to: stopping a dose level, future study planning, stopping for futility, stopping for early success, conducting a sample size re-estimation, or adapting the study after the interim analysis. Before any interim analysis is instigated, the details of the objectives, decision criteria, information dissemination plan, and method of maintaining the study blind as per Pfizer's SOPs will be documented and approved in an IRC charter. In addition, the analysis details must be documented and approved in an interim analysis SAP or final SAP.

9.5.1. PK/PD Unblinding Plan

A limited number of individuals not on the study team will be unblinded according to sponsor SOPs with the purpose of composing PK/PD analysis sets and conducting PK/PD analysis that will be made available to the study team following database lock. These data are expected to include PK, body weight, vitals and potentially other PD markers.

9.6. Data Monitoring Committee or Other Independent Oversight Committee

This study will use an IRC. The IRC is independent of the study team and includes only internal (ie, Pfizer colleague) members. The IRC charter describes the role of the IRC in more detail. The IRC will be responsible for ongoing monitoring of the safety and/or efficacy of participants in the study according to the charter. The recommendations made by the IRC to alter the conduct of the study will be forwarded to the appropriate Pfizer personnel for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of safety data, to regulatory authorities, as appropriate.

This study will not use a DMC.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

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

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

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

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

The investigator will be responsible for the following:

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

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

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

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

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study. The participant should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

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

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

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

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

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

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

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

A copy of the ICD(s) must be provided to the participant.

Participants who are rescreened are required to sign a new ICD.

Unless prohibited by local requirements or IRB/EC decision, the ICD will contain a separate section that addresses the use of samples for optional additional research. The optional additional research does not require the collection of any further samples. The investigator or authorized designee will explain to each participant the objectives of the additional research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow specimens to be used for additional research. Participants who decline to participate in this optional additional research will not provide this separate signature.

10.1.4. Data Protection

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

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

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

10.1.5. Dissemination of Clinical Study Data

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

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

www.clinicaltrials.gov

Pfizer posts clinical trial results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT

Pfizer posts clinical trial results on EudraCT for Pfizer-sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

www.pfizer.com

Pfizer posts public disclosure synopses (CSR synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

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

Data Sharing

Pfizer provides researchers secure access to patient-level data or full CSRs for the purposes of "bona-fide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials 24 months after study completion. Patient-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

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

10.1.6. Data Quality Assurance

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

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

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

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

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

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

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

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

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

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

10.1.7. Source Documents

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

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

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

Description of the use of computerized system is documented in the Data Management Plan.

10.1.8. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the date of the first participant’s first visit and will be the study start date.

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

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

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

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or GCP guidelines;

- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

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

10.1.9. Publication Policy

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

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

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

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

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

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

10.1.10. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the SToD system.

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

10.2. Appendix 2: Clinical Laboratory Tests

The following laboratory tests will be performed at times defined in the SoA section of this protocol for the applicable cohort (see SoA for Cohorts 1 and 2, and SoA for Cohort 3). Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory, or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

Table 6. Protocol Required Laboratory Assessments

Hematology	Chemistry	Urine Testing	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN Creatinine eGFR ***Plasma*** Glucose (fasting) Calcium Sodium Potassium Chloride Total CO_2 (bicarbonate) AST ALT TBili GGT Alkaline phosphatase Uric acid Albumin Total protein	Urinalysis: • pH • Glucose (qual) • Protein (qual) • Blood (qual) • Ketones • Nitrites • Leukocyte esterase • Urobilinogen • Urine bilirubin • Microscopy[a] Urine pregnancy test	HbA1c Plasma insulin (fasting) Serum pregnancy test (β hCG) Lipid panel: • Total cholesterol • Direct LDL-C • HDL-C • Triglycerides TSH Free T4 Calcitonin Amylase Lipase Total bile acids PT/INR/aPTT At V1 only: FSH[b] C-peptide (fasting) Urine drug screen
	Additional Tests (Needed for Hy's Law)		
	AST, ALT (repeat) TBili (repeat) Albumin (repeat) Alkaline phosphatase (repeat) Direct bilirubin Indirect bilirubin CK GGT PT/INR Total bile acids Acetaminophen drug and/or protein adduct levels		

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

b. For female participants to confirm post-menopausal status only.

Investigators must document their review of each laboratory safety report.

After randomization, the sponsor study team and site will be blinded to HbA1c, FPG, and FPI measured by the central laboratory, unless the FPG meets the criterion for hypoglycemia as listed in Section 8.2.5.1, or indicates hyperglycemia with an FPG ≥270 mg/dL (15.0 mmol/L).

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

10.3.1. Definition of AE

AE Definition

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

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:
  - Is associated with accompanying symptoms.
  - Requires additional diagnostic testing or medical/surgical intervention.
  - Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
- Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or SAE if they fulfill the definition of an AE or SAE and meet the requirements as per Section 8.3.8.1. Also, "lack of efficacy" or "failure of expected pharmacological action" does not constitute an AE or SAE.

Events NOT Meeting the AE Definition

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

10.3.2. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose meets one or more of the criteria listed below:

a. Results in death

b. Is life-threatening

The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is

serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

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

d. Results in persistent disability/incapacity

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

e. Is a congenital anomaly/birth defect

f. Is a suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious.

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

g. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs During the Active Collection Period

AE and SAE Recording/Reporting

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

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

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding.	All AEs/SAEs associated with exposure during pregnancy or breastfeeding **Note**: Instances of EDP or EDB not associated with an AE or SAE are not captured in the CRF.	All instances of EDP are reported (whether or not there is an associated SAE).* All instances of EDB are reported (whether or not there is an associated SAE).**
Environmental or occupational exposure to the product under study to a non-participant (not involving EDP or EDB).	None. Exposure to a study non-participant is not collected on the CRF.	The exposure (whether or not there is an associated AE or SAE) must be reported.***

* **EDP** (with or without an associated AE or SAE): any pregnancy information is reported to Pfizer Safety using CT SAE Report Form and EDP Supplemental Form; if the EDP is associated with an SAE, then the SAE is reported to Pfizer Safety using the CT SAE Report Form.

** **EDB** is reported to Pfizer Safety using the CT SAE Report Form which would also include details of any SAE that might be associated with the EDB.

*** **Environmental or Occupational exposure:** AEs or SAEs associated with occupational exposure are reported to Pfizer Safety using the CT SAE Report Form.

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

Assessment of Intensity

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

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

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

Assessment of Causality

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

Follow-up of AEs and SAEs
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers. • If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings including histopathology. • New or updated information will be recorded in the originally completed CRF. • The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

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

SAE Reporting to Pfizer Safety via CT SAE Report Form
• Facsimile transmission of the CT SAE Report Form is the preferred method to transmit this information to Pfizer Safety.

- In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the CT SAE Report Form sent by overnight mail or courier service.

- Initial notification via telephone does not replace the need for the investigator to complete and sign the CT SAE Report Form pages within the designated reporting time frames.

10.4. Appendix 4: Contraceptive Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

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

10.4.2. Female Participant Reproductive Inclusion Criteria

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

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

  OR

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), preferably with low user dependency, as described below during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate any reproductive safety risk of the study intervention(s). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), with high user dependency, as described below during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate any reproductive safety risk of the study intervention(s). In addition, a second effective method of contraception, as described below, must be used. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

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

10.4.3. Woman of Childbearing Potential

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

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

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:

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

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

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

2. Postmenopausal female:

    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition, a
        - High FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years of age and not using hormonal contraception or HRT.
        - Female on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.4. Contraception Methods

Contraceptive use by men or women should be consistent with local availability/regulations regarding the use of contraceptive methods for those participating in clinical trials.

Highly Effective Methods That Have Low User Dependency

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.
2. Intrauterine device.
3. Intrauterine hormone-releasing system.

4. Bilateral tubal occlusion.

5. Vasectomized partner.

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

Highly Effective Methods That Are User Dependent

1. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:

    - Oral;

    - Intravaginal;

    - Transdermal.

2. Progestogen-only hormone contraception associated with inhibition of ovulation:

    - Oral;

    - Injectable.

3. Sexual abstinence:

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

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

- Male or female condom with or without spermicide;

- Cervical cap, diaphragm, or sponge with spermicide;

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

10.5. Appendix 5: Genetics

Use/Analysis of DNA

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

- The scope of the genetic research may be narrow (eg, 1 or more candidate genes) or broad (eg, the entire genome), as appropriate to the scientific question under investigation.

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

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

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

- The samples will be retained as indicated:

    - Samples for banking will be stored indefinitely or for another period as per local requirements.

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

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

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

Potential Cases of Drug-Induced Liver Injury

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

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

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

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

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

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

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

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

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

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

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

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

10.7. Appendix 7: ECG Findings of Potential Clinical Concern

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

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

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

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

ECG Findings That Qualify as SAEs

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

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

10.8. Appendix 8: Prohibited Prior/Concomitant Medications

The medications listed in Table 7 may interact (at the PK level) with PF-06882961 and thus are prohibited for the provided timeframe of restriction (Table 7) and until the first follow-up visit. Additionally, the medications listed in Table 8 are also prohibited for the provided timeframe of restriction (Table 8) and until the first follow-up visit.

The Pfizer study team is to be notified of any prohibited medications taken during the study. After consulting with the sponsor, the investigator will make a judgment on the ongoing participation of any participant with prohibited medication use during the study.

Prohibited medications and timeframe of restriction may be revised during the course of the study with written notification from sponsor, to include or exclude specific drugs or drug categories for various reasons (eg, emerging DDI results for the investigational products, availability of new information in literature on the DDI potential of other drugs).

These are not all-inclusive lists. **Site staff should consult with the sponsor or designee with any questions as to whether a medication is permitted or prohibited and questions regarding potential DDI.**

Investigators should consult the product label for any other medication used during the study for information regarding medication that is prohibited for concomitant use.

Table 7. Prohibited medications that may interact (at the PK level) with PF-06882961

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

Table 8. Other Prohibited Medications

Drug Classes and/or Drugs	Timeframe of Restriction
Thiazolidinediones such as pioglitazone and rosiglitazone.	90 days prior to V1
Subcutaneously administered agents for glycemic control (eg, insulin, exenatide, liraglutide, dulaglutide, semaglutide, tirzepatide, pramlintide). ***Note***: Short-term (ie, ≤7 days) of insulin administration is permitted if participant is hospitalized.	90 days prior to V1
Pharmacological agents with approved indication for weight loss such as liraglutide, semaglutide, orlistat and sibutramine.	90 days prior to V1
Oral anti-diabetic medications, including: Metformin Sulfonylureas such as acetohexamide, chlorpropamide, tolazamide, tolbutamide, glimepiride, glipizide, glyburide. Meglitinide analogues such as repaglinide, nateglinide.	60 days prior to V1

Drug Classes and/or Drugs	Timeframe of Restriction
DPP-4 inhibitors such as sitagliptin, saxagliptin, linagliptin, vildagliptin. α-glucosidase inhibitors such as acarbose, miglitol. SGLT2 inhibitors such as canagliflozin, empagliflozin, dapagliflozin, ertugliflozin. Anti-hyperglycemic medications, including bromocriptine and colesevelam Oral GLP-1 receptor agonists (oral semaglutide).	
Systemic glucocorticoids such as prednisone, dexamethasone, triamcinolone, budesonide, betamethasone. ***Note***: As an exception, steroid-containing inhalers, nasal sprays and topical formulations are permitted. ***Note***: Intercurrent treatment with systemic corticosteroids during participation in the study may be permitted if treatment does/will not exceed 7 days.	60 days prior to V1
Immunosuppressants such as cyclosporine and tacrolimus.	60 days prior to V1
Appetite or weight modifying medications, including nonprescription or herbals and medical grade marijuana.	60 days prior to V1
Anti-psychotic medications such as olanzapine, risperidone.	60 days prior to V1
Coumarin type anticoagulants or other anticoagulants (eg, dabigatran, apixaban, edoxaban, fondaparinux, rivaroxaban).	60 days prior to V1
Anticonvulsants if prescribed for seizure disorder.	60 days prior to V1
Antiarrhythmic medications whose primary mechanism of action is sodium or potassium channel blockade (eg, procainamide, phenytoin, quinidine, propafenone; as well as amiodarone, dofetilide, sotalol). ***Note***: β-adrenergic receptor blocking agents (eg, atenolol, metoprolol) and calcium channel blockers (eg, diltiazem, amlodipine, nifedipine) are permitted.	60 days prior to V1
Sympathomimetic agents. ***Note***: Inhaled β-adrenergic receptor agonists (eg albuterol) are permitted. Methylphenidate and amphetamine medications for ADHD that are at a stable dose for at least 90 days prior to V1 are permitted.	60 days prior to V1

10.9. Appendix 9: Proposed Chronology of Procedures

For the procedures described below, where multiple procedures are scheduled at the same timepoint(s) relative to dosing, the following chronology of events should be adhered to:

- Site-based PRO assessments: should be completed by the participant at the beginning of the visit before any medical procedures or interactions with the medical staff (as much as practically possible) take place (see Section 8.1.3);

- 12-lead ECG: obtain prior to vital signs assessment, blood samples, and prior to dosing (as applicable) (see Section 8.2.3);

- Vital Signs (BP, pulse rate): obtain after 12-lead ECG collection but prior to obtaining blood samples and prior to dosing (as applicable for pre-dose collection) (see Section 8.2.2);

- Measurement of body weight, waist and hip circumference: obtain prior to dosing and food consumption (see Section 8.1.1 and Section 8.1.2);

- Fasting blood samples [for safety (see Section 8.2.4), PK (see Section 8.5), and banked biospecimens (see Section 8.7.2 and Section 8.8.4)]: after assessment of 12-lead ECG and vital signs but prior to dosing (as applicable for pre-dose collection);

- Dosing: must occur in the morning with food, and where applicable, after any pre-dose blood sample collection(s);

- For the random, post-dose PK blood collection to occur approximately 2 to 6 hours post dose (see Section 8.5): these blood samples should be collected after vital signs are measured; if collection time coincides with time of a meal/snack, these blood samples should be collected just prior to the meal/snack.

10.10. Appendix 10: Protocol Amendment History

The protocol amendment summary of changes table for the current amendment is located directly before the TOC. The protocol amendment summary of changes tables for past amendment(s) can be found below:

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Amendment 1	16 December 2021	Rationale: The protocol was amended to add Cohort 2 where approximately 49 additional participants will be randomized in a 1:2:2:2 ratio to the placebo (Arm 1, Figure 2) and 3 slow titration arms (Arms 7, 8, 9, Figure 2). This cohort was added to better characterize the tolerability and efficacy profile of the 2-week titration schemes, relative to the 1-week titration schemes, and to maintain the double-blind study design. All SoA activities will be the same for Cohort 2 as for the original Cohort of randomized participants. The following sections were revised as part of this rationale: Section 1.1 Synopsis, Overall Design: Added wording to reflect the addition of Cohort 2, including that the additional participants will be randomized to blinded study intervention in 1 of 4 arms in a 1:2:2:2 ratio (placebo: 3 slow titration arms). Section 1.1 Synopsis, Number of Participants: Added the number of participants in Cohort 2, specifying that approximately 49 additional participants will be randomized to the placebo and slow titration arms (approximately 7 in the placebo and approximately 14 in each of the 3 slow titration arms).

		Section 1.2 Schema, Figure 2 Titration Schema: Revised the "n" in the figure for the placebo and 3 slow titration arms to reflect the total number of participants in those arms, including the original Cohort plus Cohort 2. Added a footnote to explain this. Section 4.1 Overall Design: Revised the wording to reflect the addition of Cohort 2, including the subsequent enrollment into 4 of the 9 study arms (placebo and the 3 slow titration arms), and the number of participants being added as approximately 49. Section 6.3.1 Allocation to Study Intervention: Added wording to reflect the randomization for Cohort 2 is 1:2:2:2 (placebo: 3 slow titration arms). Section 9 Statistical Considerations: Added wording to reflect that the data from both cohorts (the original Cohort and Cohort 2) will be combined for final reporting. Section 9.2 Sample Size Determination: provided updated sample size for Cohort 2 including rationale. Section 9.4.1 General Considerations: Added wording to reflect that the data from both cohorts (the original Cohort and Cohort 2) will be combined for final reporting. Rationale: updated the nonclinical safety section with the most recent toxicology information, available after the original protocol. Section 2.2.1.2 Nonclinical Safety: Added that data from the 9-month toxicology study in cynomolgus monkeys (Study CCI) demonstrated no test article-related mortality, use of palliative

		care, or repeated use of dosing holidays and that this information was provided for regulatory authority and IRB/EC review and approval before initiation of Part B of C3421019, [redacted] Rationale: incorporated Protocol Administrative Clarification Letter (dated 23 November 2020) change to clarify the timeframe for the exclusion of acute pancreatitis. Section 5.2 Exclusion Criteria, #7: added timeframe as history of acute pancreatitis within 180 days (6 months) prior to V1 or any history of chronic pancreatitis. Rationale: incorporated Protocol Administrative Clarification Letter (dated 23 November 2020) change to clarify the intent to exclude participants with illicit drug use, and that certain medications that may cause a positive urine drug test, may not be representative of illicit use. Section 5.2 Exclusion Criteria, #22: clarified that the exclusion is a positive urine drug screen at V1 that is consistent with illicit drug use. Rationale: incorporated Protocol Administrative Clarification Letter (dated 23 November 2020) change to clarify that throat and neck examination (including examination of the thyroid) is part of the complete physical examination. Section 8.2.1 Physical Examinations: added throat and neck (including thyroid examination) to the list of minimum assessments as part of complete physical examination. Rationale: incorporated Protocol Administrative Clarification Letter (dated

		23 November 2020) change to clarify that continuous ECG monitoring for the referenced scenario may be either cardiac telemetry or frequent ECG ascertainment as per investigator's medical judgment for sites that do not have access to cardiac telemetry. Section 8.2.3 Electrocardiograms: added wording after continuous ECG monitoring to reflect this could be cardiac telemetry or frequent ECG ascertainment as per investigator's medical judgment. Rationale: incorporated Protocol Administrative Clarification Letter (dated 23 November 2020) change to clarify more precisely the timing following screening that blinding of the specified laboratory results will begin after randomization. Section 10.2, Appendix 2: Clinical Laboratory Tests: changed wording for blinding of the specified labs to be "after randomization" rather than "following screening". Rationale: incorporated Protocol Administrative Clarification Letter #2 (dated 21 January 2021) change to clarify that the unblinding criteria for FPG include parameters for hyperglycemia as well as hypoglycemia, and to specify the level of FPG required for unblinding. Section 10.2, Appendix 2: Clinical Laboratory Tests; added wording for unblinding for FPG that indicates hyperglycemia with an FPG ≥270 mg/dL (15.0 mmol/L). Rationale: incorporated changes from Protocol Administrative Clarification Letter #2 (dated 21 January 2021) and #3 (dated 01 Feb 2021) to clarify that the standard 30 day washout for investigational drug use

		should be interpreted to include investigational vaccines. Per FDA guidance FDA does not consider receipt under an Emergency Use Authorization as receipt of an investigational product. Section 5.2. Exclusion Criteria, criterion #16: revised wording to investigational product (eg, drug or vaccine). Rationale: clarified that serum and urine pregnancy tests are required for all females regardless of childbearing potential. Section 1.3 Schedule of Activities (SoA): in SoA table, for Pregnancy test row and Urine on-site pregnancy test row changed parenthetical content from "females only" to "all females". Revised table footnote "o" to include that serum and urine pregnancy tests are required for all females regardless of childbearing potential. Rationale: clarified that the post-dose vital sign measurements are done in triplicate. Section 1.3 Schedule of Activities (SoA): revised the wording of table footnote "i" to clarify post dose vital signs will be measured in triplicate. Section 8.2.2.1 Blood Pressure and Pulse Rate: in the bullet point that addresses post-dose BP and pulse rate measurements clarified that these are triplicate assessments. Rationale: clarified that methylphenidate and amphetamine medications for ADHD that are at a stable dose for at least 90 days prior to V1 are permitted. Section 10.8 Appendix 8: Prohibited Prior/Concomitant Medications: Added a note to the sympathomimetic agents category to clarify that methylphenidate

		and amphetamine medications for ADHD that are at a stable dose for at least 90 days prior to V1 are permitted. Rationale: clarified that MHP referral should be done for any of the reasons listed. Section 8.2.6.3 Referral to a Mental Health Professional: added "any of" before the list of reasons for MHP referral. Rationale: incorporated administrative revisions consistent with the updated Clinical Protocol Template Phase 1 2 3 4 (01 March 2021). Title page: changed to new Pfizer logo. Sections: 7.1, 8.3.1, 10.3.2, 10.3.3 and 10.4.4: editorial revisions. Rationale: entered study intervention name. Title page: entered Danuglipron in Study Intervention Name row.
Original protocol	14 September 2020	N/A

10.11. Appendix 11: Abbreviations

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

	Term
%CV	percent coefficient of variation
Abs	absolute
ADHD	Attention Deficit Hyperactivity Disorder
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{24}	area under the concentration-time curve from time 0 to 24 hours
AUC_{inf}	area under the concentration-time curve from time 0 to infinity
AV	atrioventricular
CCI [redacted]	
β-hCG	β-human chorionic gonadotropin
BID	twice daily
BMI	body mass index
BP	blood pressure
bpm	beats per minute
BUN	blood urea nitrogen
C-SSRS	Columbia-Suicide Severity Rating Scale
cAMP	cyclic adenosine monophosphate
CFB	change from baseline
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
C_{max}	maximum observed concentration
CO_2	carbon dioxide (bicarbonate)
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CT	clinical trial
CCI [redacted]	
DCT	data collection tool
DDI	drug-drug interaction
DILI	drug-induced liver injury
DMC	data monitoring committee

	Term
DNA	deoxyribonucleic acid
DPP 4	dipeptidyl peptidase 4
DU	dispensable unit
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EDB	exposure during breastfeeding
EDP	exposure during pregnancy
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EoT	End of Treatment
ePRO	electronic patient-reported outcome
ET	early termination
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FPG	fasting plasma glucose
FSH	follicle-stimulating hormone
FPI	fasting plasma insulin
FT4	free thyroxine
FU	follow-up
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GLP-1	glucagon-like peptide-1
GLP-1R	glucagon-like peptide-1 receptor
HAE	hypoglycemic adverse event
HbA1c	hemoglobin A1c
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HOMA-B	homeostatic model assessment of beta-cell function
HOMA-IR	homeostatic model assessment of insulin resistance
HR	heart rate
HRT	hormone replacement therapy
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation
ICH E9 (R1)	ICH Harmonised Guideline E9 (R1)
ID	identification
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
IP manual	investigational product manual

	Term
IPAL	Investigational Product Accountability Log
IR	immediate release
IRB	institutional review board
IRC	internal review committee
IRT	interactive response technology
ISO	International Organization for Standardization
IV	intravenous
IVGTT	intravenous glucose tolerance test
IWQOL-Lite-CT©	Impact of Weight on Quality of Life – Lite Clinical Trials Version
IWR	interactive Web-based response
K_2EDTA	dipotassium edetic acid (ethylenediaminetetraacetic acid)
LBBB	left bundle branch block
LFT	liver function test
LLN	lower limit of normal
log_e	natural logarithm
MAR	missing at random
MATE	multidrug and toxin extrusion protein
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MDR1	multidrug resistance mutation
MHP	mental health professional
MMRM	mixed model repeated measures
N/A	not applicable
NIMP	noninvestigational medicinal product
NOAEL	no-observed-adverse-effect level
CCI	[redacted]
OCT	organic cation transporter
Pbo	placebo
PCOA	patient centered outcome assessment
PD	pharmacodynamic(s)
PGI-C	patient's global impression of change
PGI-S	patient's global impression of severity
PHQ-9	Patient Health Questionnaire-9
PI	principal investigator
PK	pharmacokinetic(s)
PRO	patient-reported outcome
PROMIS®	Patient-Reported Outcomes Measurements Information System
PT	prothrombin time
PVC	premature ventricular contraction/complex
QTcF	corrected QT (Fridericia method)
qual	qualitative

	Term
R_{ac}	accumulation ratio based on AUC
RBC	red blood cell
REE	resting energy expenditure
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SF-36v2®	Short Form-36 Health Survey
SGLT2	sodium glucose cotransporter 2
SoA	schedule of activities
SOC	system organ class
SOP	standard operating procedure
SRSD	single reference safety document
SSID	study-specific subject identification
SToD	study team on demand
SUSAR	suspected unexpected serious adverse reaction
T	telephone
$t_{½}$	terminal phase half-life
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TBA	total bile acids
TBili	total bilirubin
TEAEs	treatment emergent adverse events
TEE	total energy expenditure
T_{max}	time to first occurrence of C_{max}
TSH	thyroid stimulating hormone
CCI	[redacted]
ULN	upper limit of normal
US	United States
V	visit
WBC	white blood cell
Wk	week
WOCBP	woman of childbearing potential

11. REFERENCES

1. Ørskov C, Holst JJ, Knuhtsen S, et al. Glucagon-like peptides GLP-1 and GLP-2, predicted products of the glucagon gene, are secreted separately from pig small intestine but not pancreas. Endocrinology 1986;119(4):1467-75.

2. Kreymann B, Williams G, Ghatei MA, et al. Glucagon-like peptide-1 7-36: a physiological incretin in man. Lancet 1987;2(8571):1300-4.

3. Nauck MA, Niedereichholz U, Ettler R, et al. Glucagon-like peptide-1 inhibition of gastric emptying outweighs its insulinotropic effects in healthy humans. Am J Physiol 1997;273(5):E981-8.

4. Flint A, Raben A, Astrup A, et al. Glucagon-like peptide-1 promotes satiety and suppresses energy intake in humans. J Clin Invest 1998;101(3):515-20.

5. Guh DP, Zhang W, Bansback N, et al. The incidence of co-morbidities related to obesity and overweight: a systematic review and meta-analysis. BMC Public Health 2009;9:88.

6. Flegal KM, Kit BK, Orpana H, et al. Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. JAMA 2013;309(1):71-82.

7. The GBD 2015 Obesity Collaborators. Health effects of overweight and obesity in 195 countries over 25 years. N Engl J Med 2017;377(1):13-27.

8. Ogden CL, Carroll MD, Kit BK, et al. Prevalence of childhood and adult obesity in the United States, 2011-2012. JAMA 2014;311(8):806-14.

9. Anderson JW, Konz EC, Frederich RC, et al. Long-term weight-loss maintenance: a meta-analysis of US studies. Am J Clin Nutr 2001;74(5):579-84.

10. Drucker, DL. The ascending GLP-1 road from clinical safety to reduction of cardiovascular complications. Diabetes 2018;67:1710-19.

11. Wilding JP, Overgaard RV, Jacobsen LV, et al. Exposure–response analyses of liraglutide 3.0 mg for weight management. Diabetes Obes Metab 2016;18(5): 491–9.

12. World Health Organization. Waist circumference and waist-hip ratio: report of a WHO expert consultation. Geneva, Switzerland: World Health Organization; 2008.

13. World Health Organization. WHO STEPS Surveillance Manual: The WHO STEPwise approach to chronic disease risk factor surveillance. Geneva, Switzerland: World Health Organization; 2005.

14. VICTOZA [Package insert], Drugs@FDA. 2019 Jun., Available: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/022341s031lbl.pdf <Accessed Apr 2, 2020>.

15. OZEMPIC [Package insert], Drugs@FDA. 2020 Jan., Available: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/209637s003lbl.pdf <Accessed Apr 2, 2020>.

16. TRULICITY [Package Insert], Drugs@FDA, 2020 Feb., Available: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125469s033lbl.pdf <Accessed Apr 2, 2020>.

17. SAXENDA [Package Insert], Drugs@FDA, 2020 Mar., Available: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/206321s011lbl.pdf <Accessed Apr 2, 2020>.

18. Posner K, Brown GK, Stanley B, et al. The Columbia–Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatry 2011;168(12):1266–77.

19. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med 2001;16(9):606-13.

20. Matthews DR, Hosker JP, Rudenski AS, et al. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28(7):412-9.

21. Franz MJ, VanWormer JJ, Crain AL, et al. Weight-loss outcomes: a systematic review and meta-analysis of weight-loss clinical trials with a minimum 1-year follow-up. J Am Diet Assoc 2007;107(10):1755-67.

22. American College of Cardiology/American Heart Association Task Force on Practice Guidelines, Obesity Expert Panel, 2013. Expert Panel Report: guidelines (2013) for the management of overweight and obesity in adults. Obesity (Silver Spring) 2014;22: Suppl 2:S41-410.

23. Di Benedetti D, Harris N, Rozjabek HM, et al. Assessing factors influencing eating in overweight and obese individuals. Poster presented at Endo 2019; 23-26 March 2019; New Orleans, LA.

24. Tronieri JS, Wadden TA, Walsh O, et al. Effects of liraglutide on appetite, food preoccupation, and food liking: results of a randomized controlled trial. Int J Obes (Lond) 2020;44(2):353-61.

25. Banholzer ML, Wandel C, Barrow P, et al. Clinical trial considerations on male contraception and collection of pregnancy information from female partner: update. Clin Transl Med 2016;5(1):23-37.

26. O'Neil PM, Birkenfeld AL, McGowan B, et al. Efficacy and safety of semaglutide compared with liraglutide and placebo for weight loss in patients with obesity: a randomised, double-blind, placebo and active controlled, dose-ranging, phase 2 trial. Lancet 2018;392(10148):637-49.

27. Nauck MA, Quast DR, Wefers J, et al. GLP-1 receptor agonists in the treatment of type 2 diabetes - state-of-the-art. Mol Metab. 2021;46:101102.

28. Lin PH, Proschan MA, Bray GA, et al. Estimation of energy requirements in a controlled feeding trial. Am J Clin Nutr 2003;77:639–45.

29. Patient Reported Outcomes Measurements Information System, FATIGUE: A brief guide to the PROMIS® Fatigue instruments; Feb 28, 2019.

30. HealthMeasures. http://www.healthmeasures.net/score-and-interpret/calculate-scores/scoring-instructions. 2020.

31. Patient-Reported Outcomes Measurements Information System, PHYSICAL FUNCTION, A brief guide to the PROMIS® Physical Function instruments; July 18, 2019.

32. Kolotkin RL, Williams VSL, Ervin CM, et al. Validation of a new measure of quality of life in obesity trials: Impact of Weight on Quality of Life-Lite Clinical Trials Version. Clin Obes 2019;9:e12310.

33. Ware J, Kosinski M, Bjorner J, et al. Development. User's Manual for the SF-36v2® Health Survey. Lincoln (RI): QualityMetric Incorporated;2007.

34. American Diabetes Association. Standards of medical care in diabetes -2019. Diabetes Care 2019;42(Suppl 1):S1-S193.

35. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. ICH Harmonised Guideline: Addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials: ICH E9 (R1); 2019.