CLINICAL STUDY REPORT SYNOPSIS

SYNOPSIS

Study Title: A Phase 1, Open-Label, Fixed-Sequence, 2-Period Study in Healthy Adult Male Participants to Assess the Extent of Excretion, Absolute Bioavailability, Fraction Absorbed, and Pharmacokinetics of [^{14}C]PF-06865571 Using a ^{14}C-Microtracer Approach

Study Number: C2541007

Regulatory Agency or Public Disclosure Identifier Number:

ClinicalTrials.gov ID: NCT04866225

Study Phase: Phase 1

Name of Study Intervention: ervogastat (PF-06865571)

Name of Sponsor/Company: Pfizer Inc.

CSR Version and Report Date: Final CSR (LPLV date) Version 1.0; 14 June 2022

Number of Study Center(s) and Investigator(s): A total of 6 participants were enrolled at 1 site in the United States. Details regarding the investigator and site involved in this study are available in Appendix 16.1.4.1.

Publications: None, as of issuance of this CSR

Study Period:

Study Initiation Date (First Participant First Visit): 11 May 2021

Study Completion Date (Last Participant Last Visit): 06 August 2021

This study was completed as designed.

Rationale:

Ervogastat (PF-06865571) is a potent, reversible diacylglycerol acyltransferases 2 (DGAT2) inhibitor currently being developed for the treatment of non-alcoholic steatohepatitis (NASH) with liver fibrosis. It is an oral small molecule postulated to decrease hepatic triglyceride (TG) synthesis and hepatic lipid burden in non-alcoholic fatty liver disease (NAFLD) and NASH.

The purpose of this study was to assess the extent of excretion of PF-06865571 as well as the absolute bioavailability (F), fraction absorbed (F_a) and pharmacokinetics (PK) of PF-06865571 in healthy male participants using a ^{14}C-microtracer approach.

CLINICAL STUDY REPORT SYNOPSIS

Objectives, Endpoints, and Statistical Methods:

Study objectives and endpoints are presented in Table S1.

Table S1. Study Objectives and Endpoints

Type	Objectives	Endpoints
Primary:		
Mass Balance	• To characterize the extent of excretion of total radioactivity in urine and feces following administration of a single oral dose of [^{14}C]PF-06865571.	• Total recovery of radioactivity in urine, feces and total excreta (urine + feces) as percentage of total radioactive dose administered.
Metabolites	• To characterize the metabolic profile and identify circulating and excreted metabolites following administration of a single oral dose of [^{14}C]PF-06865571.	• Metabolic profiling/identification and determination of relative abundance of [^{14}C]PF-06865571 and the metabolites of [^{14}C]PF-06865571 in plasma, urine and feces.
Secondary:		

PK	• To quantify plasma PK parameters of PF-06865571 and total radioactivity following administration of a single oral dose of [^{14}C]PF-06865571.	• Period 1: AUC_{last}, C_{max}, T_{max}, and if data permitted, AUC_{inf} and $t_{½}$ to describe single oral dose of:
		  • Total radioactivity in plasma
		  • PF-06865571 in plasma.

PK	• To quantify plasma PK parameters of PF-06865571 following administration of a single IV microtracer of [^{14}C]PF-06865571.	• [^{14}C]PF-06865571 (Period 2): AUC_{last}, C_{max}, T_{max}, and if data permitted, $t_{½}$, AUC_{inf}, CL and V_{ss}.
PK	• To determine the F of PF-06865571 following administration of a single oral dose of PF-06865571 compared to a single IV microtracer of [^{14}C]PF-06865571.	• Plasma AUC_{inf} of oral unlabeled PF-06865571 and IV microtracer of [^{14}C]PF-06865571 in Period 2 only.
PK	• To determine the F_a following administration of a single oral dose of [^{14}C]PF-06865571.	• Total urinary radioactivity following oral administration of [^{14}C]PF-06865571 in Period 1 and IV microtracer administration of [^{14}C]PF-06865571 in Period 2.
Tertiary/Exploratory:		
Mass Balance	• To characterize cumulative rate of excretion of total radioactivity in urine and feces over time following administration of a single oral dose of [^{14}C]PF-06865571.	• Cumulative recovery of radioactivity in urine and feces, and total excreta (urine + feces) over time as a percentage of total radioactive dose administered.
PK	• To quantify plasma PK parameters of PF-06865571 in plasma following administration of a single oral dose of unlabeled PF-06865571.	• PF-06865571 plasma (Period 2): AUC_{last}, C_{max}, T_{max}, and if data permitted, $t_{½}$, AUC_{inf}, CL/F, V_z/F.

CLINICAL STUDY REPORT SYNOPSIS

Table S1. Study Objectives and Endpoints

Type	Objectives	Endpoints
Other	• To evaluate the sensory and taste attributes of the PF-06865571 oral suspension in healthy participants.	• Taste Assessment Questionnaire Scoring Metrics: bitterness and tongue/mouth sensation.
Safety	• To evaluate the safety and tolerability of PF-06865571, administered as a single oral dose of [^{14}C]PF-06865571 or a single oral dose of PF-06865571 followed by administration of a single IV microtracer of [^{14}C]PF-06865571.	• AE monitoring, clinical laboratory measurements, vital signs and 12-lead ECG.

Abbreviations: AE = adverse event; AUC_{inf} = area under the plasma concentration-time profile from time zero extrapolated to infinite time; AUC_{last} = area under the plasma concentration-time profile from time zero to time of the last quantifiable concentration; CL = systemic clearance; CL/F = apparent clearance; C_{max} = maximum plasma concentration; ECG = electrocardiogram; IV = intravenous(ly); $t_{½}$= terminal elimination half-life; T_{max} = time for C_{max}; V_{ss} = steady-state volume of distribution following intravenous infusion; V_z/F = apparent volume of distribution following oral administration.

Statistical methods used in the study are as follows:

Extent of Excretion:

Participants who received 1 dose of [^{14}C]PF-06865571, had evaluable total radioactivity concentration data, and had no protocol deviations or AEs that might have affected the extent of excretion analysis were included in the extent of excretion analysis.

The percentage of the administered radioactivity excreted at each time interval, cumulatively through that interval and the total percent of dose recovered in urine and/or feces was determined based on total administered dose.

Individual participant and median data profiles were graphically presented for the cumulative recovery of radioactivity. The total recovery of radioactivity was listed and summarized using descriptive statistics. The results were detailed in the absorption, distribution, metabolism, and excretion (ADME) report and summarized in the CSR.

Metabolic Profiling/Identification:

Major metabolites of PF-06865571 in plasma, urine, and feces following oral dose of [^{14}C]PF-06865571 were identified. Results of the metabolic profiling analysis were detailed in the ADME report and summarized in the CSR.

PK:

The PK concentration population for PF-06895571 was defined as all participants who received at least 1 dose of PF-06895571 and had at least 1 measurable concentration of

CLINICAL STUDY REPORT SYNOPSIS

PF-06895571. The PK parameter analysis population for PF-06895571 was defined as all participants dosed who had at least 1 of the PF-06895571 PK parameters of interest.

Plasma PK parameters were listed and summarized descriptively by analyte (Total ^{14}C, unlabeled PF-06865571, and [^{14}C]PF-06865571) and treatment. The descriptive summary, concentration and PK parameters were presented in appropriate tables and figures.

F was estimated as the ratio of adjusted geometric means of dose-normalized AUC_{inf} for oral unlabeled PF-06865571 and IV labeled [^{14}C]PF-06865571 in plasma. Geometric mean ratio and 90% confidence interval (CI) of F were determined.

Total urine ^{14}C amounts, percent ^{14}C dose were listed by treatment (oral in Period 1 and IV in Period 2) and summarized using descriptive statistics.

F_a was estimated as the ratio of the adjusted geometric means of % of administered radioactive dose excreted into the urine following oral and IV administration of [^{14}C]PF-06865571 microtracer dose over the same collection time (up to 48 hours post-dose) in Periods 1 and 2, respectively. Geometric mean ratio and 90% CI of F_a were determined.

Taste Assessments:

The taste attributes from the taste questionnaires were listed and descriptively summarized and appropriate plots were generated.

Safety:

All participants assigned to study intervention and who received at least 1 dose of study intervention were included in the safety analysis.

AEs, ECGs, blood pressure (BP), pulse rate, and safety laboratory data were reviewed and summarized on an ongoing basis during the study. Any clinical laboratory, ECG, BP, and pulse rate abnormalities of potential clinical concern were described. Safety data were presented in tabular format and summarized descriptively, where appropriate.

Methodology:

This was a Phase 1, open-label, non-randomized, 2-period, fixed-sequence, single-dose study of PF-06865571 in healthy male participants to characterize the ADME properties of [^{14}C]PF-06865571 following oral administration, and to evaluate the F and F_a of PF-06865571 following oral administration of unlabeled PF-06865571 and IV administration of [^{14}C]PF-06865571.

In this study, each participant was to receive Regimens A and B in Periods 1 and 2, respectively.

CLINICAL STUDY REPORT SYNOPSIS

Regimen A in Period 1: PF-06865571 300 mg containing approximately 300 nCi ^{14}C (ie, radiolabeled PF-06865571) was to be administered orally.

Regimen B in Period 2: unlabeled PF-06865571 300 mg was to be administered orally followed at T_{max} (3 hours) by an IV dose of 300 nCi ^{14}C in PF-06865571 100 µg (3 µCi/mg active drug) as an infusion over approximately 15 minutes.

There was a wash-out period of 8-22 days between study intervention administration in Periods 1 and 2. Participants were to remain in the clinical research unit (CRU) from Day -1 Period 1 through the completion of Period 2. The duration of inpatient stay was between 12 days and 25 days.

Number of Participants (planned and analyzed):

Six participants were planned and dosed in the study.

All 6 participants were included in the safety analysis set and extent of excretion analysis set. All participants with evaluable plasma or urine PK for PF-06865571 and [^{14}C]PF-06865571 or Total ^{14}C were included in the PK analysis.

Diagnosis and Main Criteria for Inclusion and Exclusion:

Enrolled in this study were healthy male participants 18 to 60 years of age with a body mass index (BMI) of 17.5 to 30.4 kg/m^2 and a total body weight >50 kg (110 lb).

Study Interventions, Dose, Mode of Administration, and Batch Numbers:

On Day 1 Period 1, [^{14}C]PF-06865571 300 mg (containing approximately 300 nCi ^{14}C) was administered orally. On Day 1 Period 2, unlabeled PF-06865571 300 mg was administered orally 3 hours before the IV infusion of [^{14}C]PF-06865571 100 µg (containing approximately 300 nCi ^{14}C).

On Day 1 of Periods 1 and 2, PF-06865571 (radiolabeled or unlabeled) was to be administered orally at approximately 08:00 (± 2 hours) within approximately 10 minutes after the completion of a standard breakfast, and with approximately 240 mL water.

The study intervention information is provided in Table S2.

CLINICAL STUDY REPORT SYNOPSIS

Table S2. Study Intervention Information

Study Intervention Description	Vendor Lot Number	Pfizer Lot Number	Strength/Potency	Dosage Form
PF-06865571	GR10379 unmilled	GR10380	0.998	API
Methylcellulose (methocel A4M premium)	D180J7E011	20-EX-00293	N/A	Excipient
[^{14}C]PF-06865571 oral specific activity	20210325	21-AP-00563	1.00	RAD
[^{14}C]PF-06865571 IV specific activity	20210210	21-AP-00539	0.985	RAD

Abbreviations: API = active pharmaceutical ingredient; N/A = not applicable; RAD = radiation-absorbed dose.

Duration of Study Intervention:

Study intervention was administered on Day 1 of Periods 1 and 2.

Summary of Results:

Demographic and Other Baseline Characteristics:

All 6 participants were male with a median age of 42.0 years (range: 25 - 61 years). Median weight was 80.35 kg (range: 63.3 - 89.4 kg) and median BMI was 24.845 kg/m^2 (range: 19.56 – 29.19 kg/m^2).

Exposure:

On Day 1 Period 1, a single oral dose of [^{14}C]PF-06865571 300 mg was administered. On Day 1 Period 2, a single oral dose of PF-06865571 300 mg was administered followed 3 hours later by a single IV dose of [^{14}C]PF-06865571 100 µg.

Safety Results:

In Period 1, 4 (66.7%) participants experienced 9 all-causality treatment-emergent adverse events (TEAEs). All TEAEs were mild in severity and none of them was serious AE. The most frequently reported all-causality TEAE was diarrhoea (2 participants, 33.3%). Two treatment-related TEAEs of pruritus and flushing were reported by 1 participant in Period 1. All TEAEs resolved by the end of the study. In Period 2, none of the participants experienced TEAEs.

No participant had dose reduction or temporary/permanent discontinuation due to TEAEs.

Laboratory tests, vital signs, and ECGs had no significant safety findings.

CLINICAL STUDY REPORT SYNOPSIS

Pharmacokinetic Results:

Mass Balance

In Period 1, following a single oral dose of PF-06865571 300 mg (containing 300 nCi [^{14}C]PF-06865571), the mean ± standard deviation (SD) total recovery of the Period 1 orally administered radioactive dose over a period of up to 264 hours post-dose was 79.0 ± 16.7%, with 48.9 ± 16.3% in the urine and 30.1 ± 2.9% in the feces. The majority of radioactivity was excreted within 4 days of dosing.

In Period 2, a single IV dose of PF-06865571 100 µg (containing 300 nCi [^{14}C]PF-06865571) was administered at approximately 3 hours after a single oral dose of unlabeled PF-06865571 300 mg. The mean ± SD total recovery of the Period 2 IV administered radioactive dose over a period of up to 51 hours (48 hours post-radioactive dose) was 70.3 ± 15.1%, with 51.5 ± 15.8% in the urine and 18.8 ± 3.3% in the feces.

Metabolic Profiling and Identification

After oral dosing of [^{14}C]PF-06865571 in Period 1, the major drug-related components detected in circulation were [^{14}C]PF-06865571, M2, and M6 (representing 43.8%, 36.6%, and 11.3 % of circulating radioactivity, respectively). The major drug-related components detected in urine were M2 and coeluting M6, M7, and 584 (representing 24.9% and collectively 11.4% of administered dose, respectively). The predominant drug-related products in feces were coeluting M4 and 426, M2, M7, and M1 (representing collectively 10.0%, 7.0%, 6.3%, and 4.5% of administered dose, respectively).

Plasma Unlabeled PF-06865571 PK, [^{14}C]PF-06865571 PK, Total ^{14}C PK and Absolute Oral Bioavailability (F)

Plasma PK parameters are summarized descriptively in Table S3.

Table S3. Descriptive Summary of Plasma PK Parameters Following [14C]PF-06865571 300 mg Oral (Period 1) and PF-06865571 300 mg Oral + [14C]PF-06865571 100 ug IV (Period 2), Protocol C2541007

	[14C]PF-06865571 300 mg oral (Period 1)		PF-06865571 300 mg oral & [14C]PF-06865571 100 ug IV (Period 2)	
Parameter (Unit)[a]	PF-06865571 (N=6)	Total 14C (N=6)	PF-06865571 (N=6)	[14C]PF-06865571 (N=6)
N2, N3	6, 6	6, 6	6, 6	6, 6
AUC_{inf} (ng.hr/mL[b])	7964 (19)	20400 (15)	9546 (21)	4.209 (19)

CLINICAL STUDY REPORT SYNOPSIS

Table S3. Descriptive Summary of Plasma PK Parameters Following [14C]PF-06865571 300 mg Oral (Period 1) and PF-06865571 300 mg Oral + [14C]PF-06865571 100 ug IV (Period 2), Protocol C2541007

	[14C]PF-06865571 300 mg oral (Period 1)		PF-06865571 300 mg oral & [14C]PF-06865571 100 ug IV (Period 2)	
Parameter (Unit)[a]	**PF-06865571 (N=6)**	**Total 14C (N=6)**	**PF-06865571 (N=6)**	**[14C]PF-06865571 (N=6)**
AUC_{inf}(dn) (ng.hr/mL/mg[b])	26.25 (19)	67.26 (15)	31.46 (21)	41.92 (20)
AUC_{last} (ng.hr/mL[b])	7962 (19)	20080 (15)	9545 (21)	4.145 (20)
AUC_{last}(dn) (ng.hr/mL/mg[b])	26.22 (19)	66.09 (15)	31.45 (21)	41.25 (20)
$t_{1/2}$ (hr)	6.275±2.9246	3.622±1.9605	3.452±0.64067	1.232±0.25664
C_{max} (ng/mL[b])	2096 (15)	4417 (10)	2364 (17)	2.893 (13)
C_{max}(dn) (ng/mL/mg[b])	6.908 (15)	14.53 (10)	7.790 (17)	28.77 (13)
T_{max} (hr)	3.00 (2.00-4.00)	3.00 (3.00-4.00)	2.83 (2.82-4.00)	0.250 (0.167-0.250)
CL (L/hr)				23.88 (20)
CL/F (L/hr)	38.09 (19)	14.87 (15)	31.79 (21)	
V_{ss} (L)				38.83 (16)
V_z/F (L)	318.9 (63)	68.45 (64)	156.1 (37)	

Source: Table 14.4.5.1.1, Table 14.4.5.1.2, Table 14.4.5.1.3
N: Total number of participants in the analyte group in the indicated population;
N2: Number of participants contributed to the summary statistics;
N3: Number of participants contributed to the summary statistics for AUC_{inf}, AUC_{inf}(dn), CL/F, CL, $t_{1/2}$, V_{ss} and V_z/F.
a. Geometric mean (geometric % coefficient of variation) for all except median (range) for T_{max} and arithmetic mean±standard deviation for $t_{1/2}$.
b. Units for radioactivity parameters are ngEq/mL (Cmax), ngEq/mL/mg [Cmax (dn)], ngEq.hr/mL (AUC), ngEq.hr/mL/mg [AUC(dn)] Period 1 Total 14C only.
PFIZER CONFIDENTIAL SDTM Creation: 22FEB2022 (10:04) Source Data: adpp Table Generation: 23FEB2022 (04:02)
(Database snapshot date : 20AUG2021) Output File: ./nda1_cdisc/C2541007_PK/adpp_s101_5_i

Following administration of a single oral dose of PF-06865571 300 mg, F was 75.06% (90% CI: 71.06%, 79.29%), as measured by the ratio (oral [PO]/IV) of adjusted geometric mean dose normalized (to 1 mg equivalent) AUC_{inf} (AUC_{inf}[dn]) values.

CLINICAL STUDY REPORT SYNOPSIS

Urine Total ^{14}C Parameters and Fraction Absorbed (F_a)

Urine Total ^{14}C radioactivity parameters are summarized in Table S4.

Table S4. Descriptive Summary of Absolute and Percentage of Total 14C Excreted in Urine (Period 1 and Period 2), Protocol C2541007

Parameter [a]	[14C]PF-06865571 300 mg oral (Period 1) (N=6)	PF-06865571 300 mg oral & [14C]PF-06865571 100 ug IV (Period 2) (N=6)
N2	6	6
%^{14}C_Urine	45.92 (44)	49.50 (44)
Total ^{14}C_Urine (ngEq)	139500000 (44)	49730 (45)

Source: Table 14.4.5.1.5
N: Total number of participants in the analyte group in the indicated population;
N2: Number of participants contributed to the summary statistics;
a. Geometric mean (geometric % coefficient of variation) for all.
PFIZER CONFIDENTIAL SDTM Creation: 22FEB2022 (10:04) Source Data: adpp Table Generation: 23FEB2022 (04:02)
(Database snapshot date : 20AUG2021) Output File: ./nda1_cdisc/C2541007_PK/adpp_s101_7_i

Based on the geometric mean ratio (PO/IV) of dose-normalized Total ^{14}C_Urine values for 6 participants in PO and IV treatment with complete urine data, F_a was 92.78% (90% CI: 62.07%, 138.68%).

Taste Assessment Results:

Across the 6 participants dosed in this study, none of the mean assessment scores of taste for all 6 domains were above 50 after 5 minutes post-dose, suggesting that none of the characteristics assessed reported a strong intensity (ie, above 75). Any moderate intensity taste trait present upon dosing dissipated over the 20-minute period of assessment. In addition, taste assessment in Period 2 elicited a lower response with minimal change from 3 min to 20 min.

CLINICAL STUDY REPORT SYNOPSIS

Conclusions:

Mass Balance

- Following a single oral [^{14}C]PF-06865571 dose to healthy male participants, recovery of radioactivity was incomplete, but within the range observed in similar studies, with approximately 79% of dose recovered (~30% in feces; ~49% in urine).

Metabolic Profiling and Identification

- Following a single oral [^{14}C]PF-06865571 dose, exposure of PF-06865571 accounted for approximately 39% of total radioactivity. Two major metabolites (>10% of radioactivity in circulation) were identified, representing 36.6% (M2) and 11.3% (M6) of radioactivity in plasma.

Pharmacokinetics

- PF-06865571 absolute oral bioavailability (F) and fraction absorbed (F_a) were estimated to be 75.06% and 92.78%, respectively.

- The plasma PF-06865571 exposures were comparable after 300 mg oral dose in Period 1 and Period 2.

Safety and Taste Assessment

- PF-06865571 was generally safe and well-tolerated following either oral or simultaneous oral/IV administration.

- Administration of a single, oral dose of PF-06865571 did not result in reporting of strong taste across the 6 domains of taste tested.