CLINICAL STUDY REPORT SYNOPSIS

SYNOPSIS

Study Title: A Phase 1, Randomized, Double Blind, Sponsor-Open, Placebo-Controlled Study to Evaluate the Safety, Tolerability, Immunogenicity and Pharmacokinetics Following Single Intravenous Dose of PF-06823859 in Japanese Healthy Participants

Study Number: C0251005

Regulatory Agency or Public Disclosure Identifier Number: NCT05037409

Study Phase: Phase 1

Name of Study Intervention: PF-06823859

Name of Sponsor/Company: Pfizer Inc.

CSR Version and Report Date: Version 1.0 and 01 March 2023

Number of Study Center and Investigator: A total of 13 participants were enrolled in the study at 1 center in Japan. Principal Investigator: PPD

A list of study centers and investigators involved in this study is provided in Appendix 16.1.4.1.

Publications: None.

Study Period: 28 September 2021 (First Participant First Visit) to 27 March 2022 (Last Participant Last Visit).

This study was neither discontinued nor interrupted.

Rationale:

The purpose of this study was to evaluate the safety, tolerability, immunogenicity, and pharmacokinetics (PK) of PF-06823859 after single intravenous (IV) administration to Japanese healthy adult participants. The information of safety, tolerability, immunogenicity, and PK in Japanese healthy participants was being collected to support the development of PF-06823859 in Japan.

Objectives, Endpoints, and Statistical Methods:

The study objectives and endpoints are provided in Table S1.

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Table S1. Study Objectives and Endpoints

Type	Objectives	Endpoints
Safety	Primary: • To evaluate the safety and tolerability of single IV dose of 300 and 900 mg PF-06823859 in Japanese healthy participants.	Primary: • Assessments of AEs/SAEs including IRR, infusion sites and viral infections, vital signs, ECGs and laboratory tests.
PK/Immunogenicity	Secondary: • To evaluate the PK profile of single IV dose of 300 and 900 mg PF-06823859 in Japanese healthy participants. • To evaluate the immunogenicity of PF-06823859.	Secondary: • Serum PF-06823859 PK parameters, as permitted by data: C_{max}, C_{max} (dn), T_{max}, AUC_{inf}, AUC_{inf} (dn), AUC_{last}, AUC_{last} (dn), AUC_{14day}, AUC_{28day}, $t_{½}$, CL, V_{ss} and MRT. • Incidence of the development of ADA and NAb.

ADA = anti-drug antibodies; AE = adverse event; AUC = area under the concentration-time curve; AUC_{14day} = AUC from time 0 to 14 days post-dose; AUC_{28day} = AUC from time 0 to 28 days post-dose; AUC_{inf} = AUC from time 0 extrapolated to infinite time; AUC_{last} = AUC from time 0 to the time of the last quantifiable concentration; CL = Clearance; C_{max} = maximum observed concentration; dn = dose normalized; ECG = electrocardiogram; IRR = infusion related reaction; MRT = mean residence time; NAb = neutralizing antibodies; PK = pharmacokinetic(s); SAE = serious adverse event; T_{max} = time for C_{max}; $t_{½}$ = terminal phase half-life; V_{ss} = volume at steady state.

All safety analyses were performed on the safety analysis set, which was defined as all participants randomly assigned to study intervention and who had taken at least 1 dose of study intervention. Participants were analyzed according to the product they actually received. The primary endpoints of this study were assessments of adverse events (AEs) and serious adverse events (SAEs) including infusion related reaction (IRR), infusion sites and viral infections, vital signs, electrocardiogram (ECGs), and laboratory tests. The primary endpoints were summarized descriptively through appropriate data tabulations, descriptive statistics, categorical summaries in order to evaluate the safety and tolerability of PF-06823859. The serum PK parameters were summarized descriptively by treatment group in accordance with Pfizer data standards, as data permit. Overall, incidence of development of anti-drug antibodies (ADA), neutralizing antibodies (NAb) was calculated and summarized by treatment.

Methodology:

This was a Phase 1, randomized, double-blind, sponsor-open, placebo-controlled study to evaluate the safety, tolerability, immunogenicity, and PK of PF-06823859 following a single IV dose of PF-06823859 300 and 900 mg in Japanese healthy adult participants.

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The study consists of 2 cohorts, approximately 5 participants were planned to be randomized to receive a single IV infusion of PF-06823859 and approximately 1 participant was planned to be randomized to receive placebo in each cohort.

The participants in Cohort 2 were dosed following at least 96 hours safety pause after the participants in Cohort 1 had been dosed.

Number of Participants (planned and analyzed):

Approximately, 12 participants were to be enrolled into the study.

A total of 13 participants were enrolled in the study and were randomly assigned to the study intervention during the study. Of which, 1 participant did not receive the study intervention and 12 participants (6 in Cohort 1 and 6 in Cohort 2) received the study intervention. Overall, 12 participants who received the treatment were included in the safety analysis set. A total of 10 participants in PF-06823859 treatment group were included in the PK and immunogenicity analysis set.

Diagnosis and Main Criteria for Inclusion and Exclusion:

Enrolled in this study were male and female healthy participants who were 20 to 55 years of age, inclusive with body mass index (BMI) of 17.5 to 25 kg/m^2 and a total body weight >50 kg (110 lb); participants had 4 biologically Japanese grandparents who were born in Japan; participants who were willing and able to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures.

Participants were excluded if they had a history of autoimmune disorders and allergic or anaphylactic reaction to a therapeutic drug or any components in the study intervention; or had evidence or history of clinically significant hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurological, or allergic disease (including drug allergies, but excluding untreated, asymptomatic, seasonal allergies at the time of dosing).

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

Participants received study intervention at approximately 0800 hours on Day 1 (± 4 hours). Study intervention did not require fasting, but it was noted that the safety laboratory tests at Day -1 prior to the dose of study intervention needed a fast of at least 4 hours. Investigator site personnel administered study intervention as a 60-minute IV using a calibrated infusion pump.

The manufacturing lot numbers for the study interventions dispensed in this study are provided in Table S2.

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Table S2. Study Interventions Administered

Investigational Product Description	Vendor Lot Number	Pfizer Lot Number	Strength/Potency	Dosage Form
Placebo Solution for Injection Containing: Histidine, Sucrose, PS80, EDTA	20-DP-00117	20-000247	0 mL	Solution
PF-06823859 Solution for Injection, 100 mg/mL	21-DP-00467	21-DP-00467	100 mL	Solution

EDTA = ethylenediaminetetraacetic acid.

Duration of Study Intervention:

Within 28 days of successful completion of the screening process, eligible participants were received a single IV infusion of PF-06823859 or placebo. Participants were admitted into the clinical research unit (CRU) approximately 1 day prior to dosing and were required to stay overnight in the CRU through completion of Day 5 evaluations. Participants returned to the CRU for outpatient follow-up visits through Day 157.

Summary of Results:

Demographic and Other Baseline Characteristics:

All enrolled participants were Asian (Japanese) and not Hispanic or Latino. Across the 3 treatment groups, majority of the participants were male (8 [66.7%]). The participant's age ranged from 21 to 52 years. The mean (standard deviation[SD]) age was 36.17 (12.91) years. Across all the treatment groups, body weight ranged from 50.3 to 69.8 kg and BMI ranged from 17.6 to 24.5 kg/m^2.

Exposure:

All participants completed the treatment in Cohorts 1 and 2 except 1 participant, who did not receive the study intervention and was discontinued prior to administration due to failure to comply with site instruction.

Safety Results:

There were no deaths, SAEs, severe AEs, permanent discontinuations from study, temporary discontinuations or dose reductions due to AEs reported in this study.

In total, 9 all-causality treatment-emergent adverse events (TEAEs) were reported. Most of the TEAEs were of mild in severity. Only one TEAE (intervertebral disc protrusion) was of moderate in severity, which was considered to be unrelated to study drug by the investigator. All causalities TEAEs are summarized in Table S3.

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Table S3. Treatment-Emergent Adverse Events (All Causalities) - Safety Analysis Set (Protocol C0251005)

Number (%) of Participants	PF-06823859 300 mg n (%)	PF-06823859 900 mg n (%)	Placebo n (%)
Participants evaluable for adverse events	5	5	2
Number of adverse events	5	4	0
Participants with adverse events	4 (80.0)	1 (20.0)	0
Participants with serious adverse events	0	0	0
Participants with severe adverse events	0	0	0
Participants discontinued from study due to adverse events[a]	0	0	0
Participants with temporary discontinuation due to adverse events	0	0	0

Includes data up to lag days after last dose of study drug.
Except for the Number of Adverse Events participants are counted only once per treatment in each row.
Serious Adverse Events - according to the investigator's assessment.
a. Participants who have an AE record that indicates that the AE caused the participant to be discontinued from the study.
MedDRA v24.1 coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: 21APR2022 (17:12) Source Data: adae Table Generation: 28APR2022 (21:30)
(Database snapshot date : 19APR2022) Output File: ./cutoff2021/C0251005/adae_s010
Table 14.3.1.2.1 PF-06823859 is for Pfizer internal use.

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In the PF-06823859 300 mg group, 4 participants experienced TEAEs: of which 1 participant each experienced TEAEs of abdominal pain lower; thermal burn; vaccination site pain, and 1 participant experienced TEAEs of road traffic accident and intervertebral disc protrusion. In the PF-06823859 900 mg group, 1 participant experienced 4 TEAEs (nasopharyngitis, alanine transaminase (ALT) increased, aspartate aminotransferase (AST) increased, and arthralgia). The viral infection (nasopharyngitis) of mild severity, which was considered to be unrelated to study drug by the investigator was reported to be AE of special interest. In the placebo group, none of the participant experienced TEAEs.

One TEAE of abdominal pain lower in the PF-06823859 300 mg group was considered treatment-related by the investigator.

No IRR and infusion site reactions were reported during the study.

Though some of laboratory tests abnormalities were observed in this study, only 1 participant experienced ALT increased, and AST increased as mild TEAEs which were considered unrelated to study drug by investigator.

None of the vital signs and ECGs data met specific categorical reporting criteria. No change from baseline in vital signs and ECGs were considered clinically significant and none were reported as an AE.

Pharmacokinetic Results:

PF-06823859 PK parameters are summarized descriptively in Table S4.

Following IV infusion of PF-06823859 in Japanese healthy adult participants, the median time for C_{max} (T_{max}) were around 2 hours after the start of the infusion followed by a biphasic decline of serum concentrations over time. Exposures, as measured by geometric mean values for AUC_{inf}, AUC_{last}, and C_{max} increased in an approximately dose-proportional manner from 300 mg to 900 mg. Geometric mean clearance (CL) values were similar across doses, ranging from 0.0044 to 0.0051 L/hr. Geometric mean volume at steady state ($V_{ss)}$ values were also similar between doses, ranging from 4.30 to 4.74 L, indicative of distribution primarily in plasma volume. Arithmetic mean terminal phase half-life ($t_{½}$) values were approximately 32 and 31 days for the 300 mg and 900 mg dose, respectively.

Table S4. Summary of Serum PF-06823859 PK Parameters - PK Parameter Analysis Set (Protocol C0251005)

Parameter (unit)[a]	PF-06823859 300 mg (N=5)	PF-06823859 900 mg (N=5)

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Table S4. Summary of Serum PF-06823859 PK Parameters - PK Parameter Analysis Set (Protocol C0251005)

Parameter (unit)[a]	PF-06823859 300 mg (N=5)	PF-06823859 900 mg (N=5)
n	5	5
AUC_{14day} (ug*hr/mL)	22170 (10)	61170 (8)
AUC_{28day} (ug*hr/mL)	35040 (10)	95250 (10)
AUC_{inf} (ug*hr/mL)	68070 (12)	178000 (16)
AUC_{inf} (dn) (ug*hr/mL/mg)	227.1 (12)	197.8 (16)
AUC_{last} (ug*hr/mL)	66120 (12)	173000 (14)
AUC_{last} (dn) (ug*hr/mL/mg)	220.4 (12)	192.2 (14)
C_{max} (ug/mL)	134.4 (16)	350.1 (10)
C_{max} (dn) (ug/mL/mg)	0.4483 (16)	0.3890 (10)
CL (L/hr)	0.004406 (12)	0.005061 (16)
V_{ss} (L)	4.304 (10)	4.737 (7)
MRT (day)	40.69 (8)	38.99 (15)
$t_{1/2}$ (day)	32.42 ± 0.70852	31.42 ± 4.9505
T_{max} (hr)	2.000 (1.00 - 6.00)	2.000 (1.00 - 2.00)

a. Geometric mean (geometric %coefficient of variation) for all except median (range) for Tmax and arithmetic mean ± standard deviation for t1/2.
N = Total number of participants in the treatment group in the indicated population
n = Number of participants contributing to the summary statistics.
dn: dose normalized to a 1 mg dose
PFIZER CONFIDENTIAL SDTM Creation: 12NOV2022 (11:51) Source Data: adpp Table Generation: 15NOV2022 (09:53)
(Database snapshot date : 01APR2022) Output File: ./cutoff2021/C0251005 PK/adpp s001 I
Table 14.4.5.2 PF-06823859 is for Pfizer internal use.

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Immunogenicity Results:

For ADA, if log titer ≥1.48, the sample was deemed positive. A participant was ADA-positive, if baseline titer was missing or negative and participant had ≥1 post-treatment positive titer (treatment-induced); or there was positive titer at baseline and participant had a ≥0.602 unit increase in titer from baseline in ≥1 post-treatment sample (treatment-boosted). Participants who were ADA-positive at baseline but did not become treatment-boosted post-treatment were considered as ADA-negative. A participant was Nab-positive, if baseline was missing or negative and participant had ≥1 post-treatment positive. NAb-negative participants included participants who were ADA-negative or ADA-positive participants tested post-treatment negative in the NAb assay. Participants who were Nab-positive at baseline and had ≥1 post-treatment positive were handled as Nab-negative.

The summary of ADA and NAb incidence over time by treatment group is presented in Table S5.

Table S5. Summary of ADA and NAb incidence Over Time - Immunogenicity Analysis Set (Protocol C0251005)

	PF-06823859 300 mg (N=5) n / N (%)	PF-06823859 900 mg (N=5) n / N (%)
ADA incidence	1 / 5 (20.0)	1 / 5 (20.0)
Subjects with treatment induced ADA incidence	1 / 5 (20.0)	1 / 5 (20.0)
Subjects with treatment boosted ADA incidence	0 / 5 (0.0)	0 / 5 (0.0)
NAb incidence	1 / 5 (20.0)	1 / 5 (20.0)
Subjects with treatment induced NAb incidence	1 / 5 (20.0)	1 / 5 (20.0)
Subjects with treatment boosted NAb incidence	-	-

Treatment induced ADA: log titer < 1.48 or missing at baseline and log titer >= 1.48 post dose.
Treatment boosted ADA: log titer >= 1.48 at baseline and (log titer post dose - log titer at baseline) > 0.602.
Treatment induced NAb: negative or missing NAb at baseline and positive NAb post dose.
Treatment boosted NAb: not applicable.
N: total number of participants with at least one observation of the immunogenicity sample while on study treatment.
n: number of participants with meeting criteria while on study treatment.
PFIZER CONFIDENTIAL SDTM Creation: 19DEC2022 (23:46) Source Data: adis Table Generation: 12JAN2023 (16:28)
(Database snapshot date : 14DEC2022) Output File: ./cutoff2021/C0251005_IM/adis_s001
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There were 2 out of 10 participants who were confirmed positive for treatment induced ADA and NAb in PF-06823859 groups.

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One (20%) participant from the PF-06823859 300 mg treatment group was developed treatment induced ADA and NAb. This participant with negative ADA and NAb results at baseline (ADA log titer <1.48) was tested positive for ADA and NAb on Study Days 57 (ADA log titer = 1.48), 99 (ADA log titer = 1.48), 127 (ADA log titer = 1.48), and 157 (ADA log titer = 1.48).

The other (20%) participant from the PF-06823859 900 mg treatment group was developed treatment induced ADA and NAb. This participant with negative ADA and NAb results at baseline (ADA log titer <1.48) was tested positive for ADA and NAb on Study Days 57 (ADA log titer = 2.4), 68 (ADA log titer = 2.4), 99 (ADA log titer = 2.4) and 157 (log titer = 2.49).

Conclusions:

- A single IV dose of PF-06823859 (300 and 900 mg) was safe and well tolerated in Japanese healthy participants evaluated in this study.

- Following a single IV infusion of PF-06823859 (300 and 900 mg) in Japanese healthy adult participants, the median T_{max} were around 2 hours after the start of the infusion followed by a biphasic decline of serum concentrations over time.

- Systemic exposure increased in an approximately dose-proportional manner.

- Geometric mean CL values were similar across doses, ranging from 0.0044 to 0.0051 L/hr. Geometric mean V_{ss} values were also similar between doses, ranging from 4.30 to 4.74 L, indicative of distribution primarily in plasma volume. Arithmetic mean $t_{½}$ values were approximately 32 and 31 days for the 300 and 900 mg dose, respectively.

- Among 10 participants treated with PF-06823859, there were 2 participants who were tested confirmed positive for treatment induced ADA and NAb.