CLINICAL STUDY REPORT SYNOPSIS

SYNOPSIS

Study Title: A Phase 1, Randomized, Double-Blind, Sponsor Open, Placebo Controlled, Dose Escalating Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Single and Multiple Intravenous and Subcutaneous Doses of PF-07275315 in Healthy Participants

Study Number: C4531001

Regulatory Agency or Public Disclosure Identifier Number:

EudraCT Number: 2022-000854-27

ClinicalTraial.gov ID: NCT05411588

Study Phase: Phase 1

Name of Study Intervention: PF-07275315

Name of Sponsor/Company: Pfizer Inc.

CSR Version and Report Date: Final CSR (LPLV date) Version 1.0; 10 October 2024

Number of Study Center(s) and Investigator(s):

A total of 65 participants were enrolled at 4 centers in 2 countries (Belgium and US). A list of study centers and investigators involved in this study is provided in Appendix 16.1.4.1.

Publications: None

Study Period:

Study Initiation Date (First Participant First Visit): 09 June 2022

Study Completion Date (Last Participant Last Visit): 13 May 2024

This study was completed without study interruptions or discontinuations.

Rationale:

PF-07275315 is a recombinant humanized trispecific Immunoglobulin G1 (IgG1) antibody against Interleukin-4 (IL-4), Interleukin-13 (IL-13), and thymic stromal lymphopoietin (TSLP) that is currently being developed for treatment of patients with moderate to severe atopic dermatitis (AD).

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This was the first time that PF-07275315 was given to humans. The purpose of the study was to evaluate the safety, tolerability, pharmacokinetic(s) (PK), and pharmacodynamic(s) (PD) of escalating single and multiple doses of PF-07275315 in healthy participants.

Objectives, Endpoints, and Statistical Methods:

Type	Objective	Endpoints
Primary		
Safety	• To evaluate the safety and tolerability of PF-07275315, following single and multiple doses in healthy adults.	• Incidence and severity of AEs, SAEs. • Change from baseline in vital signs (BP, PR, RR, and temperature measurements). • Change from baseline in clinical laboratory values (chemistry and hematology including coagulation panel). • Change from baseline in ECG parameters (heart rate, QT, QTc, PR, and QRS intervals).
Secondary		

PK	• To characterize the serum exposure of PF-07275315, following single and multiple doses in healthy adults.	• PF-07275315 serum exposure as data permit:
		  • After single dose in SAD cohorts: AUC_{last}, AUC_{inf}, C_{max}, T_{max}, and $t_{½}$;
		  • After each repeat dose in MAD cohorts: AUC_{336}, C_{max}, T_{max} and $t_{½}$.

Immunogenicity	• To evaluate the immunogenicity profile of PF-07275315 following single and multiple doses in healthy adults.	• Incidence of the development of ADA and, if appropriate, NAb against PF-07275315 following single and multiple doses.

Abbreviations: ADA = antidrug antibody; AE = adverse event; AUC_{336} = area under the concentration-time curve from time 0 to 336 hours; AUC_{inf} = area under the serum concentration-time profile from time 0 extrapolated to infinite time; AUC_{last} = area under the serum concentration-time profile from time 0 to the time of the last quantifiable concentration; BP = blood pressure; C_{max} = maximum observed concentration; ECG = electrocardiogram; MAD = multiple ascending dose; NAb = neutralizing antibody; PR = pulse rate; QTc = corrected QT; RR = respiratory rate; SAD = single ascending dose; SAE = serious adverse event; $t_{½}$ = half-life; T_{max} = time for C_{max}.

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Statistical methods:

Safety:

AEs, ECGs, BP, PR and safety laboratory data were to be reviewed and summarized on an ongoing basis during the study to evaluate the safety of participants. Any clinical laboratory, ECG, BP, and PR abnormalities of potential clinical concern were to be described. Safety data were to be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

PK:

Actual PK sampling times were to be used in the derivation of PK parameters. The serum concentration of PF-07275315 was to be listed and descriptively summarized by nominal PK sampling time and treatment group. Individual subject, mean, and median profiles of the serum concentration-time data were to be plotted by treatment group using actual (for individual) and nominal (for median) times respectively. Mean and median profiles were to be presented on both linear and log scales.

Immunogenicity:

Incidence of the development of ADA and, if appropriate, NAb against PF-07275315 following single and multiple doses might be summarized by dose and presented in tabular form or graphically.

Methodology:

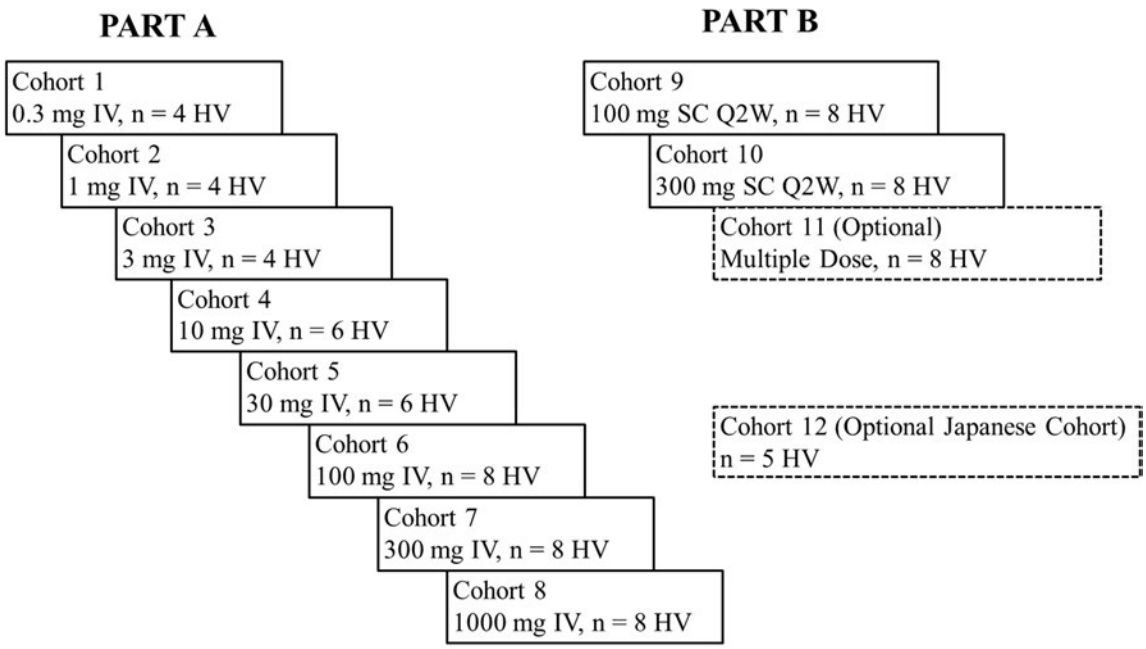
This was a first-in-human (FIH) within-cohort randomized, participant- and investigator-blind, sponsor-open, placebo-controlled study of the safety, tolerability, PK, and PD following single and multiple escalating doses of PF-07275315 that was conducted in healthy adults (Figure S1).

Approximately 77 participants were planned to be enrolled into the study. This were planned to include approximately 53 healthy participants (including 5 optional Japanese participants) in Part A, and approximately 24 healthy participants (including 8 participants in optional MAD cohort) in Part B.

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Figure S1. C4531001 Study Design With Planned Doses



Doses shown are planned doses and may be modified based on emerging data from previous cohorts. Cohort 11 was an optional MAD cohort with doses and frequency to be determined by emerging data from SAD and MAD cohorts. Cohort 12 was an optional Japanese cohort that will be conducted in Japanese healthy participants. Cohorts 2 and 11 did not enroll participants based on a study team decision.

Abbreviations: HV: healthy volunteer; IV: intravenous(ly); Q2W: every 2 weeks; SC: subcutaneous(ly).

Number of Participants (planned and analyzed):

Approximately 77 participants were planned to be enrolled and 65 were enrolled into the study (49 in SAD cohort and 16 in MAD cohort).

All participants who received PF-07275315 or placebo were included in the safety analysis set. All participants administered with at least 1 dose of PF-07275315 that had at least 1 PK parameter of interest were included in the PK analyses for both concentration and parameters.

Diagnosis and Main Criteria for Inclusion and Exclusion:

Enrolled in this study were healthy participants aged 18 to 65 years, with a body mass index (BMI) of 17.5 to 32 kg/m^2 and a total body weight >50 kg (110 lb). For the Japanese cohort, participants must have 4 Japanese biological grandparents born in Japan.

Study Interventions, Dose, Mode of Administration, and Batch Number(s):

PF-07275315 and placebo were administered IV or SC.

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Table S1. Study Intervention(s) Administered

Investigational Product Description	Vendor Lot No.	Pfizer Lot No.	Strength/ Potency	Dosage Form
Diluent Solution for Injection; [redacted]	1-FIN-3984	21-DP-00807	0 mg/mL	Solution
PF-07275315 Solution for Injection, 100 mg/mL	N/A	21-DP-00725	100 mg/mL	Solution
Placebo Solution for Injection in 6R Vial; [redacted]	1-FIN-4074	22-DP-01043	0 mg/mL	Solution

Abbreviations: [redacted]; N/A = not applicable; [redacted]

Duration of Study Intervention:

In SAD cohort, PF-07275315 or placebo was administered IV as a single dose on Day 1.

In MAD cohort, PF-07275315 or placebo was administered SC Q2W for 3 times.

Summary of Results:

Demographic and Other Baseline Characteristics:

SAD

A total of 16 participants received placebo IV (Placebo Total IV single dose [SD]); the majority of them were male (9/16 participants, 56.3%) and White (11/16 participants, 68.8%), with the mean (standard deviation [SD]) age of 41.75 (12.746) years.

A total of 33 participants received PF-07275315 IV (PF-07275315 Total IV SD); the majority of them were male (23/33 participants, 69.7%) and White (20/33 participants, 60.6%) with the mean (SD) age of 44.79 (11.194) years.

MAD

A total of 4 participants received placebo SC (Placebo SC Q2W×3); the majority of them were male (3/4 participants, 75.0%) and White (3/4 participants, 75.0%), with the mean (SD) age of 33.25 (12.148) years.

A total of 12 participants received PF-07275315 SC (PF-07275315 Total SC Q2W×3); the majority of them were female (7/12 participants, 58.3%) and White (9/12 participants, 75.0%) with the mean (SD) age of 40.00 (10.436) years.

Exposure:

In SAD cohort, all 49 participants received 1 dose of PF-07275315 or placebo.

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In MAD cohort, out of 16 participants, 1 (6.3%) participant on PF-07275315 300 mg SC Q2W×3 received 1 dose of study intervention, and all other participants received 3 doses of study intervention.

Safety Results:

SAD

placebo IV:

Six (37.5%) out of 16 participants on placebo IV (Placebo Total IV SD) experienced at least 1 all-causality treatment-emergent adverse event (TEAE). A total of 13 all-causality TEAEs were reported, and each TEAE was reported in 1 participant. A severe SAE of abortion spontaneous was reported in Placebo IV SD. No TEAEs were treatment-related. Out of 13 all-causality TEAEs, 11 were mild, 1 each was moderate (blood creatine phosphokinase increased) and severe (abortion spontaneous).

PF-07275315 IV:

Sixteen (48.5%) out of 33 participants on PF-07275315 IV (PF-07275315 Total IV SD) experienced at least 1 all-causality TEAE. A total of 31 all-causality TEAEs were reported, out of which 4 were treatment-related. No SAEs were reported. The most frequently reported all-causality TEAEs (≥ 3 participants) were within the System Organ Classes (SOCs) of Injury, Poisoning and Procedural Complications (7 participants, 21.2%), Skin and Subcutaneous Tissue Disorders (4 participants, 12.1%), General Disorders and Administration Site Conditions, and Investigations (3 participants each, 9.1%).

The most frequently reported all-causality TEAEs (≥ 2 participants) were fall, limb injury, scratch, blood creatine phosphokinase increased, and erythema (2 participants each, 6.1%). There were 4 treatment-related TEAEs reported: palpitations, infusion related reactions, pain in extremity, and erythema (1 participant each, 3.0%).

Out of 31 all-causality TEAEs, 27 were mild and 4 were moderate (blood creatine phosphokinase increased [2 events], herpes zoster, and nasopharyngitis [1 event]). All 4 treatment-related TEAEs were mild.

MAD

placebo SC:

No TEAEs were reported in participants on placebo SC (Placebo SC Q2W×3).

PF-07275315 SC:

Six (50.0%) out of 12 participants on PF-07275315 SC (PF-07275315 Total SC Q2W×3) experienced at least 1 all-causality TEAE. A total of 15 all-causality TEAEs were reported,

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out of which 3 were treatment-related. One participant on PF-07275315 300 mg SC Q2W×3 discontinued from study intervention due to an AE of coronavirus disease 2019 (COVID-19).

The most frequently reported all-causality TEAEs (≥ 3 participants) were within the SOC of General Disorders and Administration Site Conditions (3 participants, 25.0%).

The most frequently reported all-causality TEAEs (≥ 2 participants) were nausea, injection site reaction, and COVID-19 (2 participants each, 16.7%).

Out of 15 all-causality TEAEs, 13 were mild and 2 were moderate (injection site reaction and injection site erythema).

Pharmacokinetic Results:

SAD

Non-Japanese Cohorts:

In non-Japanese participants, following single 1-hour IV infusions of PF-07275315 at doses ranging from 0.3 mg to 1000 mg, C_{max} were generally observed at or within 3 hours after the end of infusion (median and individual T_{max} ranging between 1 to 4 hours after the start of a 1-hour infusion). Following attainment of C_{max}, serum concentrations exhibited a biphasic decline with a trend toward increased $t_{½}$ at the higher doses; possibly due to target mediated drug disposition observed at the low doses. Individual $t_{½}$ values ranged between 22 to 31 days for the 0.3 mg and 3 mg dose, respectively, and arithmetic mean values ranging between 28 to 40 days for doses ≥10 mg (where sufficient participants contributed to mean values). Overall, geometric mean and individual total clearance (CL) and volume of distribution at steady state (V_{ss}) values were similar across the 3 mg to 1000 mg dose groups with a higher value observed in both CL and V_{ss} for the single individual at the lowest dose of 0.3 mg.

In general, C_{max} (individual and mean values) appeared to increase dose proportional with increase in dose from 0.3 mg to 1000 mg with the exception of slightly higher C_{max} values at 10 mg. For AUC_{inf} (individual and mean values), no marked deviations from dose proportionality between 3 mg to 1000 mg while a more than proportional increase in dose between the low doses of 0.3 mg and 3 mg can be observed. However, due to <3 participants in the 0.3 mg and 3 mg dose groups, it should be noted the relationship between serum PK parameters and dose could not be fully assessed.

Participant (non-Japanese) variability in serum exposure based on geometric % coefficient of variation (CV%) ranged between 12% to 43% for $AUC_{inf,}$ AUC_{last} and $C_{max.}$

Japanese Cohort:

Overall, serum PF-07275315 pharmacokinetics was similar between Japanese and non-Japanese participants receiving a single 1000 mg IV dose. Mean $t_{½}$ values for Japanese and non-Japanese participants were equivalent (~40 days). Serum exposure based on

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geometric mean dose normalized AUC_{inf} and C_{max} for Japanese participants was comparable to non-Japanese participants.

Participant (Japanese) variability for PF-07275315 serum exposure based on geometric CV% ranged between 22% to 32% for AUC_{inf}, AUC_{last} and C_{max}.

MAD

Following SC dose administration of PF-07275315 at 100 mg or 300 mg doses Q2W for a total of 3 doses, C_{max} were reached within a median T_{max} of 96 to 166 hours on Day 1 and from 108 to 169 hours on Day 29. Following the 3rd SC dose on Day 29, geometric mean apparent clearance (CL/F) and apparent volume of distribution (V_z/F) were similar between the 100 mg and 300 mg doses, with values of 0.014 L/hr and 0.016 L/hr for CL/F, and 16 L to 19 L for V_z/F, respectively. Terminal $t_{½}$ for the 100 mg and 300 mg SC doses on Day 29 were also similar with mean values of 35 days and 34 days, respectively.

Serum PF-07275315 exposure based on area under the serum concentration time profile from time zero to time tau (τ), the dosing interval (AUC_{tau}) and C_{max} appeared to trend toward a less than dose proportional increase from 100 mg to 300 mg on Day 1 following the first dose as well as on Days 15 and 29 following multiple dose administrations; however, the range of individual participant values overlap between the dose levels. Overall, PF-07275315 exposure on Days 15 and 29 were higher than those observed following a single dose on Day 1. Following Q2W dosing for 1 month, serum PF-07275315 accumulation ratio for AUC_{tau} (R_{ac}) were 2.3 and 2.7 for the 100 mg and 300 mg SC groups, respectively, indicating some accumulation. Accumulation ratio for C_{max} ($R_{ac,Cmax}$) was similar at 2.1 for the 100 mg dose and 2.7 for the 300 mg dose.

For the 100 mg and 300 mg SC groups, bioavailability (F) was approximately 44% and 36%, respectively.

Participant variability in PF-07275315 serum exposure on Day 29 for the 100 mg and 300 mg SC doses based on geometric CV% was between 11-30% for AUC_{tau} and 13-31% for C_{max} with higher variability observed for the 300 mg dose group.

Immunogenicity Results:

SAD

Two individuals who received placebo treatment were inadvertently analyzed. Of these, in the Placebo IV (Placebo Total IV SD) group, 1 participant was positive for ADA on pre-dose Day 1 (baseline) and continued testing ADA positive through Day 271 without meaningful increase in ADA titer. The other participant was negative for ADA at baseline and tested positive for ADA only on Day 361.

In PF-07275315 IV (PF-07275315 Total IV SD) group, incidence of ADA ranged from 3% to 25.8% at various study visits. A general increase in ADAs was observed between Day 1

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(baseline) to Day 271, increasing from 3 participants (9.1%) to 8 participants (25.8%). No correlation of dose level was observed with incidence of ADA. On Day 361, 2 participants remained ADA positive, and 1 participant tested positive for ADA at early termination visit.

MAD

Placebo SC (Placebo SC Q2W×3) samples were not tested for ADA for all 4 participants from Day 1 through Day 201. ADA results were negative for the 4 and 2 participants tested on Days 291 and 381, respectively.

In PF-07275315 SC (PF-07275315 Total SC Q2W×3), ADA was negative for all participants tested during Days 1 and 29. The incidence of ADAs increased from 1 participant (8.3%) (on Days 51 and 66) to 4 participants (33.3%) (on Days 111, 201, and 291). On Day 381, 2 participants remained ADA positive. No correlation of dose level was observed with incidence of ADA.

There were no medically evaluated potential immunogenically-related AEs reported in this study.

Conclusions:

Safety

- PF-07275315 was generally safe and well-tolerated at single and multiple doses in healthy volunteers.

PK

- In healthy participants, peak serum PF-07275315 concentrations were generally observed at or within 3 hours after the end of 1-hour infusion for single IV doses. Concentrations decreased gradually over several months with terminal $t_{½}$ values between 22 to 40 days across the IV dose range of 0.3 mg to 1000 mg.

- PF-07275315 exhibits non-linear pharmacokinetics at lower doses but an approximately dose proportional increase in exposure (AUC and C_{max}) can be observed with increasing dose.

- Overall, PF-07275315 PK in Japanese participants receiving a single PF-07275315 1000 mg IV dose were comparable to PK results for non-Japanese participants. Mean terminal $t_{½}$ was approximately 40 days for both Japanese and non-Japanese cohorts.

- Following multiple PF-07275315 SC doses at 100 mg and 300 mg administered Q2W for a total of 3 doses to healthy participants, peak serum concentrations were reached within a median T_{max} of 108 and 169 hours, respectively, after the third dose. Terminal $t_{½}$ for both doses was around 34 to 35 days. Serum exposure to PF-07275315 appeared to increase less than proportionally with dose, however the

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overall exposure was higher after the 2nd and 3rd doses compared to the 1st dose. After Q2W dosing for one month, there was some accumulation of PF-07275315 with slightly higher accumulation ratios for both AUC_{tau} and C_{max} in the 300 mg dose group compared to the 100 mg group.

- Estimated bioavailability (F) for the 100 mg and 300 mg SC doses were 44% and 36%, respectively, relative to the corresponding IV doses from the SAD phase of the study.

Immunogenicity

- Following PF-07275315 IV SD, the incidence of ADAs (titer ≥20) increased from 9.1% at baseline (pre-dose on Day 1) to 25.8% on Day 271. Following PF-07275315 SC Q2W×3, the incidence of ADAs increased from 0% at baseline (pre-dose on Day 1) to 33.3% on Days 111, 201, and 291. No correlation of dose level was observed with incidence of ADA.

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