CLINICAL STUDY REPORT SYNOPSIS

Sponsor: Pfizer Inc

Investigational Product: PF-06835919

Clinical Study Report Synopsis: Protocol C1061010

Protocol Title: A Phase 1, Randomized, Double-Blind, Sponsor-Open, Placebo-Controlled Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Multiple Oral Doses of PF-06835919 in Healthy Adult Japanese Participants

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

Study Center(s): This study was conducted in 1 center in Brussels, Belgium. Refer to Appendix 16.1.4.1 for details regarding the site involved in this study.

Publications Based on the Study: None

Study Initiation Date: 24 November 2020

Study Completion Date: 31 March 2021

Report Date: 07 July 2021

Previous Report Date(s): Not Applicable

Phase of Development: Phase 1

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

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Table S1. Primary Study Objectives and Endpoints

Type	Objective	Endpoint
Primary		
Safety	• To evaluate the safety and tolerability of PF-06835919 following multiple oral doses of PF-06835919 administration in healthy adult Japanese participants.	• Assessment of AEs, clinical laboratory tests, vital signs (including BP and PR) and 12-lead ECG.
Pharmacokinetics	• To evaluate the PK of PF-06835919 following single and multiple oral doses of PF-06835919 administration in healthy adult Japanese participants.	• PK parameters for PF-06835919: • Day 1 and Day 7: C_{max}, T_{max}, AUC_{tau}; • Day 7: $t_{½}$, as data permitted.

Abbreviations: AE = adverse event; AUC_{tau} = area under the concentration-time profile from time zero to time tau, the dosing interval, where tau = 24 hours.; BP = blood pressure; C_{max} = maximum plasma concentration; ECG = electrocardiogram; PK = pharmacokinetic; PR = pulse rate; $t_{½}$ = terminal half-life; T_{max} = time at which C_{max} occurred.

METHODS

Study Design: This was a Phase 1, randomized, double-blind, sponsor-open, placebo-controlled study to evaluate the safety, tolerability and pharmacokinetic (PK) of multiple oral doses of PF-06835919 300 mg once daily (QD) in healthy adult Japanese participants. A total of approximately 8 healthy participants were planned to be enrolled and randomized to one of the 2 groups in a 3:1 ratio to receive the treatment as summarized in Table S2.

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Table S2. Study Design and Treatments

Group	Number of Participants	Treatment[a] (7 Days)
1	6	PF-06835919 300 mg QD
2	2	Placebo QD

a. Study treatment as PF-06835919 3 × 100 mg or matching placebo tablets.

Diagnosis and Main Criteria for Inclusion: Participants were healthy male or female Japanese who were 18 to 55 years of age, inclusive, at the time of signing the informed consent document (ICD), with a body mass index (BMI) of 17.5 to 30.5 kg/m^2 and a total body weight >50 kg (110 lb).

Study Treatment: The investigational products administered were PF-06835919 and matching placebo tablets. PF-06835919 was supplied by the sponsor as 100 mg tablets along with matching placebo tablets to the clinical research unit (CRU) in bulk along with individual dosing containers for unit dosing (Table S3).

On Days 1-7 at approximately 0800 hours (±2 hours), approximately 20 minutes prior to the start of breakfast, the treatments as presented in Table S2 were given to the participants following an overnight fast of at least 8 hours and in a blinded fashion. Investigator site personnel administered study intervention with ambient temperature water to a total volume of approximately 240 mL. Participants might have received additional ambient temperature water up to 100 mL, if needed. Participants swallowed the study intervention whole and did not manipulate or chew the study intervention prior to swallowing.

Table S3. Investigational Product Description

Investigational Product Description	Vendor Lot Number	Pfizer Lot Number	Strength/Potency	Dosage Form
PF-06835919 100 mg Oval White to Off-White Tablet	Not applicable	18-002838	100 mg	Tablet
Placebo Oval Tablet [redacted]	19-DP-00022	19-001254	0 mg	Tablet

Efficacy Evaluations: Not Applicable

Pharmacokinetic Evaluations: Blood samples of approximately 3 mL, to provide a minimum of 1 mL plasma, were collected for measurement of plasma concentrations of PF-06835919 at pre-specified timepoints. PF-06835919 concentrations in plasma were analyzed using a validated, sensitive and specific high-performance liquid chromatography

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coupled with tandem mass spectrometry (HPLC-MS/MS) method in compliance with Pfizer's applicable standard operating procedures (SOPs).

The PK parameters were calculated for each participant for PF-06835919, as applicable, using noncompartmental analysis (NCA) of concentration-time data. Samples below the lower limit of quantitation were set to 0 μg/mL for the PK analysis. Actual sample collection times were used for the pharmacokinetic analysis.

Safety Evaluations: Safety evaluations included adverse event (AE) and serious adverse event (SAE) monitoring, safety laboratory tests, vital signs (blood pressure and pulse rate), and 12-lead electrocardiograms (ECGs).

Statistical Methods:

Pharmacokinetic:

The PK concentration analysis set was defined as all participants who received at least 1 dose of PF-06835919 and who had at least 1 measurable concentration of PF-06835919. The PK parameter analysis set was defined as all participants treated who received at least 1 dose of PF-06835919 and had at least 1 of the PK parameters of interest calculated.

Plasma concentration of PF-06835919 were descriptively summarized and plotted by nominal PK sampling time and day. The plasma PK parameters for PF-06835919 were summarized descriptively by study day in accordance with the sponsor data standards, as data permitted.

Safety:

The safety analysis set was defined as all participants assigned to the study intervention and who took at least 1 dose of the study intervention. Safety data were reported in accordance with the sponsor reporting standards. A set of summary tables split by treatment were produced to evaluate any potential risk associated with the safety and toleration of administering PF-06835919.

RESULTS

Participant Disposition and Demography: A total of 8 participants were assigned to treatment in this study, 6 participants in PF-06835919 300 mg QD group and 2 participants in placebo group, respectively. All of them were treated and completed the study.

All 8 participants assigned to study treatments were Japanese males. The mean (standard deviation [SD]) age was 36.1 (6.81) years, ranging from 25 to 45 years. The mean (SD) body weight, height and BMI were 64.2 (7.61) kg, 169.6 (3.38) cm and 22.33 (2.21) kg/m^2, respectively.

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

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Pharmacokinetic Results:

Plasma PF-06835919 PK

PF-06835919 PK parameters for Days◦1 and 7 are summarized below.

Following single and multiple doses, PF-06835919 was absorbed rapidly with C_{max} observed in a median T_{max} of 0.834 and 0.750 hours, respectively. On Day 1, systemic exposures as measured by geometric mean values for AUC_{tau} and C_{max} were 169.3 µg•hr/mL and 23.39 µg/mL, respectively. Geometric mean values for AUC_{tau} and C_{max} following multiple dosing on Day 7, were 230.9 µg•hr/mL and 30.49 µg/mL, respectively. Following attainment of C_{max} on Day 7, plasma concentrations declined with a mean $t_{½}$ value of 14.62 hours. Based on trough plasma PF-06835919 concentrations, steady state appeared to be achieved after 4 days of daily dosing.

Similar inter-participant variability was observed for AUC_{tau} and C_{max} for single and multiple dosing. Following a single dose, percent coefficient of variation (%CV) for AUC_{tau} and C_{max} were 22% and 14%, respectively, and following multiple doses, %CV for AUC_{tau} and C_{max} were 20% and 10%, respectively.

Safety Results:

No deaths, SAEs, severe AEs, discontinuations or dose reductions due to AEs were reported during this study.

A total of 6 AEs were reported in the study and among which 2 AEs were considered treatment-related (atrioventricular block first degree and sneezing reported in 1 participant each). All AEs were of mild severity and no AEs were considered clinically significant.

There were no participants meeting pre-set laboratory test abnormality criteria. No participants met pre-defined criteria of potential clinical concern for vital signs and ECG data.

Conclusions:

- Following single dose administration on Day 1, systemic exposures of PF-06835919 as measured by geometric mean values for AUC_{tau} and C_{max} were 169.3 µg•hr/mL and 23.39 µg/mL, respectively. Geometric mean values for AUC_{tau} and C_{max} following multiple dosing on Day 7, were 230.9 µg•hr/mL and 30.49 µg/mL, respectively.

- Absorption of PF-06835919 was rapid with median T_{max} of 0.834 and 0.750 hours, respectively after single and multiple doses. The mean $t_{½}$ value of PF-06835919 was 14.62 hours on Day 7 following multiple daily doses.

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- Multiple doses of PF-06835919 300 mg were generally safe and well-tolerated in healthy Japanese participants.