Effect of Food on the Pharmacokinetics and Safety Profile of p53 Reactivator Rezatapopt in Healthy Subjects and Patients with Solid Tumors Harboring a *TP53* Y220C Mutation

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BACKGROUND

- Mutations in *TP53* result in loss of p53 tumor suppressor function and tumor progression[1-4]
- The *TP53* Y220C missense mutation is present in ~1% of all solid tumors[5]
- Tyrosine substitution by a cysteine creates a pocket in the p53 protein that destabilizes the protein structure, rendering it unable to bind to DNA and elicit tumor suppressor functions[4,5]
- Rezatapopt, an investigational agent also known as PC14586, is a first-in-class p53 reactivator that selectively binds to the pocket within the Y220C-mutated p53 protein and restores p53 wild-type conformation and transcriptional activity[6]
  - Currently being assessed in the ongoing Phase 2 registrational portion of the PYNNACLE Phase 1/2 clinical trial (NCT04585750; PMV-586-101) in patients with locally advanced or metastatic solid tumors harboring the *TP53* Y220C mutation
  - Favorable safety and anti-tumor activity in heavily pre-treated patients in PYNNACLE Phase 1
  - Administered orally and has pH-dependent solubility

OBJECTIVE

- To assess the potential effects of food on the PK, safety, and tolerability profiles of rezatapopt

METHODS

- PBPK modeling was applied to predict the effect of food on the PK profile of rezatapopt in both healthy volunteers and patients with solid tumors
- Predictions derived from the PBPK model were confirmed using clinical data from healthy volunteers (PMV-586-102 study) and patients with solid tumors (PYNNACLE Phase 1) receiving rezatapopt with and without food
- For the PMV-586-102 and PYNNACLE Phase 1 studies, noncompartmental analysis was performed to characterize the PK parameters of rezatapopt using Phoenix WinNonlin Version 8.3.4
- The clinical safety of rezatapopt was assessed using the rate of TEAEs and TRAEs observed in patients with solid tumors receiving rezatapopt at various doses as part of the PYNNACLE Phase 1 study

PBPK Model

Development

1. Inputs
   Physicochemical properties (MW, Log P, compound type, pK_a)
2. *In vitro* and clinical ADME: P_{app}, *in vitro* pH-solubility profile, *in vitro* fm estimates, Day 1 CL/F (PYNNACLE)

→
- Absorption model: ADAM[7]
- Distribution model: minimal model
- Elimination
  - Incorporated observed CL/F from patients with solid tumors
  - Renal clearance set to 0 since it is a minor clearance pathway

Verification

Verified using clinical PK data:
- From single and repeat dosing of rezatapopt (150–2500 mg QD) in patients with solid tumors (PYNNACLE study)

→ 76% of predictions from the PBPK model were within 0.67 to 1.5-fold of observed values across dose cohorts (150–2500 mg QD) in PYNNACLE

Application

Conducted virtual trials:
- 10 trials of 10 healthy volunteers (50% male; aged 20–50 years)
- 10 trials of 10 patients with solid tumors (50% male; 30–75 years)

→ Predicted **food effect** on PK exposures for healthy volunteers and patients with solid tumors following single or multiple oral doses of rezatapopt 2000 mg

PMV-586-102 Phase 1 Food Effect Study (NCT05249348)

- **Study Objective:** Assess the effect of food on the PK profile of rezatapopt after administration of a single dose of rezatapopt in healthy volunteers

Study Design: Two-part, Crossover

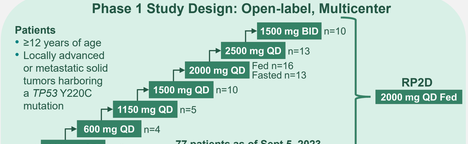
PK Sampling Timepoints: Pre-dose and over 96 h post-dose at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, 24, 48, 72, and 96 h

Primary Endpoints: AUC_{0-last}, AUC_{0-inf}, C_{max} and T_{max}

PYNNACLE Phase 1 Advanced Cancer Study (PMV-586-101, NCT04585750)

- **Study Objective:** Assess safety, tolerability, PKs, PDs, and efficacy of rezatapopt (21-day treatment cycles) in patients with locally advanced or metastatic solid tumors harboring a *TP53* Y220C mutation to determine MTD and RP2D

Phase 1 Study Design: Open-label, Multicenter



PK Sampling Timepoints: Pre-dose and over 24 h post-dose at 0.5, 1, 2, 3, 4, 6–8, 10–12, and 24 h on Cycle 1 Day 1 and Day 15 (steady state)

Endpoints for Food Effect Assessment:
Rezatapopt PK and safety profiles (including C_{max}, AUC_{0-24}, $T_{1/2}$, and AEs) in patients receiving 2000 mg QD without food vs with food (≥100 calories and 3 grams of fat)

RESULTS

PBPK Model

- The model predicts food intake increases rezatapopt exposure, AUC_{0-inf} and C_{max} by 45% and 28%, respectively, in healthy volunteers
- The model predicts food intake increases exposure following multiple doses of rezatapopt, AUC_{tau} (AUC in one dosing interval) and C_{max} by 43% and 36%, respectively, in patients with solid tumors

PMV-586-102 Phase 1 Study

PK Exposure
- Healthy volunteers (N=22) received a single oral dose of rezatapopt 2000 mg with and/or without a high-fat meal; two completed only one part of the study
- In participants who received a single oral dose of rezatapopt 2000 mg and completed the study, AUC_{0-inf}, AUC_{0-last} and C_{max} were 79%, 73% and 84% higher, respectively, in the fed vs fasted state (**Table 1; Figure 1**)

Safety and Tolerability
- Rates of GI TEAEs were similar with vs without food; all were mild

PYNNACLE Phase 1 Study

- PK data were available for 12 and 13 patients with solid tumors harboring a *TP53* Y220C mutation who received rezatapopt 2000 mg QD orally with or without food, respectively (data cutoff: Sept 5, 2023)

PK Profile
- Rezatapopt exposure was increased with food (**Table 2; Figure 2**)
  - On Day 1, geometric means of AUC_{0-24} and C_{max} were both 20% higher with vs without food after a single oral dose of rezatapopt
  - At steady state, the geometric means of AUC_{0-24} and C_{max} were 42% and 40% higher, respectively, with vs without food
- Median half-life of rezatapopt at steady state was ~19 h across dose cohorts with steady state reached by four days of dosing

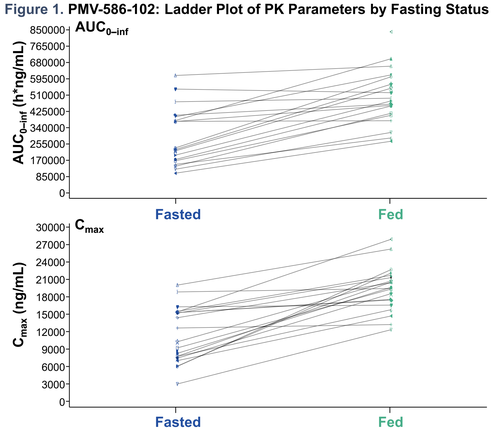
Safety and Tolerability
- Rates of GI TRAEs were reduced when rezatapopt 2000 mg QD was taken with food (**Figure 3**)
  - Frequency and severity of GI TRAEs were lowest in the 2000 mg QD fed cohort vs higher dose cohorts (2500 mg QD or 1500 mg BID without food) in the PYNNACLE Phase 1, dose-escalation study

Table 1. PMV-586-102: Effect of Food on Rezatapopt PK Parameters

Rezatapopt 2000 mg	Parameter	n[a]	Geometric Mean		GMR (%) (Fed/Fasted)	90% CI of GMR	Intra-subject CV%
			Fed[b]	Fasted			
Comparison (Fed/Fasted)	AUC_{0-inf} (h*ng/mL)	18	464526.09	259891.02	178.74	150.88, 211.74	29.74
	AUC_{0-last} (h*ng/mL)	20	448599.57	259397.05	172.94	148.55, 201.33	28.26
	C_{max} (ng/mL)	20	19085.52	10382.97	183.82	153.27, 220.46	34.08

Log transformed PK parameters were analyzed using an analysis of variance model with condition (fed/fasted) and period as fixed effects and participant as a random effect.
[a] Number of participants with non-missing and non-excluded values who received rezatapopt in both fed and fasted conditions. [b] A high-fat meal was administered 30 min prior to rezatapopt dosing.

Figure 1. PMV-586-102: Ladder Plot of PK Parameters by Fasting Status



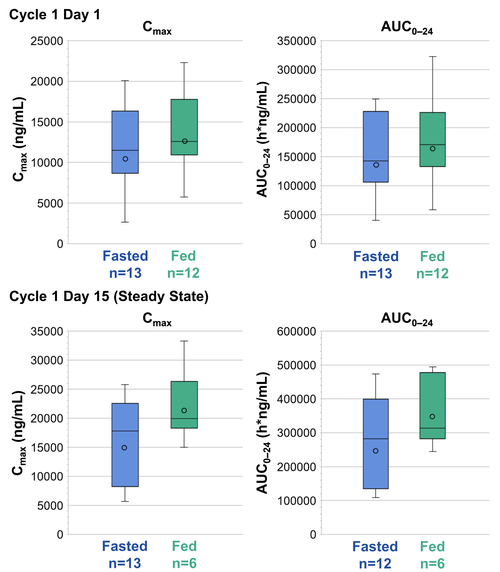
Each symbol and associated line represents a separate participant (N=22; two completed only one part of the study).

Table 2. PYNNACLE: Summary of Rezatapopt 2000 mg QD PK Parameters

Treatment	Cycle 1 Day 1			Cycle 1 Day 15 (Steady State)		
	Geometric Mean (CV%)		Median (Min–Max)	Geometric Mean (CV%)		Median (Min–Max)
	C_{max} (ng/mL)	AUC_{0-24} (h*ng/mL)	$T_{1/2}$ (h)	C_{max} (ng/mL)	AUC_{0-24} (h*ng/mL)	$T_{1/2}$ (h)
	n	n	n	n	n	n
2000 mg QD Fasted	10550 (60)	137668 (56)	12 (10–26)	14963 (55)	245956 (59)	22 (12–40)
	13	13	13	13	12	12
2000 mg QD Fed[a]	12656 (46)	164598 (48)	14 (9–16)	21268 (27)	343831 (29)	21 (17–47)
	12	12	12	6	6	6

[a] Received rezatapopt within 30 min after finishing a morning meal; the meal contained ≥ 100 calories and 3 grams of fat.

Figure 2. PYNNACLE: Boxplot of Rezatapopt 2000 mg QD PK Parameters on Cycle 1 Day 1 and Day 15 (Steady State) by Fasting Status

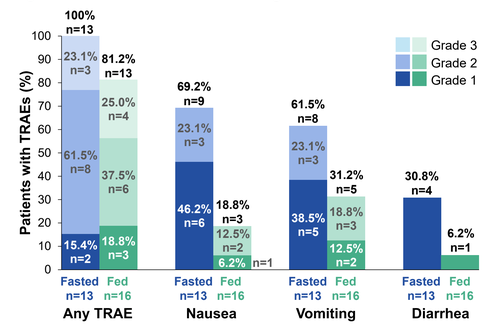


Box = interquartile range; line in box = median; whiskers = minimum and maximum; circle = geometric mean.

Abbreviations

ADAM, advanced dissolution, absorption, and metabolism; ADME, absorption, distribution, metabolism, and excretion; AE, adverse event; AUC_{0-24}, area under the plasma concentration-time curve from pre-dose to 24 hours post-dose; AUC_{0-inf}, area under the plasma concentration-time curve from pre-dose extrapolated to infinity; AUC_{0-last}, area under the plasma concentration-time curve from pre-dose to the time of the last quantifiable concentration; AUC_{tau}, area under the plasma concentration-time in one dosing interval; BID, twice daily; CI, confidence interval; CL/F, apparent clearance; C_{max}, maximum plasma concentration; CV, coefficient of variation; fm, fraction metabolized; GI, gastrointestinal; GMR, geometric mean ratio; h, hour; Log P, log of partition coefficient; max, maximum; min, minimum; MTD, maximum tolerated dose; MW, molecular weight; P_{app}, apparent permeability index; PBPK, physiologically based pharmacokinetic; PD, pharmacodynamic; PK, pharmacokinetic; pK_a, ionization constant; QD, once daily; RP2D, recommended Phase 2 dose; $T_{1/2}$, half-life; TEAE, treatment-emergent adverse event; T_{max}, time to reach C_{max}; TRAE, treatment-related adverse event.

Figure 3. PYNNACLE: TRAE at 2000 mg QD in Fasted and Fed State



CONCLUSIONS

- **PBPK modeling** predicted that rezatapopt exposure would be greater with food based on physicochemical characteristics and solubility inputs
  - This was confirmed by clinical PK data from healthy volunteers and patients with solid tumors
- In **healthy volunteers** administered a single oral dose of rezatapopt 2000 mg, AUC_{0-inf} and C_{max} were higher when rezatapopt was administered with vs without food
- **Patients with solid tumors harboring the *TP53* Y220C mutation** were administered rezatapopt 2000 mg QD orally:
  - AUC_{0-24} and C_{max} at steady state were higher and variability was lower when rezatapopt was administered with vs without food
  - Rezatapopt was well tolerated and associated with fewer GI TRAEs when administered with food (≥100 calories, ≥3 grams fat)
- The **positive food effect** may be due to enhanced solubilization with bile salt following food intake, and the decrease in GI TRAEs may be attributed to the local effect of food
- The registrational Phase 2 portion of the PYNNACLE Phase 1/2 trial is ongoing and will assess rezatapopt at 2000 mg QD with food in patients with advanced solid tumors harboring a *TP53* Y220C mutation and *KRAS* wild-type

References

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