A 16-WEEK, PHASE 2B, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL GROUP STUDY TO EVALUATE THE EFFICACY AND SAFETY OF TWICE DAILY PF-06882961 ADMINISTRATION IN ADULTS WITH TYPE 2 DIABETES MELLITUS INADEQUATELY CONTROLLED ON METFORMIN OR DIET AND EXERCISE

Investigational Product Number:	PF-06882961
Investigational Product Name:	Not Applicable (N/A)
United States (US) Investigational New Drug (IND) Number:	[redacted]
European Clinical Trials Database (EudraCT) Number:	[redacted]
Protocol Number:	C3421005
Phase:	2b

Short Title: A 16-Week Study to Evaluate the Efficacy and Safety of PF-06882961 in Adults with Type 2 Diabetes Mellitus

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Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary of Changes and Rationale**
Amendment #1	19 May 2020	Section 2.2.1.3, Nonclinical Safety has been updated with the most recent toxicology information. Rationale: Updates align with recently available toxicology information. Section 2.2.2, Clinical Overview, Section 2.2.2.1, Clinical Safety and Section 2.2.2.2 Clinical Pharmacokinetics sections have been updated to reflect the completed C3421002 study. Rationale: Updates align with the most recent clinical safety and clinical pharmacokinetics information. Section 1.3, Schedule of Activities has been updated to reduce glucagon sampling to baseline, Weeks 8 and 16 and Early Termination visit, to add a review of eligibility criteria to the Day 1 visit, and to add collection of banked biospecimens Prep B1 and B2 at the early termination visit. Rationale: Glucagon sampling has been reduced to reduce burden on sites as the glucagon tubes require special handling. Review of eligibility criteria has been added to the Day 1 visit to ensure eligibility is met prior to randomization. Collection of banked biospecimens at the early termination visit to allow for additional research in cases of early termination if applicable. Section 1.3, Schedule of Activities, revision of footnote ‘i’ to include V2. Rationale: The revision of footnote ‘i’ has

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		been made to ensure that from V2 through V9, urine pregnancy tests are reviewed and confirmed negative prior to female participant continuation in the study. Additional revisions to Section 1.3, Schedule of Activities have been made to incorporate Protocol Administrative Clarification Letter (dated 15 July 2019) including: • Revision of footnote 'c'to clarify pre- and post- dose collection of triplicate vital signs and 12 lead ECGs. • Addition of footnote 'd' to clarify that duplicate weight measurements should be separated by at least 1-2 minutes. This revision is also reflected in Section 8.2.2, Body Weight. Section 2.2.1.2, Nonclinical Pharmacokinetics and Metabolism and Appendix 8, Prohibited Prior/Concomitant Medications have been revised to include sulfasalazine. Appendix 8 also revise to extend the restriction for the use of agents with approved indication for weight loss. Rationale: Sulfasalazine is a BCRP substrate and PF-06882961 has the potential to inhibit intestinal BCRP. Extension of the restriction for use of agents with approved indication for weight loss to align with restriction of liraglutide for glycemic control. Section 3, Objectives, Estimands, and Endpoints tertiary endpoint for glucagon has been revised to change from baseline in fasting glucagon at Weeks 8 and 16. Rationale: The tertiary endpoint for glucagon has been revised to align with

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		updated glucagon sampling times. Section 4.2, Scientific Rationale for Study Design has been revised to include updates to the description of titration schemes and the rationale for contraception requirements for female participants. Rationale: Titration scheme description aligns with updates to Section 6 and the rationale for contraception requirements for female participants has been included for completeness. Section 4.3, Justification for Dose has been revised to reflect that study C3421002 has completed and data are no longer preliminary. Rationale: C3421002 was completed after initial protocol finalization. Section 4.4, Assessment of Safety and Tolerability While Study is Ongoing has been updated to indicate that an interim analysis will occur at least once during study conduct and to also include the minimum timeframe between blinded safety reviews. The triggers for pausing or stopping active dose(s) were moved to Section 6.6.1, Considerations for Pausing or Stopping Active Dose(s) Based on Observed Safety. Rationale: The minimum time frame of monthly between safety reviews has been added to ensure that there is ample time to prepare all data reports and ensure a timely review of safety data. The interim analysis of unblinded safety data permits possible updates to study conduct if needed. Section 5.2, Exclusion Criteria, criterion #15 has been revised to lower the systolic and diastolic blood pressure eligibility criteria.

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		Rationale: The cut off for blood pressure has been lowered to a more conservative level to optimize blood pressure control prior to study entry. Criterion #19 has also been revised to incorporate Protocol Administrative Clarification Letter (dated 15 July 2019) to lower the placebo run in compliance from at least 90% to at least 89% compliance for inclusion into the study. This revision is also reflected in Section 6.4, Study Intervention Compliance. Section 5.3.1, Dietary Restrictions has been revised to clarify that fasting is required prior to obtaining body weight (also a revision to Section 8.2.2, Body Weight) but is not required prior to post dose PK sample collection. Additionally, the requirement to withhold blood pressure and lipid modifying medications prior to site visits 2 through 9 has been removed. Rationale: Aligns with update to Section 8.2.2 and Appendix 9, as body weight is a secondary endpoint and must be obtained under standard conditions. Clarification that fasting is not required prior to post dose PK sample collection has been included given PF-06882961 is dosed with food. Blood pressure and lipid modifying medications may be taken prior to site visits 2 through 9 to ensure blood pressure and lipid management is maintained in participants requiring these medications. Section 6, Study Intervention and Section 6.1, Study Intervention Administered has been revised to clarify that blinded labels are used for the placebo run-in. Rationale: Updates to align with IP labeling approach and IP manual.

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		Section 6.1, Study Intervention Administered has been revised to clarify dosing administration and recording of doses administered in the dosing diary and CRF. Rationale: These revisions have been made to ensure that all doses are recorded in the dosing diary and for doses administered at the site, this is under supervision of site staff with date and time recorded in CRF. Section 6.1, Study Intervention Administered has been revised to include the final (not sample) titration and dosing scheme to be used in the study. Rationale: This revision has been made to ensure that the final dosing and titration scheme (as opposed to a sample only) is included in the protocol. Section 6.5.3, Antihypertensive Medications has been revised to remove language regarding handling of participants who enter the study with a blood pressure of ≥160/100. Rationale: This language is no longer applicable given the revision to exclusion criterion #15. Section 7.1, Discontinuation of Study Intervention has been revised to clarify that dosing activities and collection of PK samples are not required in cases where IP is permanently discontinued and the participant remains in the study. Rationale: This revision is made to ensure that additional dosing and collection of PK samples does not occur in participants who permanently discontinue IP. Section 8, Study Assessments and Procedures has been revised to incorporate Protocol Administrative Clarification Letter (dated

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		15 July 2019) and collection of additional banked biospecimens to update the total volume of blood collected. Section 8.2.3.1, Blood Pressure and Pulse Rate has been revised to allow for manual assessment of PR only if an automated device is not available and also to clarify that the same arm for BP and PR should be used throughout the study, *when possible.* Rationale: These revisions are made for clarification. Section 8.2.5.2, Management of Hypoglycemia, Section 8.2.5.2.1, Definition and Severity of Categorization of Hypoglycemic Adverse Event, and Section 8.2.5.3, Management of Hyperglycemia have been revised to incorporate Protocol Administrative Clarification Letter (dated 15 July 2019) to clarify instances of when plasma glucose is collected vs a whole blood fingerstick glucose measurement. Section 8.3.1, Time Period and Frequency for Collection AE and SAE Information has been revised to remove the requirement for medical occurrences that begin before the start of study intervention but after obtaining informed consent to be recorded on the Medical History/Current Medical Conditions section of the CRF. Rationale: This revision aligns with the requirement to collect and record all AEs and SAEs from the time informed consent is provided. Section 8.5, Pharmacokinetics has been revised to incorporate Protocol Administrative Clarification Letter (dated 15 July 2019) to clarify that the date/time of pre- and post-dose PK blood collections should be noted in source documents and

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		captured in the CRF. Section 8.8.4, Banked Biospecimens for Biomarkers, has been revised to incorporate Protocol Administrative Clarification Letter (dated 15 July 2019) to clarify the correct amount of blood collected for Prep B2 and Prep B1. Section 9.4.2.1, Electrocardiogram Analyses, has been revised to remove summarization of the number of participants with uncorrected QT values >500 msec. Rationale: This revision has been made because safety analyses and summaries will be based on QTcF intervals, not QT intervals. Section 9.4.3, Other Analyses has been revised to clarify that results from any future analyses from pharmacogenomic or biomarker data from banked biospecimens are not planned to be included in the CSR. Rationale: These results are not routinely included in CSRs. Section 9.5, Interim Analyses, wording has been updated to clarify that an IA will be performed at least once during study conduct and further details regarding the IA will be specified in the IRC Charter. Rationale: Updated to be consistent with Section 4.4 and the IRC Charter will provide details of interim analyses conducted during the study. Protocol Appendix 2, Clinical Laboratory Tests has been revised to clarify that *after randomization,* the sponsor study team and site will be blinded to HbA1c, fasting plasma glucose, glucagon, and fasting plasma insulin measured by the central laboratory, unless the fasting plasma glucose meets the criterion for

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		hypo-or hyper-glycemia. Rationale: This revision is made to clarify that the blinding of these specific analytes does not occur until after the screening period so that eligibility can be confirmed. Protocol Appendix 3, Sections 10.3.2, Definition of SAE and 10.3.3, Recording/Reporting and Follow-up of AEs and/or SAEs has been revised to align with Pfizer requirements. Protocol Appendix 4, Section 10.4.2, Female Participant Reproductive Inclusion Criteria and Section 10.4.4, Contraception Methods have been revised to clarify permitted female participant inclusion criteria and contraception requirements in cases where contraception is highly user dependent. Additionally, the requirement of females to not donate eggs has been removed. Rationale: This revision is made to align with requirements when using contraception that is highly user dependent. PF-06882961 does not have risk of genotoxicity; as such the requirement of females to not donate eggs has been removed. Protocol Appendix 9, Proposed Chronology of Procedures has been revised to clarify that body weight should be obtained prior to dosing and food consumption. Rationale: Body weight is a secondary endpoint and must be obtained under standardized conditions.
Original protocol	03 April 2019	N/A

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Short Title: A 16-Week Study to Evaluate the Efficacy and Safety of PF-06882961 in Adults with Type 2 Diabetes Mellitus

Rationale

This multicenter, randomized, double-blind, placebo controlled, parallel group study is being conducted to provide data on efficacy, safety, tolerability and pharmacokinetics (PK) of multiple dose levels of PF-06882961 in adults with type 2 diabetes mellitus (T2DM) inadequately controlled on metformin and/or diet and exercise. In addition, the study is intended to enable selection of efficacious doses for future clinical development of PF-06882961.

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Objectives, Estimands, and Endpoints

Objectives	Endpoints	Estimands
Primary:	**Primary:**	**Primary:**
To compare the effect of multiple dose levels of PF-06882961 versus placebo on glycated hemoglobin (HbA1c) in participants with T2DM on stable doses of metformin and/or diet and exercise.	Change from baseline in HbA1c at Week 16.	Estimand 1A: This estimand is intended to provide a population level estimate of the mean treatment effect (PF-06882961 versus placebo) on a continuous endpoint in participants on stable doses of metformin and/or diet and exercise without the benefit of glycemic rescue medication while on treatment.
Secondary:	**Secondary:**	**Secondary:**
To compare the effect of multiple dose levels of PF-06882961 versus placebo on glycemic control in participants with T2DM on stable doses of metformin and/or diet and exercise.	Response as defined by an HbA1c <7% at Week 16.	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 responder endpoint in participants on stable doses of metformin and/or diet and exercise without the benefit of glycemic rescue medication.
	Change from baseline in HbA1c at Weeks 2, 4, 6, 8 and 12.	Estimand 1A as above.
	Change from baseline in fasting plasma glucose at Weeks, 2, 4, 6, 8, 12 and 16.	Estimand 3: This estimand will be the same as 1A.
To compare the effect of multiple dose levels of PF-06882961 versus placebo on body weight in participants with T2DM on stable doses of metformin and/or diet and exercise.	Change from baseline in body weight at Weeks 2, 4, 6, 8, 12 and 16.	Estimand 4: This estimand will be the same as 1A.
To characterize the safety and tolerability of multiple dose levels of PF-06882961 administered to participants with T2DM on stable doses of metformin and/or diet and exercise.	Incidence of treatment emergent adverse events [adverse events (AEs) and serious adverse events (SAEs)], clinical laboratory abnormalities, vital signs (blood pressure and pulse rate) and electrocardiogram (ECG) parameters (heart rate, QT, QTcF, PR and QRS intervals).	There are no defined estimands for these endpoints and they will be analyzed using Pfizer data standards as applicable.

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Tertiary/Exploratory:	**Tertiary/Exploratory:**	**Tertiary/Exploratory:**
To compare the effect of multiple dose levels of PF-06882961 versus placebo on HbA1c in participants with T2DM on stable doses of metformin and/or diet and exercise.	Change from baseline in HbA1c at Weeks 2, 4, 6, 8, 12 and 16.	Estimand 1B: This estimand is intended to provide a population level estimate of the mean treatment effect (PF-06882961 versus placebo) on a continuous endpoint in participants on stable doses of metformin and/or diet and exercise regardless of the initiation of glycemic rescue medication or discontinuation of IP.
To compare the effect of multiple dose levels of PF-06882961 versus placebo on HbA1c in participants with T2DM on stable doses of metformin.	Change from baseline in HbA1c at Weeks 2, 4, 6, 8, 12 and 16.	Estimand 1C: This estimand is intended to provide a population level estimate of the mean treatment effect (PF-06882961 versus placebo) on a continuous endpoint in participants on stable doses of metformin without the benefit of glycemic rescue medication whilst on treatment.
To compare the effect of multiple dose levels of PF-06882961 versus placebo on metabolic parameters in participants with T2DM on stable doses of metformin and/or diet and exercise.	Change from baseline in fasting insulin, and homeostatic model assessment of insulin resistance (HOMA-IR) at Weeks 4, 8, 12 and 16. Change from baseline in fasting glucagon at Weeks 8 and 16.	There are no defined estimands for these endpoints and they will be analyzed using Pfizer data standards as applicable.
To compare the effect of multiple dose levels of PF-06882961 versus placebo on body weight in participants with T2DM on stable doses of metformin and/or diet and exercise.	Response as defined by a ≥5% body weight loss at Week 16.	There are no defined estimands for these endpoints and they will be analyzed using Pfizer data standards as applicable.
To characterize the PK of PF-06882961 to participants with T2DM on stable doses of metformin and/or diet and exercise.	Plasma concentrations of PF-06882961 at time points specified in the schedule of activities (SoA).	There is no defined estimand for these endpoints and they will be analyzed using Pfizer data standards as applicable.
To characterize the gastrointestinal tolerability during different doses and titration schemes of PF-06882961 administered to participants with T2DM on stable doses of metformin and/or diet and exercise.	Nausea burden score over 16 weeks of dosing.	There is no defined estimand for this endpoint and it will be analyzed using Pfizer data standards as applicable.
To enable exploratory research through collection of banked biospecimens, unless prohibited by local regulations or ethics committee decision.	Potential results from exploratory analysis of banked biospecimens (these results may or may not be generated in the context of the present study).	Not applicable.
For ***all*** endpoints, baseline is defined as the result closest prior to dosing at Visit 3 (Day 1). See Section 9.1.1 for additional details regarding Estimands.		

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Overall Design

This Phase 2b, multi-center, randomized, double-blind, placebo-controlled, 6 - arm, parallel group, study will assess efficacy and safety of twice daily administration of PF-06882961 in adult participants with T2DM inadequately controlled on metformin monotherapy or diet and exercise alone. At least 80% of the enrolled participants are required to be on metformin prior to screening. While a smaller proportion of participants managing their T2DM with diet and exercise only is permitted, this proportion should be no more than approximately 20% of the enrolled participants.

Following the screening period to confirm eligibility (up to 4-weeks), the study will consist of a 2-week placebo run-in period, prior to randomization on Day 1. The treatment period will be 16 weeks, followed by an approximate 4-week follow-up. The total duration of participation in the study is approximately 22 weeks, not including the screening period. Dosing will occur with food twice daily (BID), and up to 6 weeks of the 16-week dosing duration will be used for dose titration to maximize tolerability of PF-06882961.

Number of Participants

Approximately 400 participants (approximately 67 participants per treatment arm) will be randomized to ensure completion of approximately 300 participants (approximately 50 participants per treatment arm). Randomization will be stratified according to background diabetes treatment (presence or absence of metformin therapy).

Intervention Groups and Duration

Following the screening period, the study will consist of a 2-week placebo run-in period, prior to randomization on Day 1. The treatment period will be 16 weeks.

Participants will take 4 tablets of investigational product (IP) (PF-06882961 or matching placebo) in the morning with food and in the evening with food, for a total of 8 tablets of IP daily. The same dosing paradigm will be used during the placebo run-in period. Morning dosing will occur with food at the site at Visits 2 through 9. Participants will be instructed to arrive at the site in the fasted state, bring their IP with them, and to delay self-administration of IP on scheduled visit days until they arrive for their clinic visit.

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Table 1. Randomized Regimens in Study C3421005

Regimen	Regimen Description (dosed twice-daily)	Number of PF-06882961 tablets				Number of PF-06882961-matching placebo tablets	
		2.5 mg	10 mg	40 mg	100 mg	2.5 mg	10/40/100 mg
A	Placebo	-	-	-	-	1	3
B	PF-06882961 – 2.5 mg	1	-	-	-	-	3
C	PF-06882961 – 10 mg	-	1	-	-	1	2
D	PF-06882961 – 40 mg	-	-	1	-	1	2
E	PF-06882961 – 80 mg	-	-	2	-	1	1
F	PF-06882961 – 120 mg	-	2	-	1	1	-

Per the study estimands, if IP is permanently discontinued, the participant will remain in the study and continue to follow all protocol specified visits and procedures according to the SoA with the exception of dosing activities and assessment of PK.

Data Monitoring Committee

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

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 statistical analysis plan (SAP), which will be maintained by the sponsor.

The primary estimand will be the population average treatment effect on the change from baseline in HbA1c at Week 16 of PF-06882961 compared to placebo in the absence of glycemic rescue medication while on treatment and stable doses of background metformin and/or diet and exercise. Measurements after initiation of glycemic rescue medication or discontinuation of IP will be censored and treated as missing data. Missing data due to censoring, study withdrawal or other reasons (eg, laboratory failure) will have data imputed based on a missing at random (MAR) assumption. The population-based treatment effect will be the difference in the mean change from baseline in each PF-06882961 arm compared to placebo.

A secondary estimand will be the population odds ratio of the treatment effect of achieving HbA1c <7% at Week 16 of PF-06882961 compared to placebo in the absence of glycemic rescue medication in participants while on treatment and on stable doses of background metformin and/or diet and exercise. All other key secondary continuous clinical endpoints will be analyzed using the primary estimand described above.

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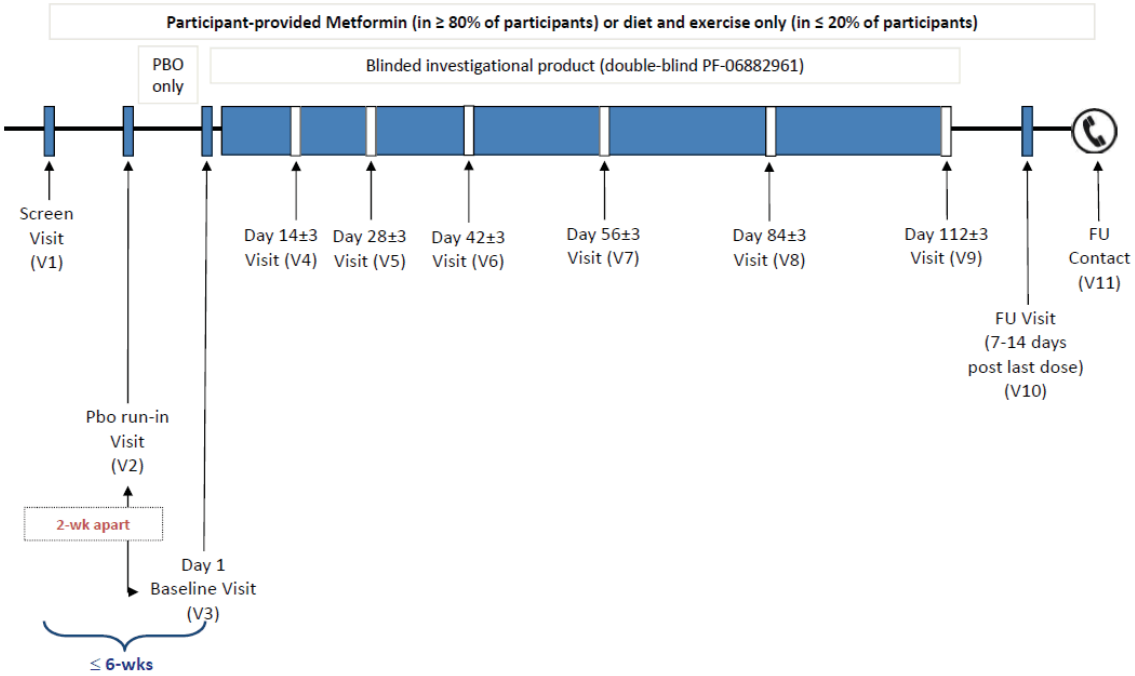
The primary analysis of the primary endpoint will be conducted using a mixed model repeated measures (MMRM) analysis of the change from baseline in HbA1c through Week 16. The primary analysis will include all participants randomly assigned to IP and who take at least 1 dose of IP. The MMRM will include treatment, time, strata (metformin vs. diet and exercise alone) 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 and no adjustments will be made for multiplicity.

1.2. Schema



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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)	**Screen**	**Pbo Run-In**	**Treatment Phase**						**End of Treatment**	**Follow Up**		**Early Termination**
Weeks Relative to Dosing on Day 1			**0**	**2**	**4**	**6**	**8**	**12**	**16**	**17-18**	**20-21**	**ET**
Days Relative to Dosing on Day 1	**-42 to -15**	**-14±3**	**1**	**14±3**	**28±3**	**42±3**	**56±3**	**84±3**	**112±3**	**119-126**	**140-147[a]**	
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	
Informed consent & demography	x											
Review of eligibility criteria	x	x	x									
Open-ended inquiry for adverse events	x	→	→	→	→	→	→	→	→	→	x	x
Medical history	x											
Review prior or concomitant treatments	x	→	→	→	→	→	→	→	→	→	x	x
Review drug, alcohol/tobacco use	x	→	→	→	→	→	→	→	→	→	x	x
Review contraception use (females only)	x	→	→	→	→	→	→	→	→	→	x	x
Counseling on diet/exercise guidelines		x										
Dispense glucometer and supplies, drug diary, glucose log & provide training		x										
Review drug diary, glucometer & glucose log			x	x	x	x	x	x	x	x		x
Glucose measurement (fasting, via glucometer, on site)		x	x	x	x	x	x	x	x	x		
Physical examination (height at Screen only)[b]	x		x						x	x		x
Supine vital signs	x	x	x[c]	x	x[c]	x	x[c]	x	x[c]	x		x
Supine 12 lead ECG	x		x[c]	x	x[c]	x	x[c]	x	x[c]	x		x
Body weight (in duplicate)[d]	x	x	x	x	x	x	x	x	x	x		x
Registration in trial (via IRT)	x											
Randomization in trial (via IRT)			x									
Dispensation of IP		x[e]	x[f]	x[f]	x[f]	x[f]	x[f]	x[f]				

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Protocol Activity (See Appendix 10 for abbreviations)	Screen	Pbo Run-In	Treatment Phase						End of Treatment	Follow Up		Early Termination
Weeks Relative to Dosing on Day 1			**0**	**2**	**4**	**6**	**8**	**12**	**16**	**17-18**	**20-21**	**ET**
Days Relative to Dosing on Day 1	**-42 to -15**	**-14±3**	**1**	**14±3**	**28±3**	**42±3**	**56±3**	**84±3**	**112±3**	**119-126**	**140-147[a]**	
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	
Dosing on site of IP (with food)		x	x	x	x	x	x	x	x			
IP/Placebo-run in compliance			x	x	x	x	x	x	x			x
Blood Sampling for:												
Fasting plasma glucose and HbA1c	x	x	x	x	x	x	x	x	x	x		x
Hematology, chemistry (inc. eGFR)	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
Lipids, TSH, free T4, calcitonin, amylase, lipase, TBA, PT/INR/aPTT, plasma insulin	x		x		x		x	x	x	x		x
Glucagon			x				x		x			x
PF-06882961 PK (pre-dose unless noted)			x	x	x[g]	x	x[g]	x	x[g]			x
Banked biospecimen: Prep B1 & B2			x		x		x		x			x
Banked biospecimen: Prep D1 (only Day 1)[h]			x									
Urine Sampling for:												
Urine drug test	x											
Urinalysis (and microscopy, if appropriate)	x		x		x		x	x	x	x		x
On-site urine pregnancy test (females only)[i]		x	x	x	x	x	x	x	x	x		x

a. Visit may be a phone call.
b. Full physical examination performed according to the SoA. A limited physical examination is performed at the follow up visit 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.
c. Measured in triplicate pre-dose (V3, V5, V7, and V9) and post-dose (***only*** V5, V7, and V9).
d. The second weight measurement should be obtained at least 1-2 minutes apart from the first weight measurement.
e. On V2 only, IP reflects single blinded placebo.
f. For V3 through V8, IP is dispensed via IRT and reflects double-blind randomized PF-06882961 or placebo.
g. PK samples collected pre-dose and within the window approximately 2-6 hours post dose.
h. 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.
i. For V2 through V9, the test result must be reviewed and deemed acceptable (ie, negative), in order to continue participation in the study.

2. INTRODUCTION

Glucagon-like peptide-1 (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-1 receptor (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 GLP-1R agonist that is currently being investigated as an adjunct to diet and exercise to improve glycemic control in adult participants with T2DM.

2.1. Study Rationale

This multicenter, Phase 2b, randomized, double-blind, placebo controlled, parallel group study is being conducted to provide data on efficacy, safety, tolerability and PK of multiple dose levels of PF-06882961 in adults with T2DM inadequately controlled on metformin and/or diet and exercise. In addition, the study is intended to enable selection of efficacious doses for future clinical development of PF-06882961.

2.2. Background

The increase in the global prevalence of T2DM is largely attributed to rising rates of excess body weight and obesity.[5] T2DM is estimated to affect more than 424 million people worldwide,[6] and the prevalence of T2DM within the United States (US) is estimated to range from 12 to 14%.[7] T2DM is characterized by insulin resistance, a disorder in which cells do not respond effectively to insulin, resulting in higher blood glucose levels. Elevated blood glucose levels and increasing severity of insulin resistance result in the need for more insulin over time, eventually resulting in progressive pancreatic β-cell failure.[8] Patients with poorly controlled T2DM have an increased risk of developing complications associated with both microvascular and macrovascular disease, including nephropathy, neuropathy, retinopathy, cardiovascular disease and stroke; and are at 2 to 4 times increased risk of mortality than adults who do not have diabetes.[9] While existing pharmacological options for the treatment of diabetes may provide satisfactory glycemic control for some patients, there remains a large number of patients who do not achieve target glycated hemoglobin (HbA1c) levels, suggesting a need for additional therapeutic options.

Marketed injectable GLP-1R agonists have demonstrated robust glycemic efficacy, weight loss, and cardiovascular safety, with at least one marketed agent demonstrating cardiovascular benefit.[10] Based on the clinical history of injectable GLP-1R agonists, an oral GLP-1R agonist is expected to improve glucose control and reduce HbA1c levels in patients with T2DM, while decreasing food intake and body weight and avoiding the subcutaneous injection required by currently available peptidic GLP-1R agonists.

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2.2.1. Nonclinical Overview

2.2.1.1. Nonclinical Pharmacology

In vitro primary pharmacodynamics (PD) studies demonstrated that, in cells expressing recombinant human and cynomolgus monkey GLP-1R, PF-06882961 dose-dependently promotes 3'-5'-cyclic adenosine monophosphate (cAMP) production. In vivo, PF-06882961 potentiated glucose-stimulated insulin secretion during an intravenous glucose tolerance test (IVGTT) in cynomolgus monkeys in a dose and concentration dependent manner. PF-06882961 was also shown to reduce food intake in cynomolgus monkeys. In all in vivo studies, efficacious plasma levels were consistent with the in vitro potency.

Refer to the Investigator's Brochure (IB) for more details on the nonclinical pharmacology of PF-06882961.

2.2.1.2. Nonclinical Pharmacokinetics and Metabolism

[redacted] In repeated oral dose toxicity studies in rats and monkeys, systemic exposure of PF-06882961 increased with increasing dose, with no accumulation.

[redacted]

[redacted] See Appendix 8 for a complete list of prohibited medications.

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In vitro data suggest that PF-06882961 is not expected to impact the PK of metformin via inhibition of OCT2, MATE1 nor MATE-2K and thus, the risk of a clinical pharmacokinetic interaction is deemed negligible.

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

2.2.1.3. 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). The exposure limits for plasma concentrations of PF-06882961 for clinical studies are based on the exposure at the no observed adverse effect level (NOAEL) dose 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, 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 34-fold (C_{max}, free) and 15-fold (AUC_{24}, free), to the observed human exposures at the highest planned clinical dose of PF-06882961, 120 mg BID.

Other toxicology studies completed in cynomolgus monkeys include a 14-week study with a 4-week lead-in (18 weeks total exposure) and a 13-week investigative toxicology study with 3-week lead-in (16 weeks total exposure), in which the NOAEL were the 100 mg/kg/day and 150 mg/kg/day (highest dose administered, respectively). At the NOAEL dose of 100 mg/kg/day in the 14-week study with 4-week lead-in, exposure margins were 1.3-fold and 0.75-fold for C_{max} and AUC_{24}, respectively, based on the lack of adverse findings in animals that survived to the scheduled necropsy. At the NOAEL dose of 150 mg/kg/day in the 13-week study with 3-week lead-in, exposure margins were 8.0- and 5.9-fold for C_{max} in males and females, respectively, and were 5.7- and 5.2-fold for AUC_{24} in males and females, repectively, based on the absence of adverse effects in the study.

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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 69-fold (C_{max}, free) and 68-fold (AUC_{24}, free), to the observed human exposures at the highest anticipated clinical dose of PF-06882961, 120 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 15-fold (C_{max}, total) and 3.6-fold (AUC_{24}, total), to the observed human exposures at the highest anticipated clinical dose of PF-06882961, 120 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 date, 3 clinical studies, C3421001, C3421002, and C3421003 have completed dosing with PF-06882961. In C3421001 and C3421003, healthy adult participants were randomized to receive single oral doses of PF-06882961 (or matching placebo). In C3421002, adult participants with T2DM were randomized to receive oral doses of PF-06882961 (or matching placebo) for 28 days, 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 (6) participants discontinued from the study, of which 2 discontinuations were due to treatment-related treatment emergent adverse events (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 (92%)] were mild in severity, 23 (7%) were moderate, and 2 (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 (1) participant experienced a mild TEAE of hypoglycemia. This AE was non-fasting, mild in severity and of limited duration.

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No deaths occurred in the C3421002 study. Two (2) participants experienced 2 severe TEAEs during the study, 1 of which occurred in the dosing period and was considered treatment related, and the other occurred during the follow-up period and was not considered treatment related. The latter participant experienced 2 non-treatment-related SAEs, 1 of which occurred in the follow-up period and was a TEAE of severe intensity, 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 heart rate have been observed, with mean increases ranging from 5 to 15 beats per minute (bpm) across doses administered to date, and most heart rate values within the normal range.

2.2.2.2. Clinical Pharmacokinetics

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

The PK properties of PF-06882961 have been evaluated in adult participants with T2DM as part of the C3421002 study. In this study, the first 6 cohorts received PF-06882961 or placebo dosed BID. Four of the 6 cohorts were titrated for various amounts of time over the 28 days, with a target maximum dose ranging between 10 and 120 mg BID across the 6 cohorts. Approximately dose proportional increases in C_{max} and AUC_{24} were observed between the doses of 10 mg BID and 120 mg BID, with C_{max} ranging from 38.38 to 685.2 ng/mL and AUC_{24} ranging from 455.9 to 8368 ng•h/mL. Percent coefficients of variance (%CV) ranged from 32 to 94 and 41 to 87 for C_{max} and AUC_{24} respectively on Day 28. Consistent with data from the completed studies, PF-06882961 was observed to have a half-life ($t_{½}$) of approximately 4.681 to 8.090 hours. Time to maximal concentration (T_{max}) ranged from 3 to 6 hours after the AM dose over the dose ranges administered.

2.3. Benefit/Risk Assessment

Based on the clinical history of injectable GLP-1R agonists, an oral GLP-1R agonist is expected to improve glucose control, reduce HbA1c levels, diminish food intake, and decrease body weight in patients with T2DM, while avoiding the requirement for subcutaneous injections that accompanies currently available peptidic GLP-1R agonists.

Considering all available clinical and nonclinical data, the benefit-risk profile of PF-06882961 is favorable and supports continued clinical development in patients with T2DM.

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 the single reference safety document (SRSD) for this study.

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3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

Objectives	Endpoints	Estimands
Primary:	**Primary:**	**Primary:**
To compare the effect of multiple dose levels of PF-06882961 versus placebo on HbA1c in participants with T2DM on stable doses of metformin and/or diet and exercise.	Change from baseline in HbA1c at Week 16.	Estimand 1A: This estimand is intended to provide a population level estimate of the mean treatment effect (PF-06882961 versus placebo) on a continuous endpoint in participants on stable doses of metformin and/or diet and exercise without the benefit of glycemic rescue medication while on treatment.
Secondary:	**Secondary:**	**Secondary:**
To compare the effect of multiple dose levels of PF-06882961 versus placebo on glycemic control in participants with T2DM on stable doses of metformin and/or diet and exercise.	Response as defined by an HbA1c <7% at Week 16.	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 responder endpoint in participants on stable doses of metformin and/or diet and exercise without the benefit of glycemic rescue medication.
	Change from baseline in HbA1c at Weeks 2, 4, 6, 8 and 12.	Estimand 1A as above.
	Change from baseline in fasting plasma glucose at Weeks 2, 4, 6, 8, 12 and 16.	Estimand 3: This estimand will be the same as 1A.
To compare the effect of multiple dose levels of PF-06882961 versus placebo on body weight in participants with T2DM on stable doses of metformin and/or diet and exercise.	Change from baseline in body weight at Weeks 2, 4, 6, 8, 12 and 16.	Estimand 4: This estimand will be the same as 1A.
To characterize the safety and tolerability of multiple dose levels of PF-06882961 administered to participants with T2DM on stable doses of metformin and/or diet and exercise.	Incidence of treatment emergent adverse events (AEs and SAEs), clinical laboratory abnormalities, vital signs (blood pressure and pulse rate) and ECG parameters (heart rate, QT, QTcF, PR and QRS intervals).	There are no defined estimands for these endpoints and they will be analyzed using Pfizer data standards as applicable.

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Tertiary/Exploratory:	**Tertiary/Exploratory:**	**Tertiary/Exploratory:**
To compare the effect of multiple dose levels of PF-06882961 versus placebo on HbA1c in participants with T2DM on stable doses of metformin and/or diet and exercise.	Change from baseline in HbA1c at Weeks 2, 4, 6, 8, 12 and 16.	Estimand 1B: This estimand is intended to provide a population level estimate of the mean treatment effect (PF-06882961 versus placebo) on a continuous endpoint in participants on stable doses of metformin and/or diet and exercise regardless of the initiation of glycemic rescue medication or discontinuation of IP.
To compare the effect of multiple dose levels of PF-06882961 versus placebo on HbA1c in participants with T2DM on stable doses of metformin.	Change from baseline in HbA1c at Weeks 2, 4, 6, 8, 12 and 16.	Estimand 1C: This estimand is intended to provide a population level estimate of the mean treatment effect (PF-06882961 versus placebo) on a continuous endpoint in participants on stable doses of metformin without the benefit of glycemic rescue medication whilst on treatment.
To compare the effect of multiple dose levels of PF-06882961 versus placebo on metabolic parameters in participants with T2DM on stable doses of metformin and/or diet and exercise.	Change from baseline in fasting insulin, and HOMA-IR at Weeks 4, 8, 12 and 16. Change from baseline in fasting glucagon at Weeks 8 and 16.	There are no defined estimands for these endpoints and they will be analyzed using Pfizer data standards as applicable.
To compare the effect of multiple dose levels of PF-06882961 versus placebo on body weight in participants with T2DM on stable doses of metformin and/or diet and exercise.	Response as defined by a ≥5% body weight loss at Week 16.	There are no defined estimands for these endpoints and they will be analyzed using Pfizer data standards as applicable.
To characterize the PK of PF-06882961 to participants with T2DM on stable doses of metformin and/or diet and exercise.	Plasma concentrations of PF-06882961 at time points specified in the SoA.	There is no defined estimand for these endpoints and they will be analyzed using Pfizer data standards as applicable.
To characterize the gastrointestinal tolerability during different doses and titration schemes of PF-06882961 administered to participants with T2DM on stable doses of metformin and/or diet and exercise.	Nausea burden score over 16 weeks of dosing.	There is no defined estimand for this endpoint and it will be analyzed using Pfizer data standards as applicable.

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To enable exploratory research through collection of banked biospecimens, unless prohibited by local regulations or ethics committee decision.	Potential results from exploratory analysis of banked biospecimens (these results may or may not be generated in the context of the present study).	Not applicable.
For ***all*** endpoints, baseline is defined as the result closest prior to dosing at Visit 3 (Day 1). See Section 9.1.1 for additional details regarding Estimands.		

4. STUDY DESIGN

4.1. Overall Design

This Phase 2b, multi-center, randomized, double-blind, placebo-controlled, 6 - arm, parallel group, study will assess efficacy and safety of twice daily administration of PF-06882961 in adult participants with T2DM inadequately controlled on metformin monotherapy or diet and exercise alone. At least 80% of the enrolled participants are required to be on metformin prior to screening. For those participants, the dose of metformin should remain the same until the first follow up visit (ie, visit 10, Week 17-18), except in circumstances where a dose change is deemed medically necessary. While a smaller proportion of participants managing their T2DM with diet and exercise only is permitted, this proportion should be no more than approximately 20% of enrolled participants.

Following the screening period to confirm eligibility (up to 4-weeks), the study will consist of a 2-week placebo run-in period, prior to randomization on Day 1. The treatment period will be 16 weeks, followed by an approximate 4-week follow-up. The total duration of participation in this study is approximately 22 weeks, not including the screening period. Dosing will occur with food twice daily, and up to 6 weeks of the 16-week dosing duration will be used for dose titration to maximize tolerability of PF-06882961. Additional details regarding dose titration are provided in the IP Manual.

Participants taking metformin will remain on self-provided metformin at the same daily dose they were receiving at the time of screening. There is no minimal metformin dose for enrollment and the metformin dose will not to exceed the highest approved dose in the country of participation.

Approximately 400 participants (approximately 67 participants per treatment arm) will be randomized to ensure completion of approximately 300 participants (approximately 50 participants per treatment arm). Randomization will be stratified according to background diabetes treatment (presence or absence of metformin therapy).

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4.2. Scientific Rationale for Study Design

This study is designed to assess the efficacy of PF-06882961 on glycemic control, measured by HbA1c, in participants with T2DM over 16 weeks of dosing. 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 blinded placebo dosing prior to randomization. Clinical laboratory tests, assessments of vital signs and 12-lead ECGs, physical examinations, and AE monitoring will provide data to evaluate the efficacy, safety and tolerability of PF-06882961.

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.[12] In addition, thyroid stimulating hormone (TSH), free thyroxine (FT4), lipids, coagulation profile and total bile acids (TBA) will be assessed, based on non-adverse findings in the nonclinical studies with PF-06882961.

The total duration of dosing in this study will be 16 weeks for all participants. Based on the tolerability data to date from C3421002, the lower doses of 2.5 and 10 mg BID are expected to be well-tolerated without the need for titration, and thus will be dosed at the same dose level for all 16 weeks of the study. The intermediate doses of 40 and 80 mg BID will involve titration and reach the target dose level within 3 to 5 weeks of initiating dosing, respectively. For the highest dose level of 120 mg BID, the target dose level will be reached in the seventh week of dosing. Downward titration or 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 IP. Titration schemes are provided in Section 6.1, and additional details regarding titration are provided in the IP Manual.

An interim analysis may be performed to assess safety, and a dose level may be dropped if deemed necessary. See Section 4.4 and Section 9.5 for additional information regarding Interim Analyses.

All doses will be blinded and consist of 4 tablets administered BID via a blister pack, and dosing regimens will look the same between the placebo run-in and the 16-week dosing duration post randomization.

While 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), blood glucose concentrations will be monitored throughout the study via glucometer; and monitoring of symptomatic hypoglycemic AEs will be performed.

Body weight will be measured at all study visits, as GLP-1R agonists have been shown to decrease food intake and body weight. The collection of blood samples, specifically fasting plasma glucose (FPG), fasting plasma insulin (FPI), and fasting plasma glucagon will assist in the time- and dose- related PD response. FPG and FPI levels will be used to calculate HOMA-IR.

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Both females of childbearing potential, as well as those who are of non-childbearing potential, will be enrolled given the availability of embryo fetal developmental (EFD) toxicity studies with PF-06882961. However, as marketed GLP-1R agonists are 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 Schedule of Activities and Appendix 4 for additional information regarding contraception use and monitoring.

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 no-observed-adverse-effect level (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.[13]

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

4.3. Justification for Dose

The PF-06882961 doses selected for this study are based on observed safety, tolerability, PK, and PD data from the C3421002 study; as well as the exposure margins relative to observed toxicology findings. Exposure margins for the highest proposed dose in this study (120 mg BID) are given in Section 2.2.1.3. As the tolerability profile of multiple doses of PF-06882961 has been assessed primarily in the setting of a BID dosing regimen, the proposed dosing regimen for the current study is BID.

This study is designed to evaluate the dose-response of PF-06882961 from low doses, predicted to have sub-maximal effects on glucose up to doses expected to have near maximal glucose lowering in the patient population, while still having an adequate tolerability profile. Mean daily glucose (MDG) levels, and change from baseline in MDG, have been assessed in C3421002 at dose levels ranging from placebo to 120 mg BID. Based on data from the C3421002 study, the glucose lowering effect of PF-06882961 is expected to be similar to that of marketed GLP-1R agonists. The proposed dose levels in this study of 2.5, 10, 40, 80, and 120 mg BID are expected to result in glucose lowering that is 25, 57, 84, 91 and 94% of maximal glucose lowering effect, respectively. The exposure of PF-06882961 increases approximately linearly, with dose and exposure-response modeling yielding similar results. Considering the uncertainty in the model parameter estimates, it is unlikely that the 2.5 mg BID dose will result in >50% of maximal response, and it is also unlikely that the 120 mg BID dose will result in <85% of maximal response. For this reason, there is high confidence that the dose range examined in this study will fully elucidate the dose-response for HbA1c in this patient population.

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4.4. Assessment of Safety and Tolerability While Study is Ongoing

During study conduct, after approximately every 25% of the total planned randomizations [for example: 100 subjects (25%), 200 subjects (50%), and 300 subjects (75%), of planned approximately 400 subjects], blinded safety review will be conducted by selected members of the Sponsor's study team. Blinded safety reviews will be separated by at least one month from the previous review. An Interim Analysis (IA) of the unblinded safety data by the IRC will occur at least once while the study is ongoing, as described in Section 9.5.

4.5. 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 follow-up visit (Visit 11), approximately 28 to 35 days post last dose of IP.

The end of the study is defined as the date of the last visit (Visit 11), by the last participant across all sites globally.

5. STUDY POPULATION

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

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

5.1. Inclusion Criteria

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

Age and Sex:

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

    - 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. Patients with T2DM who are treated with metformin and/or diet and exercise.

    - For participants taking metformin, the metformin dose must have been stable for at least 60 days prior to the screening visit (Visit 1).

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- Enrollment of participants on diet and exercise only (ie, no anti-diabetic medications) will be limited to ≤20% of total participant population.

3. HbA1c ≥7% and ≤10.5% at screening (Visit 1) as assessed by the study specific laboratory and confirmed by a single repeat test, if deemed necessary.

4. Participants who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures, including the ability to perform self-tests of blood sugar regularly (see Section 8.2.5.1) for the duration of the study and maintenance of study specific glucose logs for the duration of participation in the study.

Body Mass Index (BMI) and Weight:

5. Total body weight >50 kg (110 lb) with BMI of 24.5 to 45.4 kg/m^2 (for sites in North America and Europe) or BMI 22.5 to 45.4 kg/m^2 (for sites in Asia). Body weight must have been stable (<5% change) for 90 days prior to screening (Visit 1) as per participant report.

Informed Consent:

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

5.2. Exclusion Criteria

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

Medical Conditions:

1. Any acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or IP administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the participant inappropriate for entry into this study.

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

3. Diagnosis of type 1 diabetes mellitus or secondary forms of diabetes.

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 of screening (Visit 1).

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5. Any malignancy not considered cured (except basal cell carcinoma and squamous cell carcinoma of the skin); a subject 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 (MTC) or multiple endocrine neoplasia syndrome type 2 (MEN2), or subjects with suspected MTC per the investigator's judgment.

7. Acute pancreatitis or history of chronic pancreatitis.

8. Symptomatic gallbladder disease.

9. Participants with a known medical history of active proliferative retinopathy and/or macular edema.

10. Participants with a known medical history of active liver disease (other than non-alcoholic hepatic steatosis), including chronic active hepatitis B or C, or primary biliary cirrhosis.

11. Participants with known history of human immunodeficiency virus (HIV).

Prior/Concomitant Therapy:

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

Prior/Concurrent Clinical Study Experience:

13. 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 IP used in this study (whichever is longer).

14. Known prior participation in a trial involving PF-06882961 or known intolerance to a GLP-1R agonist.

Diagnostic Assessments:

15. Screening supine blood pressure (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. **Note:** Participants with an arm circumference greater than the largest cuff size or those with a mid-arm circumference >52 cm are not eligible.

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16. Screening 12-lead electrocardiogram (ECG) that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results (eg, baseline corrected QT interval [QTcF] >450 msec, complete left bundle branch block [LBBB], signs of an acute or indeterminate-age myocardial infarction, ST-T interval changes suggestive of myocardial ischemia, second- or third-degree atrioventricular [AV] block, or serious bradyarrhythmias or tachyarrhythmias).

    - If QTcF exceeds 450 msec, or QRS exceeds 120 msec, the ECG should be repeated 2 more times and the average of the 3 QTcF or QRS values should be used to determine the participant's eligibility.

17. A positive urine drug test. ***Note:*** Participants who have been medically prescribed opiates/opioids or benzodiazepines and report the use of these drugs to the investigator at screening (Visit 1) may be allowed to participate with notification to the sponsor.

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

    - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) level ≥2 times the upper limit of normal (ULN).
    - Total bilirubin level ≥1.5 times the ULN.
    - Fasting C peptide <0.8 ng/mL.
    - TSH >1.5 times the ULN.
    - Serum calcitonin > the ULN.
    - Amylase or lipase > the ULN.
    - Fasting plasma blood glucose >270 mg/dL (15 mmol/L) at screening (Visit 1) or placebo run-in (Visit 2).
    - Estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 as calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[14]

Other Exclusions:

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

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20. History of regular alcohol consumption exceeding 7 drinks/week for female subjects or 14 drinks/week for male subjects (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 screening (Visit 1).

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

22. Unwilling or unable to comply with the criteria in the Lifestyle Considerations section of this protocol.

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

5.3. Lifestyle Considerations

5.3.1. Dietary Restrictions

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

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

- IP 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 Visit 2 through Visit 9, participants should be instructed to arrive **without** having food/breakfast, self-administration of IP, *and* morning dose of concomitant medication for the control of glycemia, if applicable, for the given day. Note: Participants may take their morning dose of antihypertensive and/or lipid modifying medication per their usual routine, if applicable.

- At Visit 2 through Visit 9, inclusive, the above-mentioned medications will be administered at the site with food.

- Participants will be counseled on appropriate dietary and lifestyle guidelines for T2DM at Visit 2 and asked to maintain these guidelines throughout participation in the study. Counseling on dietary guidelines should be in accordance with local medical standards of care for patients with T2DM. Note; Participation in formal weight loss programs should be avoided during participation in this study.

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5.3.2. Alcohol, Caffeine and Tobacco

- Intake of alcohol is permitted in moderation (refer to exclusion criterion 20 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.

5.3.3. Physical Activity

Participants will not be permitted 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. Contraception

The investigator or his or her designee, in consultation with the participant, will confirm that female participants have selected an appropriate method of contraception from the permitted list of contraception methods (see Appendix 4, Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the 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 IP. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

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

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6. STUDY INTERVENTION

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

For the purposes of this protocol, the term IP may be used synonymously with study intervention. For this study, the IP is PF-06882961 and matching placebo tablets; and will be administered orally BID with food.

Treatment Phase IP will be packaged in blister cards containing blinded PF-06882961 or matching placebo for oral administration. Treatment assignment will be blinded, and blister cards will be labeled according to local regulatory requirements. For the placebo run-in, placebo tablets will be packaged in blister cards according to local regulatory requirements.

For participants taking metformin, they will continue taking their own metformin medication at the same total daily dose that was prescribed prior to study entry, except in circumstances where a dose change is deemed medically necessary.

6.1. Study Intervention(s) Administered

Intervention Name	PF-06882961	Placebo for PF-06882961
ARM Name	Active	Placebo
Type	Drug	Drug
Dose Formulation	Tablet	Tablet
Unit Dose Strengths	2.5 mg, 10 mg, 40 mg and 100 mg	Not applicable
Target Dosage Levels (achieved upon titration)	2.5, 10, 40, 80, 120 mg BID	0 mg BID
Route of Administration	Oral	Oral
Sourcing	Provided centrally by the sponsor. Refer to the Investigational Product Manual.	Provided centrally by the sponsor. Refer to the Investigational Product Manual.
Packaging and Labeling	Study intervention will be provided in blister packs. Each blister pack will be labeled as required per country requirement. 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. Blinded labels will be utilized for placebo run-in, titration and stable dosing blister packs.

Participants will take 4 tablets of IP (PF-06882961 or matching placebo) in the morning with food and 4 tablets of IP in the evening with food, for a total of 8 tablets of IP daily. Participants will swallow the IP whole, and will not crush, chew, break, or dissolve the IP prior to swallowing. The same dosing paradigm will be used during the placebo run-in period.

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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 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 IP. When participants self-administer the IP at home, they will record each dose, including date and time, in the dosing diary.

Morning dosing will occur with food at the site at V2-V9. Participants will be instructed to arrive at the site in the fasted state, bring their IP with them, and to delay self-administration of IP on scheduled visit days until they arrive for their clinic visit. When participants dose at the site, they will self-administer the IP under supervision by study staff. The date and time of each dose administered at the site will be recorded in the site source documents and in the dosing diary. Additionally, the date and time of the previous two doses prior to each of the blood collections related to PK (both pre- and post- dose samples) will be captured in the CRF.

Titration and dosing schemes for target doses are provided below; additional details regarding titration are provided in the IP Manual.

Table 2. Titration and Dosing Scheme

Target Dose (mg) BID	Week 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
	Titration Phase						Stable Dose Phase									
2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
40	10	20	40	40	40	40	40	40	40	40	40	40	40	40	40	40
80	10	20	40	60	80	80	80	80	80	80	80	80	80	80	80	80
120	10	20	40	60	80	100	120	120	120	120	120	120	120	120	120	120
Placebo	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

6.2. Preparation/Handling/Storage/Accountability

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

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

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must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperature since previously documented for all site storage locations upon return to business.

3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records). All study interventions will be accounted for using an IP accountability form/record. All IP that is taken home by the participant, both used and unused, must be returned to the investigator by the participant.

4. Further guidance and information for the final disposition of unused study interventions are provided in the IP manual.

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

6. Study interventions should be stored in their original containers and in accordance with the labels.

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

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

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

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

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6.2.1. Preparation and Dispensing

The IP will be dispensed using an Interactive Response Technology (IRT) drug management system at each visit according to the SoA. A qualified staff member will dispense the IP via unique container numbers in the blister cards provided, in quantities appropriate for the study visit schedule. The participant should be instructed to maintain the product in the blister cards provided throughout the course of dosing and return the blister cards to the site at the next study visit.

6.3. Measures to Minimize Bias: Randomization and Blinding

Allocation to treatment will occur via an IRT system. A randomization code using the method of random permuted blocks will be utilized to randomize eligible participants in 1:1:1:1:1:1 ratio (1 to 5 of active dosing regimens of PF-06882961 or placebo) prior to the first dose of IP.

Participants will be stratified at randomization (Day 1) by the presence or absence of metformin as background medication.

The system will be programmed with blind-breaking instructions. Refer to Section 6.3.2 for further details.

6.3.1. Allocation to Investigational Product

Participants will be randomized to receive one of the IP regimens described in Table 3.

Table 3. Randomized Regimens in Study C3421005

Regimen	Regimen Description (dosed twice-daily)	Number of PF-06882961 tablets				Number of PF-06882961-matching placebo tablets	
		2.5 mg	10 mg	40 mg	100 mg	2.5 mg	10/40/100 mg
A	Placebo	-	-	-	-	1	3
B	PF-06882961 – 2.5 mg	1	-	-	-	-	3
C	PF-06882961 – 10 mg	-	1	-	-	1	2
D	PF-06882961 – 40 mg	-	-	1	-	1	2
E	PF-06882961 – 80 mg	-	-	2	-	1	1
F	PF-06882961 – 120 mg	-	2	-	1	1	-

Allocation of participants to treatment groups will proceed through the use of an IRT system (interactive Web-based response [IWR]). The IRT system will provide a confirmation report containing the participant number, randomization number, and dispensable unit (DU) or container number assigned. The confirmation report must be stored in the site's files.

IP will be dispensed at the study visits summarized in the SoA.

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

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

6.3.2. Breaking the Blind

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

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

6.4. Study Intervention Compliance

Participant compliance with IP will be assessed at each visit. Compliance will be assessed by counting returned tablets. At V4, which occurs during the first 4 weeks of dosing when participants may be receiving titrated doses as part of their blinded regimen, 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 placebo run-in that is 11-13 days, up to 2 missed doses are allowed, and for a placebo run-in that is 14-17 days, up to 3 missed doses 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 IP from Day 1 through Week 16, 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 IP.

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.

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Treatments taken within 28 days before the first dose of IP will be documented as prior treatment. Treatments taken after the first dose of IP will be documented as concomitant treatment.

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

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

6.5.1. Metformin

At least 80% of all participants are required to be taking metformin monotherapy prior to inclusion in this study as listed in Section 5.1. For participants taking metformin, this study requires that participants have been taking stable doses of metformin for at least 60 days prior to the screening visit. Participants will continue taking their own metformin medication at the same total daily dose that was prescribed prior to study entry through the first follow up visit (ie, Visit 10, Week 17-18), except in circumstances where a change in dose is deemed medically necessary. For study visit days, participants should be instructed to refrain from morning dosing at home and to bring the metformin to the site for dosing at the same time as their blinded IP. For participants taking metformin more than once a day, the timing should be approximately the same on each day.

6.5.2. Medications for Glycemic Control

Aside from metformin, the use of other medications for glycemic control is not permitted in this study unless the participant meets the protocol defined glycemic rescue criteria (see Section 8.2.5.3).

6.5.3. 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.

6.5.4. 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.

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6.5.5. Glycemic Rescue Medicine

Participants with hyperglycemia as defined in Section 8.2.5.3 should be offered glycemic rescue medication as an add on to their randomized treatment.

Glycemic rescue medication should be prescribed according to local label and obtained locally. The following glycemic rescue medications may be used: metformin (for those participants who were not taking metformin at randomization), sulfonylureas, or sodium glucose co-transporter 2 (SGLT2) inhibitors. For participants who were taking a submaximal dose of metformin, increasing the metformin dose may be instituted as glycemic rescue medication, as long as the dose does not exceed the highest approved dose in the country of participation.

The following medication are *not* permitted as glycemic rescue medications: GLP-1R agonists, DPP-4 inhibitors, amylin analogues, thiazolediediones (TZDs) or insulin.

The date of glycemic rescue medication administration as well as the name and dosage regimen of the glycemic rescue medication must be recorded on the CRF.

Participants receiving glycemic rescue medication should continue to follow all protocol specified visits and procedures according to the SoA.

There is no rescue therapy to reverse the AEs observed with PF-06882961; standard medical supportive care must be provided to manage the AEs. Standard medical supportive care must be provided to manage the AEs, including administration of carbohydrates to treat hypoglycemic adverse events (HAE) (see Section 8.2.5.2.1).

6.6. Dose Modification

6.6.1. 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 system organ class (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.

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7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

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

Per the study estimands, if IP is permanently discontinued, the participant will remain in the study and continue to follow all protocol specified visits and procedures according to the SoA with the exception of dosing activities and assessment of PK.

The site should notify the Sponsor Medical Monitor or Sponsor Clinician if the below criteria for permanent discontinuation are met.

Note that discontinuation of IP does not represent withdrawal from the study.

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

7.1.1. Criteria for Discontinuation

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

- Criteria for a potential Hy's law case are met (see Appendix 6).
- Intent to become pregnant or pregnancy confirmed by serum beta human chorionic gonadotropin (β-hCG) testing.

7.2. Participant Discontinuation/Withdrawal From the Study

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

At the time of discontinuing from the study, if possible, an early termination 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 termination visit applies only to participants who are randomized and then are prematurely withdrawn from the study. Participants should be questioned regarding their reason for withdrawal. The participant will be permanently discontinued both from the study intervention and from the study at that time.

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

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

When a participant withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported on the Clinical Trial (CT) SAE Report.

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.

Withdrawal of Consent:

Participants who request to discontinue receipt of study treatment will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him or her or persons previously authorized by the participant to provide this information. Participants should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of IP or also from study procedures and/or post treatment study follow-up and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

7.3. Lost to Follow-up

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

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

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

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- 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.

Discontinuation of specific sites or of the study as a whole is handled as part of Appendix 1.

8. STUDY ASSESSMENTS AND PROCEDURES

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

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

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

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

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

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The total blood sampling volume for individual participants in this study is approximately 295 mL. The actual collection times of blood sampling may change. Additional blood samples may be taken for safety assessments at times specified by Pfizer, 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 HbA1c, fasting plasma glucose, and body weight which are covered in detail in Section 8.2.

8.1.1. Primary Efficacy Parameter: HbA1c

HbA1c is the primary efficacy parameter for this study. See Section 8.2.6 covering clinical laboratory tests.

8.1.2. Secondary and Tertiary Efficacy Parameters

See Section 8.2.6 (clinical laboratory assessments) for details regarding fasting plasma glucose. Participants achieving HbA1c <7% will be calculated based on HbA1c assessments as described in Section 8.2.6.

See Section 8.2.2 for details regarding assessment of body weight.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety concerns.

8.2.1. Physical Examinations

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 head, ears, eyes, nose, mouth, skin, heart and lung examinations, lymph nodes, and gastrointestinal, musculoskeletal and neurological systems.

Height will be measured at screening only.

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

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

8.2.2. Body Weight

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 measurement.

Weight will be recorded using a calibrated scale (with the same scale used if 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). The scale must be placed on a stable, flat surface.

Weight measurement should be taken under the following conditions:

- While participant is in a fasted state (see Section 5.3.1);
- After void of urine;
- After removal of shoes, bulky layers of clothing and jackets so that only light clothing remains;
- While remaining still during the measurement.

8.2.3. Vital Signs

8.2.3.1. Blood Pressure and Pulse Rate

In this study, assessment of vital signs [systolic BP, diastolic BP, and pulse rate (PR)] will occur at the nominal time points specified in the SoA per the following specifications:

- At screening, the participant's arm circumference should be measured (eg, using a flexible anthropometric tape) at the midpoint of the length of the upper arm and the appropriate cuff selected and used throughout the study.
    - ***Note:*** Participants with arm circumference greater than the largest cuff size available at the site or >52 cm are not eligible. See Section 5.2.
- BP and PR will be measured via an automated device using an oscillometric method (not auscultation).
    - Assessment of BP and PR can be manual (rather than using an automated device), only if an automated device is not available; however when done manually PR must be measured in the brachial/radial artery for at least 30 seconds.

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- Supine BP and PR will be measured with the participant's arm supported at the level of the heart, and recorded to the nearest mm Hg, following a rest of at least 5 minutes. The assessment at Visit 3 (Day 1) will serve as the participant's baseline. Triplicate assessments will be measured at V3, V5, V7 and V9 with a brief interval (eg, 1-2 minutes) between successive triplicate assessments.

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

- Participants should be instructed not to speak during BP and PR 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 PR will be permitted, as necessary, to ensure appropriate collection of safety data.

8.2.4. 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 heart rate and measures PR, QT, and QTcF intervals and QRS complex. Triplicate assessments will be measured at V3, V5, V7 and V9 with a brief interval (eg, 2-5 minutes) between successive triplicate assessments. All scheduled ECGs should be performed after the participant has rested quietly for at least 10 minutes in a supine position.

If a post dose QTcF interval remains ≥30 msec from the baseline **and** is a) >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 QTcF intervals get progressively longer, the participant should undergo continuous ECG monitoring. A cardiologist should be 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.

8.2.5. Management of Glycemic Control

Hypoglycemic adverse events (HAEs) and fasting plasma glucose will be routinely monitored during participation in the study.

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Based on this information, as well as review of the results reported by the central laboratory, an assessment of any symptomatic and asymptomatic occurrence of hypo- or hyper-glycemia must be undertaken.

8.2.5.1. Home Glucose Monitoring

- To aide in management of their T2DM, all participants will be provided home glucose monitoring supplies including a Sponsor-provided glucometer, instructions on the use of the glucometer and accompanying supplies.

- Home glucose monitoring logs will be provided to participants for completion at home and brought to each outpatient visit to the site along with the glucometers. Investigators must review the home glucose monitoring logs completed by the participants and the readings stored in the glucometer device at each visit to the site after the placebo run-in visit (V2).

- Participants must perform home glucose monitoring at least 3 times weekly following at least an 8-(preferably 10-) hour fast (except water). However, the investigator may recommend more frequent home glucose monitoring if needed.

- Less frequent glucose monitoring will NOT be considered a protocol deviation unless the participant fails to monitor his/her glucose for 3 or more consecutive days.

- If the participant experiences symptoms of hypoglycemia, home glucose monitoring should be performed, and these symptoms, along with the glucometer measurement, should be captured on the home glucose monitoring log.

- If the participant uses his/her own glucometer, and not one provided by the Sponsor, a protocol deviation will NOT be recorded provided the investigator is still able to monitor the participant's daily glucose values according to the criteria stated above.

8.2.5.2. Management of Hypoglycemia

Any episode of hypoglycemia must be captured on the Adverse Event CRF with specific details captured on the Hypoglycemia Adverse Event Form CRF. For the definition of a hypoglycemic episode and severity categorization see Section 8.2.5.2.1 below.

Participants noted to have a fasting glucose value (during home glucose monitoring) meeting the definition of hypoglycemia must be instructed to repeat the measurement the next day (following at least an 8 (preferably 10) hour fast, except water). If the second measurement also meets the below definition, participants must be asked to return to the site within 1 to 3 days (following at least an 8 (preferably 10) hour fast, except water) and have blood collected and sent to the central laboratory for analysis of fasting plasma glucose.

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8.2.5.2.1. Definition and Severity of Categorization of Hypoglycemic Adverse Event (HAE)

Based on review of the participant completed home glucose monitoring log at each site visit, as well as results reported by the central laboratory, the investigator must assess the glucose values as well as any symptoms documented.

HAE is defined as **one** of the following:[15]

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

2. **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 (or sponsor-identified central laboratory) ***and*** the clinical picture includes prompt resolution with food intake, subcutaneous glucagon, or intravenous (IV) glucose;

3. **Probable symptomatic hypoglycemia:** An event during which symptoms of HAE are *not* accompanied by a glucose determination but was presumably caused by a blood 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 **three (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 one of the following neurological symptoms:

   - Memory loss;
   - Confusion;
   - Uncontrolled behavior;
   - Irrational behavior;
   - Unusual difficulty in awakening;
   - Suspected seizure;
   - Seizure;

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- Loss of consciousness.

3. Either:

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

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

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

Any episode of HAE must be captured on the HAE CRF.

8.2.5.3. Management of Hyperglycemia

Hyperglycemia is defined as the following:

- Fasting glucose ≥270 mg/dL (15.0 mmol/L) using glucometer (or central laboratory).

After randomization, participants noted to have a fasting glucose value (during home glucose monitoring) meeting the above definition of hyperglycemia must be instructed to repeat the measurement the next day (following at least an 8 (preferably 10) hour fast, except water). If the second measurement also meets the above definition, participants must be asked to return to the site a day later (following at least an 8 (preferably 10) hour fast, except water) and have blood collected for fasting plasma glucose (and shipped to the central laboratory for analysis).

The investigator should determine if the participant collected the samples after an adequate fasting period; and if the participant is following recommended dietary guidelines. Proper dietary and collected procedures should be reinforced with the participant.

If the results from the central laboratory confirm the readings using glucometer, the participant should receive glycemic rescue medication at the discretion of the investigator (see Section 6.5.5).

8.2.6. Clinical Laboratory Assessments

See Appendix 2 for the list of clinical safety laboratory tests to be performed and the SoA for the timing and frequency.

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.

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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.

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

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

8.2.7. Pregnancy Testing

Pregnancy tests will be both urine and serum tests, 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 IP. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) and at the end of the study. Pregnancy tests may also be repeated if requested by institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations.

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 it meets the criteria for classification as an SAE or that caused the participant to discontinue the study intervention (see Section 7).

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

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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 IP), through and including a minimum of 28 calendar days, except as indicated below, after the last administration of the IP.

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

Follow-up by the investigator continues throughout and after the active collection period and until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

Investigators are not obligated to actively seek AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.1.1. Reporting SAEs to Pfizer Safety

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

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

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

During the active collection period, both nonserious AEs and SAEs are recorded on the AE section of the CRF.

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.

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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 suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

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

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

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

8.3.5.1. Exposure During Pregnancy

Details of all pregnancies in female participants will be collected after the start of study intervention and until 28 calendars days after the last administration of IP.

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

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

8.3.5.2. Exposure During Breastfeeding

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

8.3.5.3. Occupational Exposure

An occupational exposure occurs when, during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.

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

8.3.6. Medication Errors

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

Exposures to the IP 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 IP;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant.

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

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

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

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

8.4. Treatment of Overdose

For this study, any dose of IP greater than 16 blinded tablets of PF-06882961 within an approximate 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.

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. 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).

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

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

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

8.5. Pharmacokinetics

In this study, blood samples (3 mL, each) to provide sufficient ***plasma*** for PK analysis will be collected into appropriately labeled tubes containing dipotassium edetic acid (ethylenediaminetetraacetic acid) - K_2 EDTA, at times defined in the SoA – with collections occurring *prior to dosing with IP* on the given scheduled visit and between 2 and 6 hours post dose on 3 different visits: Visit 5, Visit 7 and Visit 9. The date/time of the blood

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collections related to PK (both pre- *and* post-dose samples) should be noted in source documents and captured in the CRF.

- The PK samples must be processed and shipped as indicated in the study-specific laboratory manual provided to the investigator site, prior to initiation of study, to maintain sample integrity:
    - Any deviations from the PK sample handling procedure (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 (C_{trough})] 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 IP, 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 standard operating procedures.

8.6. Pharmacodynamics

PD parameters evaluated in this study include fasting HOMA-IR, fasting plasma insulin, fasting plasma glucose and glucagon 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 blood sample of approximately 4-mL, optimized for deoxyribonucleic acid (DNA) isolation Prep D1 will be collected as local regulations and IRBs/ECs allow.

Banked biospecimens may be used for research related to drug response and T2DM. Genes and other analytes (eg, proteins, ribonucleic acid [RNA], nondrug metabolites) may be studied using the banked samples.

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

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

8.8. Biomarkers

Biomarkers are not evaluated this study.

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

Serum (Prep B2) plasma (Prep B1) samples of approximately 10-mL each will be collected according to the SoA and as local regulations and IRB/ECs allow.

Banked biospecimens may be used for research related to drug response and T2DM. Genes and other analytes (eg, proteins, RNA, nondrug metabolites) may be studied using the banked samples.

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

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

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8.9. Health Economics

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

9. STATISTICAL CONSIDERATIONS

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

9.1. Estimands and Statistical Hypotheses

9.1.1. Estimands

A summary of estimands is provided in the table below and described in detail thereafter:

Variable	Estimand	Population	Intercurrent Event	Population-level Summary	International Council for Harmonisation (ICH)-E9(R1) Strategy(ies)
HbA1c (continuous)	1A	Metformin + Diet & Exercise	Absence of glycemic rescue medication and discontinuation of study IP	Mean difference (PF-06882961 versus Placebo)	Hypothetical While on treatment
HbA1c (continuous)	1B	Metformin + Diet & Exercise	Regardless of intercurrent events	Mean difference (PF-06882961 versus Placebo)	Treatment Policy
HbA1c (continuous)	1C	Metformin	Absence of glycemic rescue medication and discontinuation of study IP	Mean difference (PF-06882961 versus Placebo)	Hypothetical While on treatment
HbA1c (categorical)	2	Metformin + Diet & Exercise	Absence of glycemic rescue medication and discontinued from IP	Odds ratio (PF-06882961 relative to Placebo)	Hypothetical While on treatment
Fasting Plasma Glucose (continuous)	3	Metformin + Diet & Exercise	Absence of glycemic rescue medication and discontinuation of IP	Mean difference (PF-06882961 versus Placebo)	Hypothetical While on treatment
Body Weight (continuous)	4	Metformin + Diet & Exercise	Absence of glycemic rescue medication and discontinuation of IP	Mean difference (PF-06882961 versus Placebo)	Hypothetical While on treatment

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Estimands related to the change from baseline in HbA1c:

The primary estimand (Estimand 1A) will be the population average treatment effect on the change from baseline in HbA1c at Week 16 of PF-06882961 compared to placebo in the absence of glycemic rescue medication while on treatment and stable doses of background metformin and/or diet and exercise. This reflects a combination of the 'Hypothetical' and 'While on treatment' strategies as outlined in the ICH-E9 (R1) draft guidance.[16]

Measurements after initiation of glycemic rescue medication or discontinuation of IP will be censored and treated as missing data. Missing data due to censoring, study withdrawal or other reasons (eg, laboratory failure) will have data imputed based on a missing at random (MAR) assumption. Participants with inadequate compliance will have their HbA1c values used as-is in the analysis. The population-based treatment effect will be the difference in the mean change from baseline in each PF-06882961 arm compared to placebo. This estimand will similarly be applied to the changes from baseline in HbA1c at Weeks 2, 4, 6, 8, and 12.

The tertiary Estimand 1B will be the population average treatment effect on the change from baseline in HbA1c at Week 16 of PF-06882961 compared to placebo, regardless of the initiation of glycemic rescue medication or discontinuation of IP in participants on stable doses of background metformin and/or diet and exercise. This reflects a 'Treatment Policy' strategy as outlined in the ICH-E9 (R1) draft guidance.[16]

Any missing data (for example due to study withdrawal or laboratory failure) will have data imputed based on a MAR assumption. The population-based treatment effect will be determined for each individual time point based on the differences in the mean change from baseline in each PF-06882961 arm compared to placebo.

The tertiary Estimand 1C is similar to 1A, except that the population will exclude participants on a background of diet and exercise only. This also reflects a combination of the 'Hypothetical' and 'While on treatment' strategies as outlined in the ICH-E9 (R1) draft guidance.[16]

Estimands related to achieving HbA1c <7% at Week 16:

A secondary estimand (Estimand 2) will be the population odds ratio of the treatment effect of achieving HbA1c <7% at Week 16 of PF-06882961 compared to placebo in the absence of glycemic rescue medication in participants while on treatment and on stable doses of background metformin and/or diet and exercise. This reflects a combination of the 'Hypothetical' and 'While on treatment' strategies as outlined in the ICH-E9 (R1) draft guidance.[16]

Measurements after initiation of glycemic rescue medication and/or discontinuation of IP 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 HbA1c <7% at Week 16 on PF-06882961 compared to the odds of achieving this on placebo (ie, odds ratio).

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Estimands related to other endpoints:

Estimands 3 and 4 will utilize the same approach as Estimand 1A for the associated endpoint(s).

Other exploratory/tertiary analyses may or may not be analyzed using these estimands and may be analyzed in a descriptive manner without reference to an estimand. Other estimands may be used for some of the primary and secondary endpoints as a means to examine the robustness of results, compare to available literative and/or be used for future study planning as needed. Details of these estimands and analyses will be presented in the SAP.

9.2. Sample Size Determination

The sample size is based on the need to have an adequately sized safety database of participants on PF-06882961 following Phase 2 clinical development. Approximately 400 participants will be randomized for an estimated total of approximately 67 participants per treatment arm. Participants who withdraw from the study will not be replaced. Evaluable participants are defined as in Section 9.3.

Once approximately 400 participants have been randomized into the study, enrollment will be halted and any participants who have signed the ICD and initiated screening procedures at this stage will be permitted to continue the study process to completion/withdrawal.

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 change from baseline (CFB) at Week 16 in HbA1c in participants on a background of stable doses of metformin and/or diet and exercise.

Assuming a conservative 25% drop-out rate there would be expected to be approximately 50 completers per arm. This yields 80% power to detect a placebo-adjusted change in HbA1c of 0.5%, using a 1-sided t-test at a 5% level and assuming a conservative standard deviation (SD) of 1.0%.

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9.3. Populations for Analysis

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign the ICD.
Randomly assigned to investigational product	All participants randomly assigned to IP regardless of whether or not IP was administered.
Evaluable	All participants randomly assigned to IP and who take at least 1 dose of IP. Participants will be analyzed according to the randomized intervention.
Safety Analysis Set	All participants randomly assigned to IP and who take at least 1 dose of IP. Participants will be analyzed according to the product they actually received.

Defined Population for Analysis	Description
Estimand Set 1A (related to estimands 1A, 2, 3, and 4)	All participants randomly assigned to IP and who take at least 1 dose of IP. For participants who discontinue IP and/or receive glycemic rescue medication, all subsequent values will be censored.
Estimand Set 1B	All participants randomly assigned to IP and who take at least 1 dose of IP.
Estimand Set 1C	This analysis set is the same as 1A, except it only includes participants assigned to the metformin strata.
PK Concentration Set	All participants randomly assigned to IP and who take at least 1 dose of PF-06882961 and in whom at least one concentration value is reported.

9.4. Statistical Analyses

The SAP will be developed and finalized before database lock and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

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9.4.1. Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary: Change from baseline in HbA1c at Week 16.	A MMRM analysis of the change from baseline in HbA1c through Week 16 will be used to estimate the treatment effect related to the primary Estimand 1A. The MMRM will include treatment, time, strata (metformin vs. diet and exercise alone) 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. The MMRM model will be fitted to change from baseline to Weeks 2, 4, 6, 8, 12 and 16 from the Estimand Set 1A. Missing values will be imputed as part of the MMRM model assumptions. No adjustments will be made for multiplicity.
Secondary: Response as defined by an HbA1c <7% at Week 16.	A logistic regression analysis of participants who reached a HbA1c goal of <7% at Week 16 and those that didn't will be used to estimate the treatment effect related to the secondary estimand 2. The logistic regression model will include a term for treatment, strata (metformin vs. diet and exercise alone), and baseline HbA1c will be included as a covariate. This model will be fitted to the Week 16 timepoint only from the Estimand Set 1A. No adjustments will be made for multiplicity.
Secondary: Change from baseline in fasting plasma glucose through and at Weeks 2, 4, 6, 8, 12 and 16.	Changes from baseline in fasting plasma glucose at Weeks 2, 4, 6, 8, 12 and 16 will be analyzed using a similar MMRM model to that used for the primary endpoint. Baseline fasting plasma glucose will be included as a covariate in the model, rather than baseline HbA1c. No adjustments will be made for multiplicity. This analysis will be applied to the Estimand Set 1A to estimate the treatment effect related to Estimand 3.
Secondary: Change from baseline in body weight at Weeks 2, 4, 6, 8, 12 and 16.	Changes from baseline in body weight will be analyzed using a similar MMRM model to that used for the primary endpoint. Baseline body weight will be included as a covariate in the model, rather than baseline HbA1c. No adjustments will be made for multiplicity. This analysis will be applied to the Estimand Set 1A to estimate the treatment effect related to Estimand 4.
Exploratory	Will be described in the SAP finalized before database lock.

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9.4.2. Safety Analyses

All safety analyses will be performed on the safety population.

Endpoint	Statistical Analysis Methods
Secondary	The safety data will be summarized in accordance with Pfizer Data Standards. All participants who receive IP (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 3. Results may also be reported by strata (metformin vs. diet and exercise alone), where details will be described in the SAP.

9.4.2.1. Electrocardiogram Analyses

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

The number (%) of participants with maximum postdose 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

9.4.3. Other Analyses

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 clinical study report (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.

9.4.3.1. Pharmacokinetic Analyses

Predose (C_{trough}) plasma PF-06882961 concentration data will be summarized descriptively by dose and visit. The post dose random plasma concentration data will *only* be listed.

In addition, as permitted by data and determined by the sponsor, PK-PD relationship between plasma concentrations of PF-06882961 and effect on primary, secondary and tertiary endpoints may be characterized using a population PK-PD approach. The objective of such an analysis, if conducted, would aim to explore potential demographic determinants (eg, age, gender, and weight) influencing the observed PK or PD variability in response to

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PF-06882961. The population PK-PD analysis, if conducted, will be reported separately from the main 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 100) 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, stopping for futility, stopping for early success, or conducting a sample size reestimation. 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 standard operating procedure (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. Data Monitoring Committee

This study will use an IRC; an external data monitoring committee will not be utilized.

9.6. 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, HbA1c, vitals, ECGs, body weight, nausea burden score and potentially other PD markers.

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10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

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

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

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

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

The investigator will be responsible for the following:

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

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

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

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

10.1.2. Financial Disclosure

Investigators and sub investigators 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 or his/her legally authorized representative and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representative defined as legal guardian will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant or his or her legally authorized representative 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 or his or her legally authorized representative 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.

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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 or the participant's legally authorized representative.

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

The ICD will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate in this optional research will not provide this separate signature.

10.1.4. Data Protection

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

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

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

10.1.5. Dissemination of Clinical Study Data

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

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

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. US Basic Results are generally submitted for posting within 1 year of the primary completion date (PCD) for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

PCD is defined as the date that the final participant was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the prespecified protocol or was terminated.

EudraCT

Pfizer posts European Union (EU) Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the PCD for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

www.pfizer.com

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

Documents within marketing authorization packages/submissions

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

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Data Sharing

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

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

10.1.6. Data Quality Assurance

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

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

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

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

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

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

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

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

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

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

10.1.7. Source Documents

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

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

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

10.1.8. Study and Site Closure

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

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

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

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

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

10.1.9. Publication Policy

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

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

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

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

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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 study team on demand (SToD) system.

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

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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 concerns.

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

a. Only if urine dipstick is positive for blood, protein, nitrites or leukocyte esterase.
b. For female subjects to confirm post-menopausal status only.

Abbreviations: Abs = absolute; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; βhCG = beta human chorionic gonadotropin; BUN = blood urea nitrogen; CO2 = carbon dioxide; eGFR = estimated glomerular filtration rate; FSH = follicle stimulating hormone; GGT = gamma-glutamyl transferase; HbA1c = glycated hemoglobin; HDL-C = high density lipoprotein cholesterol; INR = international normalized ratio; LDL-C = low density lipoprotein cholesterol; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; PT = prothrombin time; qual = qualitative; RBC = red blood cell; TSH = thyroid stimulating hormone; WBC = white blood cell.

Investigators must document their review of each laboratory safety report.

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After randomization, the sponsor study team and site will be blinded to HbA1c, fasting plasma glucose, glucagon, and fasting plasma insulin measured by the central laboratory, unless the fasting plasma glucose meets the criterion for hypo-or hyper-glycemia as listed in Section 8.2.5.2 and 8.2.5.3.

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

10.3.1. Definition of AE

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

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or SAE if they fulfill the definition of an AE or SAE.

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

10.3.2. Definition of SAE

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

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

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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 clincical 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 serous expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

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

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording adverse events on the CRF and for reporting serious adverse events on the Clinical Trial (CT) Serious Adverse Event (SAE) Report Form to Pfizer Safety. These requirements are delineated for 3 types of

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events: (1) SAEs; (2) nonserious adverse events (AEs); and (3) exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure.

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

Safety Event	**Recorded on the CRF**	**Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness**
SAE	All	All
Nonserious AE	All	None
Exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure	All AEs/SAEs associated with exposure during pregnancy or breastfeeding Occupational exposure is not recorded	All (and exposure during pregnancy [EDP] supplemental form for EDP) Note: Include all SAEs associated with exposure during pregnancy or breastfeeding. Include all AEs/SAEs associated with occupational exposure

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

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(not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

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

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

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

Assessment of Causality

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

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for every event before the initial transmission of the SAE data to the sponsor.

- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

Follow-up of AEs and SAEs

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

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.

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- The site will enter the SAE data into the electronic system as soon as the data become available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.

SAE Reporting to Pfizer Safety via CT SAE Report Form

- Facsimile transmission of the CT SAE Report Form is the preferred method to transmit this information to Pfizer Safety.
- In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the CT SAE Report Form sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the CT SAE Report Form pages within the designated reporting time frames.

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10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

10.4.1. Male Participant Reproductive Inclusion Criteria

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

10.4.2. Female Participant Reproductive Inclusion Criteria

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

- Is not a woman of child bearing potential (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 interevention.

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), with high usere 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 (WOCBP)

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

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

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Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:

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

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

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

2. Postmenopausal female:

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

10.4.4. Contraception Methods

Highly Effective Methods That Have Low User Dependency

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.
2. Intrauterine device (IUD).
3. Intrauterine hormone-releasing system (IUS).
4. Bilateral tubal occlusion.
5. Vasectomized partner.

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- 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).

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Collection of Pregnancy Information

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy (EDP) occurs if:

- A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the investigational product;
    - An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).
- A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a participant or participant's partner becomes or is found to be pregnant during the participant's treatment with the investigational product, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a participant reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) to Pfizer Safety using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

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

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

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Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

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

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

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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.

- Genetic research may consist of the analysis of 1 or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).

- The samples may be analyzed as part of a multistudy assessment of genetic factors involved in the response to PF-06882961 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 the clinical study report (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 (see Sections 8.7.2 and 8.8.4) will be stored indefinitely or other 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.

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

Potential Cases of Drug-Induced Liver Injury

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

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

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

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

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

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

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

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

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

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

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

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

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10.7. Appendix 7: ECG Findings of Potential Clinical Concern

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

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

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

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

ECG Findings That Qualify as Serious Adverse Events

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

The enumerated list of major events of potential clinical concern are not to be considered as all inclusive of what to be reported as AEs/SAEs.

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10.8. Appendix 8: Prohibited Prior/Concomitant Medications

The following medications are prohibited until the first follow-up visit (ie, Visit 10, Week 17-18), 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 Screening Visit**
Thiazolidinediones (TZDs) such as pioglitazone and rosiglitazone.	90 days
Subcutaneously administered agents for glycemic control (eg, insulin, exenatide, liraglutide, dulaglutide, semaglutide, pramlintide). ***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: Sulfonylureas such as acetohexamide, chlorpropamide, tolazamide, tolbutamide, glimepiride, glipizide, glyburide. ***Note***: These may be used as glycemic rescue medications (See Section 6.5.5). Meglitinide analogues such as repaglinide, nateglinide. Dipeptidyl peptidase 4 inhibitors (DPP 4i) such as sitagliptin, saxagliptin, linagliptin, vildagliptin. α glucosidase inhibitors such as acarbose, miglitol. Sodium glucose cotransporter 2 (SGLT2) inhibitors such as canagliflozin, empagliflozin, dapagliflozin, ertugliflozin. ***Note***: These may be used as glycemic rescue medications (See Section 6.5.5). 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. ***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).	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). ***Note***: β-adrenergic receptor blocking agents (eg, atenolol, metoprolol) and	60 days

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Drug Classes and/or Drugs	**Timeframe of Restriction Prior to Screening Visit**
calcium channel blockers (eg, diltiazem, amlodipine, nifedipine) are permitted.	
Sympathomimetic agents. ***Note***: Inhaled β-adrenergic receptor agonists (eg albuterol) are permitted.	60 days
BCRP Substrates. Rosuvastatin. ***Note***: Other statins are permitted. Sulfasalazine.	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).	Prohibited post randomization
Use of chronic agents which are clinically significant OATP inhibitors (eg, cyclosporine, gemfibrozil, rifampin).	Prohibited post randomization
Use of potent 3A4 inhibitors.	Prohibited post randomization
Paclitaxel, torsemide, amodiaquine.	Prohibited post randomization

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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:

- 12-lead ECG: obtain prior to vital signs assessment, blood samples, and prior to dosing (except for post-dose collection) (see Section 8.2.4);
- Vital Signs (BP, PR): obtain after 12-lead ECG collection but prior to obtaining blood samples and prior to dosing (except for post-dose collection) (see Section 8.2.3);
- Fasting blood samples [for Safety (see Section 8.2.6, PK (see Section 8.5), Biomarkers (see Section 8.8) 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;
- Body weight: obtain prior to dosing and food consumption (see Section 8.2.2);
- For the random, post dose PK blood collection to occur approximately 2 to 6 hours post dose (see Section 8.5): if collection time coincides with time of a meal/snack, these blood samples should be collected just prior to the meal/snack;
- Other pre-dose procedures: obtain sample/perform procedure as close as possible to the scheduled time, but may be obtained before or after blood sample collection(s);
- Dosing: must occur with food, in the morning; and where applicable, after any pre-dose blood sample collection(s).

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10.10. Appendix 10: Abbreviations

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

Abbreviation	Term
Abs	absolute
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC_{24}	area under the curve at 24 hours
AV	atrioventricular
BBS	Biospecimen Banking System
BCRP	breast cancer resistance protein
β-hCG	beta-human chorionic gonadotropin
BID	twice daily
BMI	body mass index
BP	blood pressure
bpm	beats per minute
BUN	blood urea nitrogen
cAMP	cyclic adenosine monophosphate
CFB	change from baseline
CFR	Code of Federal Regulations
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
C_{trough}	trough concentration
%CV	percent coefficients of variance
CYP	cytochrome P450
DDI	drug drug interaction
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
DU	dispensable unit
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EDP	exposure during pregnancy
eGFR	estimated glomerular filtration rate

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Abbreviation	Term
EMA	European Medicines Agency
EU	European Union
EudraCT	European Clinical Trials Database
FPG	fasting plasma glucose
FPI	fasting plasma insulin
FSH	follicle-stimulating hormone
FT4	free thyroxine
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
HbA_{1c}	glycated hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HOMA-IR	homeostatic model assessment of insulin resistance
HRT	hormone replacement therapy
IB	investigator's brochure
IR	immediate release
ICD	informed consent document
ICH	International Council for Harmonisation
ID	identification
IMP	investigational medicinal product
IND	investigational new drug application
INR	international normalized ratio
IP	investigational product
IRB	institutional review board
IRC	internal review committee
IRT	interactive response technology
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
IVGTT	intravenous glucose tolerance test
IWR	interactive Web-based response
K2 EDTA	dipotassium edetic acid (ethylenediaminetetraacetic acid)
LBBB	left bundle branch block
LFT	liver function test
MAR	missing at random
MATE	multidrug and toxin extrusion protein
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume

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Abbreviation	Term
MDG	mean daily glucose
MDR1	multidrug resistance mutation
MEN2	multiple endocrine neoplasia syndrome type 2
MMRM	mixed model repeated measures
msec	millisecond
MTC	medullary thyroid carcinoma
N/A	not applicable
NIMP	noninvestigational medicinal product
NOAEL	no-observed-adverse-effect level
OATP	organic anion transporting polypeptides
OCT	organic cation transporter
PCD	primary completion date
PD	pharmacodynamic(s)
PI	principal investigator
PK	pharmacokinetic(s)
PR	pulse rate
PT	prothrombin time
PVC	premature ventricular complex
QTc	corrected QT
QTcF	corrected QT (Fridericia method)
qual	qualitative
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation
SGLT2	sodium glucose co-transporter 2
SMP	study monitoring plan
SoA	schedule of activities
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
$t_{½}$	half life
T2DM	type 2 diabetes mellitus
TBA	total bile acids
TBili	total bilirubin
TEAE	treatment emergent adverse event
TI	therapeutic index
T_{max}	time to maximal concentration

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Abbreviation	Term
TSH	thyroid stimulating hormone
TZD	thiazolediediones
UGT	uridine 5'-diphospho-glucuronosyltransferase glucuronosyltransferase
ULN	upper limit of normal
US	United States
WBC	white blood cell
WOCBP	woman of childbearing potential

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Protocol C3421005

A 16-WEEK, PHASE 2B, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL GROUP STUDY TO EVALUATE THE EFFICACY AND SAFETY OF TWICE DAILY PF-06882961 ADMINISTRATION IN ADULTS WITH TYPE 2 DIABETES MELLITUS INADEQUATELY CONTROLLED ON METFORMIN OR DIET AND EXERCISE

Statistical Analysis Plan
(SAP)

Version: 2.0

Date: 21 JUL 2021

NOTE: *Italicized* text within this document has been taken verbatim from the Protocol.

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APPENDICES

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1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
2 21 Jul 2021	Amendment 1 19 May 2020	Updates based on SAP template update, protocol amendment, A&R plan review and Blinded Data Reviews.	Minor updates to page header and footers and addition of list of abbreviations appendix table. *Rationale:* update to latest SAP template. Sections 2.1, 3.3, 6.3.2 & 7.1: Updated glucagon analysis time points and interim analysis wording based on protocol amendment and clarified throughout that glucagon should be fasting for summaries and analysis. *Rationale:* consistent with latest protocol amendment. Sections 2.1.2.1, 3.2, 4 & 6.3.4: Updated and clarified Secondary Estimand definition in reference to intercurrent events for a response in HbA1c (and also separately, Body Weight). *Rationale:* SAP wording was not consistent with protocol, reverted back to protocol wording and added some clarifications. Section 3.2: Included HOMA-IR calculation. *Rationale:* calculation wasn't originally included. Sections 3.5.1, 3.5.1.1 & 3.5.6: Minor updates related to adverse event and burden score definitions. *Rationale:* minor clarifications based on occurrences identified during BDR reviews. Sections 3.5.3.1 & 6.6.2.1: Added %change from baseline summaries of labs of interest, added box and whisker plots, added MMRM analyses and the parameters bile acids, eGFR and GGT. *Rationale:* permit a more comprehensive review of additional safety parameters.

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			Sections 3.5.3.2 & 6.6.2.2: Added a table summarizing specific clinical laboratory parameters of interest where values met a flag or alert level. *Rationale:* permit a more comprehensive review of lab parameters of interest. Sections 3.5.4 & 3.5.5: Added that averages of triplicates would be used for baseline vitals and ECGs. *Rationale:* minor clarification. Section 4.1: Removed listing comparing randomization stratum to concomitant medication categorization. *Rationale:* clinical database was to have the correct randomization stratum included, so listing won't provide value. Sections 5.1 & Section 6.6.1: Added description of hypotheses and error rates for secondary endpoints. *Rationale:* pre-specify type I error rates for secondary objectives. Section 5.2.3: Added p-values to be reported for various outputs and clarified two-sided. *Rationale:* aid in future publication writing. Sections 5.2.7, 6.5.6, 6.6.1.3 & Appendix 4: Re-named Kaplan-Meier Curve Plots to Cumulative Incidence Plots and provided more details along with SAS code. *Rationale:* refer to the plots using the correct terminology with more clarity. Section 6.1.1.1.1: Clarified details on summaries, added box and whisker plots and added figures restricted to Week 16. *Rationale:* provide more information on primary and other key endpoints. Section 6.5.2: Added that COVID-19 related outputs would follow sponsor reporting

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			standards. *Rationale:* ensure appropriate reporting of COVID-19 related events. Section 6.5.3: Removed Demographic data summary. *Rationale:* Section duplicated information included in Section 6.5.1 Sections 6.5.2, 6.5.4, 6.5.5, 6.5.6, 6.6.1.2, 6.6.1.4, 6.6.2, 6.6.2.2 & 6.6.5: Added overall summary. *Rationale:* provide an overview of entire study population. Section 6.6.1.4: Added information on how percentage was calculated for % of participants with ongoing AEs of interest. *Rationale:* clearly specify algorithm. Section 6.6.1.5: Added summaries on time to discontinuation from IP due to gastrointestinal disorders AEs. *Rationale:* describe more information the timing of discontinuation for certain AEs. Sections 6.6.3 & 6.6.4: Removed summaries of differences to placebo for vital signs and ECG parameters and replaced with MMRM analyses. *Rationale:* provide a more comprehensive assessment of these safety parameters. Section 6.6.5: Added summary of nausea burden scores. *Rationale:* This section was omitted from the 1st version of the SAP.
1 8 Oct 2019	Original 3 Apr 2019	N/A	N/A

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2. INTRODUCTION

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study C3421005. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

2.1. Study Objectives, Endpoints, and Estimands

Objectives	***Endpoints***	***Estimands***
Primary:	***Primary:***	***Primary:***
To compare the effect of multiple dose levels of PF-06882961 versus placebo on glycated hemoglobin (HbA1c) in participants with type 2 diabetes mellitus (*T2DM*) *on stable doses of metformin and/or diet and exercise.*	*Change from baseline in HbA1c at Week 16.*	*Estimand 1A: This estimand is intended to provide a population level estimate of the mean treatment effect (PF-06882961 versus placebo) on a continuous endpoint in participants on stable doses of metformin and/or diet and exercise without the benefit of glycemic rescue medication while on treatment.*
Secondary:	***Secondary:***	***Secondary:***
To compare the effect of multiple dose levels of PF-06882961 versus placebo on glycemic control in participants with T2DM on stable doses of metformin and/or diet and exercise.	*Response as defined by an HbA1c <7% at Week 16.*	*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 responder endpoint in participants on stable doses of metformin and/or diet and exercise without the benefit of glycemic rescue medication.*
	Change from baseline in HbA1c at Weeks 2, 4, 6, 8 and 12.	*Estimand 1A as above.*
	Change from baseline in fasting plasma glucose at Weeks, 2, 4, 6, 8, 12 and 16.	*Estimand 3: This estimand will be the same as 1A.*
To compare the effect of multiple dose levels of PF-06882961 versus placebo on body weight in participants with T2DM on stable doses of metformin and/or diet and exercise.	*Change from baseline in body weight at Weeks 2, 4, 6, 8, 12 and 16.*	*Estimand 4: This estimand will be the same as 1A.*
To characterize the safety and tolerability of multiple dose levels of PF-06882961 administered to participants with T2DM on stable	*Incidence of treatment emergent adverse events [adverse events (AEs) and serious adverse events (SAEs)], clinical laboratory abnormalities, vital signs (blood pressure and pulse rate) and electrocardiogram (ECG)*	*There are no defined estimands for these endpoints and they will be analyzed using Pfizer data standards as applicable.*

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doses of metformin and/or diet and exercise.	*parameters (heart rate, QT, QTcF, PR and QRS intervals).*	
Tertiary/Exploratory:	***Tertiary/Exploratory:***	***Tertiary/Exploratory:***
To compare the effect of multiple dose levels of PF-06882961 versus placebo on HbA1c in participants with T2DM on stable doses of metformin and/or diet and exercise.	*Change from baseline in HbA1c at Weeks 2, 4, 6, 8, 12 and 16.*	*Estimand 1B: This estimand is intended to provide a population level estimate of the mean treatment effect (PF-06882961 versus placebo) on a continuous endpoint in participants on stable doses of metformin and/or diet and exercise regardless of the initiation of glycemic rescue medication or discontinuation of IP.*
To compare the effect of multiple dose levels of PF-06882961 versus placebo on HbA1c in participants with T2DM on stable doses of metformin.	*Change from baseline in HbA1c at Weeks 2, 4, 6, 8, 12 and 16.*	*Estimand 1C: This estimand is intended to provide a population level estimate of the mean treatment effect (PF-06882961 versus placebo) on a continuous endpoint in participants on stable doses of metformin without the benefit of glycemic rescue medication whilst on treatment.*
To compare the effect of multiple dose levels of PF-06882961 versus placebo on metabolic parameters in participants with T2DM on stable doses of metformin and/or diet and exercise.	*Change from baseline in fasting insulin, and homeostatic model assessment of insulin resistance (HOMA-IR) at Weeks 4, 8, 12 and 16.* *Change from baseline in fasting glucagon at Weeks 8 and 16.*	*There are no defined estimands for these endpoints and they will be analyzed using Pfizer data standards as applicable.*
To compare the effect of multiple dose levels of PF-06882961 versus placebo on body weight in participants with T2DM on stable doses of metformin and/or diet and exercise.	*Response as defined by a ≥5% body weight loss at Week 16.*	*There are no defined estimands for these endpoints and they will be analyzed using Pfizer data standards as applicable.*
To characterize the PK of PF-06882961 to participants with T2DM on stable doses of metformin and/or diet and exercise.	*Plasma concentrations of PF-06882961 at time points specified in the schedule of activities (SoA)* given in the protocol.	*There is no defined estimand for these endpoints and they will be analyzed using Pfizer data standards as applicable.*
To characterize the gastrointestinal tolerability during different doses and titration schemes of PF-06882961 administered to participants with T2DM on stable doses of metformin and/or diet and exercise.	*Nausea burden score over 16 weeks of dosing.*	*There is no defined estimand for this endpoint and it will be analyzed using Pfizer data standards as applicable.*
To enable exploratory research through collection of banked biospecimens, unless prohibited by	*Potential results from exploratory analysis of banked biospecimens (these results may or may not be*	*Not applicable.*

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local regulations or ethics committee decision.	*generated in the context of the present study).*	
*For **all** endpoints, baseline is defined as the result closest prior to dosing at Visit 3 (Day 1).*		

2.1.1. Primary Estimand(s)

The primary estimand (Estimand 1A) will be the population average treatment effect on the change from baseline in HbA1c at Week 16 of PF-06882961 compared to placebo in the absence of glycemic rescue medication while on treatment and stable doses of background metformin and/or diet and exercise. This reflects a combination of the 'Hypothetical' and 'While on treatment' strategies as outlined in the ICH-E9 (R1) draft guidance (1). It includes the following 4 attributes:

- Population: Defined by the inclusion and exclusion criteria to reflect participants with T2DM who are on a background of metformin and/or diet & exercise
- Variable: Change from baseline in HbA1c (%) at Week 16
- Intercurrent events: All data after an intercurrent event of glycemic rescue medication and/or discontinuation of investigational product (IP) will be censored
- Population-level summary: Difference of variable means between PF-06882961 (each dose considered separately) and placebo

2.1.2. Secondary Estimand(s)

2.1.2.1. Estimand Related to Achieving HbA1c <7% at Week 16

A secondary estimand (Estimand 2) will be the population odds ratio of the treatment effect of achieving HbA1c <7% at Week 16 of PF-06882961 compared to placebo in the absence of glycemic rescue medication in participants while on treatment and on stable doses of background metformin and/or diet and exercise. This reflects a combination of the 'Hypothetical' and 'While on treatment' strategies as outlined in the ICH-E9 (R1) draft guidance (1). It includes the following 4 attributes:

- Population: Defined by the inclusion and exclusion criteria to reflect participants with T2DM who are on a background of metformin and/or diet & exercise
- Variable: Response as defined by an HbA1c <7% at Week 16
- Intercurrent events: Any participant with an intercurrent event of glycemic rescue medication and/or discontinuation of IP prior to Week 16 will have all subsequent data

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censored if not missing. Missing or censored values at Week 16 will be imputed (assuming missing at random [MAR]) to determine a response classification.

- Population-level summary: Odds ratio for a response between PF-06882961 (each dose considered separately) and placebo

2.1.2.2. Estimands Related to Fasting Plasma Glucose and Body Weight

These estimands (Estimands 3 and 4) will utilize the same approach as Estimand 1A (Section 2.1.1) for the associated endpoint(s).

2.1.3. Additional Estimand(s)

Two additional estimands related to the primary endpoint have been specified under Tertiary/Exploratory objectives.

A tertiary estimand (Estimand 1B) will be the population average treatment effect on the change from baseline in HbA1c at Weeks 2, 4, 6, 8, 12 and 16 of PF-06882961 compared to placebo regardless of the initiation of glycemic rescue medication or discontinuation of IP in participants on stable doses of background metformin and/or diet and exercise. This reflects the 'Treatment Policy' strategy as outlined in the ICH-E9 (R1) draft guidance (1). It includes the following 4 attributes:

- Population: Defined by the inclusion and exclusion criteria to reflect participants with T2DM who are on a background of metformin and/or diet & exercise
- Variable: Change from baseline in HbA1c at Weeks 2, 4, 6, 8, 12 and 16
- Intercurrent events: All data collected (regardless of initiation of glycemic rescue medication or discontinuation of IP) are included
- Population-level summary: Difference of variable means between PF-06882961 (each dose considered separately) and placebo

An additional tertiary estimand (Estimand 1C) will be the same as the primary estimand (Estimand 1A), except that the population will be restricted to participants on a background of metformin only.

2.2. Study Design

This Phase 2b, multi-center, randomized, double-blind, placebo-controlled, 6 - arm, parallel group, study will assess efficacy and safety of twice daily administration of PF-06882961 in adult participants with T2DM inadequately controlled on metformin monotherapy or diet and exercise alone. At least 80% of the enrolled participants are required to be on metformin prior to screening.

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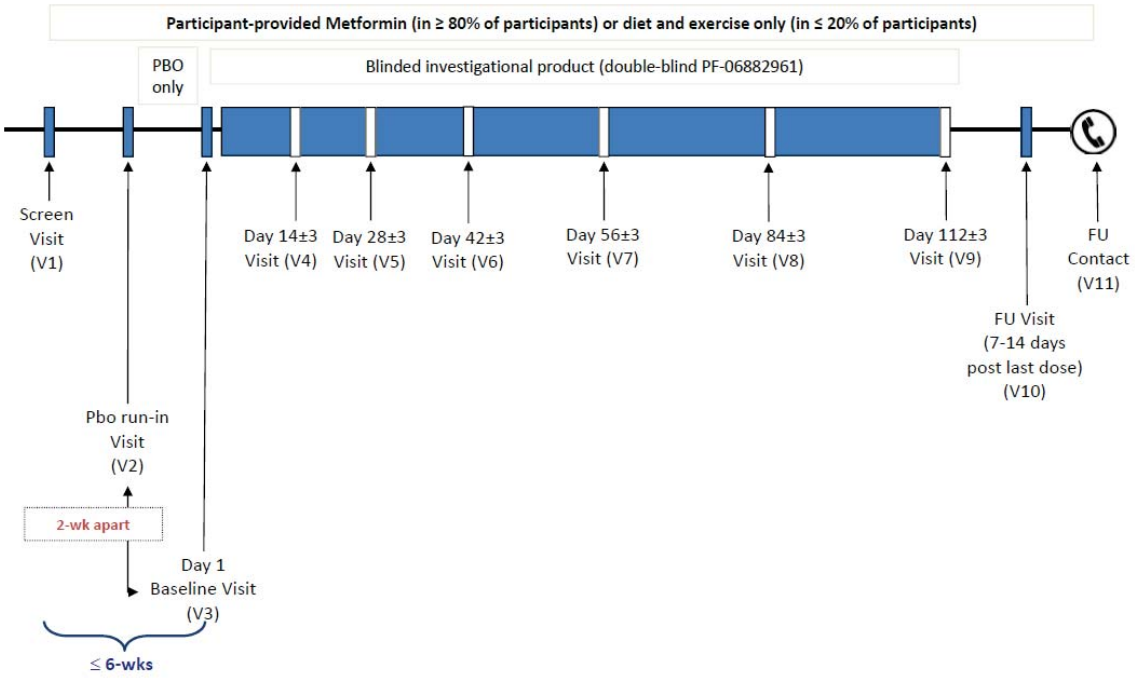
Following the screening period to confirm eligibility (up to 4-weeks), the study will consist of a 2-week placebo run-in period, prior to randomization on Day 1. The treatment period will be 16 weeks, followed by an approximate 4-week follow-up. The total duration of participation in this study is approximately 22 weeks, not including the screening period.

Participants will be randomized to one of the following 6 treatment arms (in a 1:1:1:1:1:1 ratio): placebo, 2.5 mg BID, 10 mg BID, 40 mg BID, 80 mg BID or 120 mg BID. *Dosing will occur with food twice daily, and up to 6 weeks of the 16-week dosing duration will be used for dose titration to maximize tolerability of PF-06882961.*

Approximately 400 participants (approximately 67 participants per treatment arm) will be randomized to ensure completion of approximately 300 participants (approximately 50 participants per treatment arm). Randomization will be stratified according to background diabetes treatment (presence or absence of metformin therapy).



3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

Baseline is defined as the result closest prior to dosing at Visit 3 (Day 1) for all endpoints.

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3.1. Primary Endpoint(s)

The primary efficacy endpoint is the change from baseline in HbA1c at Week 16.

3.2. Secondary Endpoint(s)

- Response as defined by an HbA1c <7% at Week 16

This endpoint will have two levels: 'Response' and 'Non-response'. The former will be based on participants having an HbA1c < 7% at Week 16, otherwise participants with a value ≥ 7% will be classed as having a 'Non-response'. Participants with an intercurrent event of starting glycemic rescue medication and/or discontinuation of IP prior to Week 16 will have all subsequent data censored if not missing. If glycemic rescue medication and/or discontinuation of IP occurs at Week 16, the data will not be censored. The intercurrent event that occurs first during the study will take precedence for determining the censoring of data. Missing or censored values at Week 16 will be imputed as described in Section 5.3.

- Change from baseline in HbA1c at Weeks 2, 4, 6, 8 and 12
- Change from baseline in fasting plasma glucose at Weeks 2, 4, 6, 8, 12 and 16
- Change from baseline in body weight at Weeks 2, 4, 6, 8, 12 and 16

The average of the duplicate body weight readings collected at each assessment time will be calculated prior to summaries/analysis. If one of the two duplicates are missing, the non-missing value will be used, and missing values will not be imputed. Both the absolute change and %change from baseline in body weight will be calculated.

3.3. Other Endpoint(s)

- Change from baseline in fasting insulin at Weeks 4, 8, 12 and 16
- Change from baseline in fasting glucagon at Weeks 8 and 16
- Change from baseline in HOMA-IR at Weeks 4, 8, 12 and 16

HOMA-IR is calculated as: (fasting plasma insulin × fasting plasma glucose)/405.

- Response as defined by a ≥5% body weight loss at Week 16

This endpoint will have two levels: 'Response' and 'Non-response'. The former will be based on participants having a ≥5% loss from baseline body weight at Week 16, otherwise participants with a value < 5% will be classed as having a 'Non-response'. Participants with an intercurrent event of starting glycemic rescue medication and/or discontinuation of IP prior to Week 16 will have all subsequent data censored if not missing. If glycemic rescue medication and/or discontinuation of IP occurs at Week 16, the data will not be censored.

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The intercurrent event that occurs first during the study will take precedence for determining the censoring of data. Missing or censored values at Week 16 will be imputed as described in Section 5.3.

- Plasma concentrations of PF-06882961 at time points specified in the SoA in the protocol.

3.4. Baseline Variables

Baseline measures will be included as a covariate in all applicable statistical models along with the stratification variable of whether or not a participant was on background metformin at screening (see Section 4.1).

The statistician may conduct further exploratory analyses into the effect of covariates and factors (such as gender, age and strata) on the efficacy endpoints. If conducted, and considered relevant to the clinical study report (CSR), the methods will be fully justified and discussed within the report.

3.5. Safety Endpoints

3.5.1. Adverse Events

An adverse event is considered treatment emergent (TEAE) relative to a given treatment if:

- the event starts during the effective duration of treatment (i.e. starting on or after the first dose but before the last dose plus lag time)

The effective duration of treatment is determined by the lag time. Any event occurring within the lag time, whether this occurs during a break in treatment or at the end of treatment, is attributed to the corresponding treatment period. The lag time is defined by the Pfizer Standard of 365 days post last dose of IP.

Adverse events occurring during the placebo run-in period (i.e. starting from Day -14, inclusive, up to and before the first dose of active treatment on Day 1) will be considered non-treatment emergent.

A 3-tier approach will be used to summarize TEAEs. Under this approach, TEAEs are classified into 1 of 3 tiers. Different analyses will be performed for different tiers (see Section 6.6.1).

Tier 1 events: These are prespecified events of clinical importance and are maintained in a list in the product's Safety Review Plan (or similar, e.g. Safety Surveillance Review Plan).

Tier 2 events: These are events that are not tier 1 but are "common." A Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT) is defined as a Tier 2 event if there are at least 5% of participants reporting the event in any treatment group.

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Tier 3 events: These are events that are neither Tier 1 nor Tier 2 events.

3.5.1.1. Subset Reporting Interval

A summary of adverse events occurring during a subset of the main reporting interval will be based on a shorter reporting window. This will include all TEAEs starting after or on the first dose, but doesn't start more than two days after the last dose of IP (defined as either completing the 16 weeks of treatment or discontinuing from IP earlier).

3.5.2. Hypoglycemic Monitoring

Hypoglycemia AEs will be recorded in the AE Case Report Form (CRF) with details of the event captured on the Hypoglycemic Event Details CRF. Details of when these will be recorded are given in the protocol Section 8.2.5.2.

For programming purposes, the hypoglycemic AE categories are based on the following:

- Severe Hypoglycemia: Severe is checked in the severity criteria of the CRF. This assessment will be made by the PI based on the protocol definition.
- Documented Symptomatic Hypoglycemia: If (1 – Did the participant have symptoms of hypoglycemia?) Yes and (2 – Was the blood glucose measured?) Yes and result <70 mg/dL on the CRF, but hypoglycemia is not classified as severe.
- Asymptomatic Hypoglycemia: If (1) No and (2) Yes and result <70 mg/dL on the CRF, but hypoglycemia is not classified as severe.
- Probable Symptomatic Hypoglycemia: If (1) Yes and (2) No and (2b – If blood glucose was not measured, did symptoms resolve when treated with carbohydrate or glucagon?) Yes on the CRF, but hypoglycemia is not classified as severe.

3.5.3. Laboratory Data

Safety laboratory tests (hematology, chemistry, urine testing and other clinical laboratory tests) will be performed as described in the protocol.

To determine if there are any clinically significant laboratory abnormalities, the safety tests will be assessed against the criteria specified in the sponsor reporting standards. The assessment will take into account whether each participant's baseline test result is within or outside the laboratory reference range for the particular laboratory parameter.

Baseline for all laboratory measurements will be defined as the result closest prior to dosing at Visit 3 (Day 1).

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3.5.3.1. Change from Baseline Summaries

Focused change from baseline summaries (including both absolute changes from baseline and percent change from baseline, calculated separately) of the following safety laboratory endpoints will be assessed:

- Change from baseline in calcitonin to all post-dose time points as per the SOA
- Change from baseline in amylase to all post-dose time points as per the SOA
- Change from baseline in lipase to all post-dose time points as per the SOA
- Change from baseline in thyroid stimulating hormone (TSH) to all post-dose time points as per the SOA
- Change from baseline in free thyroxine (free T4) to all post-dose time points as per the SOA
- Change from baseline in lipid profile (total cholesterol, direct LDL cholesterol, HDL cholesterol and triglycerides) to all post-dose time points as per the SOA
- Change from baseline in liver function tests (ALT, AST, alkaline phosphatase, total bilirubin, bile acids and gamma-glutamyl transferase [GGT]) to all post-dose time points as per the SOA
- Change from baseline in estimated glomerular filtration rate (eGFR) to all post-dose time points as per the SOA

3.5.3.2. Clinical Laboratory Parameters of Interest

For the specific laboratory parameters listed in the table below, the following endpoints will be derived:

- Abnormalities defined as either a “Flag Level” or “Alert Level” as in the table below

Parameter	Flag Level	Alert Level	Conventional Units
Fasting Plasma Glucose	< 70	≤ 54	mg/dL
	≥ 270	≥ 270	
Amylase	>ULN	Pfizer standard flag for PCC	U/L
Lipase	>ULN	Pfizer standard flag for PCC	U/L
Calcitonin	>ULN	Pfizer standard flag for PCC	pg/mL

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Alanine Aminotransferase	≥ 2 ULN	Pfizer standard flag for PCC	U/L
Aspartate Aminotransferase	≥ 2 ULN	Pfizer standard flag for PCC	U/L
Alkaline Phosphatase	≥ 2 ULN	Pfizer standard flag for PCC	U/L
Gamma Glutamyl Transferase	≥ ULN	Pfizer standard flag for PCC	U/L
Total Bilirubin	> 1.5 ULN	Pfizer standard flag for PCC	mg/dL
Serum Total Bile Acids	>ULN	Pfizer standard flag for PCC	µmol/L

PCC – potential clinical concern
ULN – upper limit of normal as determined by the central laboratory

These endpoints will be derived using both pre and post-dose data separately. Post-dose will include all post-baseline data including unplanned readings and pre-dose will include all data from the placebo run-in defined by including all values from Visit 2 to pre-dose, including the baseline measurement and unplanned readings. Note, both pre- and post-dose populations will be from the safety analysis set (defined in Section 4).

3.5.4. Vital Signs

Vital sign measurements (blood pressure and pulse rate) will be taken as detailed in the Schedule of Activities given in the protocol. The average of the triplicate measurements collected at each appropriate assessment time will be calculated for each vital sign parameter.

Baseline will be defined as the average of the triplicate measurements at the visit closest prior to dosing at Visit 3 (Day 1).

Changes from baseline for supine systolic and diastolic blood pressure and pulse rate will be calculated for each post baseline measurement.

3.5.5. Electrocardiogram (ECG)

Standard 12-lead ECG (including heart rate, QT, QTcF, PR and QRS interval) will be obtained at times detailed in the Schedule of Activities given in the protocol. The average of the triplicate readings collected at each appropriate assessment time will be calculated for each ECG parameter.

Baseline will be defined as the average of the triplicate measurements at the visit closest prior to dosing at Visit 3 (Day 1).

Change from baseline for heart rate, QT, QTcF, PR and QRS interval will be calculated for each post baseline measurement.

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3.5.6. Nausea burden score over 16 weeks of dosing

The nausea burden score is based on the incidence of TEAEs of nausea reported during the dosing period over 16 weeks (i.e. starting on or after the first dose on Day 1 to Week 16, inclusive). The nausea burden score is defined as the sum across all occurrences within a participant (with each occurrence being the product of the severity [mild=1, moderate=2, and severe=3] and duration of nausea), normalized by the total duration of therapy. The duration related to the nausea TEAE will not be truncated to the total duration of therapy and so will be the total duration of the adverse event (i.e. it may be greater than 16 weeks of dosing).

The percentage of time participants experience nausea will be calculated based on the above dosing period. If a participant does not experience nausea, the value will be 0%.

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

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

Population	***Description***
Enrolled	*All participants who sign the ICD.*
Randomly assigned to investigational product (IP)	*All participants randomly assigned to IP regardless of whether or not IP was administered.*
Evaluable	*All participants randomly assigned to IP and who take at least 1 dose of IP. Participants will be analyzed according to the randomized intervention.*
Safety Analysis Set	*All participants randomly assigned to IP and who take at least 1 dose of IP. Participants will be analyzed according to the product they actually received.*

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Defined Population for Analysis	***Description***
Estimand Set 1A	*All* evaluable *participants. For participants who discontinue IP and/or receive glycemic rescue medication, all subsequent values will be censored.*
Estimand Set 1B	*All* evaluable *participants.*
Estimand Set 1C	*This analysis set is the same as 1A, except it only includes participants assigned to the metformin strata.*
Estimand Set 2	All evaluable participants. Participants who receive glycemic rescue medication and/or discontinue IP prior to Week 16 will have their Week 16 value censored (if not missing). Missing or censored values at Week 16 will be imputed as described in Section 5.3.
PK Concentration Set	*All participants* from the PK Analysis Set *and in whom at least one concentration value is reported.*

4.1. Strata Misallocations

Participants who are randomized to the wrong stratum, in error, will have the incorrect stratum assignment remain in IMPALA but the clinical database will include the correct stratum. The latter will subsequently be used for all relevant analyses.

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

Statistical inference will be based on the primary endpoint: change from baseline in HbA1c at Week 16.

The null hypothesis is that there is no difference between PF-06882961 and placebo on the primary endpoint. The alternative hypothesis is that PF-06882961 is superior (i.e. greater reduction) to placebo on the primary endpoint.

The Type I error rate (α-level) used for the statistical inference will be 5% (1-sided).

Each dose of PF-06882961 will be tested separately compared to placebo.

No adjustment for multiple comparisons will be made.

Similar hypotheses will be applied to the secondary endpoints (change from baseline in fasting plasma glucose/body weight at Week 16 & response as defined by an HbA1c <7% at Week 16), where the type I error rate will also be 5% (1-sided). Note the alternative

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hypothesis for the response endpoint is that PF-06882961 is superior to placebo as shown by an odds ratio > 1. As above, each dose of PF-06882961 will be tested separately compared to placebo with no adjustment for multiple comparisons.

5.2. General Methods

The efficacy analyses will be based on the appropriate population for analysis (see Section 4).

5.2.1. Summary Analyses for Continuous Data

Continuous variables will be presented using summary statistics: number of observations, arithmetic mean, standard deviation, median, minimum and maximum values.

5.2.2. Summary Analyses for Categorical Data

Categorical variables will be presented using summary statistics: number of observations, counts and percentages.

5.2.3. Mixed Model Repeated Measures (MMRM)

The MMRM model *will include treatment, time, strata* (defined as *metformin vs. diet and exercise alone* – this factor is not included in analyses of metformin-only participants, or diet and exercise only) *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 covariance matrix will be used to estimate the variances and covariance within participant across time points. If convergence is not obtained or model fit is not adequate, then other covariance structures will be investigated as necessary. The Kenward-Roger approximation will be used for estimating degrees of freedom for the model parameters.

Missing values (e.g. due to censoring) *will be* implicitly *imputed as part of the MMRM model* fitting.

The Least Squares Means (LSMeans) together with 90% confidence intervals, standard errors and 2-sided p-values will be obtained for each treatment at each time point.

Differences in LSMeans between each dose of PF-06882961 relative to placebo at each time point, together with 90% confidence intervals, standard errors and 2-sided p-values, will also be obtained.

Example SAS code is provided in Appendix 4.

Statistical Model Diagnostics

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The presence of outliers will be investigated for this model. An outlier will be defined as any response data value with a studentized (conditional) residual greater than 3, or less than -3. A listing will be presented of any participants meeting these criteria and will be included with standard SAS outputs. The assumptions of normality will be verified graphically using residual plots. For each fitted model, a set of conditional studentized residual plots will be produced, including residual plot, histogram of normality, QQ plot and summary of fit statistics. The residual plots will not be included in the clinical study report.

If there are outliers or major deviations from normality, then the effect of these on the conclusions may be investigated through alternative transformations and/or analyses excluding outliers. Justification for any alternative to the planned analysis will be given in the report of the study.

5.2.4. Logistic Regression

The logistic regression model will include a term for treatment, strata (metformin vs. diet and exercise alone), and baseline will be included as a covariate. The model will be fitted to the Week 16 timepoint only.

Missing values (e.g. due to censoring) will be imputed for missing data using a multiple imputation method as described in Section 5.3.

The odds ratio for each dose of PF-06882961 relative to placebo and corresponding 90% confidence interval will be obtained.

Example SAS code is provided in Appendix 4.

5.2.5. Emax Model (no baseline interaction)

The 4-parameter dose-response Emax model will be used to characterize change from baseline (CFB) dose-response relationships with dose included as a continuous variable.

The model structure will take the form:

$$CFB = E_0 + \frac{E_{max} \times dose^{Hill}}{ED_{50}{}^{Hill} + dose^{Hill}}$$

E_0 is the placebo effect, *dose* is the target randomized dose, E_{max} is the maximum effect, ED_{50} is the dose producing 50% of the maximum effect and *Hill* is the slope parameter.

The model will be applied to the LSMean results from the primary MMRM model (Section 6.1.1.1) utilizing a Bayesian methodology approach with weakly informative priors as described in Appendix 3.

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Estimates of the model parameters of E_0, E_{max}, ED_{50} and *Hill* and their 95% credible intervals will be produced.

The posterior medians and 90% credible intervals (5th and 95th percentiles of the relevant posterior distribution) will be reported for each target randomized dose (including Placebo) and their differences relative to placebo. Both will be reported in tables and plotted in separate figures.

If convergence cannot be obtained or visual inspection of the data does not support a dose-response Emax relationship the following options will be considered in order: (1) assume the hill parameter is 1 and remove from the model (giving a 3-parameter dose-response Emax model); (2) utilize alternative priors to those provided in the appendix; (3) otherwise an Emax model (no baseline interaction) will not be reported and alternative model structures may be investigated and the subsequent analyses may be included in the CSR with rationale for the eventual model selected.

5.2.6. Emax Model (baseline interaction)

An additional 4-parameter dose-response Emax model will be used to characterize change from baseline (CFB) dose-response relationships, assuming an interaction between baseline HbA1c and dose.

The model structure will be the same as Section 5.2.5.

The model will be applied to the LSMean results from individual MMRM models that have been applied to each treatment separately. The MMRM models will include time and strata 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 covariance matrix will be used to estimate the variances and covariance within participant across time points for each separate MMRM. If convergence is not obtained or model fit is not adequate, then other covariance structures will be investigated as necessary. The Kenward-Roger approximation will be used for estimating degrees of freedom for the model parameters.

The LSmean results from the separate MMRM models will be calculated for the overall baseline HbA1c (i.e. across all participants in the Estimand Set 1A) and then fitted with the Emax model above utilizing a Bayesian methodology approach with weakly informative priors as described in Appendix 3.

Estimates of the model parameters of E_0, E_{max}, ED_{50} and *Hill* and their 95% credible intervals will be produced.

The posterior medians and 90% credible intervals (5th and 95th percentiles of the relevant posterior distribution) will be reported for each target randomized dose (including Placebo)

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and their differences relative to placebo. Both will be reported in tables and plotted in separate figures.

If convergence cannot be obtained or visual inspection of the data does not support a dose-response Emax relationship the following options will be considered in order: (1) assume the hill parameter is 1 and remove from the model (giving a 3-parameter dose-response Emax model); (2) utilize alternative priors to those provided in the appendix; (3) otherwise an Emax model (with a baseline interaction) will not be reported.

5.2.7. Cumulative Incidence Plots

Cumulative Incidence Plots will be produced based on the time to the event of interest (starting from the time of start of dosing on Day 1) for each treatment separately and will be plotted on the same graph up to Week 18 (i.e. including the follow-up visit 10). This will be based on plotting the cumulative incidence function (with no competing risks), which will be presented as a % on the y-axis. No statistical testing for differences between treatment will be considered.

Details of censoring are included in Section 6 and example SAS code is provided in Appendix 4.

5.3. Methods to Manage Missing Data

Details of efficacy data to be censored is described in Sections 3.2 and 3.3.

For applicable continuous endpoints modelled with an MMRM, missing/censored values will be imputed as part of the analysis method.

In all PK data presentations (except listings), concentrations below the limit of quantification (BLQ) will be set to zero. In listings BLQ values will be reported as "<LLQ", where LLQ will be replaced with the value for the lower limit of quantification (LLQ).

5.3.1. Multiple Imputation

For summarizing the proportion of responses in HbA1c or Body Weight, all data from Estimand Set 2 (or similar for body weight) will be included (i.e. all time points up to and including Week 16). A multiple imputation (MI) method will be implemented, using a multivariate imputation method by chained equations, which is still valid with an arbitrary missing data pattern. The model will include: treatment, baseline (HbA1c or Body Weight as appropriate) and strata. Twenty sets of imputations of each missing value will be constructed from the MI method and the proportion of responses by treatment will be determined with associated standard errors utilizing a normal approximation and will be combined using standard multiple imputation techniques proposed by Rubin (2) to yield overall estimates. If there is more missing data in the study than anticipated, the number of imputation sets may be increased as required.

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For logistic regression of HbA1c or Body Weight, all data from Estimand Set 2 (or similar for body weight) will be included (i.e. all time points up to and including Week 16). The same imputed datasets as produced for the proportion of responses above will be utilized, where a Logistic Regression model (as described in Section 5.2.4) will be applied to each of the 20 imputed datasets separately. Parameter estimates of the log odds ratios for each dose relative to placebo will be combined using standard multiple imputation techniques proposed by Rubin (2) to yield overall estimates of the log odds ratios and their associated standard errors will be used to create 90% confidence intervals on the log-odds scale. The log odds ratios and log odds 90% confidence intervals will be back transformed into odds ratios and associated 90% confidence intervals for final reporting.

6. ANALYSES AND SUMMARIES

Data collected before baseline will only be listed, unless otherwise stated.

6.1. Primary Endpoint(s)

6.1.1. Change from Baseline in HbA1c at Week 16

6.1.1.1. Main Analysis

In all cases the Estimand Set 1A as specified in Section 4 will be utilised.

Absolute values and changes from baseline in HbA1c will be summarised descriptively by treatment and time point as described in Section 5.2.1. Tables will present all data from the screening (visit 1, absolute tables only), beginning of the placebo run-in (visit 2, absolute tables only), baseline and post-baseline time points (including follow-up, which will be restricted to participants who completed 16 weeks of treatment and did not initiate glycemic rescue medication). Box and whisker plots of absolute values and changes from baseline will also be separately produced.

The primary analysis will be an MMRM (as described in Section 5.2.3) applied to the change from baseline at Weeks 2, 4, 6, 8, 12 and 16 that will be used to estimate the treatment effect related to the primary Estimand 1A (as described in Section 2.1.1).

The following results from the above primary analysis will be plotted:

- Profile plots of the LSMeans (including 90% confidence intervals) over time, with a separate line for each treatment
- Profile plots of the LSMean differences to Placebo (including 90% confidence intervals) over time, with a separate line for each dose of PF-06882961
- Plot of the LSMeans (including 90% confidence intervals) at Week 16, with a separate point for each treatment (applicable to analyses related to HbA1c only)

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- Plot of the LSMean differences to Placebo (including 90% confidence intervals) at Week 16, with a separate point for each dose of PF-06882961 (applicable to analyses related to HbA1c only)

Standard SAS output will be provided to support the main statistical summary table for the primary analysis model but will not be included in the CSR.

In addition, a waterfall plot of the individual changes from baseline in HbA1c at Week 16 in the Estimand Set 1A will be created, ordered in increasing reductions from baseline and coloured by treatment.

6.1.1.2. Sensitivity/Supplementary Analyses

For all of the following analyses, standard SAS output will be provided to support the statistical summaries produced but will not be included in the CSR.

The following supplementary analyses to the primary endpoint will be carried out:

- To assume a dose-response relationship with HbA1c (without a baseline interaction) an Emax model will be applied to the LSmeans at Week 16 from the main MMRM analysis as described in Section 5.2.5.

- To assume a dose-response relationship with HbA1c, including an interaction between baseline HbA1c and dose, an Emax model will be applied to the LSMeans at Week 16 from separate MMRM models at the overall baseline HbA1c as described in Section 5.2.6.

The following supplementary estimands to the primary endpoint will be carried out:

1. Estimand 1B

An analysis that assesses the primary endpoint using a treatment policy estimand strategy (Section 2.1.3) will be performed to estimate the treatment effect related to the exploratory Estimand 1B (as described in Section 2.1.3). The same summary and analysis output as the main analysis (excluding the waterfall plot) will be performed and reported but applied to the Estimand Set 1B (as described in Section 4). Note follow-up summaries will include all evaluable participants.

2. Estimand 1C

An analysis that assesses the primary endpoint using a similar estimand approach for intercurrent events, but is limited to participants on a background of metformin (Section 2.1.3) will be performed to estimate the treatment effect related to the exploratory Estimand 1C (as described in Section 2.1.3). A similar model as described in Section 6.1.1.1 will be applied except that the strata term will not be included in the MMRM model. The same

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summary and analysis output (excluding the waterfall plot) as the main analysis will be performed and reported but applied to the Estimand Set 1C (as described in Section 4). Note follow-up summaries will include participants from the metformin strata who completed 16 weeks of treatment and did not initiate glycemic rescue medication.

6.2. Secondary Endpoint(s)

6.2.1. Response as defined by an HbA1c <7% at Week 16

6.2.1.1. Main Analysis

In all cases the Estimand Set 2 as specified in Section 4 will be utilised.

The proportion of responses at Week 16 will be summarised descriptively by treatment as described in Section 5.2.2, where no imputation for missing values will be conducted. The proportion of responses at Week 16 will also be reported after multiple imputation for missing values as per Section 5.3.

A logistic regression model (as described in Section 5.2.4) will be applied to the response at Week 16 that will be used to estimate the treatment effect related to the secondary Estimand 2 (as described in Section 2.1.2.1), where missing values will be imputed using multiple imputation as per Section 5.3. Baseline HbA1c and strata will be included in the model.

In addition, standard SAS output will be provided to support the main statistical summary table for the logistic regression model and multiple imputation approach but will not be included in the CSR.

6.2.2. Change from Baseline in HbA1c at Weeks 2, 4, 6, 8 and 12

Summaries and analysis results will be reported as per the primary analysis approach (Section 6.1.1).

6.2.3. Change from Baseline in Fasting Plasma Glucose at Weeks 2, 4, 6, 8, 12 and 16

In all cases the Estimand Set 1A as specified in Section 4 will be utilised.

Absolute values and changes from baseline in fasting plasma glucose will be summarised similar to HbA1c in Section 6.1.1.1.

The analysis will be an MMRM (as described in Section 5.2.3) applied to the change from baseline at Weeks 2, 4, 6, 8, 12 and 16 that will be used to estimate the treatment effect related to the primary Estimand 3 (as described in Section 2.1.1). Results similar to HbA1c in Section 6.1.1.1 (excluding the waterfall plot) will be reported along with standard SAS output (where the latter will not be included in the CSR).

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6.2.4. Change from Baseline in Body Weight at Weeks 2, 4, 6, 8, 12 and 16

In all cases the Estimand Set 1A as specified in Section 4 will be utilised.

Absolute values and changes from baseline in body weight will be summarised similar to HbA1c in Section 6.1.1.1.

The analysis will be an MMRM (as described in Section 5.2.3) applied to the change from baseline at Weeks 2, 4, 6, 8, 12 and 16 that will be used to estimate the treatment effect related to the primary Estimand 4 (as described in Section 2.1.1). Results similar to HbA1c in Section 6.1.1.1 (including the waterfall plot for changes from baseline at Week 16) will be reported along with standard SAS output (where the latter will not be included in the CSR).

6.2.4.1. Supplementary Analyses

The percentage change from baseline in body weight at Weeks 2, 4, 6, 8, 12 and 16 will similarly be summarised and analysed to absolute changes as per Section 6.2.4.

For the MMRM model, all body weight values (including baseline) will be $\log_e$-transformed prior to analysis (i.e. the outcome in the model will be the difference of the $\log_e$ absolute value at the time point of interest minus the $\log_e$ baseline). All LSMeans and LSMean differences (including confidence intervals) will be back-transformed to give geometric LSMeans and ratios of geometric LSMeans.

The percent change will then be calculated as follows:

- Percent change = 100*(back-transformed LSMean – 1)

6.3. Other Endpoint(s)

6.3.1. Change from Baseline in Fasting Insulin at Weeks 4, 8, 12 and 16

In all cases a dataset similar to Estimand Set 1A as specified in Section 4 will be utilised.

Absolute values and changes from baseline in fasting insulin will be summarised similar to HbA1c in Section 6.1.1.1.

An MMRM (as described in Section 5.2.3) will be applied to the change from baseline at Weeks 4, 8, 12 and 16. Results similar to HbA1c in Section 6.1.1.1 (excluding the waterfall plot) will be reported along with standard SAS output (where the latter will not be included in the CSR).

6.3.2. Change from Baseline in Fasting Glucagon at Weeks 8 and 16

In all cases the Estimand Set 1A as specified in Section 4 will be utilised.

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Absolute values and changes from baseline in fasting glucagon will be summarised similar to HbA1c in Section 6.1.1.1.

An MMRM (as described in Section 5.2.3) will be applied to the change from baseline at Weeks 8 and 16. Results similar to HbA1c in Section 6.1.1.1 (excluding the waterfall plot) will be reported along with standard SAS output (where the latter will not be included in the CSR).

6.3.3. Change from Baseline in HOMA-IR at Weeks 4, 8, 12 and 16

In all cases the Estimand Set 1A as specified in Section 4 will be utilised.

Absolute values and changes from baseline in HOMA-IR will be summarised similar to HbA1c in Section 6.1.1.1.

An MMRM (as described in Section 5.2.3) will be applied to the change from baseline at Weeks 4, 8, 12 and 16. Results similar to HbA1c in Section 6.1.1.1 (excluding the waterfall plot) will be reported along with standard SAS output (where the latter will not be included in the CSR).

6.3.4. Response as Defined by a ≥5% Body Weight Loss at Week 16

In all cases a dataset similar to the Estimand Set 2 as specified in Section 4 will be utilized.

The proportion of responses at Week 16 will be summarised descriptively by treatment as described in Section 5.2.2, where no imputation for missing values will be conducted. The proportion of responses at Week 16 will also be reported after multiple imputation for missing values as per Section 5.3.

A logistic regression model (as described in Section 5.2.4) will be applied to the response at Week 16, where missing values will be imputed using multiple imputation as per Section 5.3. Baseline body weight will be included in the model.

In addition, standard SAS output will be provided to support the main statistical summary table for the logistic regression model and multiple imputation approach but will not be included in the CSR.

6.3.5. Pharmacokinetic Endpoints

PF-06882961 concentrations will be characterized by C_{trough} and will be summarized by dose and by time point using the following descriptive statistics: number of participants contributing at each time point, arithmetic mean, median, minimum, maximum, Q1, Q3, standard deviation, geometric mean, and geometric CV (%).

Median C_{trough} versus time point will be plotted by dose including error bars representing the inter-quartile range (i.e. Q1 to Q3).

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The post dose random plasma concentration data will only be listed. PF-06882961 concentrations assessed during random collection will only be listed (and not summarized); these data are noted for use in supplemental population-PK analyses.

In addition, as permitted by data and determined by the sponsor, PK-PD relationship between plasma concentrations of PF-06882961 and effect on primary, secondary and tertiary endpoints may be characterized using a population PK-PD approach. The objective of such an analysis, if conducted, would aim to explore potential demographic determinants (eg, age, gender, and weight) influencing the observed PK or PD variability in response to PF-06882961. The population PK-PD analysis, if conducted, will be reported separately from the main CSR.

6.4. Subset Analyses

Planned subset analyses for HbA1c are described in Section 6.1.1.2.

Further subset analyses restricted to participants on a background of metformin and/or diet & exercise may be added for other efficacy and/or safety endpoints if required for the CSR and would be included as part of an update to this SAP with an amendment prior to database lock or documented in the CSR under changes to planned analysis.

6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline Summaries

A baseline table (or separate tables, as required) summarizing the following will be produced by treatment and overall: age; gender; race; ethnicity; height; weight; body mass index; duration of T2DM; stratification factor; country; HbA1c; fasting plasma glucose; fasting glucagon; fasting insulin; HOMA-IR; eGFR; systolic blood pressure; diastolic blood pressure; and duration of metformin.

This table will also be re-produced limited to each strata. The table restricted to participants on a background of metformin only will not include the strata summary. The table restricted to diet and exercise will not include the metformin dose and strata summary.

6.5.2. Study Conduct and Participant Disposition

Participant evaluation groups will show participant disposition for each phase of the study (screening, placebo-run in, double-blind treatment and follow-up) and will additionally show which participants were analysed for efficacy (Estimand Set 1A, 1B, 1C and 2) as well as for safety. Frequency counts and percentages will be supplied for participant discontinuation(s) by treatment and overall.

Data will be reported in accordance with the sponsor reporting standards (including creation of COVID-19 related outputs).

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6.5.3. Banked Biospecimens

Banked biospecimens will be collected and retained for future analyses, but will not be analyzed specifically for this study and will not be included in the CSR.

6.5.4. Concomitant Medications and Nondrug Treatments

All prior and concomitant medication(s) as well as non-drug treatment(s) will be reported according to current sponsor reporting standards.

A separate table listing the use of rescue medication will be produced according to current sponsor reporting standards. The use of rescue medication (grouped by class of medication) will be summarized descriptively by treatment and overall as described in Section 5.2.2. The classes will be defined based on medications used in the study.

6.5.5. Treatment Compliance

A summary table of treatment compliance (by treatment and overall) will be produced according to current sponsor reporting standards.

6.5.6. Discontinuations

Participant discontinuations, temporary discontinuations or dose reductions due to adverse events will be detailed and summarised by treatment and overall.

Data will be reported in accordance with the sponsor reporting standards.

Exploratory summaries on the time to discontinuation from the study and time to discontinuation of IP (regardless of study discontinuation or continuation) will be produced separately using Cumulative Incidence Plots as described in Section 5.2.7. For both, participants who discontinue from the study/IP will be censored at the associated discontinuation date.

6.6. Safety Summaries and Analyses

The three AEs of interest are: diarrhoea, nausea and vomiting (based on preferred term).

6.6.1. Adverse Events

Adverse events (Tier 1, 2 and 3 AEs as described in Section 3.5.1) will be summarized by treatment and overall and in accordance with sponsor reporting standards using the safety analysis set defined in Section 4. The adverse events (AEs) will be sorted in descending frequency within a system organ class.

Incidence and severity of treatment emergent adverse event (TEAE) tables will additionally be produced ('All causality' and 'Treatment related', separately) to summarise the total number of adverse events by preferred term, which will be reported by treatment and overall.

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The following tables and figures related to TEAEs classed as Tier 1 or 2 will be ordered in descending point estimate of risk difference within System Organ Class. If two or more events have the same frequency they will be sorted alphabetically by preferred term.

TEAEs classed as Tier 1 events will be tabulated by treatment. Number of participants and percent will be presented, along with the risk difference between each dose of PF-06882961 and placebo. 95% confidence intervals and 2-sided p-values will also be presented for the comparison. No adjustment for multiplicity will be used.

Tier 1 TEAEs will also be presented graphically. The TEAEs will be presented in a two-panel plot, the left panel will give the proportions of TEAEs observed in a dose of PF-06882961 and separately placebo while the right panel will display the 95% confidence interval for the risk differences for each TEAE. A vertical line corresponding to the value of 0 will be added to the right-hand plot. For the graphical display for tier 1 events, a column containing the 2-sided p-value for each event will be added to the right-hand side of the forest plot in the right panel. Each panel will be paged by dose of PF-06882961.

TEAEs classed as Tier 2 events will be summarised and graphically presented similar to Tier 1 events, but no p-values will be presented. No adjustments for multiplicity will also be used.

For Tier 1 and Tier 2 outputs, footnotes will be included on the tables to provide proper interpretation of p-values (Tier 1 only) and confidence intervals and to describe how the comparison was conducted, e.g. “P-values and confidence intervals are not adjusted for multiplicity and should be used for screening purpose only. 95% Confidence intervals are provided to help gauge the precision of the estimates for Risk Difference. Risk Difference is computed as PF-06882961 versus placebo.”

It should be recognized that most studies are not designed to reliably demonstrate a causal relationship between the use of a pharmaceutical product and an adverse event or a group of adverse events. Except for select events in unique situations, studies do not employ formal adjudication procedures for the purpose of event classification. As such, safety analysis is generally considered as an exploratory analysis and its purpose is to generate hypotheses for further investigation. The 3-tier approach facilitates this exploratory analysis.

6.6.1.1. Subset reporting interval

The subset adverse events, described in Section 3.5.1.1, will be summarised as above (excluding the 3-tier reporting system) where standard tables and incidence tables will be produced for both ‘All causality’ and ‘Treatment related’.

6.6.1.2. Hypoglycemic Adverse Events

The hypoglycemic AEs will be listed in a separate table and summarized categorically by treatment and overall as per Section 5.2.2.

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6.6.1.3. Time to First Occurrence/Recurrence of AEs of Interest

Exploratory summaries on the time to the first occurrence of AEs of interest will be produced in Cumulative Incidence Plots as described in Section 5.2.7. Participants who discontinue from the study, discontinue from IP or initiate glycemic rescue medication prior to the start of the AE event of interest will be censored at the discontinuation/initiation date.

The three AEs of interest are: diarrhoea, nausea and vomiting (based on preferred term). A separate plot for each AE will be produced separately.

The above will also be produced separately for the time to the first recurrence of the three AEs of interest.

6.6.1.4. Percentage of Participants with Ongoing AEs of Interest

Exploratory summaries on the percentage of participants reporting AEs of interest will be produced by week and treatment and overall as per Section 5.2.2 from Week 1 up to Week 18 (i.e. including the follow-up visit 10).

To calculate the percentage each week, the total number of participants who experience the TEAE of interest at any time during the respective week will be the numerator and the total number of participants who had not discontinued from IP and/or the study prior to that respective week will be the denominator (note if a participant did discontinue from IP and/or the study during that respective week they would be included in the denominator).

A line plot of the percentages over each week will be produced based on the summary statistics with a separate line for each treatment.

The AEs of interest are diarrhoea, nausea and vomiting (based on preferred term); where a separate table and plot will be produced for each AE.

6.6.1.5. Time to discontinuation from IP due to Gastrointestinal Disorders AEs

Exploratory summaries on the time to discontinuation from IP (regardless of study discontinuation or continuation) due to Gastrointestinal Disorders AEs (defined as based on System Organ Class) will be produced with a Cumulative Incidence Plot as described in Section 5.2.7. Participants who discontinue will be censored at the associated discontinuation date.

6.6.2. Laboratory Data

Laboratory data from will be listed and summarized by treatment and overall, in accordance with the sponsor reporting standards. Baseline is as defined in Section 3.5.3.

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6.6.2.1. Focused Laboratory Summaries on Endpoints of Interest

Absolute values, changes from baseline and percent changes from baseline in calcitonin, amylase, lipase, TSH, free T4, lipid profile, liver function tests and eGFR (as outlined in Section 3.5.3.1) will be summarized by treatment and time point as per Section 5.2.1 (unplanned readings will not be included in these summaries). Follow-up data will be included in the summaries with data from all participants in the safety analysis set. Tables will be paged by parameter. Baseline is as defined in Section 3.5.3.

The following box and whisker plots for each parameter will be produced:

- Absolute values over time by treatment
- Change from baseline over time by treatment
- Percentage change from baseline over time by treatment

MMRM models (as described in Section 5.2.3) will be applied to the change from baseline at Weeks 2 (only for liver function tests and eGFR), 4, 6 (only for liver function tests and eGFR), 8, 12 and 16 for each parameter separately using the safety analysis set (as defined in Section 4). From each model, the LSMeans together with 90% confidence intervals, standard errors and 2-sided p-values will be obtained for each treatment at each time point. Differences in LSMeans between each dose of PF-06882961 relative to placebo at each time point, together with 90% confidence intervals, standard errors and 2-sided p-values will also be obtained. A plot of the LSMean differences to Placebo (including 90% confidence intervals) over time, with a separate line for each dose of PF-06882961 will be produced separately for each parameter. Standard SAS outputs will be provided to support the main statistical summary tables but will not be included in the CSR.

Additionally, MMRM models will be applied to the changes from baseline in Triglycerides, ALT, AST, Alkaline Phosphatase and GGT for each parameter separately on the natural log scale at the same above relevant weeks using the safety analysis set. This parameter list may be expanded after review of unblinded tables if MMRM diagnostics reveal any other residuals that deviate substantially from a normal distribution and require log transformation for interpretation. In the models, the related baseline will be included on the natural log scale also. Similar outputs will be reported as above, where the percent change from baseline or percent difference to placebo (as applicable) will be reported as calculated using:

Percent change = 100*(back-transformed LSMean – 1)

6.6.2.2. Clinical Laboratory Parameters of Interest

An additional summary table of the number of participants (from the Safety Analysis Set as defined in Section 4) with “Flag Level” or “Alert Level” abnormalities for each of the clinical laboratory parameters of interest as specified in Section 3.5.3.2 will be produced.

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This table will summarise the number of participants with “Flag level” or “Alert level” abnormalities separately and by treatment group and placebo run-in and overall (i.e. post-dose), as per Section 5.2.2.

6.6.3. Vital Signs

Average of the triplicate measurements (where applicable) will be used in analyses.

Absolute values and changes from baseline in supine systolic and diastolic blood pressure and pulse rate will be summarized by treatment and time point, according to sponsor reporting standards. Tables will be paged by parameter. Baseline is as defined in Section 3.5.3.2.

Mean changes from baseline for systolic and diastolic blood pressure and pulse rate will be plotted against time point. On each plot there will be 1 line for each treatment with all treatments on the same plot including placebo.

MMRM models (as described in Section 5.2.3) will be applied to the change from baseline at Weeks 2, 4 (0 and 2H separately), 6, 8 (0 and 2H separately), 12 and 16 (0 and 2H separately) for supine systolic and diastolic blood pressure and pulse rate separately using the safety analysis set (as defined in Section 4). From each model, the LSMeans together with 90% confidence intervals, standard errors and 2-sided p-values will be obtained for each treatment at each time point. Differences in LSMeans between each dose of PF-06882961 relative to placebo at each time point, together with 90% confidence intervals, standard errors and 2-sided p-values will also be obtained. A plot of the LSMean differences to Placebo (including 90% confidence intervals) over time, with a separate line for each dose of PF-06882961 will be produced separately for each parameter. Standard SAS outputs will be provided to support the main statistical summary tables but will not be included in the CSR.

Maximum absolute values and maximum changes from baseline for vital signs, over all measurements taken post dose will also be tabulated by treatment using categories as defined in the Appendix 5. Numbers and percentages of participants meeting the categorical criteria will be provided. All planned and unplanned post dose time points will be counted in these categorical summaries. All values meeting the criteria of potential clinical concern will be listed.

Maximum decrease and increase from baseline for supine systolic and diastolic blood pressures, and maximum increase from baseline for supine pulse rate will be summarized by treatment, according to sponsor reporting standards.

6.6.4. Electrocardiograms

Average of the triplicate measurements (where applicable) will be used in analyses. Absolute values and changes from baseline in QT, heart rate, QTcF, PR and QRS will be summarized

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by treatment and time point using sponsor reporting standards. Tables will be paged by parameter. Baseline is as defined in Section 3.5.5.

Mean changes from baseline in QT, heart rate and QTcF will be plotted against time point. On each plot there will be 1 line for each treatment with all treatments included on the same plot including placebo.

MMRM models (as described in Section 5.2.3) will be applied to the change from baseline at Weeks 2, 4 (0 and 2H separately), 6, 8 (0 and 2H separately), 12 and 16 (0 and 2H separately) for QT, heart rate and QTcF separately using the safety analysis set (as defined in Section 4). From each model, the LSMeans together with 90% confidence intervals, standard errors and 2-sided p-values will be obtained for each treatment at each time point. Differences in LSMeans between each dose of PF-06882961 relative to placebo at each time point, together with 90% confidence intervals, standard errors and 2-sided p-values will also be obtained. A plot of the LSMean differences to Placebo (including 90% confidence intervals) over time, with a separate line for each dose of PF-06882961 will be produced separately for each parameter. Standard SAS outputs will be provided to support the main statistical summary tables but will not be included in the CSR.

ECG endpoints and changes from baseline (QTcF, PR and QRS) will also be summarized descriptively by treatment using categories as defined in the Appendix 5 (for QTc these correspond to the Pfizer Guidance (3) as referenced in Section 8). Numbers and percentages of participants meeting the categorical criteria will be provided. All planned and unplanned postdose time points will be counted in these categorical summaries. All values meeting the criteria of potential clinical concern will be listed.

Maximum absolute value (post dose) and the maximum increase from baseline for QTcF, PR and QRS will be summarized by treatment according to sponsor reporting standards.

Listings of participants with any single post dose value > 500 msec will also be produced for QTcF.

6.6.5. Nausea Burden Score

The nausea burden score will be summarized descriptively by treatment and overall as per Section 5.2.1. The percentage of days that participants experienced nausea during the dosing period will also be summarized descriptively by treatment and overall as per Section 5.2.1.

7. INTERIM ANALYSES

7.1. Introduction

An interim analysis will be performed at least once while the study is ongoing, after at least 25% of participants (ie, approximately 100) are randomized, with further details provided in the IRC charter. This interim analysis will assess, at a minimum, unblinded safety of the

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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, stopping for futility, stopping for early success, or conducting a sample size reestimation. 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 standard operating procedure (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.

7.2. Interim Analyses and Summaries

The interim analyses will be performed using the methodology specified in this SAP and will be outlined in this SAP (with an amendment) or the interim analysis SAP. Any substantial deviations from the SAP's methodology will be fully justified and outlined. Details of the ongoing unblinded safety reviews will be provided in the IRC Charter and/or the interim analysis SAP.

8. REFERENCES

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3. Pfizer Guidance for Evaluation of QT / QTc Interval Prolongation and Proarrhythmic Potential for Non-antiarrhythmic Drugs; Members of the Cardiovascular Safety & Advisory Council (CVSAC); January 26, 2018.

4. Thomas, N. and Wu, J. (2019). clinDR: Simulation and Analysis Tools for Clinical Dose Response Modeling. R package version 1.9. https://CRAN.R-project.org/package=clinDR

5. Wu, J, Banerjee, A., Jin, B., Menon, S., Martin, S., and Heatherington, A., (2017), Clinical dose-response for a broad set of biological products: A model-based meta-analysis, *Statistical Methods in Medical Research,* Vol. 7, No. 9, 2694-2721.

6. Thomas, N., and Roy, D. (2017). Analysis of clinical dose-response in small-molecule drug development: 2009-2014. *Statistics in Biopharmaceutical Research,* Vol. 9, No. 2, 137-146.

7. Thomas, N., Sweeney, K., and Somayaji, V. (2014). Meta-analysis of clinical dose response in a large drug development portfolio, *Statistics in Biopharmaceutical Research,* Vol. 6, No.4, 302-317.

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9. APPENDICES

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Appendix 1. Summary of Efficacy Analyses

Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
Change from baseline at Week 16 in HbA1c	Summary	Estimand Set 1A	GRM: Censor all values post first use DFI: Censor all values post discontinuation MV: Not imputed	N/A
	Primary analysis			MMRM
	Supplementary analyses			Emax
	Supplementary analysis (summary)	Estimand Set 1B	GRM: Not censored DFI: Not censored MV: Not imputed	N/A
	Supplementary analysis			MMRM
	Supplementary analysis (summary)	Estimand Set 1C	GRM: Censor all values post first use DFI: Censor all values post discontinuation MV: Not imputed	N/A
	Supplementary analysis			MMRM
Response as defined by an HbA1c <7% at Week 16	Summary	Estimand Set 2	GRM: Censor all values post first use DFI: Censor all values post discontinuation MV: Not imputed	N/A
	Summary		GRM: Censor all values post first use DFI: Censor all values post discontinuation MV: Imputed using multiple imputation	N/A
	Secondary analysis			Logistic regression
Change from baseline in HbA1c at Weeks 2, 4, 6, 8 and 12	Summary	Estimand Set 1A	GRM: Censor all values post first use DFI: Censor all values post discontinuation MV: Not imputed	N/A
	Secondary analysis			MMRM
Change from baseline in fasting plasma glucose at Weeks 2, 4, 6, 8, 12 and 16	Summary	Estimand Set 1A	GRM: Censor all values post first use DFI: Censor all values post discontinuation MV: Not imputed	N/A
	Secondary analysis			MMRM
Change from baseline in body weight at Weeks 2, 4, 6, 8, 12 and 16	Summary	Estimand Set 1A	GRM: Censor all values post first use DFI: Censor all values post discontinuation MV: Not imputed	N/A
	Secondary analysis			MMRM

%Change from baseline in body weight at Weeks 2, 4, 6, 8, 12 and 16	Supplementary summary	Not applicable	GRM: Censor all values post first use DFI: Censor all values post discontinuation MV: Not imputed	N/A
	Supplementary analysis			MMRM
Change from baseline in fasting insulin at Weeks 4, 8, 12 and 16	Summary	Similar to Estimand Set 1A	GRM: Censor all values post first use DFI: Censor all values post discontinuation MV: Not imputed	N/A
	Exploratory analysis			MMRM
Change from baseline in fasting glucagon at Weeks 8 and 16	Summary	Similar to Estimand Set 1A	GRM: Censor all values post first use DFI: Censor all values post discontinuation MV: Not imputed	N/A
	Exploratory analysis			MMRM
Change from baseline in HOMA-IR at Weeks 4, 8, 12 and 16	Summary	Similar to Estimand Set 1A	GRM: Censor all values post first use DFI: Censor all values post discontinuation MV: Not imputed	N/A
	Exploratory analysis			MMRM
Response as defined by a ≥5% body weight loss at Week 16	Summary	Similar to Estimand Set 2	GRM: Censor all values post first use DFI: Censor all values post discontinuation MV: Not imputed	N/A
	Summary		GRM: Censor all values post first dose DFI: Censor all values post discontinuation MV: Imputed using multiple imputation	N/A
	Exploratory analysis			Logistic regression

Abbreviations: DFI = discontinuation from IP; GRM = glycemic rescue medication; MV = missing values (note this includes missing values produced through censoring).

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Appendix 2. Data Set Descriptions

To explore the data further and to assess the goodness-of-fit of all statistical models, separate SAS datasets and .CSV files will be provided by the clinical programmer to the statistician.

The dataset requirements for the Dataset (Snapshot PD Dataset, SNAP_PD) are specified in the table below. Note, the variable names and labels are suggested labels only and the actual names and labels and code levels should be consistent with current sponsor reporting standards:

Suggested Variable Name	Suggested Variable Label	Specifications	Order in the dataset
USUBJID	Unique Subject ID		1
Treattxt	Treatment Label		2
Leg_sort	Treatment Code		3
Dose	Dose (mg)		4
Site	Site		5
Age	Age	Age	6
Agecat	Age Category	1 = <18. 2 = 18 – 44, 3 = 45 – 64, 4 = >=65	7
Gender	Gender	1 = Female 2 = Male	8
Height	Height	Height	9
Weight_Screen	Weight (Screening)	Weight (Screening value)	10
Race	Race	Race	11
Strata	Strata	1 = Background Metformin 0 = Diet & Exercise	12
Time point	Time point (weeks)	Time point (in Weeks)	13
Rescue	Glycemic Rescue Medication	1 = Started using glycemic rescue medication 0 = Not started glycemic rescue medication	14
HbA1c	HbA1c	HbA1c value	15
HbA1c_bas	Baseline (HbA1c)	Baseline for HbA1c	16
HbA1c_Resp	Responder (HbA1c)	1 = Response 0 = Non-response (Only valid for Week 16, otherwise missing values)	17
FPG	Fasting Plasma Glucose	Fasting Plasma Glucose value	18
FPG_bas	Baseline (Fasting Plasma Glucose)	Baseline for Fasting Plasma Glucose	19
Weight	Body Weight	Body Weight value	20
Weight_bas	Baseline (Body Weight)	Baseline for Body Weight	21

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Suggested Variable Name	Suggested Variable Label	Specifications	Order in the dataset
Weight_Resp	Responder (Weight)	1 = Response 0 = Non-response (Only valid for Week 16, otherwise missing values)	22

The dataset(s) should contain each of the primary and secondary efficacy variables and the format can be amended as long as each variable is included along with the respective baseline variables.

Appendix 3. Bayesian Statistical Methodology Details

Emax model without baseline interaction (Section 5.2.5)

A dataset (either .txt or .csv) of the following format should be produced by programming for use in R by the reporting statistician and QC statistician. Note, column headers should be labelled as specified below (including capitalization), as R is case sensitive:

Dose	Mean	SE
0	0	0.3
2.5	-0.2	0.4
10	-0.4	0.5
40	-0.8	0.3
80	-1.0	0.4
120	-1.2	0.5

The residual standard deviation at Week 16 from the unstructured covariance matrix from the associated MMRM will also be provided to the statisticians.

The 4-parameter Emax model will be fit using the latest version (currently v2.1) of the clinDR package (4). This analysis will be conducted by the study statistician. A different statistician will conduct QC of the analysis. The outputs of the analysis will be provided as .txt files to the programming team for inclusion in the final CSR table and figure formats.

Compound-specific information will be used to specify independent prior distributions for the placebo response (E_0), and the difference in response between the highest dose (*dTarget*=120 mg) and placebo, denoted by *difTarget*, based on data from the C3421002 study. Non-informative priors will be used for these parameters. Note that the E_{max} parameter is derived from the other parameters and is thus not explicitly supplied. The residual standard deviation, *sigma*, is assigned a uniform prior distribution over a range we are confident will include the population value.

Parameter	Prior
E_0	Normal(Mean = 0, SD = 100)

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difTarget	Normal(Mean = -1.52, SD = 100)
sigma	Uniform(lb = 0.25, ub = 4)

In addition, the projected ED_{50} is P_{50} = ~6mg based on data from the C3421002 study. It will be combined with the predictive prior distribution for the log(ED_{50}/P_{50}), obtained from meta-data on approximately 225 compounds (from 3 references: 5, 6 & 7), to specify an informative prior distribution for the ED_{50}. The distribution of the Hill parameter is the predictive distribution from the meta-data. The current distributions are listed below. They are the default distributions in clinDR. These default distributions will be updated if the meta-data and their analysis are updated before the completion of the current study.

Parameter	Prior
log(Hill)	*t*(Mean = 0, SD = 0.84, df = 5)
log(ED_{50})	log(P_{50}) + *t*(Mean = 0, SD = 1.74, df = 5)

The bivariate predictive distribution of these parameters also includes a prior correlation, which is currently -0.43 based on the analysis of the meta-data, which also would be updated if the historical analysis is updated.

The default burn-in and number of samples will be utilized along with thinning of 20, which will include 3 chains to assess convergence. Model diagnostics will be examined including trace and auto-correlations plots. If these raise concerns over model convergence, additional burn-ins, samples and thinning will be attempted to improve convergence. Changes to the priors above may also be considered (e.g. increase precision of E_0 and *difTarget*) to improve convergence if deemed necessary. The final diagnostic plots will not be included in the clinical study report.

The following R code is included as an example that will be used as a basis for the analysis:

```
library(clinDR)
compileStanModels()
mmrmRes <- read.csv("LSmeans.csv",header=T,stringsAsFactors=F)
# Determine 'effective' subject numbers based on MMRM SD at Week 16:
mmrm_sd <- 0.825 # Provided by programming
mmrmRes$N <- trunc((mmrm_sd/mmrmRes$StdErr)^2,0)

# Set-up priors and MCMC options:
prior_mmrm <- emaxPrior.control(epmu=0,epsca=100,difTargetmu=-
1.52,difTargetsca=100,dTarget=120,effDF=9999,p50=6,sigmalow=0.25,sigmaup=4)
mcmc_mmrm <- mcmc.control(chains=3,thin=20,seed=169)

### Run Emax model: ###
```

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```
emaxMMRM <-
fitEmaxB(mmrmRes$Estimate,mmrmRes$dose,prior_mmrm,modType=4,count=mmrmRes$N,msSat=mmrm_s
d^2,mcmc=mcmc_mmrm)

# Diagnostics and output:
stan_trace(emaxMMRM$estanfit) # Look at trace
stan_dens(emaxMMRM$estanfit) # Look at densities
stan_ac(emaxMMRM$estanfit) # Look at autocorrelation
summary(emaxMMRM) # Summary of model parameters
plot(emaxMMRM) # Look at fitted vs. observed data
emaxMMRMout <- predict(emaxMMRM,dosevec=mmrmRes$dose,clev=0.90) # Get dose predictions
```

Model parameters, posterior medians and 90/95% credible intervals as specified in Section 5.2.5 will be output and provided back to the programming team after QC is complete.

Emax model with baseline interaction (Section 5.2.6)

A dataset of the same format to above should be produced by programming for use in R by the reporting statistician and QC statistician. Note, column headers should be labelled as specified (including capitalization), as R is case sensitive.

The residual standard deviations at Week 16 from the unstructured covariance matrices from each of the associated MMRM models will also be provided to the statisticians.

The same process for priors, model fitting, checking of model convergence and QC as above will be implemented for this model along with similar R code as to above. The only major difference in R code is the requirement to take the average of the residual standard deviations from the separate MMRM outputs which will be used as the global standard deviation in model fitting:

```
mmrmDoseRes <- read.csv(Dose_LSmeans.csv",header=T,stringsAsFactors=F)
# Covariance matrix:
mmrmDoseCov <- read.csv(Dose_CovParams.csv",header=T,stringsAsFactors=F)
# Calculate global SD:
mmrm_global_sd <- mean(mmrmDoseCov$SD)
# Merge datasets:
mmrmDoseRes <- merge(mmrmDoseRes,mmrmDoseCov,by="dose")
mmrmDoseRes$N1 <- trunc((mmrmDoseRes$SD/mmrmDoseRes$StdErr)^2,0)
mmrmDoseRes$Glob_SD <- mmrm_global_sd
mmrmDoseRes$N <- trunc((mmrmDoseRes$Glob_SD/mmrmDoseRes$StdErr)^2,0)
…
emaxMMRM_Int <-
fitEmaxB(mmrmDoseRes$Estimate,mmrmDoseRes$dose,prior_mmrm,modType=4,count=mmrmDoseRes$N,
msSat=mmrm_global_sd^2,mcmc=mcmc_mmrm)
```

Model parameters, posterior medians and 90/95% credible intervals as specified in Section 5.2.6 will be output and provided back to the programming team after QC is complete.

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Appendix 4. Traditional Statistical Methodology Details

The following SAS code is to be used as a guide for implementation.

Example SAS code for MMRM Model (strata included):

```
proc mixed data = dataset method=reml;
        class subject treatment time strata;
        model cfb = treatment base time base* time time *treatment strata/ddfm=kr residual outp=resid_out;
        repeated time /subject=subjid type = un;
        lsmeans treatment*time/diff cl alpha=0.1;
        ods output lsmeans=lsmeans_out;
        ods output diffs=diffs_out;
        ods output CovParms=CovParms_out;
run;
```

Example SAS code for Cumulative Incidence Plots:

```
proc lifetest data = dataset method=km plots=cif(test) outcif=cifatrisk intervals=0 to 20 by 2;
        strata treatment;
        time day*censor(1)/eventcode=0;
run;
```

NOTE: the censor variable has a value = 1 when the related time is censored and has a value = 0 when the event of interest occurs. There should be no other values available for this censored variable in this dataset (including missing values). If required, missing observations should be removed prior to analysis.

Example SAS code for Proportion of Responses (with multiple imputation):

Assume the SAS dataset is in a long format. The variable 'treatment' should be coded similar to 'Placebo', 'PF-06882961 2.5 mg BID', 'PF-06882961 10 mg BID',… 'PF-06882961 120 mg BID', so that when sorted in descending order 'Placebo' comes first.

```
proc sort data=analysis out= analysisl;
        by subjid time treatment base strata;
run;

* Create wide dataset for multiple imputation;
proc transpose data= analysisl out=analysisw  prefix=week;
        by subjid treatment base strata;
        id time;
        var cfb;
run;

* Perform multiple imputation;
proc mi data=analysisw seed=169 nimpute=20 out= analysis_mi;
        class treatment strata;
```

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```
        fcs nbiter=10 reg(/details);
        var base treatment strata week2 week4 week6 week8 week12 week16;
run;

* Determine responders and non-responders at Week 16 for all imputed datasets;
data analysis_mi_16;
        set analysis_mi;
        value = week16 + base;
        if value < 7 and week16 ne . then resp = 1;
        if value >= 7 and week16 ne . then resp = 0;
run;

* Create datasets and combine proportions;
proc freq data=analysis_mi_16;
        tables _imputation_*dose*resp/out=prop_mi outpct;
run;

data prop_mi_0;
        set prop_mi;
        if resp=0;
        keep _imputation_ treatment count;
        rename count=count_0;
run;
data prop_mi_1;
        set prop_mi;
        if resp=1;
        keep _imputation_ treatment count;
        rename count=count_1;
run;
data prop_mi_combined;
        merge prop_mi_0 prop_mi_1;
        by _imputation_ treatment;
        total = count_0 + count_1;
        p = count_1/total;
        q = count_0/total;
        se_p = sqrt((p*q)/total);
run;

proc sort data=prop_mi_combined;
        by treatment _imputation_;
proc mianalyze data=prop_mi_combined  alpha=0.1;
    by treatment;
    modeleffects p;
    stderr se_p;
    ods output parameterestimates=prop_mi_out;
run;
```

Example SAS code for Logistic Regression Model (with multiple imputation):

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The same imputed datasets as produced above for the 'Proportion of Responses' will be utilized. Note: the imputed dataset should be ordered so that the group 'Placebo' and 'Resp'=1 comes first to ensure that the reference group is Placebo and the odds ratios are for a response = 1.

```
* Fit logistic regressions to each imputed dataset and combine results;
proc sort data=analysis_mi_16;
        by _imputation_ descending treatment descending resp;
proc logistic data = analysis_mi_16 order=data;
        by _imputation_;
        class resp treatment strata;
        model resp = treatment strata base/alpha=0.1;
        oddsratio dose/diff=all;
        ods output OddsRatiosWald=OddsRatiosWald_mi;
run;

data OddsRatiosWald_mi;
        set OddsRatiosWald_mi;
        if Effect = 'treatment 2.5 mg BID vs Placebo' then treatment = 2.5;
        if Effect = 'treatment 10 mg BID vs Placebo' then treatment = 10;
        if Effect = 'treatment 40 mg BID vs Placebo' then treatment = 40;
        if Effect = 'treatment 80 mg BID vs Placebo' then treatment = 80;
        if Effect = 'treatment 120 mg BID vs Placebo' then treatment = 120;
        if treatment = . then delete;
        estimate = log(OddsRatioEst);
        SE = (log(UpperCL) - log(LowerCL))/(2*QUANTILE('NORMAL',0.95));
run;

proc sort data=OddsRatiosWald_mi;
        by treatment _imputation_;
proc mianalyze data=OddsRatiosWald_mi  alpha=0.1;
    by treatment;
    modeleffects estimate;
    stderr SE;
    ods output parameterestimates=OddsRatiosWald_mi_out;
run;
```

Appendix 5. Categorical Classes for ECG and Vital Signs of Potential Clinical Concern

Categories for QTcF

Absolute value of QTcF (msec)	>450 and ≤480	>480 and ≤500	>500
Increase from baseline in QTcF (msec)	>30 and ≤60	>60	

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Categories for PR and QRS

PR (ms)	max. ≥300	
PR (ms) increase from baseline	Baseline >200 and max. ≥25% increase	Baseline ≤200 and max. ≥50% increase
QRS (ms)	max. ≥140	
QRS (ms) increase from baseline	≥50% increase	

Categories for Vital Signs

Supine Systolic BP (mm Hg)	min. <90	
Supine Systolic BP (mm Hg) change from baseline	max. decrease ≥30	max. increase ≥30
Supine diastolic BP (mm Hg)	min. <50	
Supine diastolic BP (mm Hg) change from baseline	max. decrease ≥20	max. increase ≥20
Supine pulse rate (bpm)	min. <40	max. >120

Appendix 6. List of Abbreviations

Abbreviation	Term
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BLQ	below the limit of quantitation
BOCF	baseline observation carried forward
CFB	change from baseline
CRF	case report form
CSR	clinical study report
CV	coefficient of variation
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
Free T4	free thyroxine
GGT	gamma-glutamyl transferase
HbA1c	hemoglobin A1C
HDL	high-density lipoprotein
HOMA-IR	homeostatic model assessment of insulin resistance
ICD	informed consent document

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Abbreviation	Term
IP	investigational product
LDL	low-density lipoprotein
LLQ	lower limit of quantitation
LSMean	least-squares mean
MedDRA	Medical Dictionary for Regulatory Activities
MCMC	Markov Chain Monte–Carlo
MI	multiple imputation
MMRM	mixed model repeated measures
PCC	potential clinical concern
PK	pharmacokinetic(s)
PR	pulse rate
PT	preferred term
QC	quality control
QQ	quantile-quantile
QTcF	corrected QT (Fridericia method)
SAE	serious adverse event
SAP	statistical analysis plan
SOA	schedule of activities
SOP	standard operating procedure
T2DM	type 2 diabetes mellitus
TEAE	treatment emergent AE
TSH	thyroid-stimulating hormone
ULN	upper limit of normal

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