CLINICAL STUDY REPORT SYNOPSIS

Study Title:	A Phase 1, Open-Label, Randomized, Single-Dose, Parallel Design, Study to Evaluate Pharmacokinetic Comparability of Two PF-07940367 Film-Coated Tablet Formulations Administered as 150 mg Under Fasted Conditions in Healthy Participants
Study Number:	C5351008
Study Phase:	Phase 1
Regulatory Agency or Public Disclosure Identifier Number:	NCT #: NCT06190561 EU CT #: Not Applicable
Pediatric Investigational Plan Number:	Not Applicable
Study Intervention:	Osivelotor (PF-07940367)
Indication:	Sickle Cell Anemia
Study Sponsor:	Pfizer Inc. 66 Hudson Boulevard East New York, NY 10001
Study Initiation Date (First Participant First Visit [FPFV]):	15 January 2024
Primary Completion Date (PCD):	07 May 2024
Presentation of data in this CSR synopsis based on Study Completion (Last Participant Last Vist [LPLV]) Date:	07 May 2024
Early Termination Status:	This study was not terminated early and was completed as per protocol.
CSR Version and Report Date:	**Document Version** / **Report Date** Final LPLV CSR Version 1.0 / 23 September 2024 Final LPLV CSR (Amendment to / 06 December 2024

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	23 September 2024) Version 2.0		

GOOD CLINICAL PRACTICE STATEMENT

This study was conducted in compliance with GCP guidelines and, where applicable, local country regulations relevant to the use of new therapeutic agents in the country/countries of conduct, including the archiving of essential documents.

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

Study C5351008 was conducted at 1 site in the United States (US).

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

Publications:

None.

Brief Description of the Trial Design and Methodology:

This was an open-label, single-dose, randomized, parallel-group study in adult healthy participants. The study aimed to evaluate the pharmacokinetic (PK) comparability of the tablet Formulation II (1×150 mg) compared to the tablet Formulation I (1×100 mg and 2×25 mg) using a 150 mg PF 07940367 single dose administered under fasted condition.

Number of Participants (planned and analyzed):

Approximately 40 participants were planned to be enrolled. PK data variability was evaluated after the collection of PK on Day 15 had been completed for the (approximately) 40 participants. If the geometric CV for AUC_{0-336} was >30%, up to 20 additional participants were planned to be enrolled, subjected to the Sponsor's discretion.

Based on the analysis of preliminary PK data, the %CV for AUC_{0-336} did not exceed 30%. Consequently, the decision was made not to enroll additional participants in the C5351008 study. A total of 40 participants were enrolled in the study and treated.

Table S1. Number of Participants (Planned and Analyzed)

Population	N	Definition
Enrolled	40	"Enrolled" meant a participant's, or their legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process and randomization/assignment to study intervention. A participant was considered enrolled if the informed consent was not withdrawn prior to participating in any study activity after screening. Potential participants who were screened for the purpose of determining eligibility for the study, but did not participate in the study, were not considered enrolled, unless otherwise specified by the protocol.
FAS	40	All participants randomly assigned to study intervention and who took at least 1 dose of study intervention. Participants were analyzed according to the treatment they are randomized to.
SAS	40	All participants who took at least 1 dose of study intervention. Participants were analyzed according to the treatment they actually received.
PK Concentration Set	40	The PK concentration population was defined as all participants who received any amount of PF-07940367 and in whom at least 1 measurable concentration value was

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Table S1. Number of Participants (Planned and Analyzed)

		reported. Participants were analyzed according to the treatment they actually received.
PK Parameter Set	40	The PK parameter analysis population was defined as all participants who received any amount of PF-07940367 and had at least 1 of the PK parameters of interest calculated. Participants were analyzed according to the treatment they actually received.

Abbreviations: FAS=full analysis set; PK=Pharmacokinetic; SAS=safety analysis set.

Diagnosis and Main Criteria for Inclusion and Exclusion:

This study enrolled healthy male and female participants aged 18 years or older (or the minimum age of consent in accordance with local regulations) at screening.

Study Intervention:

For eligible participants, the total duration of participation was up to 112 days from Screening (28-day screening window) to the final Follow-up Visit (Day 84). The study consisted of an initial screening period of up to 28 days (while allowing for the return and review of all results, including laboratory tests), a 5-day inpatient stay at the clinical research unit (CRU) which included administration of a single oral dose of PF-07940367, and 5 follow-up visits. The first 2 follow-up visits were in-clinic, whereas the remaining 3 follow-up visits were performed remotely (telephone call).

Study Intervention(s)		
Intervention Name	PF-07940367	PF-07940367
Use	Experimental	Experimental
Investigational Medicinal Product (IMP) or Non-investigational Medicinal Product / Auxiliary Medicinal Product (NIMP/AxMP)	IMP	IMP
Dose Formulation	Film-coated tablet; Formulation II	Film-coated tablet; Formulation I
Unit Dose Strength(s)	150 mg/tablet	100 mg/tablet and 25 mg/tablet
Route of Administration	Oral	Oral

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Study Arm(s)		
Arm Title	Treatment A	Treatment B
Arm Description	Participants will receive a single dose of 150 mg on Day 1 orally as 1×150 mg tablet. (test)	Participants will receive a single dose of 150 mg on Day 1 orally as 1×100 mg tablet and 2×25 mg tablets. (reference)

The manufacturing lot numbers for the study intervention(s) dispensed in this study are provided in Table S2.

Table S2. Study Intervention(s) Administered

Investigational Product Description	Vendor Lot No.	Pfizer Lot No.	Strength/ Potency	Dosage Form
PF-07940367 150 mg Tablet	N/A	23-DP-01774	150 mg	Tablet
PF-07940367 100 mg Bottle 30 ct (L-GBT)	124761L0	23-UU-01051	100 mg	Tablet
PF-07940367 25 mg Bottle 30 ct (L-GBT)	124761K0	23-UU-01097	25 mg	Tablet

Global Substantial Modifications

Table S3. Global Substantial Modifications

Date of Protocol Amendment	Amendment
31 January 2024	The protocol was amended due to a strategic shift.
07 November 2023	The protocol was amended to eliminate non-essential activities to decrease clinical site and participant burden.

Global Interruptions and Re-starts

Not applicable.

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Endpoints And Statistical Methods:

Objectives	Endpoints	Analysis Type	Analysis Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
Primary	**Primary:**				
• To evaluate the PK comparability of a single dose of a PF-07940367 150 mg film-coated tablet Formulation II (test) to the PF-07940367 film-coated tablet Formulation I (1×100 mg/tablet and 2×25 mg/tablet) (reference) administered under fasted conditions to healthy participants.	• AUC_{0-336} (if data permit, otherwise AUC_{last}) for PF-07940367 in whole blood	• Primary PK analysis	• PK parameter set	• Missing PK data were not imputed.	• ANOVA model • Descriptive statistics
Secondary	**Secondary:**				
• To evaluate the safety and tolerability of PF-07940367 in healthy participants following a single dose.	• Incidence of TEAEs[a], clinically significant changes in laboratory assessments, ECGs, and vital signs	• Secondary safety analysis	• Safety analysis set	Safety data were reported in accordance with the CaPS.	• Descriptive statistics
• To evaluate the single-dose whole blood PK of PF-07940367 in healthy participants	• C_{max}, AUC_{last} and T_{max} for PF-07940367 in whole blood	• Secondary PK analysis	• PK parameter set	• Missing PK data were not imputed.	• ANOVA model • Descriptive statistics

a. TEAE: A TEAE is an AE that occurs during the effective duration of treatment, defined as the period from the dose of study drug and through the minimum of either Study Day 57, study discontinuation or study completion date.
Abbreviations: ANOVA = analysis of variance; AUC_{0-336} = Area under the whole blood concentration-time profile from time 0 to time = 336 hours post-dose; AUC_{last} = Area under the whole blood concentration-time profile from time zero to the time of the last quantifiable concentration (C_{last}); CaPS = CDISC Aligned Pfizer Standards; C_{max} = maximum whole blood concentration; TEAE = treatment emergent adverse event ;T_{max} = Time for C_{max}

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SUMMARY OF RESULTS:

Participant Disposition

A total of 40 participants were enrolled in the study and treated. All participants (40) completed the study.

Demographic and Other Baseline Characteristics:

The majority of participants were male (57.5%), Black or African American (77.5%), and not Hispanic or Latino (82.5%). The median (range) age was 43.50 (29, 73) years. The mean (standard deviation [SD]) BMI was 27.69 (2.62) kg/m^2.

Exposure:

All enrolled participants received a single dose of PF-07940367 150 mg orally. Twenty participants received Formulation I (1 x 100 mg/tablet and 2 x 25 mg/tablet), and 20 participants received Formulation II (PF-07940367 150 mg/tablet).

Summary of PK/Safety Results

Table S4. Study C5351008 PK/Safety Results

Endpoints	Results
Primary:	
• AUC_{0-336} (if data permit, otherwise AUC_{last}) for PF-07940367 in whole blood	• When Formulation II is compared to Formulation I, the ratio (90% CI) of the adjusted geometric means was 102.33% (92.60% - 113.09%) for AUC_{0-336}. • As the 90% CI for the ratio of the AUC_{0-336} (test/reference) falls within the range of 70%-143%, PK comparability between the test and reference treatment was established. Also, note that the 90% CI was entirely contained within the BE acceptance limits of 80% - 125%. • Variability of PF-07940367 exposure based on geometric CV% for AUC_{0-336} did not exceed 30%, ranging between 17% to 22%.
Secondary:	
• Incidence of TEAEs, clinically significant changes in laboratory assessments, ECGs, and vital signs	• There were 2 TEAEs reported by 2 (10.0%) participants after dosing of Formulation I, and 3 TEAEs reported by 2 participants (10.0%) after dosing with Formulation II. All the TEAEs (Blepharitis, Alanine aminotransferase increased, Asparate aminotransferase increased and Headaches) are non-serious AEs. No deaths, SAEs, Grade ≥3 TEAEs, or TEAEs leading to study discontinuation or study intervention discontinuations were reported in the study. • Aspartate aminotransferase increased and Alanine aminotransferase increased reported in 1 participant receiving

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Table S4. Study C5351008 PK/Safety Results

Endpoints	Results
	Formulation II (PF-07940367 150 mg/tablet) were assessed as clinically significant and reported as treatment-related AEs. No other clinically significant laboratory abnormalities as assessed by the investigators were observed during the study. • No clinically significant vital signs or ECG findings as assessed by the investigators were observed during the study.
• C_{max}, AUC_{last} and T_{max} for PF-07940367 in whole blood	• Following administration of single oral doses of PF-07940367 150 mg in healthy adult participants, similar whole blood concentration-time profiles were observed between Formulation I and II. The median T_{max} for the Formulation II (150 mg/tablet) was 24.0 hours and Formulation I (1 x 100 mg/tablet and 2 x 25 mg/tablet) was 24.1 hours. • When Formulation II is compared to Formulation I, the ratios (90% CI) of the adjusted geometric means were 102.74% (92.96% - 113.55%) for AUC_{last}, and 102.11% (91.36% - 114.12%) for C_{max}. • Variability based on geometric CV% for C_{max} ranged from 21% to 23%.

CONCLUSIONS:

PK:

- Bioavailability of Formulation II (PF-07940367 150 mg/tablet) relative to Formulation I (PF-07940367 1 x 100 mg/tablet and 2 x 25 mg/tablet) was comparable with the 90% CI for AUC_{0-336} falling within the prespecified PK comparability range of 70%-143%. Furthermore, the 90% CIs for both AUC_{0-336} and C_{max} were entirely contained within the BE acceptance limits of 80% - 125%.

Safety:

- A single oral dose of PF-07940367 150 mg in both Formulation I (PF-07940367 1 x 100 mg/tablet and 2 x 25 mg/tablet) and Formulation II (PF-07940367 150 mg/tablet) were found to be safe and well-tolerated in healthy adult participants.

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