# A 26-WEEK, PHASE 2B, 2-PART, 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:** | N/A |
| **US IND Number:** | 148671 |
| **EudraCT Number:** | 2020-001312-19 |
| **Protocol Number:** | C3421019 |
| **Phase:** | 2b |

**Short Title:** A 26-Week, 2-Part Study to Evaluate the Efficacy and Safety of PF-06882961 in Adults With Obesity

This document and accompanying materials contain confidential information belonging to Pfizer. Except as otherwise agreed to in writing, by accepting or reviewing these documents, you agree to hold this information in confidence and not copy or disclose it to others (except where required by applicable law) or use it for unauthorized purposes. In the event of any actual or suspected breach of this obligation, Pfizer must be promptly notified.

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

## Protocol Amendment Summary of Changes Table

| Document History | | |
|---|---|---|
| **Document** | **Version Date** | **Summary and Rationale for Changes** |
| Original protocol | 14 September 2020 | N/A |

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

## TABLE OF CONTENTS

LIST OF TABLES ..... 8
LIST OF FIGURES ..... 8
1. PROTOCOL SUMMARY ..... 9
1.1. Synopsis ..... 9
1.2. Schema ..... 15
1.3. Schedule of Activities (SoA) ..... 17
2. INTRODUCTION ..... 20
2.1. Study Rationale ..... 20
2.2. Background ..... 21
2.2.1. Nonclinical Overview ..... 21
2.2.1.1. Nonclinical Pharmacokinetics and Metabolism ..... 21
2.2.1.2. Nonclinical Safety ..... 22
2.2.2. Clinical Overview ..... 23
2.2.2.1. Clinical Safety ..... 23
2.2.2.2. Clinical Pharmacokinetics ..... 24
2.3. Benefit/Risk Assessment ..... 25
2.3.1. Risk Assessment ..... 25
2.3.2. Benefit Assessment ..... 28
2.3.3. Overall Benefit/Risk Conclusion ..... 28
3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS ..... 28
4. STUDY DESIGN ..... 30
4.1. Overall Design ..... 30
4.1.1. Assessment of Safety and Tolerability While Study is Ongoing ..... 31
4.2. Scientific Rationale for Study Design ..... 32
4.3. Justification for Dose ..... 33
4.4. End of Study Definition ..... 34
5. STUDY POPULATION ..... 34
5.1. Inclusion Criteria ..... 35
5.2. Exclusion Criteria ..... 35
5.3. Lifestyle Considerations ..... 38

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

5.3.1. Dietary Restrictions ....38
5.3.2. Dietary Counseling ....39
5.3.3. Physical Activity Counseling ....39
5.3.4. Alcohol, Caffeine, and Tobacco ....40
5.3.5. Contraception ....40
5.4. Screen Failures ....40
6. STUDY INTERVENTION ....41
6.1. Study Intervention(s) Administered ....41
6.1.1. Administration ....41
6.2. Preparation/Handling/Storage/Accountability ....44
6.2.1. Preparation and Dispensing ....45
6.3. Measures to Minimize Bias: Randomization and Blinding ....45
6.3.1. Allocation to Study Intervention ....45
6.3.2. Breaking the Blind ....46
6.4. Study Intervention Compliance ....47
6.5. Concomitant Therapy ....47
6.5.1. Antihypertensive Medications ....48
6.5.2. Lipid Modifying Medications ....48
6.5.3. Rescue Medicine ....48
6.6. Dose Modification ....48
6.6.1. Dose Titration ....48
6.6.2. Considerations for Pausing or Stopping Active Dose(s) Based on Observed Safety ....48
6.7. Intervention After the End of the Study ....48
7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL ....49
7.1. Discontinuation of Study Intervention ....49
7.2. Participant Discontinuation/Withdrawal From the Study ....49
7.2.1. Withdrawal of Consent ....50
7.3. Lost to Follow-up ....51
8. STUDY ASSESSMENTS AND PROCEDURES ....51
8.1. Efficacy Assessments ....52

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

8.1.1. Primary Efficacy Parameter: Body Weight ....52
8.1.2. Secondary Efficacy Parameters: Waist and Hip Circumference ....53
8.1.3. Tertiary Efficacy Parameters: Patient Centered Outcome Assessments (PCOAs) ....53
8.1.3.1. Eating-Related Factors Daily Diary ....55
8.1.3.2. Patient's Global Impression of Severity (PGI-S) ....55
8.1.3.3. Patient's Global Impression of Change (PGI-C) ....55
8.1.3.4. PROMIS® Fatigue Custom 9-item Version ....55
8.1.3.5. PROMIS® Physical Function Custom 13-item Version ....55
8.1.3.6. Impact of Weight on Quality of Life–Lite (IWQOL-Lite) Clinical Trials Version ....55
8.1.3.7. SF-36v2® Health Survey ....56
8.2. Safety Assessments ....56
8.2.1. Physical Examinations ....56
8.2.2. Vital Signs ....56
8.2.2.1. Blood Pressure and Pulse Rate ....56
8.2.3. Electrocardiograms ....57
8.2.4. Clinical Safety Laboratory Assessments ....58
8.2.5. Management of Hypoglycemia ....58
8.2.5.1. Definition and Severity of Hypoglycemic Adverse Event (HAE) ....59
8.2.6. Mental Health Questionnaires ....60
8.2.6.1. Columbia Suicide Severity Rating Scale (C-SSRS) ....60
8.2.6.2. Patient Health Questionnaire-9 (PHQ-9) ....60
8.2.6.3. Referral to a Mental Health Professional ....61
8.2.7. Pregnancy Testing ....61
8.3. Adverse Events and Serious Adverse Events ....61
8.3.1. Time Period and Frequency for Collecting AE and SAE Information ....62
8.3.1.1. Reporting SAEs to Pfizer Safety ....62
8.3.1.2. Recording Nonserious AEs and SAEs on the CRF ....62
8.3.2. Method of Detecting AEs and SAEs ....63
8.3.3. Follow-up of AEs and SAEs ....63

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

8.3.4. Regulatory Reporting Requirements for SAEs....63
8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure....64
8.3.5.1. Exposure During Pregnancy....64
8.3.5.2. Exposure During Breastfeeding....65
8.3.5.3. Occupational Exposure....66
8.3.6. Cardiovascular and Death Events....66
8.3.7. Disease Related Events and/or Disease Related Outcomes Not Qualifying as AEs or SAEs....66
8.3.8. Adverse Events of Special Interest....66
8.3.8.1. Lack of Efficacy....66
8.3.9. Medical Device Deficiencies....66
8.3.10. Medication Errors....67
8.4. Treatment of Overdose....67
8.5. Pharmacokinetics....68
8.6. Pharmacodynamics....69
8.7. Genetics....69
8.7.1. Specified Genetics....69
8.7.2. Banked Biospecimens for Genetics....69
8.8. Biomarkers....69
8.8.1. Specified Gene Expression (RNA) Research....69
8.8.2. Specified Protein Research....69
8.8.3. Specified Metabolomic Research....69
8.8.4. Banked Biospecimens for Biomarkers....69
8.9. Immunogenicity Assessments....70
8.10. Health Economics....70
9. STATISTICAL CONSIDERATIONS....70
9.1. Estimands and Statistical Hypotheses....70
9.2. Sample Size Determination....72
9.3. Analysis Sets....72
9.4. Statistical Analyses....74
9.4.1. General Considerations....74

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

9.4.1.1. Analyses for Continuous Endpoints ..... 74
9.4.1.2. Analyses for Categorical Endpoints ..... 74
9.4.2. Primary Endpoint(s) ..... 74
9.4.3. Secondary Endpoint(s) ..... 75
9.4.4. Tertiary/Exploratory Endpoint(s) ..... 76
9.4.5. Other Safety Analyses ..... 76
9.4.5.1. Electrocardiogram Interval Analyses ..... 77
9.4.6. Other Analyse(s) ..... 77
9.5. Interim Analyses ..... 77
9.5.1. PK/PD Unblinding Plan ..... 77
9.6. Data Monitoring Committee or Other Independent Oversight Committee ..... 78
10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS ..... 79
10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations ..... 79
10.1.1. Regulatory and Ethical Considerations ..... 79
10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP ..... 79
10.1.2. Financial Disclosure ..... 80
10.1.3. Informed Consent Process ..... 80
10.1.4. Data Protection ..... 81
10.1.5. Dissemination of Clinical Study Data ..... 81
10.1.6. Data Quality Assurance ..... 83
10.1.7. Source Documents ..... 84
10.1.8. Study and Site Start and Closure ..... 84
10.1.9. Publication Policy ..... 85
10.1.10. Sponsor's Qualified Medical Personnel ..... 86
10.2. Appendix 2: Clinical Laboratory Tests ..... 87
10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting ..... 89
10.3.1. Definition of AE ..... 89
10.3.2. Definition of SAE ..... 90
10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs ..... 92

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

10.3.4. Reporting of SAEs ..... 95
10.4. Appendix 4: Contraceptive Guidance ..... 96
10.4.1. Male Participant Reproductive Inclusion Criteria ..... 96
10.4.2. Female Participant Reproductive Inclusion Criteria ..... 96
10.4.3. Woman of Childbearing Potential ..... 96
10.4.4. Contraception Methods ..... 97
10.5. Appendix 5: Genetics ..... 99
10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments ..... 100
10.7. Appendix 7: ECG Findings of Potential Clinical Concern ..... 102
10.8. Appendix 8: Prohibited Prior/Concomitant Medications ..... 104
10.9. Appendix 9: Proposed Chronology of Procedures ..... 106
10.10. Appendix 10: Abbreviations ..... 107
11. REFERENCES ..... 111

## LIST OF TABLES

Table 1. Target Doses for Randomized Regimens ..... 14
Table 2. Titration and Dosing Schemes ..... 43
Table 3. Target Doses for Randomized Regimens ..... 46
Table 4. Patient Reported Outcome Measures ..... 54
Table 5. Protocol Required Laboratory Assessments ..... 87

## LIST OF FIGURES

Figure 1. Overall Study Schema ..... 15
Figure 2. Titration Schema ..... 16

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

# 1. PROTOCOL SUMMARY

## 1.1. Synopsis

**Short Title:** A 26-Week, 2-Part Study to Evaluate the Efficacy and Safety of PF-06882961 in Adults With Obesity

### Rationale

This multicenter, Phase 2b, 2-part, randomized, double-blind, placebo-controlled, parallel group, dose-ranging study is being conducted in adults with obesity. After completion of the screening period, this study is designed as a 2-part trial:

- 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;
- Part B (Weeks 17-26): participants in Part A will continue in Part B (according to randomization from Part A) contingent upon supportive nonclinical data through 26 weeks from the ongoing 9-month toxicology study in monkeys (Study 19GR370) and formal agreement with regulatory authorities and IRBs/ECs.

A 2-part study design is utilized, as the 16-week dosing duration of Part A is supported by the currently available nonclinical toxicology data (Section 2.2.1.2), and dosing in Part B over Weeks 17 through 26 is contingent on availability of supportive nonclinical data Study 19GR370 as described above. Based on the projected timeline for conduct of this clinical study and the anticipated date of availability of the 26-week data from Study 19GR370, it is expected that formal agreement for Part B will occur in time to allow participants to proceed directly from Part A to Part B. In the event participants reach the end of Part A prior to formal approval to initiate Part B of the study, these participants will not continue to Part B but instead will end treatment at Week 16 (ie, V10 will be considered the End of Treatment visit) and will continue directly to the follow-up phase, completing Follow-up visits relative to Week 16 (ie, V14 will occur at Weeks 17-18 and V15 at Weeks 20-21) (see SoA). The primary endpoint for this study will be determined by the planned End of Treatment visit for the study, which is expected to be Week 26, based on conducting Part B after formal agreement with regulatory authorities and IRBs/ECs. However, in the event that Part B is not approved, then Week 16 will serve as the End of Treatment visit, as described above. 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.

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

## 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.<br>• 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. | • Percent CFB in body weight at Weeks 2, 4, 6, 8, 10, 12, 16,[b] 18 and 22.[c] |
| | • 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 | • Absolute CFB in waist-to-hip |

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

| Objectives | Estimands | Endpoints |
|---|---|---|
| | will be similar to 3 above. | 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. | • Absolute CFB in HbA1c at Weeks 16 and 26.[c] |
| | • Estimand 6: This estimand will be similar to 3 above. | • Absolute CFB in FPG at Weeks 2, 4, 6, 8, 10, 12, 16, 18, 22 and 26.[c] |
| **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 Weeks 2, 4, 6, 8, 10, 12,16, 18, 22 and 26.[c] |
| • 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. |
| • 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. | • CFB in fasting plasma insulin, HOMA-IR and HOMA-B at Weeks 4, 8, 12, 16, 22 and 26.[c] |
| • 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. | • Absolute CFB in waist circumference at Weeks 2, 4, 6, 8, 10, 12, 16,[b] 18 and 22.[c] |
| | • Estimand 4: This estimand will be similar to 3 above. | • Absolute CFB in waist-to-hip ratio at Weeks 2, 4, 6, 8, 10, 12, 16,[b] 18 and 22.[c] |
| • 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] |

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

| Objectives | Estimands | Endpoints |
|---|---|---|
| • 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 Weeks 2, 4, 6, 8, 10, 12, 16, 18, 22 and 26.[c]<br>• CFB in lipid parameters at Weeks 4, 8, 12, 16, 22 and 26.[c] |
| • 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. | • CFB in SF-36v2® subscales and summary scores at Weeks 16 and 26.[c] |
| • 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. | • CFB in Eating-Related Factors Daily Diary at Weeks 4, 8, 12, 16, 22 and 26.[c]<br>• CFB in PGI-S at Weeks 2, 4, 6, 8, 10, 12, 16, 18, 22 and 26.[c]<br>• CFB in PROMIS® Fatigue at Weeks 16 and 26.[c]<br>• CFB in PROMIS® Physical Function at Weeks 16 and 26.[c]<br>• CFB in IWQOL-Lite-CT© at Weeks 16 and 26.[c]<br>• PGI-C at Weeks 4, 16 and 26.[c] |

***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.

a. End of Treatment defined as Week 26 if agreement to complete Part B. In the event that Part B is not conducted, then End of Treatment will be defined as Week 16.

b. In the event that Part B is not conducted and Week 16 is designated as End of Treatment, then Week 16 will not be included in this endpoint.

c. CFB for timepoints after Week 16 is contingent on approval to conduct Part B.

## Overall Design

This is a 2-part Phase 2b, multicenter, randomized, double-blind, placebo-controlled, 9-arm, parallel group, study to assess the efficacy and safety of twice daily oral administration of PF-06882961 in adult participants with obesity. Eligible participants who maintain acceptable compliance during a 2-week placebo run-in period will be randomized on Day 1, of Part A, to double-blinded study intervention in 1 of 9 arms in a 3:3:3:3:3:3:1:1:1 ratio (placebo: 5 standard titration PF-06882961 arms: 3 slow titration arms). Randomization will be 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

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

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. In Part A, dosing with double-blinded study intervention will occur with food twice daily for 16 weeks. Upon formal approval, dosing in Part B (Weeks 17-26) will occur according to the randomization in Part A. All dosing regimens will include dose titration to enhance tolerability of PF-06882961 (see Table 2).

**Number of Participants**

Approximately 420 participants (approximately 60 in each of the placebo and 5 standard titration PF-06882961 arms and approximately 20 participants in each of the 3 slow titration arms) will be randomized to ensure completion of approximately 315 evaluable participants (approximately 45 participants in each of the placebo and standard titration PF-06882961 arms and 15 in each of the slow titration arms). If formal agreement with regulatory authorities and IRBs/ECs for Part B is delayed such that initial participants are not allowed to continue to Part B, but subsequent formal agreement is obtained, the sample size may be increased up to a maximum of 460 randomized participants to enable the completion of approximately 315 evaluable participants in Part B.

**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 will 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. The morning and evening doses should be taken approximately 10-12 hours apart and at approximately the same time each day.

Target dose levels, achieved after completion of titration, for the 9 arms of the study are placebo and PF-06882961 doses of 40 mg BID, 80 mg BID, 120 mg BID, 160 mg BID, and 200 mg BID (see Table 1 below). For the 5 standard titration PF-06882961 groups, 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, and titration will occur at 1-week intervals from a starting dose of 10 mg BID. For the 3 slow titration PF-06882961 groups, target dose levels for each of the arms are 120 mg BID, 160 mg BID, and 200 mg BID, and titration will occur at 2-week intervals from a starting dose of 10 mg BID.

Following the initial screening period to confirm eligibility (up to 4-weeks), screening will continue with a 2-week placebo run-in period. The double-blind treatment period will consist of 2 parts: Part A, which will involve dosing from weeks 1 through 16; and Part B, (contingent upon agreement with regulatory authorities and IRBs/ECS), which will involve further dosing from Weeks 17 through 26 according to the randomization in Part A. For participants who complete both Part A and Part B, the total dosing duration will be approximately 26 weeks, followed by an approximate 4-week follow-up. The total duration of participation in this study for these participants is approximately 32 weeks, including the

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

2-week single-blind run-in period, but excluding the initial screening period. If applicable, for participants who reach the end of Part A but are not allowed to continue to Part B because formal agreement with regulatory authorities and IRBs/ECs for Part B has not yet been obtained, the total dosing duration will be approximately 16 weeks, followed by an approximate 4-week follow-up. The total duration of participation in the study for these participants is approximately 22 weeks, including the 2-week single-blind run-in period, but excluding the initial screening period. For the standard titration arms, up to 10 weeks of the dosing duration will be used for dose titration. For the slow titration arms, up to 20 weeks will be used for dose titration (see Table 2).

**Table 1. Target Doses for Randomized Regimens**

| Regimen Description (dosed twice-daily) | Number of PF-06882961 Tablets | | | Number of Matching Placebo Tablets | Total Number of Tablets |
|---|---|---|---|---|---|
| | 10 mg | 40 mg | 100 mg | 10/40/100 mg | |
| Placebo | - | - | - | 4 | 4 |
| PF-06882961 – 40 mg (standard titration) | - | 1 | - | 3 | 4 |
| PF-06882961 – 80 mg (standard titration) | - | 2 | - | 2 | 4 |
| PF-06882961 – 120 mg (standard titration) | 2 | - | 1 | 1 | 4 |
| PF-06882961 – 160 mg (standard titration) | 2 | 1 | 1 | - | 4 |
| PF-06882961 – 200 mg (standard titration) | - | - | 2 | 2 | 4 |
| PF-06882961 – 120 mg (slow titration) | 2 | - | 1 | 1 | 4 |
| PF-06882961 – 160 mg (slow titration) | 2 | 1 | 1 | - | 4 |
| PF-06882961 – 200 mg (slow titration) | - | - | 2 | 2 | 4 |

**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 outlined in Section 9 and further detailed in a SAP, which will be maintained by the sponsor.

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. End of Treatment is defined as Week 26 if formal agreement to conduct Part B is obtained, otherwise End of Treatment will be defined as Week 16. Measurements after discontinuation of study intervention will be censored and treated as missing data. Missing data due to censoring, study withdrawal or other reasons

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

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.

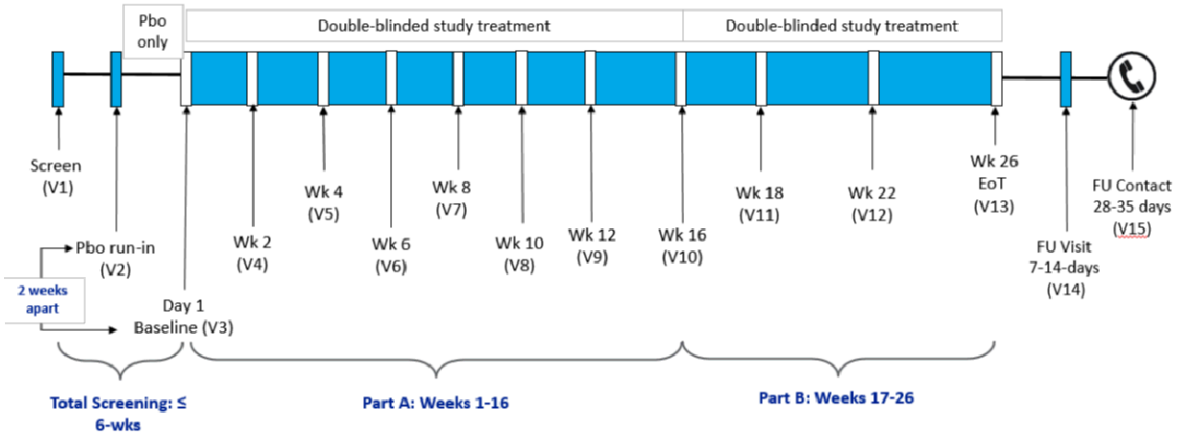
A secondary estimand will be the population odds ratio of the treatment effect of achieving a body weight loss ≥5% from baseline at End of Treatment of PF-06882961 compared to placebo in all evaluable participants while on treatment. All other key secondary continuous clinical endpoints will be analyzed 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. The MMRM model will be fitted to the CFB of $\log_e$-transformed values to Weeks 2, 4, 6, 8, 10, 12, 16, 18, 22 and 26. Inclusion of timepoints after Week 16 is contingent on formal agreement to conduct Part B.

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 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.

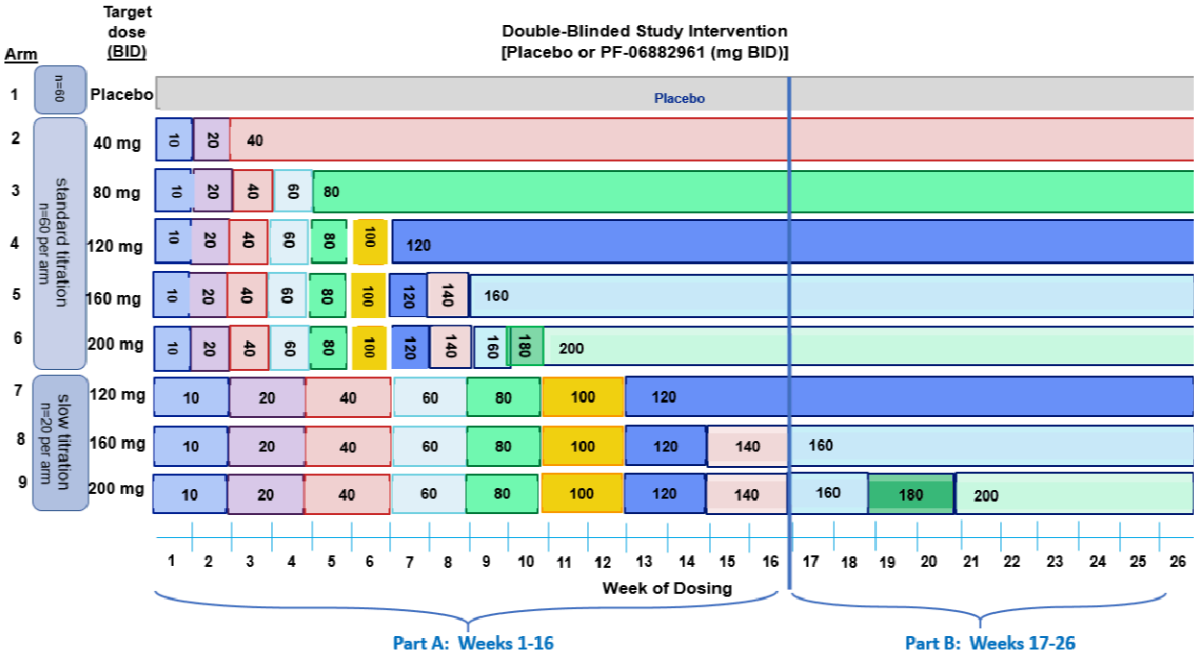
## 1.2. Schema

**Figure 1. Overall Study Schema**




090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

**Figure 2. Titration Schema**




090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

### 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.

| **Protocol Activity** (See Appendix 10 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 |
| Registration in trial (via IRT) | x | | | | | | | | | | | | | | | |

| Protocol Activity (See Appendix 10 for abbreviations) | Screening Phase | | Treatment Phase | | | | | | | | | | End of Treat-ment[a] | Follow-up[b] | | Early Term/ Dis-contin-uation[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] | |
| 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 (females only) | 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 (females only)[o] | | x | x | x | x | x | x | x | x | x | x | x | x | x | | x |

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

a. **End of Treatment:** Defined as Week 26 if agreement to complete Part B. In the event that Part B is not conducted, then End of Treatment will be defined as Week 16.

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, contingent upon supportive nonclinical data and formal agreement with regulatory authorities and IRBs/ECs (see Section 4). In the event participants reach the end of Part A prior to formal approval to initiate Part B of the study, these participants will not continue to Part B but instead will end treatment at Week 16 (ie, V10 will be considered the End of Treatment visit) and will continue directly to the follow-up phase, completing Follow-up visits relative to Week 16 (ie, V14 will occur at Weeks 17-18 and V15 at Weeks 20-21).

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* one 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. **Urine pregnancy test:** At each visit V2 through V14, the test result must be negative in order to continue participation in the study.

# 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, 2-part, randomized, double-blind, placebo-controlled, parallel group, dose-ranging study is being conducted in adults with obesity. After completion of the screening period, this study is designed as a 2-part trial:

- 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;
- Part B (Weeks 17-26): participants in Part A will continue in Part B (according to randomization from Part A) contingent upon supportive nonclinical data through 26 weeks from the ongoing 9-month toxicology study in monkeys (Study 19GR370) and formal agreement with regulatory authorities and IRBs/ECs.

A 2-part study design is utilized, as the 16-week dosing duration of Part A is supported by the currently available nonclinical toxicology data (Section 2.2.1.2), and dosing in Part B over Weeks 17 through 26 is contingent on availability of supportive nonclinical data from the ongoing Study 19GR370 as described above. Based on the projected timeline for conduct of this clinical study and the anticipated date of availability of the 26-week data from Study 19GR370, it is expected that formal agreement for Part B will occur in time to allow participants to proceed directly from Part A to Part B. In the event participants reach the end of Part A prior to formal approval to initiate Part B of the study, these participants will not continue to Part B but instead will end treatment at Week 16 (ie, V10 will be considered the End of Treatment visit) and will continue directly to the follow-up phase, completing Follow-up visits relative to Week 16 (ie, V14 will occur at Weeks 17-18 and V15 at Weeks 20-21). The primary endpoint for this study will be determined by the planned End of Treatment visit for the study, which is expected to be Week 26, based on conducting Part B after formal agreement with regulatory authorities and IRBs/ECs. However, in the event Part B is not approved, then Week 16 will serve as the End of Treatment visit, as described above.

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

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 vitro studies indicate that at doses planned for this study (200 mg BID), there is a risk of weak PK interaction via time dependent inhibition of CYP3A4 by PF-06882961, and therefore sensitive CYP3A4 substrates with a narrow therapeutic index will be excluded. Based on in vitro data, PF-06882961 has the potential to inhibit intestinal BCRP, and therefore, rosuvastatin and sulfasalazine, BCRP sensitive substrates, are excluded from this study.

In vitro data also suggest a risk of PF-06882961 interaction with drugs for which CYP2C8 and UGT1A1 mediated metabolism constitutes the primary mechanism of clearance. At the dose of 200 mg BID, there is also a possibility of weak inhibition of hepatic OATP1B3, OATP2B1, OCT1 and uptake transporter MDR1. Given the potential for weak inhibition of OATP, statins exposures may be modestly higher when administered with PF-06882961; therefore statins administered at the top approved dose are excluded in this study. Static modeling of in vitro data also indicate that PF-06882961 has a low potential to cause DDIs as a result of induction of CYP3A4, or inhibition of other CYP enzymes (1A2, 2B6, 2C9, 2C19 or 2D6), other UGT enzymes (1A4, 1A6, 1A9, 2B7, 2B15), and uptake transporters (OATP1B1, OCT2, MATE1, MATE 2K, OAT1 and OAT3). See Appendix 8 for a complete list of prohibited medications.

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

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

#### 2.2.1.2. Nonclinical Safety

General toxicology studies have been completed in cynomolgus monkeys up to 6 months in duration (with a 3-week lead-in and 1-month recovery) and in rats up to 6 months in duration with a 1-month recovery. As the monkey is the only nonclinical species for which PF-06882961 is known to activate the receptor, toxicology studies in rats were conducted to evaluate off-target effects. The exposure limits for plasma concentrations of PF-06882961 for clinical studies are based on exposure at the NOAEL of 250 mg/kg/day in the 6-month with 1-month recovery toxicology study in rats, due to the fact that findings in monkeys such as decreased food intake and body weight loss are reversible and monitorable in a clinical setting. In the 6-month toxicity study in rats with 1-month recovery (Study 18GR006) the NOAEL was 250 mg/kg/day based on species-specific toxicity at a higher dose. The exposure margins at 250 mg/kg/day were 41-fold ($C_{max}$, free) and 23-fold ($AUC_{24}$, free), to the predicted human exposures at the highest planned dose of PF-06882961 in this study, which is 200 mg BID.

A NOAEL was not established in the cynomolgus monkey 6-month toxicity study with 3-week lead-in and 1-month recovery (Study 8400521), due to early euthanasia of 3 animals administered ≥50 mg/kg/day that was attributed to study-specific factors, as this had not occurred in animals exposed for longer duration in previous studies with similar doses (Studies 17GR068 and 18GR007). Based on the available data, none of the adverse microscopic findings in the kidney and heart observed in these moribund animals appeared to be consistent with primary toxicological effects. Rather, they were more consistent with secondary events related to prolonged inanition and the resulting negative energy state. Exposure margins at 50 mg/kg/day were 0.71- and 5.1-fold for $C_{max}$ (free) in males and females, respectively, and were 0.41- and 2.2-fold for $AUC_{24}$ (free) in males and females, respectively, to the predicted human exposures at the highest planned dose of PF-06882961 in this study (200 mg BID). Data through 26-weeks of dosing from the ongoing 9-month toxicology study in cynomolgus monkeys (Study 19GR370) will be provided for regulatory authority and IRB/EC review and approval prior to initiation of Part B of C3421019.

Other toxicology studies completed in cynomolgus monkeys include a 14-week study with a 4-week lead-in (up to 18 weeks total exposure) (Study 18GR007) and a 13-week investigative toxicology study with 3-week lead-in (16 weeks total exposure) (Study 19GR251), in which the NOAELs were 100 mg/kg/day and 150 mg/kg/day, respectively. At the NOAEL dose of 100 mg/kg/day in the 14-week study with 4-week lead-in, exposure margins were 1.6-fold and 1.2-fold for $C_{max}$ (free) and $AUC_{24}$ (free), respectively, based on dose-limiting inappetence and decreases in body weight observed in 1 animal at the highest dose of 200 mg/kg/day. At the NOAEL dose of 150 mg/kg/day in the 13-week study with 3-week lead-in, exposure margins were 9.5- and 6.9-fold for $C_{max}$ (free) in males and females, respectively, and were 8.8- and 7.9-fold for $AUC_{24}$ (free) in males and females, respectively, based on the absence of adverse effects at any dose in the study. These exposure margins are versus the predicted human exposures at the highest planned dose of PF-06882961 in this study (200 mg BID).

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

Embryo-fetal developmental studies were completed in rats and rabbits. Based on the lack of maternal toxicity or adverse effects on embryo-fetal development, the NOAEL for maternal and developmental toxicity in rats was 500 mg/kg/day (highest dose evaluated). The exposures at 500 mg/kg/day provide margins of approximately 81-fold ($C_{max}$, free) and 105-fold ($AUC_{24}$, free), to the predicted human exposures at the highest dose of PF-06882961 in this study (200 mg BID).

In embryo-fetal studies conducted in rabbits, the NOAEL for maternal and developmental toxicity was 250 mg/kg/day, with margins of approximately 18-fold ($C_{max}$, free) and 5.5-fold ($AUC_{24}$, free), to the predicted human exposures at the highest dose of PF-06882961 in this study (200 mg BID).

PF-06882961 was negative in genetic toxicity testing and photosafety endpoints. A risk assessment of the target organ toxicities noted in the repeat-dose toxicity studies is provided in the IB.

Refer to the IB for more details on the nonclinical safety of PF-06882961.

### 2.2.2. Clinical Overview

As of the protocol finalization date, 3 clinical studies, C3421001, C3421002 and C3421003 have completed dosing with PF-06882961. In C3421001 and C3421003, single oral doses of PF-06882961 up to 300 mg (or matching placebo) were generally safe and well tolerated in healthy adult participants. In the multiple dose study C3421002, PF-06882961 doses up to 120 mg BID (or matching placebo) for 28 days were generally safe and well-tolerated in adult participants with T2DM on a background of metformin therapy, and safety results from this study are provided in Section 2.2.2.1. 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

Clinical data from the completed C3421001, C3421002 and C3421003 studies are provided in the IB for PF-06882961.

In study C3421002, PF-06882961 doses ranging from 10 mg BID to 120 mg BID were generally safe and well tolerated. A total of 98 participants with T2DM on a background of metformin were randomized to receive PF-06882961 or matching placebo in a 3:1 randomization ratio, and 92 participants completed the study. Six participants discontinued from the study, of which 2 discontinuations were due to treatment-related TEAEs, and 4 withdrew during the treatment or follow-up period for non-treatment related reasons.

A total of 319 TEAEs were reported, of which the majority of the AEs (294 or 92%) were mild in intensity, 23 (or 7%) were moderate, and 2 (or 1%) were severe in intensity. The most frequently reported TEAEs were nausea (49.0%), dyspepsia (32.7%), vomiting (26.5%), diarrhea (24.5%), headache (23.5%), and constipation (20.4%). One participant experienced a TEAE of hypoglycemia, which was non-fasting, mild in severity and of

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

limited duration. No deaths occurred in the C3421002 study. Two participants experienced 2 severe TEAEs during the study, 1 of which occurred in the dosing period and was considered treatment related, the other occurred during the follow-up period and was not considered treatment related. One participant experienced 2 non-treatment-related SAEs, 1 of which occurred in the follow-up period and the other occurred outside of the study reporting period.

While there were isolated values for laboratory tests, vital signs and ECG intervals outside of the reference ranges, no clear adverse trends were apparent in these parameters. As has been reported for marketed GLP-1R agonists,[10,11] increases in HR have been observed, with mean increases ranging from 5 to 15 bpm across doses administered to date, and most HR values within the normal range.

#### 2.2.2.2. Clinical Pharmacokinetics

The clinical PK of PF-06882961 in adult participants has been evaluated in 3 completed studies: C3421001, C3421002, and C3421003. The results of these completed studies are summarized in the PF-06882961 IB.

In study C3421001, following a single, oral dose administration of PF-06882961 to healthy participants at doses ranging from 3 mg to 300 mg under fasted conditions, median $T_{max}$ ranged from 2.0 to 6.0 hours post dose. Mean $t_{½}$ values ranged from 4.3 to 6.1 hours. Plasma exposure, as assessed by dose-normalized geometric mean $AUC_{inf}$ and $C_{max}$ values, appeared to increase in a dose proportional manner across the 3 mg to 300 mg doses. Variability in PF-06882961 exposure based on geometric percent coefficient of variation (%CV) ranged from 50% to 91% for $C_{max}$ and 28% to 60% for $AUC_{inf}$ across the 3 mg to 300 mg dose range.

In study C3421002, following 28 days of dosing to participants with T2DM, accumulation was modest for the BID IR formulation treatments, with mean ratios based on dose normalized $AUC_{24}$ ($R_{ac}$) values ranging from 1.203-2.009. Day 28 plasma exposure as measured by geometric mean $AUC_{24}$ values appeared to increase in an approximate dose proportional manner across all IR treatments. Mean $t_{½}$ values on Day 28 across all treatments ranged between 4.681 to 8.090 hours, and no apparent trends were observed across various treatments, regimens, or doses administered. Inter-participant variability for PF-06882961 exposure was based on geometric mean was 31%-87% for $AUC_{24}$ and 32%-94% for $C_{max}$ and on Day 28 across all treatments and cohorts. A population PK model based on data from C3421001 and C3421002 indicated that the exposure in T2DM participants (C3421002) was approximately 1.7-fold higher than that observed in healthy participants (C3421001) after accounting for differences in body weight between the participants in each study.

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

## 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 injectable GLP-1R agonists (ie, 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.<br>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 injectable GLP-1R agonists (ie, liraglutide, exenatide and dulaglutide).<br>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 injectable 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.<br>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.<br>Only one AE of mild hypoglycemia has been reported in the 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. |

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

| Potential Risk of Clinical Significance | Summary of Data/Rationale for Risk | Mitigation Strategy |
|---|---|---|
| Impairment in renal function | In rats, minimal renal tubular vacuolation was observed, but this finding was considered to be non-adverse.<br>In the clinical trial program only 1 mild AE (Blood creatinine increased) has been observed in the clinical trial program. | 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 injectable GLP-1R agonists (ie, liraglutide, exenatide and dulaglutide).<br>In addition, 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 injectable GLP-1R agonist semaglutide for T2DM. This risk has not been listed in the prescribing information for other marketed GLP-1R agonists.<br>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 agonist liraglutide for obesity. This risk has not been listed in the prescribing information for other marketed GLP-1R agonists for T2DM.<br>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. |
| Increase in HR | The potential risk is based on the product labeling for the injectable GLP 1R agonist liraglutide for obesity.<br>Increases in HR have been noted in the clinical program with PF-06882961 with most values within the normal range. There have been no incidences of HR >120 bpm in the clinical program to date and no AEs related to elevations in HR. | Vital signs, including HR and BP, and ECGs are assessed at all onsite study visits in all participants. |

| Potential Risk of Clinical Significance | Summary of Data/Rationale for Risk | Mitigation Strategy |
|---|---|---|
| Acute gallbladder disease | The potential risk is based on the product labeling for the injectable GLP 1R agonist liraglutide for obesity and also exenatide.<br>Acute gallbladder disease has not been observed in the PF-06882961 clinical trial program to date. | 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. |

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

### 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.<br>• 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. | • Percent CFB in body weight at Weeks 2, 4, 6, 8, 10, 12, 16,[b] 18 and 22.[c] |
| | • 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 | • Absolute CFB in waist-to-hip ratio at |

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

| Objectives | Estimands | Endpoints |
|---|---|---|
| | be similar to 3 above. | 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. | • Absolute CFB in HbA1c at Weeks 16 and 26.[c] |
| | • Estimand 6: This estimand will be similar to 3 above. | • Absolute CFB in FPG at Weeks 2, 4, 6, 8, 10, 12, 16, 18, 22 and 26.[c] |
| **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 Weeks 2, 4, 6, 8, 10, 12, 16, 18, 22 and 26.[c] |
| • 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. |
| • 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. | • CFB in fasting plasma insulin, HOMA-IR and HOMA-B at Weeks 4, 8, 12, 16, 22 and 26.[c] |
| • 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. | • Absolute CFB in waist circumference at Weeks 2, 4, 6, 8, 10, 12, 16,[b] 18 and 22.[c] |
| | • Estimand 4: This estimand will be similar to 3 above. | • Absolute CFB in waist-to-hip ratio at Weeks 2, 4, 6, 8, 10, 12, 16,[b] 18 and 22.[c] |
| • 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 Weeks 2, 4, 6, 8, 10, 12, 16, 18, 22 and 26.[c]<br>• CFB in lipid parameters at Weeks 4, 8, 12, 16, 22 and 26.[c] |
| • 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. | • CFB in SF-36v2® subscales and summary scores at Weeks 16 and 26.[c] |

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

| Objectives | Estimands | Endpoints |
|---|---|---|
| • 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. | • CFB in Eating-Related Factors Daily Diary at Weeks 4, 8, 12, 16, 22 and 26.[c]<br>• CFB in PGI-S at Weeks 2, 4, 6, 8, 10, 12,16, 18, 22 and 26.[c]<br>• CFB in PROMIS® Fatigue at Weeks 16 and 26.[c]<br>• CFB in PROMIS® Physical Function at Weeks 16 and 26.[c]<br>• CFB in IWQOL-Lite-CT© at Weeks 16 and 26.[c]<br>• PGI-C at Weeks 4, 16 and 26.[c] |

***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.

a. End of Treatment defined as Week 26 if agreement to complete Part B. In the event that Part B is not conducted, then End of Treatment will be defined as Week 16.

b. In the event that Part B is not conducted and Week 16 is designated as End of Treatment, then Week 16 will not be included in this endpoint.

c. CFB for timepoints after Week 16 is contingent on approval to conduct Part B.

# 4. STUDY DESIGN

## 4.1. Overall Design

This 2-part, Phase 2b, multicenter, randomized, double-blind, placebo-controlled, 9-arm, parallel group, study will assess efficacy, safety, tolerability and PK of twice daily oral administration of PF-06882961 in adult participants with obesity.

Following the initial screening period to confirm eligibility (up to 4 weeks), screening will continue 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 will be randomized on Day 1 to double-blinded study intervention in 1 of 9 arms. The double-blinded treatment period will consist of 2 parts:

- 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;

- Part B (Weeks 17-26): participants in Part A will continue in Part B (according to randomization from Part A) contingent upon supportive nonclinical data through 26 weeks from the ongoing 9-month toxicology study in monkeys (Study 19GR370) and formal agreement with regulatory authorities and IRBs/ECs.

For participants who complete both parts of the study, the total duration of dosing with double-blinded study medication is 26 weeks, followed by an approximate 4-week follow-up. The total duration of participation in this study for these participants is approximately 32 weeks, including the 2-week single-blind run-in period, but excluding the initial screening period. For participants who reach the end of Part A but are not allowed to continue to

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

Part B because formal agreement with regulatory authorities and IRBs/ECs for Part B has not yet been obtained, the total dosing duration will be approximately 16 weeks, followed by an approximate 4-week follow-up. The total duration of participation in the study for these participants is approximately 22 weeks, including the 2-week single-blind run-in period, but excluding the initial screening period.

Dosing will occur with food twice daily, and target dose levels, achieved after completion of titration, for the 9 arms of the study are placebo and PF-06882961 doses of 40 mg BID, 80 mg BID, 120 mg BID, 160 mg BID, and 200 mg BID. Dose titration will be used to enhance tolerability of PF-06882961. For the 5 standard titration PF-06882961 groups, 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, and titration will occur at 1-week intervals from a starting dose of 10 mg BID. For the 5 groups with the standard, 1-week titration steps, up to 10 weeks of the dosing duration will be used for dose titration. For the 3 slow titration PF-06882961 groups, target dose levels for each of the arms are 120 mg BID, 160 mg BID, and 200 mg BID, and titration will occur at 2-week intervals from a starting dose of 10 mg BID. For these 3 slow titration groups, up to 20 weeks will be used for dose titration to reach the target dose. All dosing arms, including placebo, will be enrolled simultaneously. Additional details regarding dose titration are provided in Section 6.1 and in the IP Manual.

Approximately 420 participants (approximately 60 in each of the placebo and 5 standard titration PF-06882961 arms and approximately 20 participants in each of the 3 slow titration arms) will be randomized to ensure completion of approximately 315 evaluable participants (approximately 45 participants in each of the placebo and standard titration PF-06882961 arms and 15 in each of the slow titration arms). If formal agreement with regulatory authorities and IRBs/ECs for Part B is delayed such that initial participants are not allowed to continue to Part B, but subsequent formal agreement is obtained, the sample size may be increased up to a maximum of 460 randomized participants to enable the completion of approximately 315 evaluable participants in Part B.

Randomization will be stratified according to biological gender (female versus male), as both tolerability and efficacy may be different between men and women.[12] 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

During study conduct, after approximately every 25% of the total planned randomizations [for example: 105 (25%), 210 (50%), and 315 participants (75%), of planned approximately 420 participants], blinded safety reviews will be conducted by selected members of the sponsor's study team. Blinded safety reviews will be separated by at least 1 month from the previous review. An interim analysis of the unblinded safety data by the IRC will occur at least once while the study is ongoing, as described in Section 9.5.

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

### 4.2. Scientific Rationale for Study Design

This 2-part study is designed to assess the efficacy and safety of PF-06882961 in adult participants with obesity over 26 weeks of dosing. As described in Section 2.1, a 2-part study design is utilized, as the 16-week dosing duration of Part A is supported by the currently available nonclinical toxicology data Section 2.2.1.2, and dosing in Part B over Weeks 17 through 26 is contingent on availability of supportive nonclinical data through 26 weeks of dosing of PF-06882961 from the ongoing 9-month toxicology study in monkeys (Study 19GR370) and agreement with regulatory authorities and IRBs/ECs.

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. 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.[13-16] 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[17] and PHQ-9[18] will also be performed based on the potential risk related to the product labeling for the injectable GLP-1R agonist liraglutide for obesity.[16]

In this 2-part study, the total duration of dosing with randomized double-blinded study intervention will be 26 weeks for all participants who complete both Part A and Part B of the study. As described previously, if only Part A is completed, then the total duration of dosing will be 16 weeks. The study design was chosen to permit sufficient efficacy[19] and tolerability assessment of both standard titration arms (with 1-week titration steps) and slow titration arms (with 2-week steps). The titration schemes utilized in this study are informed by the doses administered and tolerability data from the C3421002 study. 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. Slow titration arms are primarily utilized to compare tolerability differences between the arms with 1-week titration steps and 2-week titration steps.

In accordance with guidelines for the management for obesity,[20] all participants will receive dietary and physical activity counseling.

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

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.

Body weight will be measured in duplicate at all study visits, as GLP-1R agonists have been shown to decrease food intake and body weight. Waist and hip circumference[21,22] will be measured in triplicate, according to the SoA as additional parameters of body weight. 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.[23]

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.[24,25]

An interim analysis will be performed at least once 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 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 ≥100 fold between the estimated partner exposure due to seminal transfer and the NOAEL for serious manifestations of developmental toxicity in nonclinical studies. The safety margin of ≥100-fold is based on applying a 10-fold safety factor for interspecies extrapolation and a 10-fold safety factor for susceptible populations.[26]

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 from the C3421002 study, 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

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

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 modeling on Phase 1 data from C3421002 indicate the proposed target dose levels in this study 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 46%, 69%, 84%, 94% and 100% of the projected body weight loss at the highest dose in this study (200 mg BID). 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. The 200 mg BID dose is projected to result in comparable weight loss to that observed in a Phase 2 clinical study with an injectable peptidic GLP-1R agonist.[27]

Based on population pharmacokinetic modeling, an approximately 1.7-fold higher exposure was identified in T2DM versus non-T2DM participants after adjusting for body weight differences. If this relationship is observed in this study, the exposures at the top dose in this study (200 mg BID) are expected to be similar to that observed at the top dose in the completed multiple ascending dose study C3421002 (120 mg BID). Based on population PK analysis, the predicted exposure at 200 mg BID in participants with obesity and without T2DM is expected to have a 41- and 23-fold margin under the unbound NOAEL for the 6-month rat toxicology study for $C_{max}$ and AUC, respectively (Section 2.2.1.2). Even if the exposures in this study are ~1.7-fold higher than these projections indicate (ie, consistent with exposures in T2DM), acceptable margins under the rat NOAEL are still expected.

As the duration in the multiple ascending dose study C3421002 was limited to 4 weeks, the time course of titration in this study was less than 4 weeks. In the current study, the doses will be titrated to the highest doses over a 10- to 20-week duration, which is expected to improve the tolerability of PF-06882961, and therefore doses of up to 200 mg BID are viewed as appropriate for assessment in this study.

### 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 (V15), 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.

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

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).

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

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 or 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 drug within 30 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of study intervention used in this study (whichever is longer).

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

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. ***Note:*** Participants who have been medically prescribed 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;

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

- 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.

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

- 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 V2 through V13, 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 V2 through V13, inclusive, 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 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, 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,[20] 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, 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.[20]

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

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, 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.

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

# 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)** | 10 mg, 40 mg, and 100 mg | Not applicable |
| **Target Dosage Level(s) (achieved upon titration)** | 40 mg BID, 80 mg BID, 120 mg BID, 160 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** | Study intervention will be provided in blister packs. Each blister pack will be labeled as required per country requirement.<br><br>Blinded labels will be utilized for placebo run-in, titration and stable dosing blister packs. | Study intervention will be provided in blister packs. Each blister pack will be labeled as required per country requirement.<br><br>Blinded labels will be utilized for placebo run-in, titration and stable dosing blister packs. |

### 6.1.1. Administration

Participants will be provided with blinded study intervention, consisting of identical tablets packaged in blister packs. The same dosing paradigm will be used for the single-blind placebo run-in and the randomized double-blind study intervention administered in Part A and Part B of the study. For V10-12 only, during which the study intervention for Part B is dispensed, dispensation via IRT will be permitted only after formal agreement with regulatory authorities and IRBs/ECs as described in Section 2.1 and Section 4.

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

Participants will 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 will be 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. Participants will be instructed to arrive at the site in the fasted state for each of these visits. For V3-V13, 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. 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 2. Details regarding dose titration are provided in the IP Manual.

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

## Table 2. Titration and Dosing Schemes

| | | Arm 1 | Arm 2 | Arm 3 | Arm 4 | Arm 5 | Arm 6 | Arm 7 | Arm 8 | Arm 9 |
|---|---|---|---|---|---|---|---|---|---|---|
| | 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) Standard Titration[b] | | | | | PF-06882961 (mg BID) Slow Titration[c] | | |
| Part A: Weeks 1-16 | 1 | 0 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | 2 | 0 | 20 | 20 | 20 | 20 | 20 | 10 | 10 | 10 |
| | 3 | 0 | 40 | 40 | 40 | 40 | 40 | 20 | 20 | 20 |
| | 4 | 0 | 40 | 60 | 60 | 60 | 60 | 20 | 20 | 20 |
| | 5 | 0 | 40 | 80 | 80 | 80 | 80 | 40 | 40 | 40 |
| | 6 | 0 | 40 | 80 | 100 | 100 | 100 | 40 | 40 | 40 |
| | 7 | 0 | 40 | 80 | 120 | 120 | 120 | 60 | 60 | 60 |
| | 8 | 0 | 40 | 80 | 120 | 140 | 140 | 60 | 60 | 60 |
| | 9 | 0 | 40 | 80 | 120 | 160 | 160 | 80 | 80 | 80 |
| | 10 | 0 | 40 | 80 | 120 | 160 | 180 | 80 | 80 | 80 |
| | 11 | 0 | 40 | 80 | 120 | 160 | 200 | 100 | 100 | 100 |
| | 12 | 0 | 40 | 80 | 120 | 160 | 200 | 100 | 100 | 100 |
| | 13 | 0 | 40 | 80 | 120 | 160 | 200 | 120 | 120 | 120 |
| | 14 | 0 | 40 | 80 | 120 | 160 | 200 | 120 | 120 | 120 |
| | 15 | 0 | 40 | 80 | 120 | 160 | 200 | 120 | 140 | 140 |
| | 16 | 0 | 40 | 80 | 120 | 160 | 200 | 120 | 140 | 140 |
| Part B: Weeks 17-26 | 17 | 0 | 40 | 80 | 120 | 160 | 200 | 120 | 160 | 160 |
| | 18 | 0 | 40 | 80 | 120 | 160 | 200 | 120 | 160 | 160 |
| | 19 | 0 | 40 | 80 | 120 | 160 | 200 | 120 | 160 | 180 |
| | 20 | 0 | 40 | 80 | 120 | 160 | 200 | 120 | 160 | 180 |
| | 21 | 0 | 40 | 80 | 120 | 160 | 200 | 120 | 160 | 200 |
| | 22 | 0 | 40 | 80 | 120 | 160 | 200 | 120 | 160 | 200 |
| | 23 | 0 | 40 | 80 | 120 | 160 | 200 | 120 | 160 | 200 |
| | 24 | 0 | 40 | 80 | 120 | 160 | 200 | 120 | 160 | 200 |
| | 25 | 0 | 40 | 80 | 120 | 160 | 200 | 120 | 160 | 200 |
| | 26 | 0 | 40 | 80 | 120 | 160 | 200 | 120 | 160 | 200 |

a. Target dose achieved after titration from starting dose.

b. Standard titration refers to titration schemes with 1-week of dosing at each titration step.

c. Slow titration refers to titration schemes with 2-weeks of dosing at each titration step.

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

## 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.

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

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 provided, in quantities appropriate according to the SoA. The participant should be instructed to maintain the product in the blister cards provided throughout the course of dosing and bring the blister cards 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.

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 standard 1-week titration PF-06882961 arms: 3 slow titration 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.

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

**Table 3. Target Doses for Randomized Regimens**

| Regimen Description (dosed twice-daily) | Number of PF-06882961 Tablets | | | Number of Matching Placebo Tablets | Total Number of Tablets |
|---|---|---|---|---|---|
| | 10 mg | 40 mg | 100 mg | 10/40/100 mg | |
| Placebo | - | - | - | 4 | 4 |
| PF-06882961 – 40 mg (standard titration) | - | 1 | - | 3 | 4 |
| PF-06882961 – 80 mg (standard titration) | - | 2 | - | 2 | 4 |
| PF-06882961 – 120 mg (standard titration) | 2 | - | 1 | 1 | 4 |
| PF-06882961 – 160 mg (standard titration) | 2 | 1 | 1 | - | 4 |
| PF-06882961 – 200 mg (standard titration) | - | - | 2 | 2 | 4 |
| PF-06882961 – 120 mg (slow titration) | 2 | - | 1 | 1 | 4 |
| PF-06882961 – 160 mg (slow titration) | 2 | 1 | 1 | - | 4 |
| PF-06882961 – 200 mg (slow titration) | - | - | 2 | 2 | 4 |

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.

Study intervention will be dispensed at the study visits summarized in the SoA.

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.

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

### 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. If a participant is continuing doses from their current blister cards, sites should assess the blister cards for compliance, however the cards should remain in the possession of the participant.

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 Week 26, 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.

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

See Appendix 8 for details regarding prohibited concomitant medications, as well as medications with timeframes for restriction prior to V1. 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. However, each dosing regimen will be provided in blister packs, and dose adjustment, either during dose titration or steady state dosing, will not be permitted per protocol.

### 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.

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

# 7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

## 7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention (definitive discontinuation). Reasons for definitive 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, with the exception of dosing activities and assessment of PK. See the SoA 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;

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

- 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 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.

Participants who reach the end of Part A prior to formal approval to initiate Part B of the study will not continue to Part B but instead will end treatment at Week 16 (ie, V10 will be considered the End of Treatment visit) and continue directly to the follow-up phase, completing the Follow-up visits relative to Week 16 (ie, V14 will occur at Weeks 17-18 and V15 at Weeks 20-21).

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.

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

### 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. 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, 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

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

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 in this study who complete only Part A (including follow-up) is approximately 210 mL; for participants who complete Part A and Part B (including follow-up), the blood sampling volume 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. 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.

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

### 8.1.2. Secondary Efficacy Parameters: Waist and Hip Circumference

Waist and hip circumference will be measured at the times specified in the SoA 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.[21,22]

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,[21] 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 and Table 4.

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

**Table 4. 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] | Daily, starting at V2 (Pbo run-in) to V13 (Week 26) | 5 | 2 minutes | At home, (handheld device) | N/A |
| PGI-S | At each site visit, starting at V2 (Pbo run-in) to V13 (Week 26) | 4 | 1 minute | At the clinic (electronic tablet) | |
| PGI-C | V5 (Week 4)<br>V10 (Week 16)<br>V13 (Week 26) | 4 | 1 minute | | |
| PROMIS® Fatigue Custom 9-item | V2 (Pbo run-in)<br>V3 (Day 1)<br>V10 (Week 16)<br>V13 (Week 26) | 9 | 11 minutes | | |
| PROMIS® Physical Function Custom 13-item | V2 (Pbo run-in)<br>V3 (Day 1)<br>V10 (Week 16)<br>V13 (Week 26) | 13 | | | |
| IWQOL-Lite-CT© | V2 (Pbo run-in)<br>V3 (Day 1)<br>V10 (Week 16)<br>V13 (Week 26) | 20 | | | |
| SF-36v2® | V2 (Pbo run-in)<br>V3 (Day 1)<br>V10 (Week 16)<br>V13 (Week 26) | 36 | 9 minutes | At the clinic (electronic tablet) | At the clinic (electronic tablet) |

Note: Assessment of timepoints after Week 16 is contingent on approval to conduct Part B.

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. 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.

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

#### 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.

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

#### 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. 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.

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, 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 follow-up V14 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 per the following specifications:

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

- 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 visit. At V3, V7, V10 and V13, these 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 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. A cardiologist should be

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

consulted if QTcF intervals do not return to less than the criterion listed above after 8 hours of monitoring (or sooner, at the discretion of the investigator).

In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads be placed in the same positions each time in order to achieve precise ECG recordings. If a machine-read 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 timing and frequency. All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

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

All laboratory tests with values considered clinically significantly abnormal during participation in the study 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.

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

#### 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.

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

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.[17] 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. 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.[18] The PHQ-9 will be completed by participants and reviewed by site staff at the pre-defined time points outlined in the SoA. 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).

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

#### 8.2.6.3. Referral to a Mental Health Professional

A participant should be referred to a MHP for 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. 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).

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

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 and Pfizer concurs with that assessment.

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

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

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

Investigators are not obligated to actively seek AEs or SAEs after 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.

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

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.

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

### 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.

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

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.

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

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.

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

### 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 12 tablets within a 24-hour time period ±2 hours 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.

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

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 $K_2$EDTA, at times defined in the SoA and according to the chronology in Appendix 9, with collections occurring prior to dosing with study intervention on the given scheduled visit, and 1 time within the window of approximately 2 to 6 hours post-dose at V3, V7, V10 and V13. 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 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.

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

## 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. 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:

- 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.

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

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.

### 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. End of Treatment is defined as Week 26 if formal agreement to conduct Part B is obtained, otherwise End of Treatment will be defined as Week 16. 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. As noted previously, percent CFB for timepoints after Week 16 is contingent on formal agreement to conduct Part B. All randomized participants in Part A of the study who take at least 1 dose of study intervention will be included. Participants who complete Part A, but are unable to initiate Part B due to delays in gaining formal agreement with regulatory authorities and IRBs/ECs (as described in Section 4.1) will still be included in this Estimand Set. An additional exploratory estimand removing such participants may be explored if required, where further details will be provided in the SAP.

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

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.

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

### 9.2. Sample Size Determination

The sample size is 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 participants in each of the placebo and 5 standard titration PF-06882961 arms and 20 participants in each of the 3 slow titration arms) will be randomized to ensure completion of approximately 315 evaluable participants (assuming all participants are able to continue to Part B and a conservative discontinuation rate of 25%), with approximately 45 participants in each of the placebo and standard titration PF-06882961 arms and 15 participants in each of the slow titration arms. Participants who withdraw from the study will not be replaced. Evaluable participants are defined as in Section 9.3.

If formal agreement with regulatory authorities and IRBs/ECs for Part B (as described in Section 4.1) is delayed such that initial participants are not allowed to continue to Part B, but subsequent formal agreement is obtained, the sample size may be increased up to a maximum of 460 randomized participants to enable the completion of approximately 315 evaluable participants in Part B.

The above sample size also provides acceptable operating characteristics for decision making based on the primary endpoint as justified below.

The primary analysis for this study is based on the primary endpoint, the percent CFB at End of Treatment in body weight. Assuming a conservative 25% drop-out rate (where all participants are able to continue into Part B of the study) there would be expected to be approximately 315 completed participants, with approximately 45 completed participants per arm for each of the placebo and standard titration PF-06882961 treatment arms as above. If End of Treatment is defined as Week 26, this yields 80% power to detect a placebo-adjusted reduction in body weight of 3.5% (comparing 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 0.068 based on historical internal studies. Similarly, if End of Treatment is defined as Week 16, there would be 80% power to detect a reduction of 2.8% assuming a conservative SD on the $\log_e$-scale of 0.053 based on historical internal studies.

### 9.3. Analysis Sets

For purposes of analysis, the following analysis sets are defined:

| 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. |

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

| | |
|---|---|
| Randomly assigned to study intervention | All participants randomly assigned to study intervention in Part A of the study regardless of whether or not study intervention was administered. |
| Evaluable | All participants randomly assigned to study intervention in Part A of the study 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 in Part A of the study and who take at least 1 dose of study intervention. Participants will be analyzed according to the study intervention they actually received. Participants who complete Part A, but are unable to initiate Part B will still be included in this Analysis Set. |

| **Defined Analysis Set** | **Description** |
|---|---|
| Estimand Set 1 (related to estimands 1, 2, 3, 4, 5 and 6) | All participants randomly assigned to study intervention in Part A and who take at least 1 dose of study intervention. For participants who discontinue study intervention, all subsequent values will be censored. Participants who complete Part A, but are unable to initiate Part B will still be included in this Estimand Set. |
| 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. Participants who complete Part A, but are unable to initiate Part B will still be included in this Estimand Set. |
| 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. Participants who complete Part A, but are unable to initiate Part B will still be included in this Estimand Set. |

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

## 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

All treatment arms of PF-06882961 and placebo will be reported separately.

As noted above, End of Treatment is defined as Week 26 if formal agreement to conduct Part B is obtained, otherwise End of Treatment will be defined as Week 16.

#### 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. 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 Week 26 (or Week 16, as applicable) will be used to estimate the treatment effect related to the primary Estimand 1. Baseline body weight will be included on the $\log_e$-scale. The MMRM model will be fitted to the CFB of $\log_e$-transformed values to Weeks 2, 4, 6, 8, 10, 12, 16, 18, 22 and 26 from the Estimand Set 1. Inclusion of timepoints after Week 16 is contingent on formal agreement to conduct Part B. 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.

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

### 9.4.3. Secondary Endpoint(s)

Note, inclusion of timepoints after Week 16 in the applicable models described in the table below are contingent on formal agreement to conduct Part B.

| 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.<br>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 | Results related to this endpoint will be obtained from the Primary Analysis model.<br>No adjustments will be made for multiplicity.<br>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 Weeks 2, 4, 6, 8, 10, 12, 16, 18, 22 and 26 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.<br>This analysis will be applied to Estimand Set 1 to estimate the treatment effect related to Estimand 3. |
| Secondary: Absolute CFB in waist-to-hip ratio at End of Treatment | Absolute CFB in waist-to-hip ratio at Weeks 2, 4, 6, 8, 10, 12, 16, 18, 22 and 26 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.<br>This analysis will be applied to Estimand Set 1 to estimate the treatment effect related to Estimand 4. |

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

| Endpoint | Statistical Analysis Methods |
|---|---|
| Secondary: CFB in HbA1c at Weeks 16 and 26 | CFB in HbA1c at Weeks 16 and 26 will be analyzed using an MMRM model (as per Section 9.4.1.1). Inclusion of Week 26 is contingent on formal agreement to conduct Part B and if not obtained, an ANCOVA model will instead be applied to Week 16 only and treatment, baseline and strata will be included in the model. Baseline HbA1c will be included as a covariate in the selected model. No adjustments will be made for multiplicity.<br>This analysis will be applied to Estimand Set 1 to estimate the treatment effect related to Estimand 5. |
| Secondary: CFB in FPG at Weeks 2, 4, 6, 8, 10, 12, 16, 18, 22 and 26 | CFB in FPG at 2, 4, 6, 8, 10, 12, 16, 18, 22 and 26 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.<br>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.

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

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 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. Data draws are expected at approximately 50%, and 100% of total study data. These data are expected to include PK, body weight, vitals and potentially other PD markers.

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

### 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.

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

# 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.

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

### 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.

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

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.

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

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.

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

### 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.

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

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;

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

- 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.

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

### 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.

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

## 10.2. Appendix 2: Clinical Laboratory Tests

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

**Table 5. Protocol Required Laboratory Assessments**

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

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

Investigators must document their review of each laboratory safety report.

Following the screening period, 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.

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

## 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.

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

- 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

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

**An SAE is defined as any untoward medical occurrence that, at any dose:**

**a. Results in death**

**b. Is life-threatening**

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

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

**c. Requires inpatient hospitalization or prolongation of existing hospitalization**

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

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

**d. Results in persistent disability/incapacity**

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

**e. Is a congenital anomaly/birth defect**

**f. Other situations:**

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.
- Suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

considered for reporting as product defects, if appropriate.

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

**AE and SAE Recording/Reporting**

The table below summarizes the requirements for recording 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, and occupational exposure | All AEs/SAEs associated with exposure during pregnancy or breastfeeding<br><br>Occupational exposure is not recorded. | All (and EDP supplemental form for EDP)<br>Note: Include all SAEs associated with exposure during pregnancy or breastfeeding. Include all AEs/SAEs associated with occupational exposure. |

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the CT SAE Report

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

Form/AE/SAE CRF page.

- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.

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

**Assessment of Intensity**

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

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.

- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.

- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

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

**Assessment of Causality**

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.

- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

- The investigator will use clinical judgment to determine the relationship.

- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

- 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.

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

### 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.<br><br>• 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.<br><br>• The site will enter the SAE data into the electronic system as soon as the data become available.<br><br>• 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.<br><br>• 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.<br><br>• 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.<br><br>• 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. |

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

## 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 ≥100-fold between the estimated maternal exposure due to seminal transfer and the NOAEL for serious manifestations of developmental toxicity in nonclinical studies.

### 10.4.2. Female Participant Reproductive Inclusion Criteria

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

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

  OR

- Is a WOCBP and using 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.

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

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.

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

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;

    - Injectable.

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).

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

## 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.

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

## 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).

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

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.

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

## 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.<br>• New PR interval prolongation >280 msec.<br>• New prolongation of QTcF to >480 msec (absolute) or by ≥60 msec from baseline.<br>• New-onset atrial flutter or fibrillation, with controlled ventricular response rate: ie, rate <120 bpm.<br>• New-onset type I second-degree (Wenckebach) AV block of >30 seconds' duration.<br>• 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.<br>• New ST-T changes suggestive of myocardial ischemia.<br>• New-onset LBBB (QRS >120 msec).<br>• New-onset right bundle branch block (QRS >120 msec).<br>• Symptomatic bradycardia.<br>• Asystole:<br>  • 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;<br>  • In awake, symptom-free patients with atrial fibrillation and bradycardia with 1 or more pauses of at least 5 seconds or longer;<br>  • Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120 bpm.<br>• Sustained supraventricular tachycardia (rate >120 bpm) ("sustained" = short duration with relevant symptoms or lasting >1 minute).<br>• Ventricular rhythms >30 seconds' duration, including idioventricular rhythm (HR <40 bpm), accelerated idioventricular rhythm (HR 40 bpm to <100 bpm), and |

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

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.

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

## 10.8. Appendix 8: Prohibited Prior/Concomitant Medications

The following medications are prohibited until the first follow-up visit (ie, V14), unless stated otherwise. If a participant receives a prohibited medication, the investigator should contact the sponsor Clinician or sponsor Medical Monitor to determine if the participant may remain in the study.

| **Drug Classes and/or Drugs** | **Timeframe of Restriction Prior to V1** |
|---|---|
| Thiazolidinediones such as pioglitazone and rosiglitazone. | 90 days |
| Subcutaneously administered agents for glycemic control (eg, insulin, exenatide, liraglutide, dulaglutide, semaglutide, pramlintide).<br>***Note***: Short-term (ie, ≤7 days) of insulin administration is permitted if participant is hospitalized. | 90 days |
| Pharmacological agents with approved indication for weight loss such as liraglutide, orlistat and sibutramine. | 90 days |
| Oral anti-diabetic medications, including:<br>Metformin<br>Sulfonylureas such as acetohexamide, chlorpropamide, tolazamide, tolbutamide, glimepiride, glipizide, glyburide.<br>Meglitinide analogues such as repaglinide, nateglinide.<br>DPP-4 inhibitors such as sitagliptin, saxagliptin, linagliptin, vildagliptin.<br>α-glucosidase inhibitors such as acarbose, miglitol.<br>SGLT2 inhibitors such as canagliflozin, empagliflozin, dapagliflozin, ertugliflozin.<br>Anti-hyperglycemic medications, including bromocriptine and colesevelam. | 60 days |
| Systemic glucocorticoids such as prednisone, dexamethasone, triamcinolone, budesonide, betamethasone. ***Note***: As an exception, steroid-containing inhalers, nasal sprays and topical formulations are permitted.<br>***Note***: Intercurrent treatment with systemic corticosteroids during participation in the study may be permitted if treatment does/will not exceed 7 days. | 60 days |
| Immunosuppressants such as cyclosporine and tacrolimus. | 60 days |
| Appetite or weight modifying medications, including nonprescription or herbals and medical grade marijuana. | 60 days |
| Anti-psychotic medications such as olanzapine, risperidone. | 60 days |
| Coumarin type anticoagulants or other anticoagulants (eg, dabigatran, apixaban, edoxaban, fondaparinux, rivaroxaban). | 60 days |
| Anticonvulsants if prescribed for seizure disorder. | 60 days |
| Antiarrhythmic medications whose primary mechanism of action is sodium or potassium channel blockade (eg, procainamide, phenytoin, quinidine, propafenone; as well as amiodarone, dofetilide, sotalol). | 60 days |

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

| Drug Classes and/or Drugs | Timeframe of Restriction Prior to V1 |
|---|---|
| ***Note***: β-adrenergic receptor blocking agents (eg, atenolol, metoprolol) and calcium channel blockers (eg, diltiazem, amlodipine, nifedipine) are permitted. | |
| Sympathomimetic agents.<br><br>***Note***: Inhaled β-adrenergic receptor agonists (eg albuterol) are permitted. | 60 days |
| Sensitive BCRP Substrates:<br><br>Rosuvastatin. ***Note***: Other statins are permitted (except at top approved dose as noted below).<br><br>Sulfasalazine | Prohibited post randomization |
| Due to potential weak inhibition of OATP, statins (other than rosuvastatin which is excluded at any dose) at the top approved dose in the country of the clinical site. Statin use at lower doses is permitted. | Prohibited post randomization |
| Use of CYP3A4/5 substrates with narrow therapeutic index – eg, alfentanil, astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, and terfenadine. | Prohibited post randomization |
| Use of chronic agents which are potent inducers of CYP3A (eg, rifampin, carbamazepine, phenobarbital, phenytoin). | Prohibited post randomization |
| Use of chronic agents which are clinically significant OATP inhibitors (eg, cyclosporine, gemfibrozil, rifampin). | Prohibited post randomization |
| Use of potent CYP3A4 inhibitors (eg, clarithromycin, conivaptan, ketoconazole, mibefradil, nefazodone, telithromycin, troleandomycin). | Prohibited post randomization |
| Paclitaxel, torsemide, amodiaquine. | Prohibited post randomization |

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

## 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.

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

## 10.10. Appendix 10: Abbreviations

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

| | **Term** |
|---|---|
| %CV | percent coefficient of variation |
| Abs | absolute |
| 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 |
| BCRP | breast cancer resistance protein |
| 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 |
| CYP | cytochrome P450 |
| DCT | data collection tool |
| DDI | drug-drug interaction |
| DILI | drug-induced liver injury |
| DMC | data monitoring committee |
| DNA | deoxyribonucleic acid |

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

| | **Term** |
|---|---|
| DPP 4 | dipeptidyl peptidase 4 |
| DU | dispensable unit |
| EC | ethics committee |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| EDP | exposure during pregnancy |
| eGFR | estimated glomerular filtration rate |
| EMA | European Medicines Agency |
| ePRO | electronic patient-reported outcome |
| ET | early termination |
| EU | European Union |
| EudraCT | European Clinical Trials Database |
| 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 |
| IPAL | Investigational Product Accountability Log |
| IR | immediate release |
| IRB | institutional review board |
| IRC | internal review committee |

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

| | Term |
|---|---|
| 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 |
| $K_2$EDTA | 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 |
| OATP | organic anion transporting polypeptides |
| 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 |
| $R_{ac}$ | accumulation ratio based on AUC |
| RBC | red blood cell |
| REE | resting energy expenditure |
| RNA | ribonucleic acid |

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

| | **Term** |
|---|---|
| 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 |
| $t_{½}$ | 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 |
| UGT | uridine 5'-diphospho glucuronosyltransferase |
| ULN | upper limit of normal |
| US | United States |
| V | visit |
| WBC | white blood cell |
| Wk | week |
| WOCBP | woman of childbearing potential |

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

## 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. Lorenz M, Lawson F, Owens D, et al. Differential effects of glucagon-like peptide-1 receptor agonists on heart rate. Cardiovasc Diabetol 2017;16(1):6.

12. 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.

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

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

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

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

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

17. 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.

18. 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.

19. 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.

20. 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.

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

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

23. 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.

24. 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.

25. 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.

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)

26. 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.

27. 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.

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.

090177e194f25577\Approved\Approved On: 17-Sep-2020 16:08 (GMT)