CLINICAL STUDY REPORT SYNOPSIS

Sponsor: Pfizer Inc.

Investigational Product: PF-07258669

Clinical Study Report Synopsis: Protocol C4541001

Protocol Title: A Phase 1, Randomized, Double-Blind, Sponsor-Open, Placebo-Controlled, First-in-Human Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Single Ascending Oral Doses of PF-07258669 Administered to Healthy Adult Participants

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

Study Center(s): One site in the United States was involved in this study. 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 2021

Study Completion Date: 25 August 2021

Report Date: 25 February 2022

Previous Report Date(s): Not applicable

Phase of Development: Phase 1

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

Table S1. Primary and Secondary Study Objectives and Endpoints

Objective	Endpoint
Primary	
• To evaluate the safety and tolerability of single ascending doses of PF-07258669 administered orally to healthy adult participants.	• Assessment of AEs, clinical safety laboratory tests, vital signs, continuous cardiac monitoring, 12-lead ECGs, respiratory rate, oral body temperature, physical examinations, and neurological examinations.
Secondary	
• To evaluate the PK of PF-07258669 following single doses of PF-07258669 administered orally to healthy adult participants.	• PK parameters derived from plasma PF-07258669 concentrations: C_{max}, AUC_{last}, AUC_{inf}, T_{max}, and $t_{½}$, if data permitted.

Abbreviations: AE = adverse event; AUC_{inf} = area under the plasma concentration-time profile from time 0 extrapolated to infinite time; AUC_{last} = area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration; C_{max} = maximum observed concentration; ECG = electrocardiogram; PK = pharmacokinetic(s); $t_{½}$ = terminal half-life; T_{max} = time for C_{max}.

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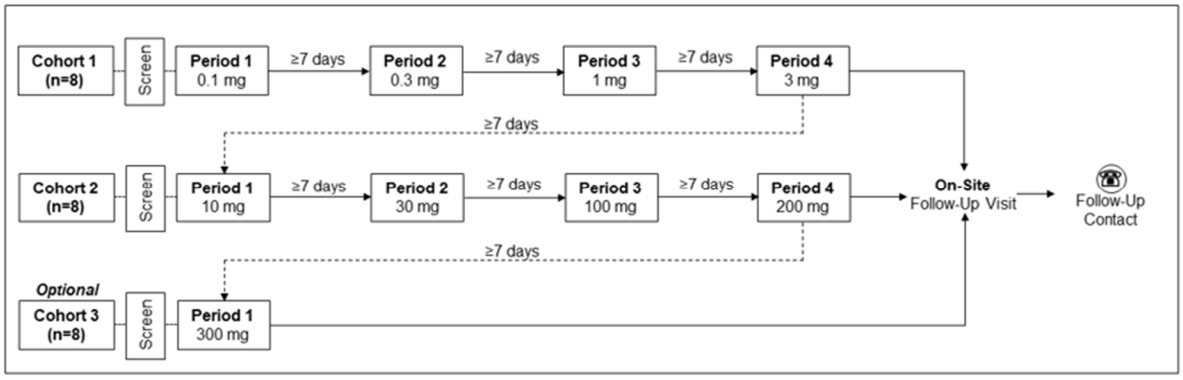
METHODS

Study Design: This study was a randomized, investigator- and participant-blind, sponsor-open, placebo-controlled, first-in-human, single ascending oral dose study of PF-07258669 administered to healthy adult participants. Up to approximately 24 healthy adult participants (up to 3 cohorts of approximately 8 participants each) were planned to be enrolled in this study. Each participant was planned to undergo 4 treatment periods receiving 3 doses of PF-07258669 and 1 dose of placebo. There was a washout interval of at least 7 days after each period.

Precautionary sentinel dosing was used in each period of each cohort. Two participants (1 receiving PF-07258669 and 1 receiving placebo) within a period were dosed initially. Safety and tolerability data, through at least 24 hours post-dose for the sentinel participants, were reviewed prior to dosing the remaining participants of that period.

An overview of the study, as it was conducted, is shown in Figure S1. Dose levels were escalated to bracket the expected clinical dose range, but projected exposures did not exceed the pre-defined human exposure limits. The optional third cohort was only to be used if the objectives of the study were not fulfilled in Cohorts 1 and 2; ultimately, a third cohort was required for a single period only. The total duration of participation from the screening visit to the telephone follow-up contact was approximately 14 weeks for each participant.

Figure S1. Overall Study Design



Screening to dosing on Day 1 in Period 1: Maximum of 28 days for each cohort.
Inpatient stay in each period: Day -1 to minimum of Day 3 (ie, 48 hours post-dose).
In each period, 6 participants were planned to be randomized to receive PF-07258669, and 2 participants were planned to receive matching-placebo.
PF-07258669 doses ≤1 mg were administered as solutions; PF-07258669 doses ≥3 mg were administered as suspensions.
On-site follow-up visit was planned to occur on Day 8±2 days in Period 4 only, with an additional follow-up contact planned for 28-35 days after administration of the final dose of study intervention.

Diagnosis and Main Criteria for Inclusion: Healthy female participants of nonchildbearing potential and male participants 18 to 55 years of age, inclusive, at the time

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of signing the Informed Consent Document, with body mass index of 17.5 to 30.5 kg/m^2 and a total body weight >50 kg (110 lb).

Study Treatment: The study interventions were PF-07258669 and its matching placebo. PF-07258669 and placebo were provided by Pfizer as bulk powders for extemporaneous preparation of oral solutions or suspensions at the site. Lot numbers and formulation identification/dosage material identifications are presented in Table S2.

Table S2. Investigational Product Description

Investigational Product Description	Vendor Lot Number	Pfizer Lot Number	Strength/Potency	Dosage Form
Hydrochloric Acid Solution 0.1 M Oral Solution 20 mL Glass Vial (20 mL)	N/A	18-001691	N/A	Solution
Methylcellulose (Methocel A4M Premium)	D180J7E011	20-EX-00293	N/A	Excipient
PF-07258669	N/A	20-AP-00346	0.992	API
Titanium Dioxide (Titanium Dioxide BC 3328)	5722315	19-EX-00055	N/A	Excipient

Abbreviations: API = active pharmaceutical ingredient; N/A = not applicable.

Efficacy Evaluations: Not Applicable

PK Evaluations: Blood samples were collected for measurement of plasma concentrations of PF-07258669 using a validated, sensitive, and specific high performance liquid chromatography coupled with tandem mass spectrometry (HPLC-MS/MS) method in compliance with Pfizer's standard operating procedures (SOPs).

The following PF-07258669 PK parameters (Table S3) were calculated for each participant and treatment using noncompartmental analysis (NCA) of plasma concentration-time data.

Table S3. Pharmacokinetic Parameters Determined in Study C4541001

Parameter	Definition	Method of Determination
AUC_{last}	Area under the plasma concentration-time profile from time 0 to the time of C_{last}	Linear/Log trapezoidal method
AUC_{inf}[a]	Area under the plasma concentration-time profile from time 0 extrapolated to infinite time	$AUC_{last} + (C_{last}*/k_{el})$, where $C_{last}*$ is the predicted plasma concentration at the last quantifiable timepoint estimated from the log-linear regression analysis
C_{max}	Maximum observed concentration	Observed directly from data

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Table S3. Pharmacokinetic Parameters Determined in Study C4541001

Parameter	Definition	Method of Determination
T_{max}	Time for C_{max}	Observed directly from data as time of first occurrence
$t_{½}$[a]	Terminal half-life	$Log_e(2)/k_{el}$, where k_{el} is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve.

Pharmacokinetic parameter values were calculated using an internally validated software system, open noncompartmental analysis (oNCA; version 2.4.33).
a. If data permitted.

Safety Evaluations: Safety evaluations mainly included AE monitoring, clinical safety laboratory tests, vital signs, and 12-lead ECGs.

Statistical Methods: The safety analysis set was defined as all participants randomly assigned to study intervention and who received a dose of study intervention. Participants were analyzed according to the product they actually received. All safety analyses were performed on the safety population. Safety data were presented in tabular and/or graphical format and summarized descriptively, where appropriate.

The PK concentration analysis set was defined as all participants randomly assigned to study intervention, who received a dose of study intervention, and in whom at least 1 PF-07258669 plasma concentration value was reported. The PK parameter analysis set was defined as all participants randomly assigned to study intervention, who received a dose of study intervention and had at least 1 of the PK parameters of interest calculated.

The plasma PK parameters in Table S3 were summarized descriptively by dose in accordance with Pfizer data standards, as data permitted.

RESULTS

Participant Disposition and Demography: A total of 29 participants were enrolled into the study, and all received study intervention.

Ten participants in Cohort 1 were randomized to PF-07258669 dose levels of 0.1, 0.3, 1, 3 mg, and/or placebo; 11 participants in Cohort 2 were randomized to PF-07258669 dose levels of 10, 30, 100, 200 mg, and/or placebo; 8 participants in Cohort 3 were randomized to PF-07258669 dose level of 300 mg or placebo (Figure S1 and Table S4).

Sixteen of the 29 participants completed the double-blind treatment phase, and 15 participants completed the follow-up phase. Two participants in Cohort 1 and 3 participants in Cohort 2 withdrew from the study for reasons other than an AE and were replaced by alternate participants in subsequent periods (Table S4). All 8 participants in Cohort 3 discontinued from the double-blind treatment phase and follow-up phase when the

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study was terminated after the first period given that the geometric mean C_{max} for this cohort with study intervention of PF-07258669 300 mg approached the pre-defined human exposure limit and the primary and secondary objectives of the study had been achieved.

The median age of the participants was 40.0 years (range: 20.0 to 56.0 years); most of the participants were male (20/29). The majority (26/29) of participants were White, and all participants were Hispanic or Latino.

Table S4. Disposition Events Summary (Protocol C4541001)

Number (%) of Participants	COHORT 1 (N=10) n (%)	COHORT 2 (N=11) n (%)	COHORT 3 (N=8) n (%)	Total (N=29) n (%)
Disposition phase: screening				
Participants Entered:	10 (100.0)	11 (100.0)	8 (100.0)	29 (100.0)
Discontinued	0	0	0	0
Reason for discontinuation				
Lost to follow-Up	0	0	0	0
Study terminated by sponsor	0	0	0	0
Withdrawal by subject	0	0	0	0
Completed	10 (100.0)	11 (100.0)	8 (100.0)	29 (100.0)
Disposition phase: Double-Blind Treatment				
Participants Entered:	10 (100.0)	11 (100.0)	8 (100.0)	29 (100.0)
Discontinued	2 (20.0)	3 (27.3)	8 (100.0)	13 (44.8)
Reason for discontinuation				
Lost to follow-Up	0	0	0	0
Study terminated by sponsor	0	0	8 (100.0)	8 (27.6)
Withdrawal by subject	2 (20.0)	3 (27.3)	0	5 (17.2)
Completed	8 (80.0)	8 (72.7)	0	16 (55.2)
Disposition phase: follow-up				
Participants Entered:	8 (80.0)	8 (72.7)	8 (100.0)	24 (82.8)
Discontinued	0	1 (9.1)	8 (100.0)	9 (31.0)
Reason for discontinuation				
Lost to follow-Up	0	1 (9.1)	0	1 (3.4)
Study terminated by sponsor	0	0	8 (100.0)	8 (27.6)
Withdrawal by subject	0	0	0	0
Completed	8 (80.0)	7 (63.6)	0	15 (51.7)

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Table S4. Disposition Events Summary (Protocol C4541001)

Number (%) of Participants	COHORT 1 (N=10) n (%)	COHORT 2 (N=11) n (%)	COHORT 3 (N=8) n (%)	Total (N=29) n (%)

PF-07258669 dose levels in Cohort 1 were 0.1, 0.3, 1, and 3 mg. Dose levels of 10, 30, 100, and 200 mg were evaluated in Cohort 2. In Cohort 3, 300 mg was evaluated.
PFIZER CONFIDENTIAL SDTM Creation: 22SEP2021 (00:41) Source Data: adds Table Generation: 28NOV2021 (05:05)
Output File: ./nda1 cdisc/C4541001/adds s001
Table 14.1.1.2.1 PF-07258669 is for Pfizer internal use.

Efficacy Results: Efficacy evaluations were not done for this study.

PK Results: Following administration of single oral doses of PF-07258669 to healthy adult participants, PF-07258669 was rapidly absorbed with a median T_{max} of 0.750 to 1.25 hours across all dose levels. [redacted]

PF-07258669 plasma exposures (AUC_{last}, AUC_{inf}, and C_{max}) increased with increasing dose. Exposures increased in an approximately dose-proportional manner within each cohort (0.1 mg to 3 mg in Cohort 1; 10 mg to 200 mg in Cohort 2). However, exposures in Cohort 2 were less than dose proportional when compared to Cohort 1. Exposures observed at 300 mg in Cohort 3 were consistent with those of Cohort 2.

Safety Results:

Adverse events:

No deaths, serious adverse events (SAEs), severe AEs, discontinuations from study due to AEs, discontinuations from study drug due to AEs, or dose reduction or temporary discontinuation due to AEs were reported. No medical errors were reported.

A total of 19 treatment-emergent adverse events (TEAEs) were reported in 14 of 29 participants in the study. Seven of the 19 AEs were reported in 6 participants when receiving placebo, and 12 AEs were reported in 10 participants when receiving PF-07258669 at 1 mg to 300 mg. Five TEAEs were considered as treatment-related by the investigator (4 AEs in PF-07258669 groups and 1 AE in the placebo group). All TEAEs were graded as mild in severity.

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The incidence rates of AEs were similar across treatment groups (33.3% for placebo and 16.7%-50.0% for PF-07258669 ≥1 mg groups; no AEs were reported in PF-07258669 <1 mg groups). The TEAEs occurring in ≥2 participants, regardless of System Organ Classes, were increased blood triglycerides (2 AEs each in 2 participants), contact dermatitis (3 AEs in 2 participants), and upper respiratory tract infection (1 AE each in 2 participants). Five AEs (1 AE of orthostatic hypotension for 1 participant in Cohort 1 and 2 AEs of increased blood triglycerides each for 2 participants in Cohort 2) were considered as related to study drug.

Clinical laboratory tests:

The number of participants with laboratory abnormalities in PF-07258669 and placebo groups were generally comparable. There was no definitive dose-dependent increase in frequency of laboratory abnormalities.

The most frequently reported laboratory abnormalities were high-density lipoprotein cholesterol <0.8× lower limit of normal (incidence rates ranging from 33.3% to 100% across treatment groups) and low-density lipoprotein cholesterol >1.2× upper limit of normal (incidence rates ranging from 16.7% to 83.3% across treatment groups), which was observed pre- and post-dose, and occurred across the treatment groups (PF-07258669 and placebo), with no apparent dose-related increase in the frequency of values outside the normal range. Four AEs related to increase in blood triglycerides were reported in 2 participants in Cohort 2, which were considered as related to study drug, as described above.

Vital signs:

Overall, there were no clinically significant adverse trends observed in vital signs in participants receiving PF-07258669 compared to placebo. A single AE of asymptomatic orthostatic hypotension was reported in 1 participant 6 hours post-dose of PF-07258669 3 mg as described above.

The vital sign (absolute value), meeting the categorical criterion in the greatest number of participants, was standing diastolic blood pressure ≥90 mm Hg reported in a total of 10 participants (including 6 participants in placebo group, 2 participants each in PF-07258669 3 mg, 10 mg, and 200 mg groups, and 1 participant each in PF-07258669 0.3 mg, 1 mg, 30 mg, 100, and 300 mg groups).

ECGs:

There were no clinically significant adverse trends observed in ECG parameters. There was no evidence of a relationship between change from baseline in QTcF and plasma PF-07258669 concentration.

First degree atrioventricular heart block was reported as an AE in 1 participant in Cohort 1 post-dose of PF-07258669 1 mg, and was not considered as related to study drug. Otherwise, no ECG abnormalities were reported as AEs. No participants had absolute values or

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maximum changes from baseline meeting any categorical criteria for any ECG parameter, and no participants had uncorrected QT values >500 msec.

Conclusion(s):

Safety:

- Oral administration of PF-07258669 at single ascending doses from 0.1 mg to 300 mg to healthy adult participants was considered safe and well-tolerated. All AEs were mild, and the incidence rates of AEs were similar across treatment groups (33.3% for placebo and 16.7%-50.0% for PF-07258669 ≥1 mg groups; no AEs were reported in PF-07258669 <1 mg groups). The most frequently reported AE was increased blood triglycerides (2 AEs each in 2 participants).

- No deaths, SAEs, severe AEs, discontinuation from study due to AEs, discontinuation from study drug due to AEs, or dose reduction or temporary discontinuation due to AEs were reported in this study.

- No adverse or clinically significant trends were observed in any safety parameters, including clinical laboratory data, vital signs, and ECG parameters. There was no apparent dose-dependent increase in frequency of abnormalities in any of the safety parameters assessed.

PK:

- Following administration of single oral PF-07258669 doses of 0.1 mg to 300 mg to healthy adult participants, PF-07258669 was absorbed rapidly with a median T_{max} of 0.750 to 1.25 hours. AUC_{last}, AUC_{inf} and C_{max} increased with increasing dose from 0.1 mg to 300 mg. The exposure increases were approximately dose-proportional within each cohort, but exposures were less than dose proportional in Cohort 2 (doses of 10 mg to 200 mg) and Cohort 3 (dose of 300 mg) when compared to Cohort 1 (doses of 0.1 mg to 3 mg). [redacted]