CLINICAL STUDY REPORT SYNOPSIS

Sponsor: Pfizer, Inc.

Investigational Product: PF-07081532

Clinical Study Report Synopsis: Protocol C3991002

Protocol Title: A Phase 1, Randomized, Double-Blind, Sponsor-Open, Placebo-Controlled Study to Assess the Safety, Tolerability, and Pharmacokinetics of Multiple Escalating Oral Doses of PF-07081532 in Adult Participants With Type 2 Diabetes Mellitus

Investigators: Refer to Appendix 16.1.4.1 for a list of investigators involved in this study.

Study Center(s): 2 centers in the United States. Refer to Appendix 16.1.4.1 for a list of sites involved in this study.

Publications Based on the Study: None

Study Initiation Date: 16 March 2020

Study Completion Date: Primary Completion Date and Last Participant Last Visit: 14 Jul 2021

Report Date: 08 April 2022

Previous Report Date: 04 March 2022

Phase of Development: Phase 1

Primary and Secondary Study Objectives and Endpoints: The primary and secondary study objectives and endpoints are presented in Table S1.

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Table S1. Primary and Secondary Study Objectives and Endpoints

Type	Objective	Endpoint
Primary		
Safety	To evaluate the safety and tolerability of escalating, multiple doses of PF-07081532, orally administered to adult participants with T2DM inadequately controlled by metformin and, if conducted, to non-diabetic obese participants.	Assessment of AEs, safety laboratory tests, vital signs and 12-lead ECGs.
Secondary		
PK	To characterize plasma PK of PF-07081532 following multiple doses administered orally to adult participants with T2DM inadequately controlled on metformin and, if conducted, to non-diabetic obese participants.	PF-07081532 plasma PK parameters AUC_{24}, C_{max}, T_{max}, $t_{½}$ on Day 1 and following multiple, oral dose administration, as data permit.
	To characterize the urine PK of PF-07081532 following multiple doses administered orally to adult participants with T2DM inadequately controlled on metformin.	Urine PK parameters for PF-07081532, as data permit: Ae_{24}, Ae_{24}%, and CL_r following multiple, oral dose administration, as data permit.

Abbreviations: AE = adverse event; Ae_{24} = cumulative amount of drug recovered unchanged in urine over 24 hours; Ae_{24}% = percent of dose recovered unchanged in urine over 24 hours; AUC_{24} = area under the concentration-time profile from time 0 to 24 hours; CL_r = renal clearance; C_{max} = maximum plasma concentration; ECG = electrocardiogram; PK = pharmacokinetic(s); $t_{½}$ = terminal half-life; T2DM = type 2 diabetes mellitus; T_{max} = time for C_{max}.

METHODS

Study Design:

This was a randomized, double-blind (investigator- and participant-blind), sponsor-open, placebo-controlled, multiple oral dose-escalating study of PF-07081532. There were 2 participant populations enrolled in this study: participants with T2DM and participants with Obesity, without diabetes. The study was conducted in 3 parts, portions of which could be conducted concurrently. Figure S1 shows an overview of the study, as it was conducted. As described in the protocol, dose levels were selected based on emerging data.

Part A: adult participants with T2DM inadequately controlled on metformin who received PF-07081532 or placebo daily for 28 days, with approximately 10 participants (8 PF-07081532: 2 placebo) per cohort. The duration of the study from the Screening visit to the on-site follow-up visit was approximately 10 weeks, of which approximately 33 days were inpatient at the clinical research unit (CRU).

Part B: adult participants with Obesity (without diabetes) who received PF-07081532 or placebo daily for 42 days, with approximately 15 participants with Obesity (12 PF-07081532: 3 placebo) per cohort. [redacted]

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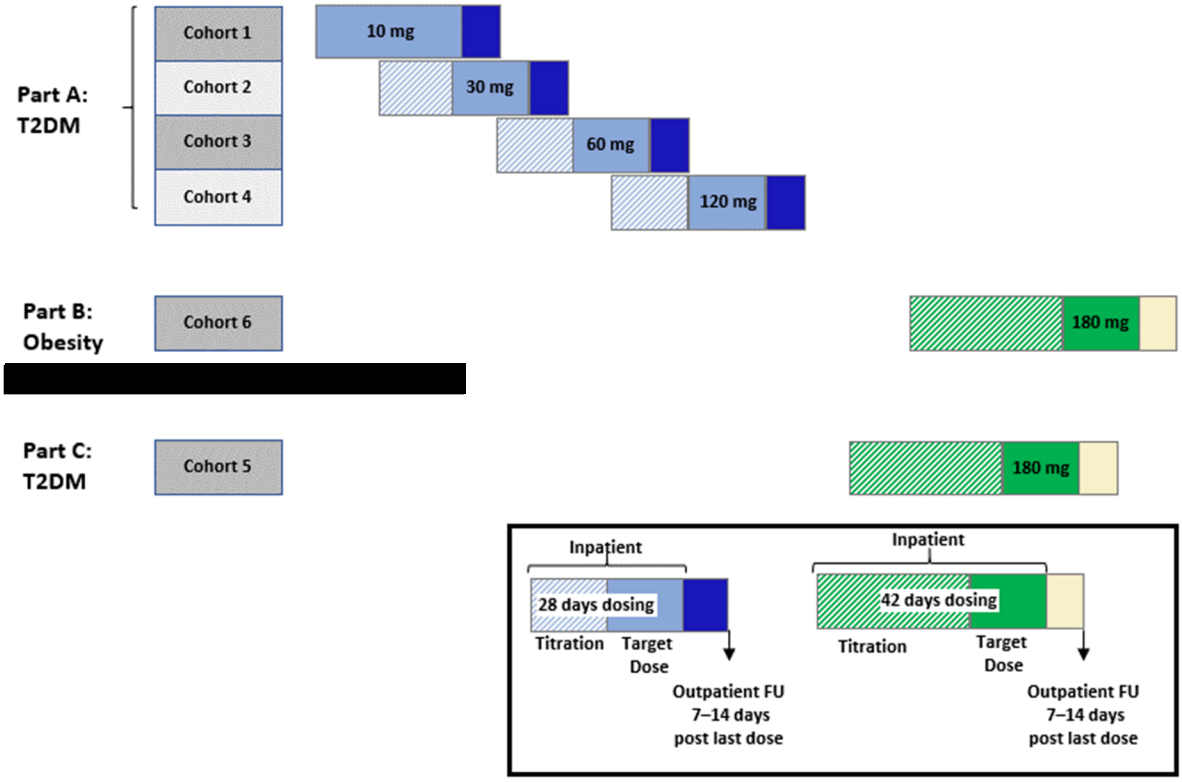
[redacted] The duration of the study from the Screening visit to the on-site follow-up visit was approximately 12 weeks, of which approximately 48 days were inpatient at the CRU.

Part C: adult participants with T2DM inadequately controlled on metformin who received PF-07081532 or placebo daily for 42 days, with approximately 10 participants (8 PF-07081532: 2 placebo) per cohort. The duration of the study from the Screening visit to the on-site follow-up visit was approximately 12 weeks, of which approximately 47 days were inpatient at the CRU.

Figure S1. Overall Study Design With Actual Implementation



Abbreviation: [redacted] FU = follow-up.

Diagnosis and Main Criteria for Inclusion: Adults with inadequately controlled T2DM on metformin monotherapy, and participants with Obesity (without diabetes) were enrolled in this study. Females must have been of non-childbearing potential.

Study Treatment:

Participants received PF-07081532 or matching placebo at approximately 0800 hours (±2 hours) each day from Day 1 to Day 28 (Part A) or Day 42 (Parts B and C). Investigator

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site personnel administered study intervention with approximately 240 mL ambient temperature water.

[redacted]

Metformin was required for participants with T2DM. On all study days while in the CRU, participants were given their morning dose of metformin at the same time as PF-07081532/placebo. For participants taking metformin more frequently than once a day, the investigator determined the appropriate times during the day to administer those doses. For metformin and other permitted concomitant medications, the timing of administration should have been the same between inpatient days, and care should have been taken to minimize changes to the participants' stable medication routine.

Study intervention information is provided in Table S2. PF-07081532 and matching placebo were supplied by Pfizer as tablets to the CRU in bulk along with individual dosing containers for unit dosing. [redacted]

Table S2. Study Intervention Information

Study Intervention Description	Vendor Lot Number	Pfizer Lot Number	Strength/Potency	Dosage Form
PF-07081532-82 100 mg Tablet	20-DP-00097	19-004901	100 mg	Tablet
PF-07081532-82 10 mg Tablet	20-DP-00096	19-004900	10 mg	Tablet
PF-07081532-82 10 mg Tablet	20-DP-00147	20-000975	10 mg	Tablet
PF-07081532-82 1 mg Tablet	20-DP-00095	19-004899	1 mg	Tablet
Placebo 6 mm Tablet	N/A	18-004178	0 mg	Tablet
Placebo Oval Tablet	B19053	19-002564	0 mg	Tablet

Efficacy Evaluations: Not Applicable

Pharmacokinetic Evaluations: Samples collected for analysis of PF-07081532 PK were analyzed using validated analytical methods in compliance with applicable standard

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operating procedures (SOPs). PF-07081532 plasma PK parameters (AUC_{24}, C_{max}, T_{max}, $t_{½}$ on Day 1 and following multiple dose administration, as data permitted) were calculated for each participant and each treatment using non-compartmental analysis of plasma concentration-time data. In addition, urine PK parameters (Ae_{24}, Ae_{24}%, and CL_r following multiple dose administration) were calculated as data permitted.

Safety Evaluations: Safety evaluations included AEs and serious adverse events (SAEs) monitoring, laboratory assessments, vital signs, 12-lead ECGs and physical examinations.

Statistical Methods:

Pharmacokinetics

The PF-07081532 concentration and PK parameter analysis populations were defined as all randomized participants who received at least 1 dose of PF-07081532, and in whom at least 1 plasma concentration value and 1 PK parameter value was reported, respectively. Each PK parameter was summarized by matrix (plasma/urine), treatment, and Study Day. Samples below the lower limit of quantitation were set to 0 for the PK analysis. Actual sample collection times were used for the PK analysis. PK samples from participants randomized to placebo were not routinely analyzed.

Safety

The safety analysis set included all randomized participants who received at least 1 dose of study intervention (PF-07081532 or placebo). Safety data were summarized descriptively by treatment in accordance with sponsor reporting standards.

RESULTS

Subject Disposition and Demography: A total of 66 participants were assigned to treatment and received at least 1 dose of study intervention; of these, 61 participants completed the blinded treatment. Of the 5 participants who discontinued, 3 were due to treatment-related AEs: 1 participant from Part A PF-07081532 60 mg group discontinued on Day 13 at a dose of 40 mg due to nausea; this participant did not complete the follow-up visit due to withdrawal by participant. One participant from Part A PF-07081532 120 mg group discontinued on Day 5 at a dose of 40 mg due to hypoglycemia. One participant from Part B PF-07081532 180 mg group discontinued study drug on Day 32 at a dose of 150 mg due to upper abdominal pain; this participant continued in the study. In addition, 1 participant from Part A placebo group and 1 participant from Part C PF-07081532 180 mg group discontinued during the treatment phase due to other reasons.

Demographic characteristics were generally comparable across groups. The gender distribution of the 66 participants was well-balanced, with 53% male and 47% female. The majority (more than 80%) of the participants were White, and a majority had Hispanic or Latino ethnicity (approximately 75% of participants with T2DM, and 87% of participants with Obesity). Overall, the mean age of participants was 57.4 years (range: 29 to 70 years),

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with generally similar average age and range across the populations studied. The mean weight and BMI for participants enrolling with T2DM were 89.7 kg (range: 52 to 152 kg) and 32.7 kg/m^2 (range: 25 to 45 kg/m^2), respectively. The mean duration of T2DM for participants with T2DM was 10.7 years (range: 1.6 to 22.8 years) and the median HbA1c at Screening in these participants was 8.4% (range: 7.0% to 10.5 %). The mean weight and BMI for participants enrolling with Obesity was 98.2 kg (range: 74 to 122 kg) and 35.1 kg/m^2 (range: 31 to 44 kg/m^2), respectively.

Efficacy Results: Efficacy evaluations were not done

Pharmacokinetic Results:

The PK of PF-07081532 were assessed on Day 1, then on Day 14 (Part A 10 mg) or 21 (Part A 30 mg, 60 mg and 120 mg) or 28 (Part B 180 mg and Part C 180 mg) and finally following last dose on Day 28 or 42. PF-07081532 was absorbed with C_{max} achieved at a median T_{max} of 1 to 2 hours for all treatments on Day 1, and 2 to 8 hours following last dose on Day 28 or 42. In general, plasma PF-07081532 exposure (C_{max} and area under the concentration-time profile from time 0 to time tau, the dosing interval, where tau = 24 hours [AUC_{tau}]) appeared to increase in an approximately dose-proportional manner following multiple oral doses across the dose range studied. Mean $t_{½}$ following last dose on Day 28 or 42 ranged from 20.70 to 26.50 hours for all treatments.

No substantial differences were observed in the achieved exposures (both C_{max} and AUC_{tau}) between participants with T2DM and Obesity (Part C and Part B, respectively) either after single dose administration (Day 1, 10 mg) or multiple dose administration (Day 28, 120 mg, and Day 42, 180 mg).

Urinary recovery of unchanged PF-07081532 was low, with less than 0.2% of the dose recovered in the 24-hour dosing interval following last dose on Day 28 or 42. CL_r was also low with geometric mean values of 0.00027 and 0.00019 L/hr for Part A 120 mg and Part C 180 mg groups, respectively, where CL_r could be reported.

Inter-participant variability for PF-07081532 exposure based on geometric percent coefficient of variation (%CV) ranged between 15% to 62% for AUC_{tau} and 17% to 51% for C_{max}, across all treatment groups for Day 1 and following last dose on Day 28 or 42.

Safety Results:

Adverse Events

The majority of all-causality treatment-emergent adverse events (TEAEs) (214 out of 240) were mild in severity (AEs described hereafter were all TEAEs if not specifically identified. The AE causality was assessed by the investigator unless specified). Twenty-four AEs were moderate, of which 20 were considered treatment-related. There were no deaths. Two severe AEs were reported in PF-07081532 30 mg group as described below.

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In participants with T2DM, a total of 174 TEAEs were reported in 44 (86.3%) participants. The majority of AEs (128 occurred in 38 participants) were considered treatment-related by the investigator. In PF-07081532 treatment groups, the 10 mg group had the lowest number of all-causality AEs with 5 events, and the 180 mg group had the highest number of all-causality AEs with 47 events. One participant in the 30 mg group had an SAE of obstructive pancreatitis (considered treatment-related by the investigator but considered unrelated by the sponsor). This participant also experienced severe AEs of hypotension (not related to study treatment but related to pancreatitis) and increased transaminases (treatment-related) on the same day of the SAE onset.

In participants with T2DM, 2 participants discontinued from the blinded treatment phase due to AEs: 1 in PF-07081532 60 mg group (Day 13, 40 mg dose) due to moderate nausea, and 1 in PF-07081532 120 mg group (Day 5, 40 mg dose) due to mild hypoglycemia. Both AEs were considered treatment-related. One participant in PF-07081532 120 mg group had a dose reduction to 100 mg due to moderate nausea and moderate dyspepsia, both considered treatment-related.

In participants with Obesity, a total of 66 AEs were reported in 14 (93.3%) participants. The majority of AEs (59 occurred in 13 participants) were considered treatment-related. No SAEs, severe AEs, or permanent discontinuation from study due to AEs were reported in these participants. In PF-07081532 180 mg group, 1 participant discontinued study drug due to moderate treatment-related upper abdominal pain and continued study; 1 participant had a dose reduction to 150 mg due to mild nausea (treatment-related).

In this study, all-causality TEAEs in the system organ class (SOC) of Gastrointestinal Disorders were most frequently reported (56.1% of events in participants with T2DM, 56.4% of events in participants with Obesity). The most frequently reported all-causality TEAE by preferred term (PT) was nausea in participants with T2DM, and nausea and constipation in participants with Obesity.

A total of 12 participants (6 participants with T2DM and 6 participants with Obesity) experienced hypoglycemic AEs (all treatment-related). All of these AEs were considered mild in severity, with the exception of 1 moderate documented symptomatic hypoglycemia reported in Part A PF-07081532 120 mg group. No participant had blood glucose <55 mg/dL. All hypoglycemic AEs were resolved.

Clinical Laboratory Evaluation

Without regard to baseline abnormality, 46 (70.8%) of the 65 participants evaluable for laboratory tests experienced laboratory abnormalities. Though there were isolated occurrences of laboratory abnormalities reported as AEs, no clinically significant adverse trends were observed in laboratory test parameters across treatment groups.

Vital Signs

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The most frequently reported post-baseline vital signs across all treatment groups that met pre-specified categorical analysis criteria in each study part were: Part A: supine systolic BP decreased ≥30 mmHg (12 participants); Part B: supine systolic BP increased ≥30 mmHg, and supine diastolic BP increased ≥20 mmHg (3 participants each); Part C: supine systolic BP decreased ≥30 mmHg (2 participants).

There were no apparent dose-related trends in the frequency of values meeting these criteria. There were no clinically significant adverse trends and no treatment-related AEs related to changes in vital signs.

In participants with T2DM, on Day 1, time-matched double differences in pulse rate for most PF-07081532 doses were similar to placebo. Modest increases were noted in most PF-07081532 doses across the dosing interval to Day 28 (Part A) or Day 42 (Part C), compared with Day 1, with mean heart rate remaining within the normal range. Across the dosing interval, the maximum mean time-matched double difference for pulse rate was 6.8 bpm in placebo, ranged from 3.9 to 8.3 bpm in Part A PF-07081532 groups, and 10.1 bpm in Part C 180 mg group. One participant in 120 mg group had pulse rate >120 bpm, in the setting of an episode of hypoglycemia.

In participants with Obesity, on Day 1, time-matched double differences in pulse rate for 180 mg dose group were similar to placebo. Across the dosing interval to Day 42, increases in the 180 mg group were observed compared with Day 1. The maximum mean time-matched double difference in pulse rate in the 180 mg group was 13.9 bpm on Day 42 compared to 6.7 bpm in placebo. While these increases in pulse rate were observed, there were no occurrences of pulse rate >120 bpm.

ECG

The following participants reported post-baseline ECG data meeting pre-specified categorical analysis criteria: 1 participant in Part A 30 mg group had QRS duration ≥140 msec; 5 participants in Part A had QTcF interval >450 msec and ≤480 msec (1 in placebo, 2 in 10 mg, 1 in 30 mg, and 1 in 60 mg); 3 participants had QTcF interval change from baseline >30 msec and ≤60 msec (1 in Part A 30 mg, and 2 in Part B placebo).

While there were isolated ECG measures outside the reference range, there were no clinically significant adverse trends observed in ECG parameters across treatment groups and no apparent dose-related increase in frequency of ECG abnormalities.

The mean time-matched double differences in heart rate demonstrated similar trends to those of pulse rate, with modest increases in heart rate observed on Day 28 or 42 in PF-07081532 treated groups. There were no clear dose-dependent trends noted for PR interval, QRS duration and QT and QTcF interval.

Conclusions:

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Safety

- Ascending, multiple, oral doses of PF-07081532 were considered safe in adult participants with T2DM or with Obesity, with a tolerability profile consistent with the mechanism of action.

- In both participants with T2DM and with Obesity, most TEAEs reported were mild in intensity and within the Gastrointestinal Disorders SOC. The most frequently reported all-causality TEAEs were nausea in participants with T2DM, and nausea and constipation in participants with Obesity. Doses of PF-07081532 <120 mg were considered well tolerated, with greater incidence of gastrointestinal TEAEs observed in the higher dose groups of PF-07081532 (120 mg and 180 mg) compared to placebo.

- There were no clinically significant adverse trends in safety laboratory tests, vital signs or ECG parameters with increasing PF-07081532 doses.

PK

- Following administration of PF-07081532 QD, C_{max} was observed at 1 to 2 hours on Day 1, and 2 to 8 hours following last dose on Day 28 or 42.

- $T_{½}$ averaged 20.70 to 26.50 hours following last dose on Day 28 or 42.

- PF-07081532 exposure (C_{max} and AUC_{tau}) generally increased in an approximately dose-proportional manner across the dose range studied.

- No substantial differences in PF-07081532 exposure (C_{max} and AUC_{tau}) were observed between participants with T2DM and obesity either after single dose (Day 1, 10 mg) or multiple dose (Day 28, 120 mg and Day 42, 180 mg) administration.

- Urinary recovery of unchanged PF-07081532 was low, with less than 0.2% of the dose recovered in the 24-hour dosing interval following last dose on Day 28 or 42.