S-076

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

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Objective

To evaluate the potential exposure-response (E-R) relationships between PF-07248144 and safety endpoints of interest.

Conclusions

- PF-07248144 exhibits a positive E-R relationship for neutrophil count time course and Grade ≥ 3 treatment-emergent adverse events (TEAEs), which are primarily influenced by neutropenia.
- Dysgeusia and Grade ≥ 3 anemia do not appear dependent on exposure in the dose range tested.
- The E-R characterization across a variety of safety endpoints identified neutropenia as the primary safety endpoint to inform the benefit:risk assessment, and a longitudinal model was developed for differentiation of various dosing regimens of PF-07248144.

Background

- KAT6A and its paralog, KAT6B, are histone lysine acetyltransferases (KATs) that regulate lineage-specific gene transcription via H3K23 acetylation (H3K23Ac).
- PF-07248144 is a novel, potent and selective catalytic KAT6A and KAT6B inhibitor currently being developed in ER+ HER2– metastatic breast cancer.
- A phase 1 study (C4551001) to evaluate the safety, pharmacokinetics (PK), and early signs of efficacy of PF-07248144 is ongoing (NCT04606446).
- Understanding the potential E-R relationships for safety of PF-07248144 was vital to the benefit:risk assessment for dose selection and dose optimization.

Materials and Methods

- E-R analyses for PF-07248144 were conducted using relevant clinical data from the ongoing phase 1 study.
- Patients included in this analysis received PF-07248144 once daily (QD) as monotherapy or in combination with fulvestrant at doses ranging from 1 mg to 15 mg QD, with expansion cohorts at 1 mg and 5 mg.

LOGISTIC REGRESSION ANALYSES OF SELECT SAFETY ENDPOINTS

- Logistic regression analyses were conducted for safety endpoints of interest including any grade dysgeusia, Grade 2 dysgeusia, Grade ≥ 3 anemia, and Grade ≥ 3 TEAEs.
- All participants included in logistic regression analyses had at least 6 months of follow-up.
- PF-07248144 exposure metrics evaluated in logistic regression were generated from a population PK (PopPK) model and included C_{max}, C_{avg}, and C_{trough} following single dose and at steady state (day 15).
- The following covariates were explored for E-R analysis for safety: race, sex, baseline ECOG score, concomitant fulvestrant therapy, prior chemotherapy, age, baseline neutrophil count, baseline serum creatinine, baseline albumin, and baseline alanine aminotransferase (ALT).

LONGITUDINAL NEUTROPENIA MODEL

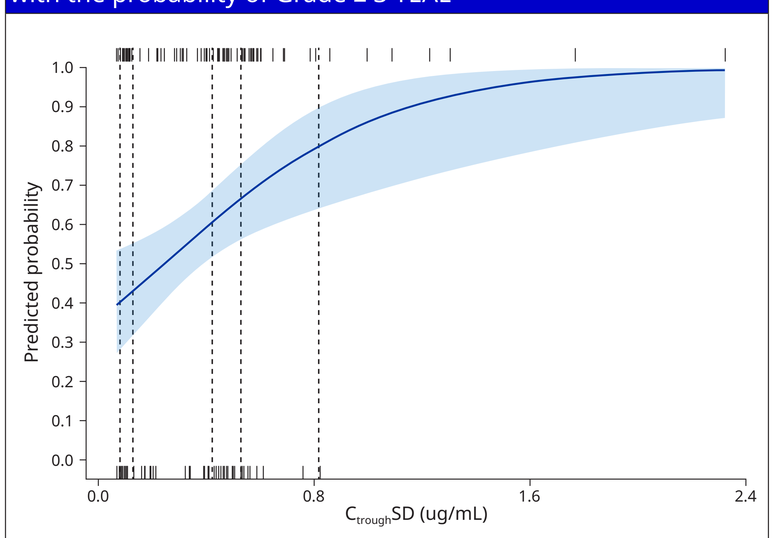
- Due to the dose modifications seen in the C4551001 study, longitudinal pharmacokinetic-pharmacodynamic (PK-PD) models were pursued.
- Since Grade ≥ 3 neutropenia was the main adverse event and driver of dose modifications; a nonlinear mixed effect semi-mechanistic model of myelosuppression was used to characterize the E-R relationship.[1]
- Simulations of absolute neutrophil count (ANC) over time were conducted for virtual patients over 6 months at various dosing regimens. If a virtual patient had a simulated ANC less than 1.0 (x 1000/uL) at any point, they were considered to have experienced Grade ≥ 3 neutropenia.
- Dosing regimens with alternative schedules were dose intensity-matched to the corresponding QD dosing regimen.
- Grade ≥ 3 neutropenia rates were compared across dosing regimens.

Results

LOGISTIC REGRESSION ANALYSES OF SELECT SAFETY ENDPOINTS

- A positive E-R relationship was found between PF-07248144 single-dose C_{trough} and Grade ≥ 3 TEAE (**Figure 1**).
  - The majority of Grade ≥ 3 TEAEs were neutropenia, which was further explored through a longitudinal neutropenia model.
- No significant E-R relationship was found via logistic regression for any grade dysgeusia, Grade 2 dysgeusia, or Grade ≥ 3 anemia after backward selection.
  - Graphical comparisons of exposure metrics versus endpoints showed no obvious trends (**Figure 2**).

Figure 1. Simulations of the PF-07248144 exposure relationship with the probability of Grade ≥ 3 TEAE



Solid blue line is the predicted probability of event and shaded area is the 95% confidence interval.
The vertical dashed lines represent the observed 0.05, 0.25, 0.5, 0.75, and 0.95 quantiles of the dependent variable.
TEAE, treatment-emergent adverse event.

LONGITUDINAL NEUTROPENIA MODEL

- The longitudinal PK-PD model of neutrophil count over time used a typical semi-mechanistic myelosuppression model structure (**Figure 3**) with circulating cells representing the neutrophil count, an E_{max} drug concentration effect on cell proliferation rate, and random effects on baseline neutrophil count and E_{max}.
- Model diagnostics indicated an adequate fit to the data (**Figure 4**), and the model was considered appropriate for further PK-PD simulations using the fixed and random effects from the associated PopPK model and the PK-PD neutropenia model.
- Simulations of Grade ≥ 3 neutropenia rates showed a clinically meaningful difference in central tendency between 1 mg and 5 mg that was in agreement with clinical observations from the C4551001 study.[2]
- Alternative regimens did not show a meaningful difference in Grade ≥ 3 neutropenia rates compared to the dose intensity-matched QD regimen (**Table 1**).
- Simulations from this model were leveraged through adaptive dosing simulation methods[3] to inform the predicted safety risk for various dosing regimens, as part of a benefit:risk assessment through clinical utility index.[4,5] This quantitative benefit:risk assessment supported 5 mg QD as the recommended phase 3 dose (RP3D).[2]

Figure 3. Myelosuppression model structure[1]

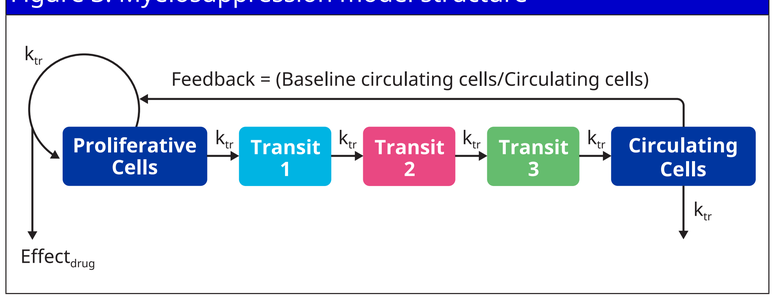
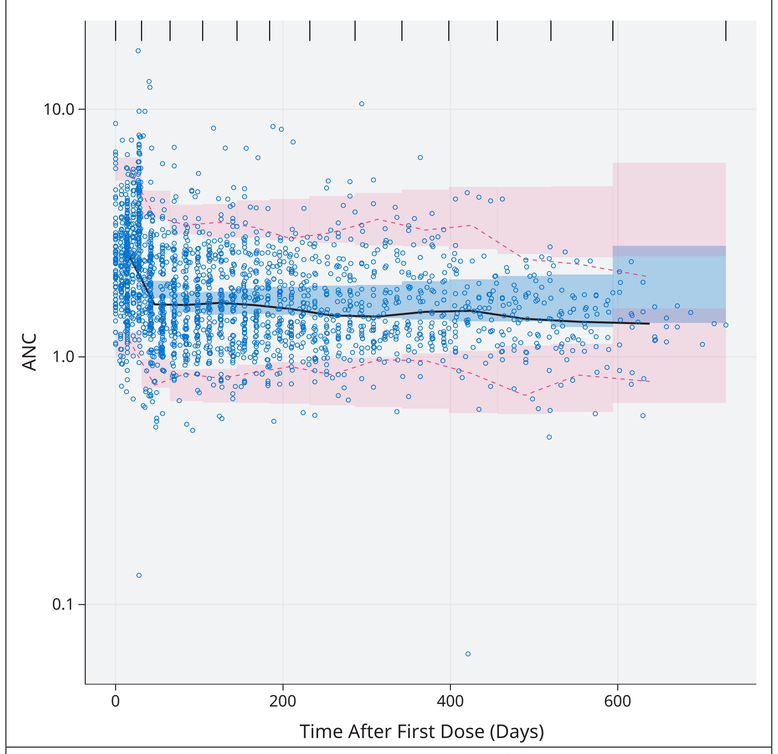


Figure 4. Prediction-corrected visual predictive check (pcVPC) of PF-07248144 longitudinal neutropenia model



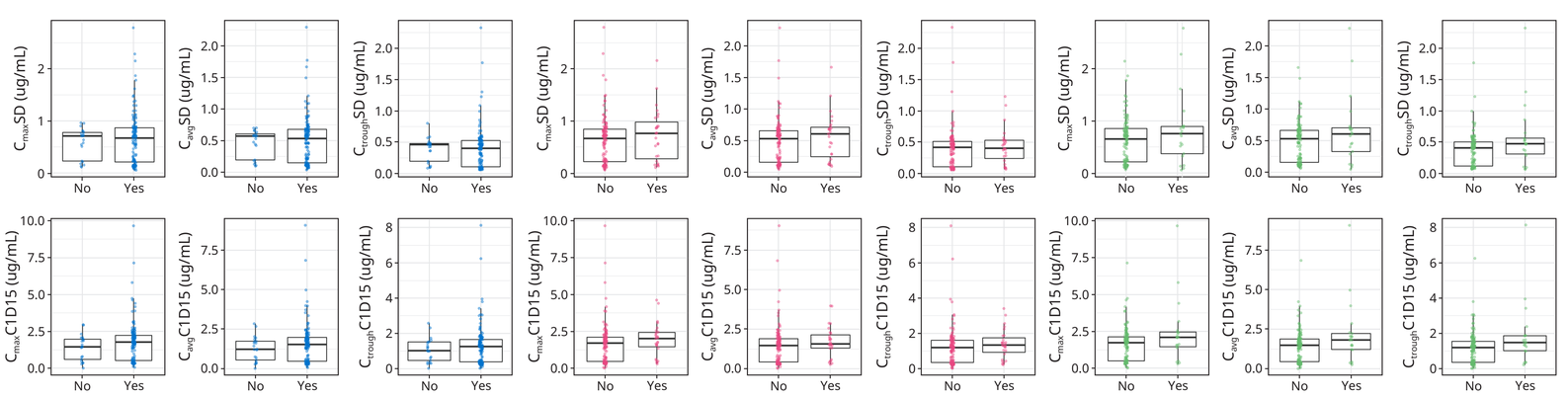
Solid blue line is the predicted probability of event and shaded area is the 95% confidence interval.
The vertical dashed lines represent the observed 0.05, 0.25, 0.5, 0.75, and 0.95 quantiles of the dependent variable.
TEAE, treatment-emergent adverse event.

Table 1. Simulated Grade ≥ 3 neutropenia rates with various regimens

Average dose intensity per day of PF-07248144 over 1 cycle	Daily (QD)	Weekly (QW)	3 weeks on (QD) 1 week off	4 days on (QD) 3 days off
1 mg	18.3%	13.5%	21.9%	17.4%
3 mg	39.4%	33.8%	41.8%	37.7%
5 mg	47.0%	43.9%	48.3%	45.1%

Simulated ANC less than 1.0 (x 1000/uL) at any point was considered Grade ≥ 3 neutropenia.
ANC, absolute neutrophil count.

Figure 2. PF-07248144 exposure metrics vs select safety endpoints



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