Poster PII-115

Evaluation of the Effect of Vepdegestrant, a PROteolysis TArgeting Chimera (PROTAC) Estrogen Receptor Degrader, on Rosuvastatin Pharmacokinetics in Healthy Adult Participants

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Objective

- To evaluate the impact of vepdegestrant (ARV-471) on the pharmacokinetics (PK) of the breast cancer resistance protein (BCRP) substrate rosuvastatin in healthy adult participants (NCT05652660)

Key Findings

- In healthy adult participants (N=12), co-administration of rosuvastatin (10 mg) with a single dose of vepdegestrant (200 mg) increased rosuvastatin plasma area under the concentration-time curve from time 0 to time of the last measurable concentration (AUC_{last}) by 11% and maximum plasma concentration (C_{max}) by 21%
- Treatment-emergent adverse events (TEAEs) occurred in 1 (8.3%) participant after rosuvastatin treatment alone and 3 (25.0%) participants after rosuvastatin and vepdegestrant combination treatment
- Treatment-related adverse events (TRAEs) occurred in 2 (16.7%) participants after rosuvastatin and vepdegestrant combination treatment (dizziness and headache; 1 [8.3%] each)

Conclusions

- Co-administration of vepdegestrant had a minor effect on rosuvastatin exposure, suggesting vepdegestrant to be a weak BCRP inhibitor; dose reductions of BCRP substrate drugs are not warranted in patients taking vepdegestrant
- The study treatments were well tolerated in healthy adult participants; no new safety issues were identified

References

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Background

- Vepdegestrant (ARV-471) is a selective, orally administered PROTAC estrogen receptor (ER) degrader that directly binds an E3 ubiquitin ligase and ER to trigger ubiquitination of ER and its subsequent proteasomal degradation[1]
- In the first-in-human phase 1/2 study (NCT04072952), vepdegestrant was well tolerated and had encouraging clinical activity in patients with ER+/human epidermal growth factor 2-negative (HER2-) breast cancer[2-4]
- Vepdegestrant 200 mg once daily is currently under clinical development in 2 phase 3 studies as monotherapy and in combination with palbociclib for patients with ER+/HER2- advanced breast cancer[5,6]
- Based on in vitro data, vepdegestrant is a BCRP inhibitor (data on file); therefore, it is possible that administration of a BCRP substrate with vepdegestrant may lead to increased plasma exposure of the BCRP substrate
- Rosuvastatin is a known substrate of BCRP[7] and has been recommended as a probe for BCRP inhibition by regulatory agencies[8]
- This study (NCT05652660) was conducted to estimate the effect of vepdegestrant on the PK of rosuvastatin following a single oral dose of rosuvastatin 10 mg with and without co-administration of a single dose of vepdegestrant 200 mg in healthy adult participants

Methods

- This study was conducted at the Pfizer Clinical Research Unit (CRU) in New Haven, CT, in compliance with the ethical principles outlined in the Declaration of Helsinki and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines. Approval was received from the local Independent Ethics Committee, and all local regulatory requirements were followed

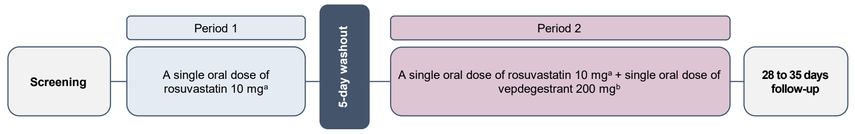
Participants

- Eligible participants included females (of non-childbearing potential) and males who are overtly healthy as determined by medical evaluation between the ages of 18–65 years with body mass index of 17.5–32.0 kg/m^2 and total body weight ≥45 kg (99 lb)
- Exclusion criteria included but were not limited to evidence or history of clinically significant conditions, known history of hypersensitivity to study drugs, and administration of investigational products (drug or vaccine) within 30 days or 5 half-lives (whichever was longer) preceding the first dose of study intervention

Study Design

- This was a phase 1, open-label, 2-period, fixed-sequence study in healthy adult participants (**Figure 1**). Participants were confined to the CRU on the day before initiating treatment until the day of clinic discharge

Figure 1: Study design



For each period, serial blood PK samples were collected predose and at 1, 2, 3, 4, 6, 8, 12, 24, 36, 48, and 72 hours post rosuvastatin dose to determine the single-dose rosuvastatin PK parameters without or with vepdegestrant

[a]Administered as 1 tablet of 10 mg ≈2 hours after starting the standard breakfast
[b]Administered as 2 tablets of 100 mg ≈30 minutes after starting the standard breakfast
PK=pharmacokinetics

- Healthy participants received 2 single doses of rosuvastatin 10 mg. The first dose was administered alone followed by at least 5 days of washout (period 1). The second dose was administered ≈1.5 hours after vepdegestrant 200 mg single dose (period 2). A standard breakfast was provided in period 1 and 2

Assessment and Analyses

- Rosuvastatin PK parameters were estimated using a noncompartmental approach. Natural log–transformed PK parameters (C_{max}, area under the concentration-time curve from time 0 extrapolated to infinity [AUC_{inf}], and AUC_{last}) of rosuvastatin were analyzed using a mixed-effects model, which included treatments as fixed effects and participant as a random effect
- Plasma concentrations of rosuvastatin were determined by a validated, sensitive, and specific high-performance liquid chromatography-tandem mass spectrometric (HPLC-MS/MS) method at Syneos Health (Princeton, NJ)
- Participants underwent physical examinations and were monitored for adverse events (AEs), vital signs, and electrocardiogram (ECG) changes throughout the study, including follow-up or early termination/discontinuation. Blood samples for safety laboratories were collected at screening, day −1 of period 1 (admission), and last day of each period

Results

Demographics and Baseline Characteristics

- Baseline characteristics of the 12 healthy adult participants enrolled and treated in the study are shown in **Table 1**
- All participants were included in the PK and safety analyses

Table 1: Demographics and baseline characteristics

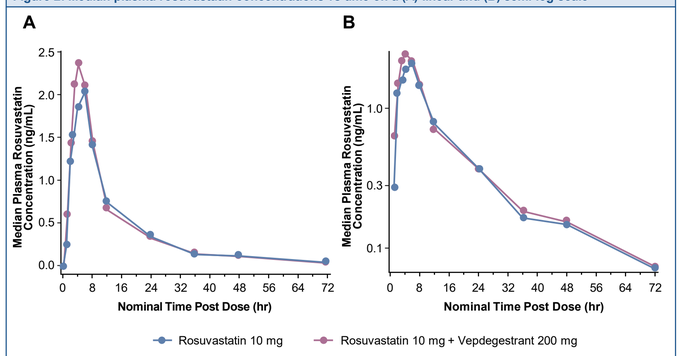
Characteristic	Total (N=12)
Age, median (range), y	52 (30–63)
Sex, n (%)	
Female	3 (25.0)
Male	9 (75.0)
Race, n (%)	
Asian	1 (8.3)
Black or African American	3 (25.0)
White	8 (66.7)
Ethnicity, n (%)	
Hispanic or Latino	4 (33.3)
Not Hispanic or Latino	8 (66.7)
BMI, median (range), kg/m^2	27.7 (21.9–31.7)
Weight, median (range), kg	83.0 (55.3–114.6)

BMI=body mass index

Pharmacokinetics

- The plasma concentration-time profiles of rosuvastatin with and without vepdegestrant are presented in **Figure 2**
- Summaries of rosuvastatin PK parameters with and without vepdegestrant are summarized in **Table 2** and displayed in **Figure 3**
  - Co-administration of rosuvastatin with vepdegestrant increased AUC_{last} by 11% and C_{max} by 21%
    - Interparticipant variability in rosuvastatin exposure based on AUC_{last} (N=12) and C_{max} (N=12) was similar when rosuvastatin was administered alone (40% and 53%, respectively) and when administered with vepdegestrant (40% and 48%, respectively)
  - Median time to reach C_{max} (T_{max}) was 4.0 hours when rosuvastatin was administered alone and when administered with vepdegestrant
  - Apparent first-order terminal elimination half-life ($t_{1/2}$) was similar, with mean values of 21.6 hours and 20.5 hours for rosuvastatin alone and rosuvastatin with vepdegestrant, respectively

Figure 2: Median plasma rosuvastatin concentrations vs time on a (A) linear and (B) semi-log scale



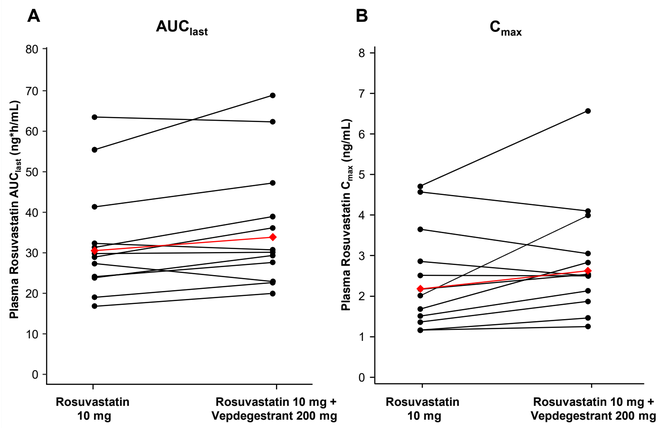
Data from PK analysis set: participants who received ≥1 dose of rosuvastatin
PK=pharmacokinetics

Table 2: Descriptive summary of plasma rosuvastatin PK parameters

PK parameter, unit	n	Rosuvastatin 10 mg reference	n	Rosuvastatin 10 mg + vepdegestrant 200 mg test	Ratio of adjusted geometric means (90% CI) test/reference
AUC_{inf}, ng*h/mL	8	36.7 (40)	8	38.5 (42)	116.9 (108.6–125.7)
AUC_{last}, ng*h/mL	12	31.4 (40)	12	34.7 (40)	110.6 (103.5–118.1)
C_{max}, ng/mL	12	2.2 (53)	12	2.6 (48)	120.5 (104.8–138.6)
T_{max}, h	12	4.0 (2.0–8.0)	12	4.0 (2.0–6.0)	-
$t_{1/2}$, h	8	21.6 ±8.16	8	20.5 ±5.08	-
CL/F, L/h	8	272.1 (40)	8	260.2 (42)	-
V_z/F, L	8	8016 (64)	8	7492 (66)	-

Data from PK analysis set: participants who received ≥1 dose of rosuvastatin. Data are presented as geometric mean (CV%) except for T_{max}, which is presented as median (min–max) and $t_{1/2}$, which is presented as arithmetic mean ± standard deviation. Rosuvastatin AUC_{inf}, $t_{1/2}$, CL/F, and V_z/F were not reported for 4 participants in period 1 and for 4 participants in period 2 due to a lack of a well-characterized terminal phase as defined by prespecified criteria (≥3 data points, r^2 ≥0.9, and AUC_{extrap}% ≤20)
AUC_{extrap}%=percent of the area under the concentration-time curve from time 0 to infinite time, obtained by forward extrapolation; AUC_{inf}=area under the concentration-time curve from time 0 extrapolated to infinity; AUC_{last}=area under the concentration-time curve from time 0 to time of the last measurable concentration of rosuvastatin; CL/F=apparent total clearance after extravascular administration; C_{max}=maximum plasma concentration; CV=coefficient of variation; PK=pharmacokinetics; r^2=goodness-of-fit statistic from the regression; $t_{1/2}$=apparent first-order terminal elimination half-life; T_{max}=time to reach C_{max}; V_z/F=apparent volume of distribution during the terminal elimination phase after extravascular administration

Figure 3: Individual and geometric mean (A) AUC_{last} and (B) C_{max} of rosuvastatin by treatment



Data from PK analysis set: participants who received ≥1 dose of rosuvastatin. Red data points indicate geometric mean for each parameter. Black data points indicate individual values
AUC_{last}=area under the concentration-time curve from time 0 to time of the last measurable concentration of rosuvastatin; C_{max}=maximum plasma concentration; PK=pharmacokinetics

Safety

- A total of 1 TEAE was reported in 1 (8.3%) participant following a single dose of rosuvastatin, and a total of 3 TEAEs were reported in 3 (25.0%) participants following a single dose of rosuvastatin and vepdegestrant; all were mild
- TRAEs were reported in 2 (16.7%) participants who received rosuvastatin 10 mg in combination with vepdegestrant 200 mg; both were mild (**Table 3**)
- No serious or severe AEs occurred, and no discontinuations or dose modifications due to AEs were reported
- No clinically meaningful changes in vital sign, ECG, or laboratory measurements were observed

Table 3: Summary of TRAEs

AEs by preferred term, n (%)	Rosuvastatin 10 mg (N=12)	Rosuvastatin 10 mg + vepdegestrant 200 mg (N=12)
Any TRAE	0	2 (16.7)
Dizziness	0	1 (8.3)
Headache	0	1 (8.3)

Data from safety analysis set: participants who received ≥1 dose of rosuvastatin or vepdegestrant
AE=adverse event; TRAE=treatment-related adverse event