Poster PII-109

Drug-Drug Interaction Study of the PROteolysis TArgeting Chimera (PROTAC) Androgen Receptor Degrader Bavdegalutamide in Combination With the P-glycoprotein Substrate Fexofenadine in Healthy Male Volunteers

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Objectives

- To evaluate the impact of a single dose of bavdegalutamide (ARV-110) 420 mg on the pharmacokinetics (PK) of a single dose of the P-glycoprotein (P-gp) substrate fexofenadine 60 mg in healthy male volunteers
- To evaluate the safety and tolerability of co-administration of bavdegalutamide with fexofenadine as single doses

Key Findings

- In healthy male volunteers, co-administration of bavdegalutamide with fexofenadine (n=16) resulted in an approximately 2.8-fold higher extent of exposure and 2.4-fold higher peak exposure of fexofenadine compared with fexofenadine alone (N=20)
- Bavdegalutamide-related adverse events (AEs) were reported in 15 (78.9%) participants who received bavdegalutamide co-administered with fexofenadine (n=19), with nausea being the most commonly reported in 10 (52.6%) participants
- No AEs were considered related to fexofenadine

Conclusions

- Co-administration of bavdegalutamide with fexofenadine increased the extent of systemic exposure and the peak exposure of fexofenadine
  - In ongoing clinical studies, bavdegalutamide should not be co-administered with sensitive P-gp substrates or P-gp substrates that have a narrow therapeutic index
- A single dose of fexofenadine 60 mg in combination with bavdegalutamide 420 mg was generally safe and well tolerated by healthy male volunteers

References

1. Békés M, et al. *Nat Rev Drug Discov*. 2022;21(3):181-200. **2**. Petrylak DP, et al. Presented at ESMO; Oct 20-24, 2023; Madrid, Spain. Poster 1803P. **3**. Allegra. Prescribing information. Aventis Pharmaceuticals Inc; 2000. **4**. FDA. Accessed January 12, 2024. https://www.fda.gov/media/161199/download **5**. EMA. Accessed January 12, 2024. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-drug-interactions-revision-1_en.pdf.

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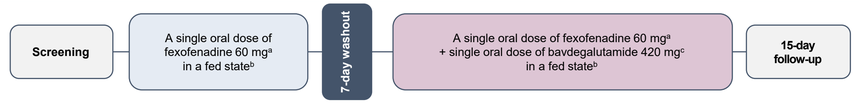
Background

- Bavdegalutamide (ARV-110) is a small-molecule, orally bioavailable PROTAC androgen receptor (AR) degrader[1,2]
- Bavdegalutamide creates a trimer complex with AR and an E3 ubiquitin ligase to directly trigger ubiquitination and subsequent degradation of AR by the proteasome[1]
- In a phase 1/2 study in men with metastatic castration-resistant prostate cancer, bavdegalutamide demonstrated an acceptable safety profile[2]
- In vitro assessment indicated that bavdegalutamide has an inhibitory effect on the efflux transporter pump P-gp and may potentially impact the PK of P-gp substrates (data on file)
- Fexofenadine, an antihistamine,[3] is a known sensitive substrate of P-gp and has been recommended as a probe for intestinal P-gp inhibition by regulatory agencies[4,5]

Methods

- This was a phase 1, open-label, 2-period, fixed-sequence, drug-drug interaction (DDI) study in healthy males (**Figure 1**)
- Blood samples were collected at predetermined time points for PK analyses (**Figure 1**)
- Plasma concentrations were determined by liquid chromatography-tandem mass spectrometry at the bioanalytical laboratory of Q^2 Solutions (Ithaca, NY), with a lower limit of quantification of 1 ng/mL
- Primary PK endpoints were AUC_{last} and C_{max}, and secondary PK endpoints included AUC_{inf} and other PK parameters[a]; safety was also evaluated
  - Safety evaluation included assessment of type, frequency, and severity of AEs and laboratory abnormalities
- Appropriate noncompartmental PK parameters were calculated for plasma fexofenadine concentration-time data using Phoenix® WinNonlin®, and descriptive statistics were used for safety and PK assessments

Figure 1: Study design



In both treatment periods, PK samples for fexofenadine were collected at predose and 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 16, 24, 36, and 48 hours post dose

[a]Administered as a single 60 mg tablet
[b]Participants received a moderate-fat meal of ≈700 calories with ≈35% fat content 30 minutes prior to doses of fexofenadine and bavdegalutamide
[c]Administered as three 140 mg tablets
PK=pharmacokinetics

- Comparisons of the natural log–transformed PK parameters C_{max}, AUC_{last}, and AUC_{inf} of fexofenadine were made to evaluate the PK of fexofenadine + bavdegalutamide (test) vs fexofenadine alone (reference) using mixed effects models, which included treatments as fixed effects and participant as a random effect
  - Inferential results (least squares means [LSMs], difference between LSMs, and 90% CI of the difference) were constructed for the natural log-scale values of each parameter, back transformed, and expressed as the ratio of geometric means

[a]$t_{1/2}$, CL/F, T_{max}, and V_z/F
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 fexofenadine; CL/F=apparent total clearance after extravascular administration; C_{max}=maximum plasma concentration of fexofenadine; $t_{1/2}$=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

Results

Participants

- A total of 20 healthy men participated in the study (**Table 1**), with 16 participants completing both study treatment periods
- Analysis sets were the PK analysis population (fexofenadine 60 mg alone [N=20] and fexofenadine 60 mg + bavdegalutamide 420 mg [n=16]) and safety analysis populations (N=20 and n=19, respectively)

Plasma Concentration-Time Profiles

- Geometric mean plasma concentration-time profiles of fexofenadine with and without bavdegalutamide are presented in **Figure 2**

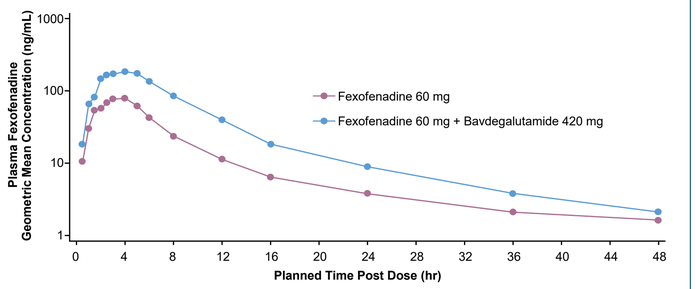
DDI Evaluation

- PK parameters of fexofenadine with and without bavdegalutamide are summarized in **Table 2** and displayed in **Figure 3**
  - AUC_{last} and C_{max} increased ≈2.8-fold and ≈2.4-fold, respectively, with co-administration of bavdegalutamide
  - Mean $t_{1/2}$ was comparable between treatments (11–13 hours), median T_{max} occurred at ≈2–4 hours, and geometric mean values for CL/F and V_z/F decreased 2.6-fold and 2.9-fold, respectively

Safety

- Treatment-emergent AEs occurred in 17 (85.0%) participants who received fexofenadine alone or in combination with bavdegalutamide, and were all grade 1/2
- Bavdegalutamide-related AEs were reported in 15 (78.9%) participants, with nausea being the most common (**Table 3**)
- No AEs were considered related to fexofenadine
- 1 (5.0%) participant discontinued the study after a single dose of fexofenadine 60 mg due to grade 2 AEs of leukopenia and neutropenia

Figure 2: Fexofenadine plasma concentrations vs time on a semi-log scale



Data from PK analysis set: participants who received ≥1 dose of the study drug and had sufficient concentration-time data to reliably determine PK parameters
PK=pharmacokinetics

Table 2: Bavdegalutamide effects on fexofenadine PK

PK parameter	Geometric LS mean: Fexofenadine 60 mg (reference) (N=20)	Geometric LS mean: Fexofenadine 60 mg + bavdegalutamide 420 mg (test) (n=16)	Geometric mean ratio (test/reference): Ratio (%)	Geometric mean ratio (test/reference): 90% CI	Intra-participant CV%
AUC_{inf} (ng*h/mL)	655.9	1754	267.3	237.8–300.6	19.8
AUC_{last} (ng*h/mL)	622.2	1717	276.0	245.1–310.7	20.0
C_{max} (ng/mL)	101.3	241.6	238.5	203.5–279.6	27.1

Data from PK analysis set: participants who received ≥1 dose of the study drug and had sufficient concentration-time data to reliably determine PK parameters
CV=coefficient of variation; LS=least squares; PK=pharmacokinetics

Table 1: Healthy male participant demographics and baseline characteristics

Characteristic	Total (N=20)
Age, median (range), y	33.5 (19–57)
Race, n (%)	
Black or African American	9 (45.0)
White	11 (55.0)
Ethnicity, n (%)	
Hispanic or Latino	4 (20.0)
Not Hispanic or Latino	16 (80.0)
BMI, median (range), kg/m^2	25.2 (20.8–29.9)
Weight, median (range), kg	80.5 (62.5–102.9)

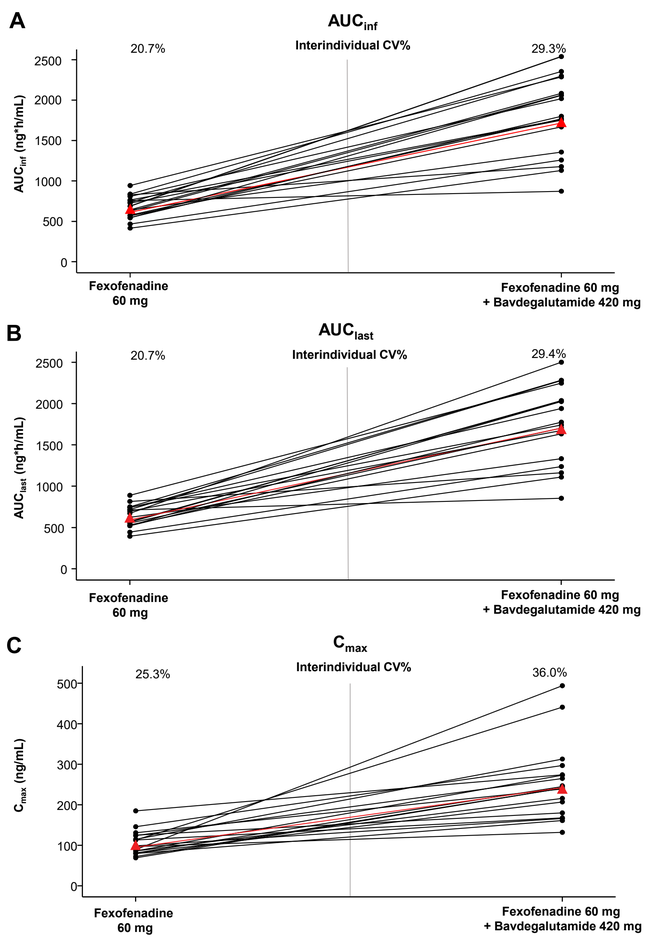
BMI=body mass index

Table 3: Summary of TRAEs[a]

Category, n (%)	Fexofenadine 60 mg + bavdegalutamide 420 mg (n=19)[b]
Any grade TRAE	15 (78.9)[c]
Nausea	10 (52.6)
Headache	4 (21.1)
Vomiting	3 (15.8)
Dizziness	2 (10.5)
Fatigue	2 (10.5)
Upper abdominal pain	2 (10.5)
Abdominal distension	1 (5.3)
Decreased appetite	1 (5.3)
Diarrhea	1 (5.3)
Feeling abnormal	1 (5.3)

Data from safety analysis set: participants who received ≥1 dose of fexofenadine or bavdegalutamide
[a]No TRAEs were reported in the fexofenadine 60 mg alone group
[b]TRAEs in this period were considered related to bavdegalutamide; none were considered related to fexofenadine
[c]No TRAEs grade ≥3 were reported
TRAE=treatment-related adverse event

Figure 3: Pairwise comparisons of bavdegalutamide effects on fexofenadine PK



Data from PK analysis set: participants who received ≥1 dose of the study drug and had sufficient concentration-time data to reliably determine PK parameters. Red data points/line indicate geometric mean for each parameter. Black data points/line indicate individual values
CV=coefficient of variation; PK=pharmacokinetics