M-071

Model-Informed Phase 3 Dose Selection for a Novel KAT6 Inhibitor, PF-07248144, Following Dose Optimization in 2L+ ER+/HER2– Metastatic Breast Cancer (mBC) Population

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Objective

To evaluate the range of plasma exposures from clinical study C4551001 to characterize the exposure-response (E-R) relationships for endpoints of interest for PF-07248144 to inform the benefit-risk across dose levels in order to select the phase 3 dose.

Conclusions

Novel methodology

- The quantitative assessment based on comprehensive E-R analyses incorporated dose modifications into longitudinal simulations to enable safety and efficacy projections across dose levels.

Evaluation of alternative regimens

- Simulations were in line with observed data, and alternative regimens including intermediate doses were projected.

Quantitative risk-benefit for RP3D

- The clinical utility index supports the 5 mg QD starting dose of PF-07248144 in combination with fulvestrant as having an optimal benefit-risk profile compared with lower dose levels in this disease setting.

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References: 1. Mukohara T, Park YH, Sommerhalder D, et al. Inhibition of lysine acetyltransferase KAT6 in ER+HER2– metastatic breast cancer: a phase 1 trial. *Nat Med*. 2024;30:2242–2250. **2.** Liyanage M, Jermain B, Masters JC. Population modeling framework with adaptive dosing for optimizing clinical utility of compounds in development for treatment of solid tumors. Poster presented at: 2024 ACCP Annual Meeting, Sep 8–10, 2024, Bethesda, MD. **3.** LoRusso PM, Mukohara T, Sommerhalder D, et al. Dose optimization of PF-07248144, a first-in-class KAT6 inhibitor, in patients (pts) with ER+/HER2– metastatic breast cancer (mBC): Results from phase 1 study to support the Recommended Phase 3 Dose (RP3D). Oral Presentation at ASCO May 30–June 3, 2025, Chicago IL. **4.** Liyanage M, Kowalski K, Williams JH, et al. Exposure-response characterization of the safety profile for a novel KAT6 inhibitor, PF-07248144, for use in dose optimization during a phase 1 first-in-patient study. Abstract Accepted. 2025 ACoP Annual Meeting. Oct 18–21, 2025, Aurora, CO. **5.** Jermain B, et al. ACoP13 2022. **6.** Jermain B, Kowalski K, Liyanage M, et al. Clinical utility index leveraging results from clinical trial simulation for safety and efficacy outcomes derived from longitudinal models. Abstract Accepted. 2025 ACoP Annual Meeting. Oct 18–21, 2025, Aurora, CO.

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Background

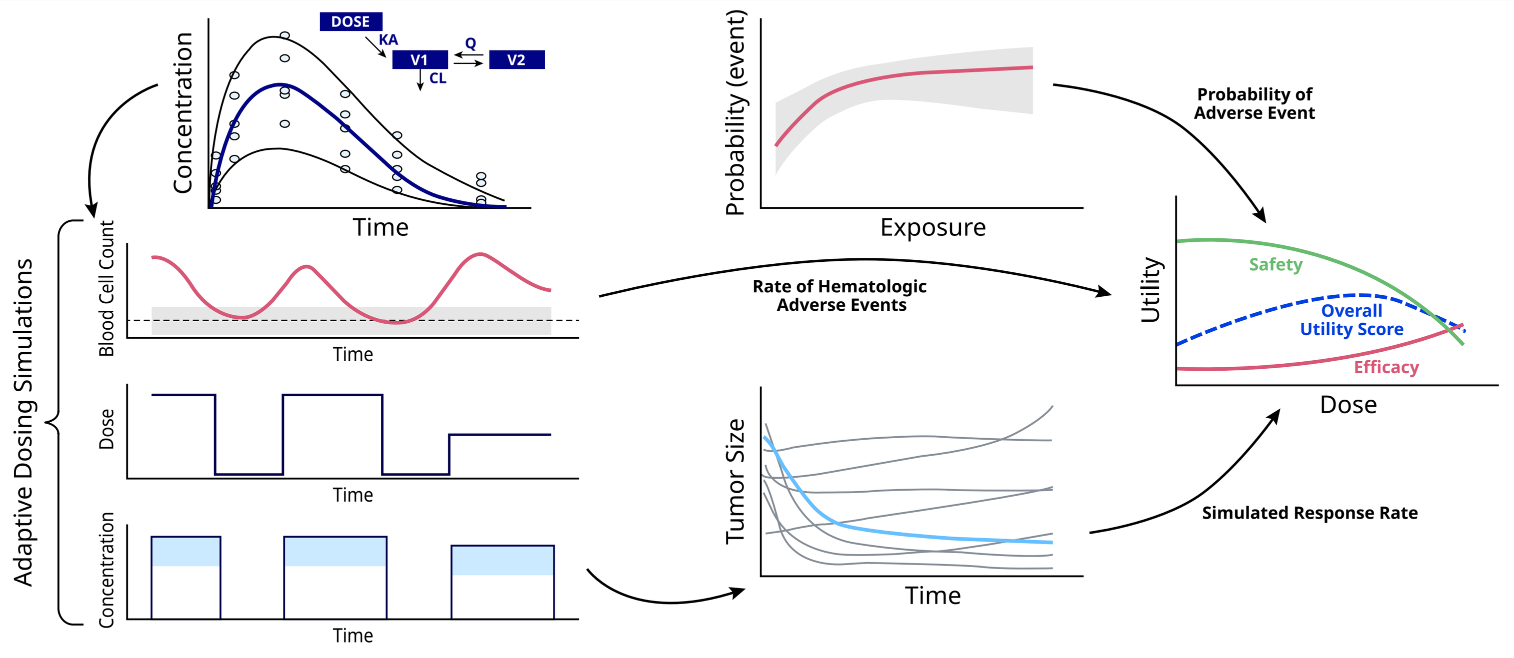
- PF-07248144 is a first-in-class, selective catalytic inhibitor of KAT6, a histone lysine acetyltransferase. C4551001 is a first-in-human, phase 1 study in patients with heavily pretreated estrogen receptor-positive/human epidermal growth factor receptor 2-negative (ER+/HER2–) mBC evaluating PF-07248144 monotherapy or in combination with fulvestrant within Part 1 dose escalation and Part 2 dose expansion (NCT04606446).
  - PF-07248144 in monotherapy or combination with fulvestrant across a wide range of doses including 1–15 mg QD in the Part 1 dose escalation were evaluated.[1] In addition to QD regimens, a 7 mg QW regimen was assessed in a small sample size.
- 1 and 5 mg QD in combination with fulvestrant were selected as the recommended doses for expansion (RDEs) in the Part 2 dose expansion phase in the second-line or later (2L+) ER+/HER2– mBC population for dose optimization, based on preclinical efficacious dose prediction, clinical PK, PD, and preliminary safety and efficacy from dose escalation.[1]

Materials and methods

MODELING AND SIMULATION WORKFLOW

- Information across a wide range of dose levels, including a large number of participants dosed at the 5 mg QD dose level (up to 88 patients) and 1 mg QD dose level (up to 37 patients) with sufficient follow-up (minimum 6 months from last subject first dose [LSFD] across RDE cohorts), was integrated into various popPK and E-R analyses.
  - A popPK model, longitudinal E-R models for tumor dynamics and absolute neutrophil count (ANC) and logistic regression models for safety and efficacy endpoints of interest were developed.
- Based on the observed dose-dependent rate of dose modifications primarily driven by neutropenia, the longitudinal neutropenia model was integrated into an adaptive dosing framework (**Figure 1**) to assess the impact of exposures over time on tumor dynamics for a given dose level using the dose modification schedule per protocol.[2] The clinical utility score of each dosing regimen was calculated with sensitivity analyses conducted for weightings of efficacy versus safety.

Figure 1: Illustration of adaptive MIDD dose optimization framework[2]



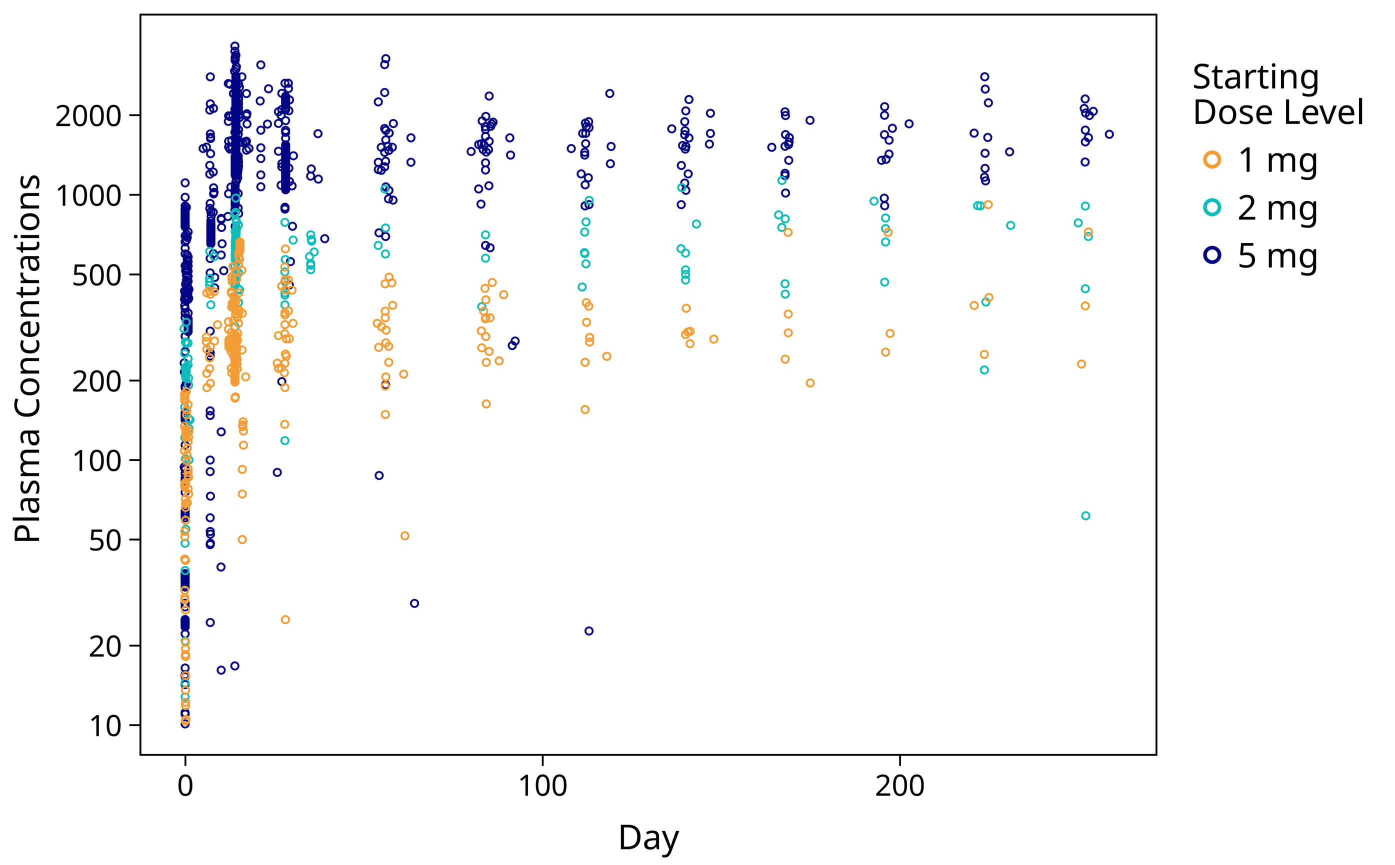
MIDD, Model-informed drug development.

Results

CLINICAL OBSERVATIONS

- PF-07248144 plasma exposure increased proportionally across the evaluated dose range, and the selected RDEs were pharmacokinetically distinct (**Figure 2**).

Figure 2. Wide range of exposures represented across RDE range within dataset



- Efficacy data indicated deeper and more durable antitumor activity at the 5 mg QD dose level compared with monotherapy or the evaluated lower dose (1 mg QD).[3]
- The most frequent treatment-related adverse event (TRAE) was dysgeusia (Grade [G] 1, G2, no treatment discontinuations at 5 mg QD). The most frequent G3/4 TRAE was neutropenia.[3]
- Across RDEs, a dose-dependent rate of dose reductions was observed with 55.8% of participants at the 5 mg QD dose level, with fulvestrant incurring TRAEs leading to dose reductions.[3]
  - Correspondingly, a wide range of exposures were observed including exposures at intermediate dose levels.[3]
  - 80% of dose reductions were due to neutropenia, which was manageable and reversible with no febrile neutropenia reported.[3]

EXPOSURE-RESPONSE ANALYSES AND PROJECTIONS

- PF-07248144 PK was characterized via popPK by a 2-compartment model with first order absorption and lag-time, which was used for simulating PK for subsequent E-R analyses of efficacy and safety endpoints.
- The E-R models for ≥ G3 anemia, any grade dysgeusia and G2 dysgeusia did not demonstrate a relationship. Based on low clinical relevance and shallow/flat E-R trends for dysgeusia and anemia, these endpoints were not considered in further assessment of benefit-risk across dose levels.[4]
  - Based on clinical relevance and dose dependency, ≥ G3 neutropenia and tumor response rate were selected as endpoints of interest to inform the risk-benefit across starting dose levels of interest.
- Longitudinal models were developed to describe ANC and tumor dynamic changes with PF-07248144 treatment. Both the neutropenia and tumor dynamic models demonstrated positive E-R relationships. The projected rates of ≥ G3 neutropenia and simulated tumor response from adaptive dosing simulations were consistent with the observed clinical data at the tested dose levels (**Table 1**).[3,5]

Table 1. Simulated safety and efficacy events across observed and intermediate dose levels, incorporating dose modifications

Starting Dose	Grade 3+ Neutropenia	*Observed Grade 3+ Neutropenia*	Tumor Response	*Observed ORR*
mg, QD	**Mean, % (90% CI)**	%	**Mean, % (90% CI)**	% (95% CI)
1	**18 (10–28)**	20.7	**17 (10–30)**	20.7 (8.0–39.7)
2	32 (22–45)	–	23 (12–35)	
3	39 (28–50)	–	27 (18–42)	
5	**46 (35–60)**	46.5	**35 (22–48)**	37.2 (23.0–53.3)

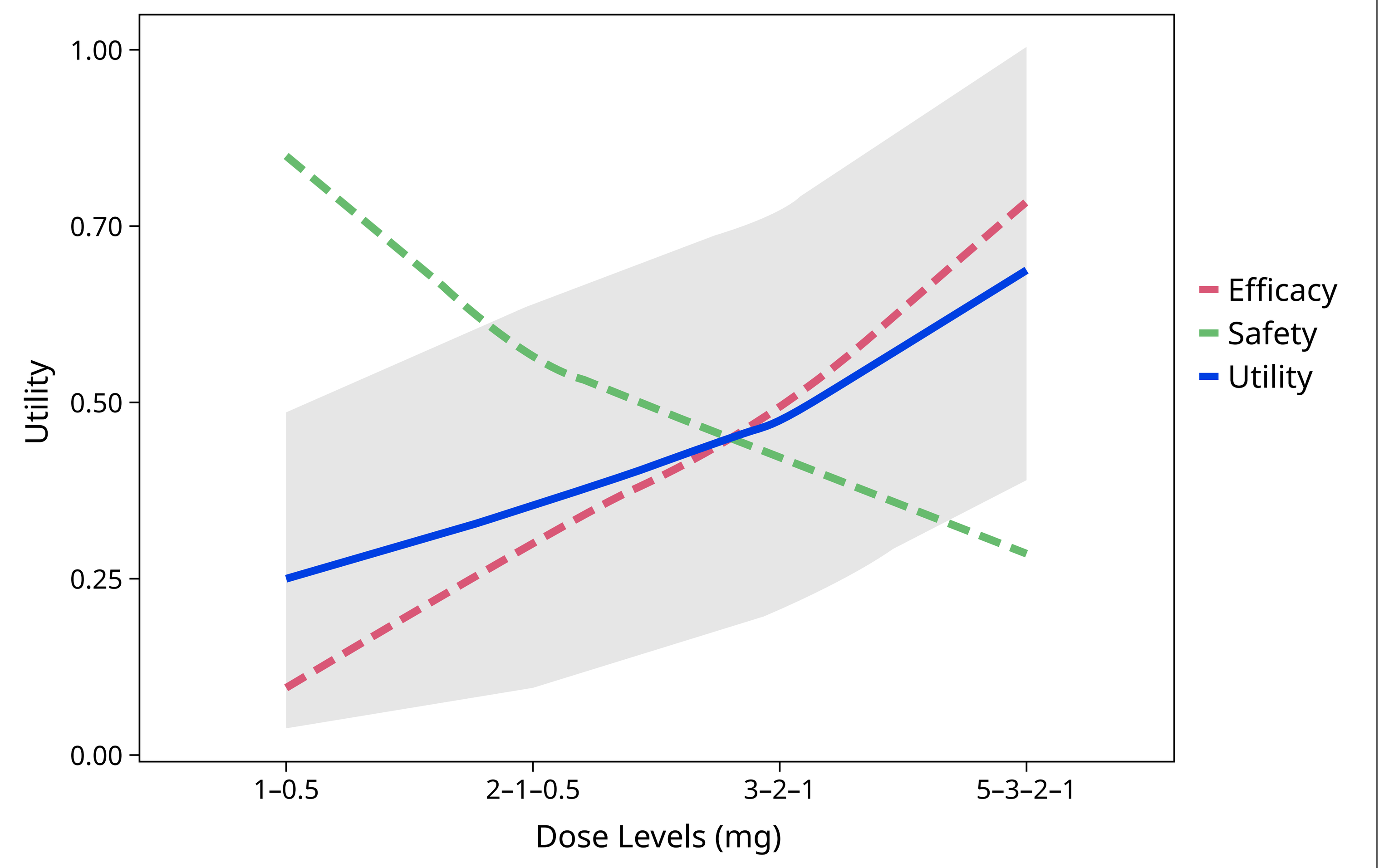
Response defined as 30% or more decrease from baseline in target lesion sum of longest diameter simulated out to 24 weeks.
Based on data cutoff date of 30 April 2024.
CI, confidence interval; ORR, objective response rate; QD, once daily.

- In addition to intermediate dose levels, alternative PF-07248144 dose regimens on rates of ≥ G3 neutropenia were evaluated, indicating alternative regimens (ie, QW, 3 weeks on/1 week off, 4 days on/3 days off) do not meaningfully reduce the rates of neutropenia relative to the QD regimen of equivalent time-matched dose intensity.

QUANTITATIVE RISK-BENEFIT ASSESSMENT

- Clinically relevant endpoints (≥ G3 neutropenia and tumor response rate) were integrated into a derived clinical utility index for the RDEs and intermediate dose levels in combination with fulvestrant (ie, 2 mg QD, 3 mg QD), indicating an optimal benefit-risk for the 5 mg QD dose level (**Figure 3**).[6]

Figure 3. Clinical utility of simulated PF-07248144 QD dose levels in combination with fulvestrant



The following regimens were assessed (listed with the starting dose followed by dose reductions available for each regimen, in mg): regimen 1: 1–0.5; regimen 2: 2–1–0.5; regimen 3: 3–2–1; and regimen 4: 5–3–2–1.

Efficacy utility (red dashed line); safety utility (green dashed line); overall utility (solid blue line) with 80% prediction interval around the overall utility (blue shading) quantified using simulated data across dose regimens and a specified target product profile using a weighting of 80:20 (efficacy:safety).

QD, once daily.

- The clinical utility score of each dosing regimen was calculated based on simulated safety and efficacy outcomes to guide dosing decisions. Sensitivity analyses were conducted by varying the weight of efficacy and safety components (eg, 60:40, 50:50).
- Across the range of sensitivity analyses, there were no scenarios in which an intermediate dose level was optimal. In all scenarios where efficacy was weighted higher than safety, the 5 mg QD dose level was optimal.