Evaluating the Effects of Acid-Reducing Agents and CYP3A4 Inhibition on the Pharmacokinetics of Rezatapopt in Healthy Volunteers: Two Phase 1 Studies

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Poster 220

BACKGROUND

- The *TP53* Y220C missense mutation is present in ~1% of all solid tumors[1,2]
- The tyrosine to cysteine substitution forms a pocket in the mutated protein that destabilizes p53 and results in loss of p53 function[1,2]
- Rezatapopt is an investigational, first-in-class, oral, selective p53 reactivator that binds to the mutated p53 Y220C protein and stabilizes it in the p53 wild-type conformation, which restores the tumor suppressor activity of p53[2,3]
- Rezatapopt is currently being assessed in the ongoing, pivotal, Phase 2 PYNNACLE clinical trial (NCT04585750) in patients with locally advanced or metastatic solid tumors harboring a *TP53* Y220C mutation[4,5]
- Rezatapopt dissolution is pH dependent
  - Acid-reducing agents (ARAs), which are often used by patients with cancer,[6] may impact rezatapopt absorption and PK parameters
- In vitro metabolism profiling studies suggest that metabolism by CYP3A4 is a key metabolic pathway of rezatapopt
  - CYP3A4 inhibitors may increase rezatapopt exposure

OBJECTIVES

- To assess the effect of rabeprazole, an ARA, on rezatapopt PK parameters in healthy participants
- To assess the effect of itraconazole, a strong CYP3A4 and P-gp inhibitor, on rezatapopt PK parameters in healthy participants

METHODS

- Two Phase 1, open-label, fixed-sequence studies were conducted in **healthy adult volunteers** to assess the impact of co-administration of rezatapopt with an ARA or CYP3A4 inhibitor on the PKs of rezatapopt (**Figure 1-2**)

- **PMV-586-104:** ARA
  - Assessed impact of rabeprazole, a PPI with prolonged effects on gastric pH
  - Participants were healthy and 18–55 years of age with a BMI of 18.5–30.0 kg/m^2
- **PMV-586-105**: CYP3A4 inhibitor
  - Assessed impact of itraconazole, a strong CYP3A4 inhibitor
  - Participants were healthy and 18–55 years of age with a BMI of 18.0–32.0 kg/m^2
- Each participant served as their own control
- All rezatapopt doses were administered following a low-fat meal
- Linear mixed-effects modeling assessed drug-drug interactions
  - A linear mixed effect model was fitted to log-transformed PK parameters to assess the effect of rabeprazole or itraconazole on rezatapopt
  - Model included treatment as a fixed effect and participant as a random effect
  - LSM for each treatment, difference in LSM, and 90% CI were calculated; these values were used to provide the GMR and 90% CI

Figure 1. PMV-586-104: ARA study (N=25 planned)

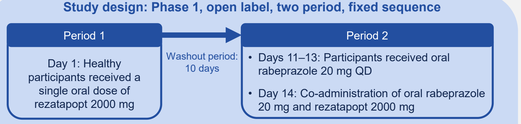
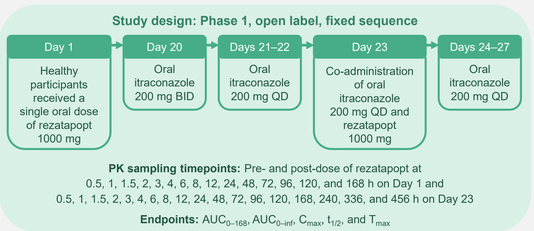


Figure 2. PMV-586-105: CYP3A4 inhibitor study (N=12 planned)



RESULTS

PMV-586-104: ARA study

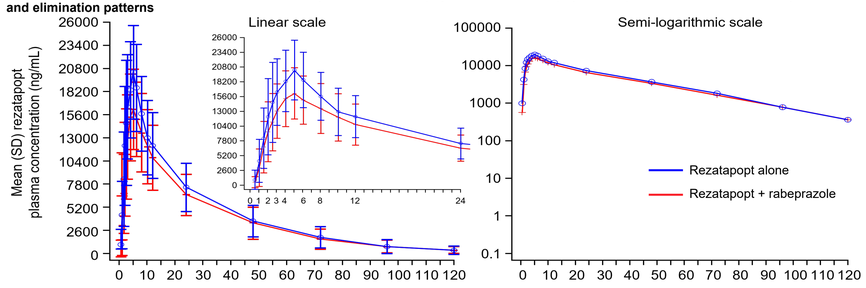
- In total, 28 participants were enrolled, including five female participants and 23 male participants
  - Mean (SD) age was 35.4 (7.9) years; mean (SD) BMI was 25.9 (2.6) kg/m^2
  - 26 participants completed both treatment periods; two participants treated in Period 1 withdrew before treatment in Period 2 and were excluded from the statistical analysis
- Statistical analysis estimated the GMR of test (rezatapopt + rabeprazole) to reference (rezatapopt alone), showing the effect of rabeprazole on a single 2000-mg dose of rezatapopt as follows (**Table 1**):
  - Geometric mean C_{max} was ~19% lower, and geometric mean AUC_{0-inf} was ~11% lower; 90% CIs for GMRs were within the no effect/alteration bounds
- Median T_{max} and geometric mean $t_{1/2}$ were similar for rezatapopt alone (4.01 and 17.9 h; N=28) and when co-administered with rabeprazole (4.52 and 18.6 h; n=26) (**Figure 3**)
- Most TEAEs were mild (47/53 events; moderate: 6/53 events)
  - 36 TEAEs in 10 participants were considered related to rezatapopt (15 TEAEs in Period 1; 21 TEAEs in Period 2). One TEAE in Period 2 was considered related to both rezatapopt and rabeprazole; none were considered related to rabeprazole alone
  - The most common TEAEs were diarrhea and headache, occurring in six participants each (21.4%)
  - No TEAEs leading to study or treatment discontinuation were reported
- No deaths, SAEs, or significant AEs were reported
- There were no clinically relevant changes from baseline in clinical laboratory evaluations, vital signs, ECGs, or physical examination findings

Table 1. Summary of rezatapopt PK parameters for rezatapopt alone and rezatapopt + rabeprazole

Parameter	Rezatapopt 2000 mg (reference)	Rezatapopt 2000 mg + rabeprazole 20 mg (test)	(Rezatapopt + rabeprazole)/ rezatapopt
	Geometric mean (90% CI)		GMR (90% CI), %[a]
C_{max}, ng/mL	21,600 (20,100–23,200)	17,500 (16,300–18,800)	81.1 (77.9–84.4)
N	26	26	26
AUC_{0-inf}, h•ng/mL	485,000 (423,000–555,000)	429,000 (375,000–491,000)	88.6 (83.6–93.8)
N	26	26	26
$t_{1/2}$, h	17.9 (27.0)	18.6 (26.7)	–
N	28	26	
	Median (min–max)		
T_{max}, h	4.01 (2.37–8.02)	4.52 (1.51–6.07)	–
N	28	26	

[a] Estimated difference of the LSMs and the corresponding CI obtained on the log scale was exponentiated to provide an estimate of the test to reference GMR and its associated two-sided 90% CI.

Figure 3. Rezatapopt plasma concentration vs time profiles for rezatapopt alone and rezatapopt + rabeprazole show similar absorption and elimination patterns



PMV-586-105: CYP3A4 inhibitor study

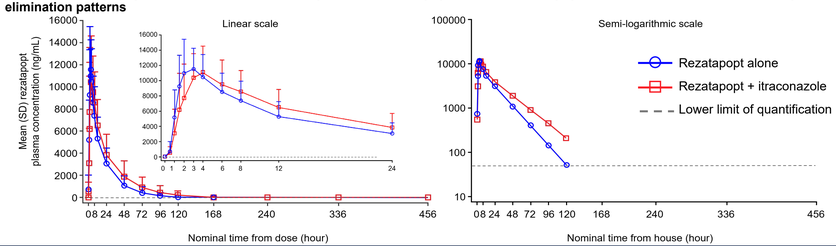
- In total, 12 participants were enrolled and completed the study, including one female participant and 11 male participants
  - Mean (SD) age was 32.3 (10.2) years; mean (SD) BMI was 25.9 (2.3) kg/m^2
- Geometric mean C_{max} of rezatapopt was similar when administered alone or with itraconazole; 90% CIs for GMRs spanned unity (**Table 2**)
  - C_{max} was reached later with rezatapopt + itraconazole vs rezatapopt alone (median T_{max}, 3.5 vs 2.0 h)
- Geometric mean AUC_{0-168} and AUC_{0-inf} of rezatapopt were ~29% higher when co-administered with itraconazole vs rezatapopt alone
- Geometric mean $t_{1/2}$ was longer when rezatapopt was co-administered with itraconazole (17.2 h) vs rezatapopt alone (13.5 h) (**Figure 4**)
- All TEAEs were mild; the most common TEAE was headache, occurring in three participants (25%)
  - One TEAE was considered related to itraconazole; none were considered related to rezatapopt
  - No participants discontinued from the study due to a TEAE
- No deaths, SAEs, or significant AEs were reported
- There were no clinically significant findings in clinical laboratory evaluations, vital signs, ECGs, or physical examinations

Table 2. Summary of rezatapopt PK parameters for rezatapopt alone and rezatapopt + itraconazole

Parameter	Rezatapopt 1000 mg (reference)	Rezatapopt 1000 mg + itraconazole 200 mg (test)	(Rezatapopt + itraconazole)/ rezatapopt
	Geometric mean (gCV%)		GMR, % (90% CI)[a]
C_{max}, ng/mL	12,000 (24.8)	12,100 (23.2)	100 (93.9–107)
N	12	12	12
AUC_{0-inf}, h•ng/mL	197,000 (40.7)	255,000 (49.1)	129 (118–142)
N	12	12	12
AUC_{0-168}, h•ng/mL	197,000 (40.6)	254,000 (48.4)	129 (118–141)
N	12	12	12
$t_{1/2}$, h	13.5 (20.4)	17.2 (23.3)	–
N	12	12	
	Median (min–max)		
T_{max}, h	2.00 (1.50–6.20)	3.50 (1.50–6.02)	–
N	12	12	

[a] Estimated difference of the LSMs and the corresponding CI obtained on the log scale was exponentiated to provide an estimate of the test to reference GMR and its associated two-sided 90% CI.

Figure 4. Rezatapopt plasma concentration vs time profiles for rezatapopt alone and rezatapopt + itraconazole show similar absorption and elimination patterns



CONCLUSIONS

- Under fed conditions with a low-fat meal, co-administration of multiple doses of an ARA (rabeprazole) or a strong CYP3A4 and P-gp inhibitor (itraconazole) with a single rezatapopt dose did not have a clinically meaningful impact on rezatapopt PK parameters, considering no effect boundaries, safety findings, and PK variability in the target population
  - Food intake may enhance rezatapopt absorption by improving solubility through bile salt-mediated mechanisms. This potentially buffers the drug's pH sensitivity, making it less susceptible to the effects of ARAs
- Based on the study results, no dose adjustment of rezatapopt is needed when concomitantly administered with ARAs (e.g., PPIs, H2 blockers, antacids), CYP3A4 inhibitors, or P-gp inhibitors

Abbreviations: AE, adverse event; ARA, acid-reducing agent; AUC_{0-168}/AUC_{0-inf}, area under the plasma concentration-time curve from pre-dose to 168 hours post-dose/extrapolated to infinity; BID, twice daily; BMI, body mass index; C_{max}, maximum plasma concentration; CYP3A4, cytochrome P450 3A4; ECG, electrocardiogram; gCV, geometric coefficient of variation; GMR, geometric mean ratio; LSM, least squares mean; max, maximum; min, minimum; P-gp, P-glycoprotein; PK, pharmacokinetics; PPI, proton pump inhibitor; QD, once daily; SAE, serious adverse event; $t_{1/2}$, half-life; TEAE, treatment-emergent adverse event; T_{max}, time to reach C_{max}.

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Acknowledgments: We thank all the patients, their families, and caregivers who have participated, and continue to participate, in the clinical trials; investigators and research staff; PPD; Resolution Biosciences; and Foundation Medicine. This study and the clinical trials are sponsored by PMV Pharmaceuticals, Inc. Medical writing was provided by Nucleus Global and funded by PMV Pharmaceuticals, Inc.

Disclosures: HCDK/AW/MF: PMV Pharmaceuticals employees (with stock options and shares). RG/KD: nothing to disclose.

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