

Drug-Drug Interaction Study of the PROteolysis Targeting Chimera (PROTAC) Androgen Receptor Degradar 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 proteasome¹
- In a phase 1/2 study in men with metastatic castration-resistant prostate cancer, bavdegalutamide demonstrated an acceptable safety profile²
- 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 Q² 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 parameters⁶; 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

^at_{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

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	

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

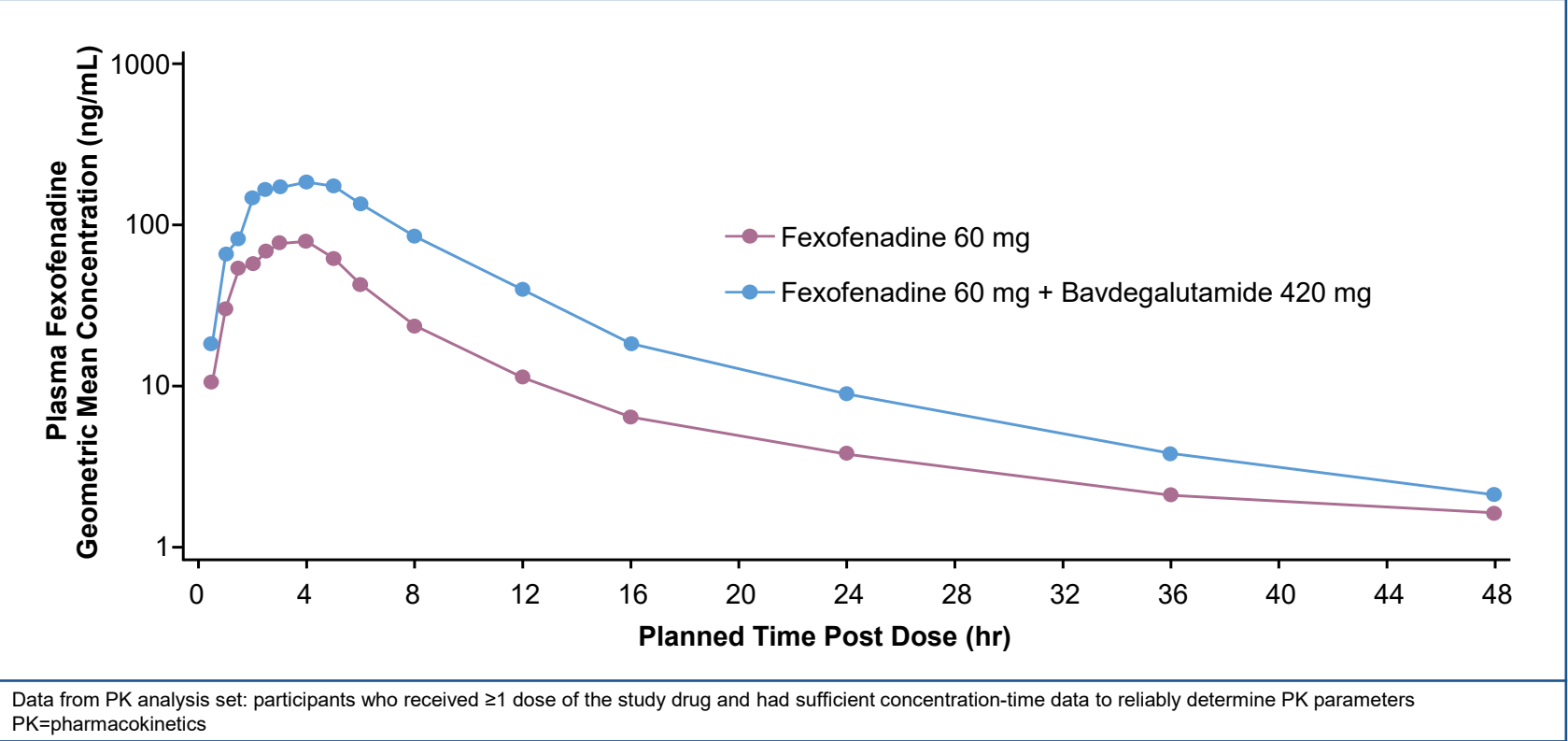


Table 2: Bavdegalutamide effects on fexofenadine PK

PK parameter	Geometric LS mean		Geometric mean ratio (test/reference)		Intra-participant CV%
	Fexofenadine 60 mg (reference) (N=20)	Fexofenadine 60 mg + bavdegalutamide 420 mg (test) (n=16)	Ratio (%)	90% CI	
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

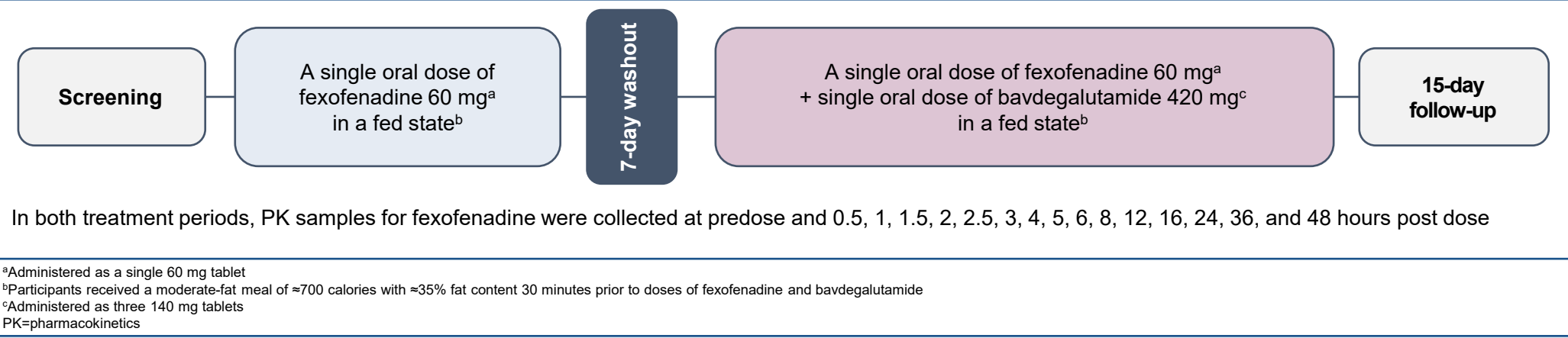
Data from PK analysis set: participants who received ≥1 dose of the study drug and had sufficient concentration-time data to reliably determine PK parameters
CV=coefficient of variation; LS=least squares; PK=pharmacokinetics

Table 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
^aNo TRAEs were reported in the fexofenadine 60 mg alone group
^bTRAEs in this period were considered related to bavdegalutamide; none were considered related to fexofenadine
^cNo TRAEs grade ≥3 were reported
TRAE=treatment-related adverse event

Figure 1: Study design



- 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

Figure 3: Pairwise comparisons of bavdegalutamide effects on fexofenadine PK

