Poster 175

Drug-Drug Interaction Study of the PROteolysis TArgeting Chimera (PROTAC) Androgen Receptor Degrader Bavdegalutamide in Combination With the CYP3A4 Inhibitor Itraconazole in Healthy Volunteers

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Objectives

- To evaluate the impact of multiple dosing of the cytochrome P450 (CYP) 3A4 inhibitor itraconazole 200 mg on the pharmacokinetics (PK) of a single dose of bavdegalutamide (ARV-110) 280 mg in healthy male participants
- To evaluate bavdegalutamide safety with and without itraconazole

Key Findings

- In healthy male volunteers (N=20), co-administration of bavdegalutamide with itraconazole resulted in an approximately 2-fold higher extent of exposure and 1.5-fold higher peak exposure of bavdegalutamide
- The presence of itraconazole also delayed median T_{max} by 2 hours (8.0 hours vs 6.0 hours)
- A total of 7 treatment-related adverse events (TRAEs) were reported, with fatigue (n=3) being most common

Conclusions

- Co-administration of bavdegalutamide with itraconazole increased the peak concentration and extent of systemic exposure of bavdegalutamide; in ongoing clinical studies bavdegalutamide is not co-administered with strong CYP3A4 inhibitors
- A single oral dose of bavdegalutamide 280 mg alone or in combination with itraconazole 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.
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4. EMA. Accessed Jun 26, 2023. https://www.ema.europa.eu/en/investigation-drug-interactions-scientific-guideline#current effective-version---under-revision-section.
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Acknowledgments

We thank the volunteers who participated in this study, as well as the investigators, researchers, and coordinators who contributed to this study. This study is sponsored by Arvinas Androgen Receptor, Inc. Medical writing and editorial support were provided by Nathan Yardley, PhD, and Melissa Austin of Apollo Medical Communications, part of Helios Global Group, and funded by Arvinas Operations, Inc.

Please scan this QR code to **download a copy of the poster** and **supplementary material**

For additional information on bavdegalutamide PK, see poster 163: "The Effect of Food and the Proton Pump Inhibitor Esomeprazole on the Single-Dose Pharmacokinetics and Safety of the PROteolysis TArgeting Chimera (PROTAC) Androgen Receptor Degrader Bavdegalutamide in Healthy Volunteers" presented by J Alicea et al

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American College of Clinical Pharmacology (ACCP) Annual Meeting, Bellevue, WA, September 10–12, 2023

Background

- Bavdegalutamide (ARV-110) is a small molecule, orally bioavailable PROTAC androgen receptor (AR) degrader being investigated as a potential prostate cancer treatment[1,2]
- Bavdegalutamide creates a trimer complex with AR and the cereblon E3 ubiquitin ligase to directly trigger ubiquitination and subsequent degradation of AR by the proteasome[1] (**Supplemental Figure**)
- In a phase 1/2 study in men with metastatic castration-resistant prostate cancer, bavdegalutamide demonstrated an acceptable safety profile[2,3]
- In vitro, bavdegalutamide was cleared through multiple pathways, including hydrolysis and CYP-mediated metabolism; assessment indicated CYP3A4 as the principal isoform contributing to CYP-based metabolism for bavdegalutamide (data on file)
- Itraconazole, a synthetic triazole antifungal agent, is a strong inhibitor of CYP3A4[4,5] and was selected as the perpetrator drug for this study

Methods

- This was a phase 1, open-label, 2-treatment, fixed sequence study in healthy male volunteers (**Figure 1**)
- Blood samples were collected at predetermined time points for PK analyses (**Figure 1**)
- A single dose of bavdegalutamide 280 mg was considered adequate to establish the potential for drug-drug interaction (DDI) with a CYP3A inhibitor and to mitigate the risk of increased bavdegalutamide exposure expected with co-administration of itraconazole
- Plasma concentrations of bavdegalutamide were determined by liquid chromatography-tandem mass spectrometry (LC-MS/MS) at the bioanalytical laboratory of Q^2 Solutions (Ithaca, NY), with lower limit of quantification of 1 ng/mL
- Primary PK endpoints were AUC_{last} and C_{max} and secondary PK endpoints were 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

Figure 1: Study design

In both treatment periods, PK samples for bavdegalutamide were collected at predose and 1, 2, 4, 6, 8, 12, 24, 36, 48, 60, 72, 96, 144, 168, 216, 264, and 312 hours post bavdegalutamide dose

[a]Administered as two 140 mg tablets
[b]Participants received a moderate-fat meal of ≈700 calories 30 minutes prior to the bavdegalutamide dose
[c]Administered as a 200 mg oral solution twice on day 1 and once daily thereafter until day 16; on day 4, itraconazole was administered 30 minutes prior to a moderate-fat meal and 1 hour prior to the single dose of bavdegalutamide
PK=pharmacokinetics

- The appropriate noncompartmental PK parameters were calculated from plasma bavdegalutamide concentration-time data using Phoenix® WinNonlin®, and descriptive statistics were used for safety and PK assessments
  - Calculation of the actual time for plasma bavdegalutamide was with respect to the start of dose administration time of bavdegalutamide on days 1 and 4
- Comparisons of the natural log–transformed PK parameters C_{max}, AUC_{last}, and AUC_{inf} of bavdegalutamide were made to evaluate the relative bioavailability of bavdegalutamide + itraconazole (test) vs bavdegalutamide alone (reference) using an analysis of variance model, which included treatments as fixed effects and subject as a random effect
  - The inferential results (least squares means [LSMs], difference between LSMs, and 90% CI of the difference) were exponentiated to the original scale; geometric LSMs, geometric mean ratios, and 90% CIs were calculated

[a]$T_{1/2}$, CL/F, T_{max}, V_z/F, λ_z, T_{last}, and C_{last}
%AUC_{tr-inf}=percent of AUC_{inf} extrapolated; λ_z=apparent first-order terminal elimination rate constant; AUC_{inf}=area under the concentration-time curve from time 0 extrapolated to infinity; AUC_{last}=area under the curve from time 0 to time of the last measurable concentration of bavdegalutamide; CL/F=apparent total clearance after extravascular administration; C_{last}=observed concentration corresponding to T_{last}; C_{max}=maximum plasma concentration of bavdegalutamide; $T_{1/2}$=apparent first-order terminal elimination half-life; T_{last}=time of last measurable observed concentration; 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 17 participants completing both treatments
- Analysis sets were PK analysis population (bavdegalutamide 280 mg alone [n=19]; bavdegalutamide 280 mg + itraconazole 200 mg [n=17]) and safety analysis population (N=20)

Plasma Concentration-Time Profiles

- Geometric mean plasma concentration-time profiles of bavdegalutamide were similarly shaped for both treatments (**Figure 2**)

DDI Evaluation

- Bavdegalutamide PK parameters with and without itraconazole are summarized in **Table 2** and the **Supplemental Table** and displayed in **Figure 3**
  - C_{max} and AUC increased 1.5-fold and ≈2.0-fold, respectively, with co-administration of itraconazole
  - Mean $T_{1/2}$ was prolonged (by ≈40 hours), median T_{max} was delayed (by ≈2 hours), and geometric mean values for CL/F and V_z/F decreased (by ≈2.0-fold and ≈1.4-fold, respectively)

Safety

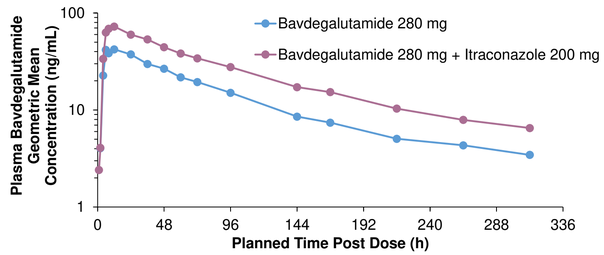
- Treatment-emergent AEs occurred in 10 (50.0%) participants and were all grade 1/2
- A total of 7 TRAEs were reported, with fatigue (10.7%) being most common (**Table 3**)
- 1 (5%) participant in the bavdegalutamide 280 mg alone group discontinued the study due to grade 1 (mild) COVID-19, which was considered unrelated to treatment

Table 1: Healthy male participant demographics and baseline characteristics

Characteristic	Total (N=20)
Age, median (range), y	39.5 (25–65)
Race, n (%)	
White	11 (55.0)
Black or African American	8 (40.0)
Native Hawaiian or other Pacific Islander	1 (5.0)
Ethnicity, n (%)	
Hispanic or Latino	2 (10.0)
Not Hispanic or Latino	18 (90.0)
BMI, median (range), kg/m^2	26.2 (20.5–29.2)
Weight, median (range), kg	84.5 (62.6–94.3)

BMI=body mass index

Figure 2: Bavdegalutamide 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: Itraconazole effects on bavdegalutamide PK

PK parameter	Bavdegalutamide 280 mg (reference) n	Bavdegalutamide 280 mg (reference) Geometric LS mean	Bavdegalutamide 280 mg + itraconazole 200 mg (test) n	Bavdegalutamide 280 mg + itraconazole 200 mg (test) Geometric LS mean	Geometric mean ratio (test/reference) Estimate (%)	Geometric mean ratio (test/reference) 90% CI	Intra-participant CV%
AUC_{inf}[a] (ng*h/mL)	19	4358	13	9000	206.5	149.8–284.8	56.4
AUC_{last} (ng*h/mL)	19	3920	17	7168	182.9	134.3–248.9	57.0
C_{max} (ng/mL)	20	51	17	80	156.7	113.4–216.6	63.4

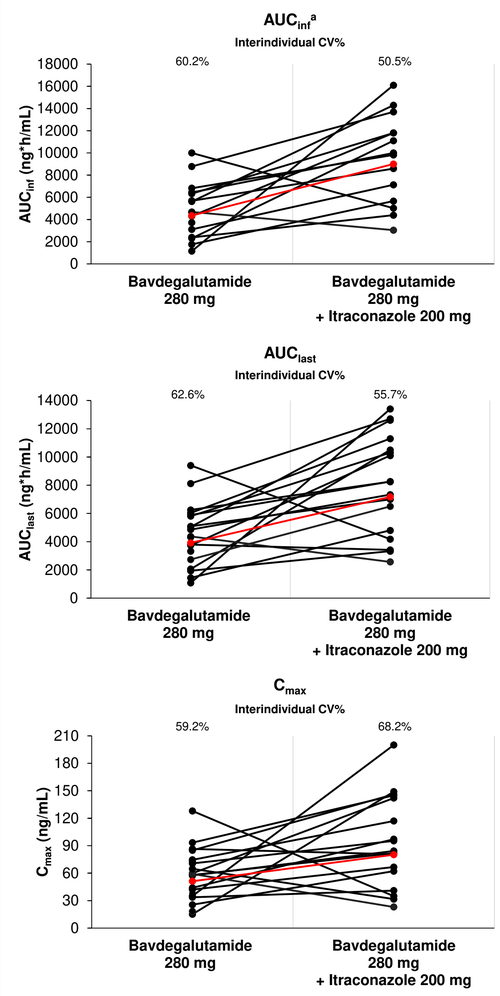
Data from PK analysis set, participants who received ≥1 dose of the study drug and had sufficient concentration-time data to reliably determine PK parameters
[a]Excluding participants whose %AUC_{tr-inf} was >20%
CV=coefficient of variation; LS=least squares; PK=pharmacokinetics

Table 3: Summary of TRAEs

Category, n (%)	Bavdegalutamide 280 mg (N=20)	Bavdegalutamide 280 mg + itraconazole 200 mg (n=17)	Overall (N=20)
Any grade TRAE[a]	7 (53.8)	0	7 (25.0)
Fatigue	3 (23.1)	0	3 (10.7)
Headache	1 (7.7)	0	1 (3.6)
Dizziness	1 (7.7)	0	1 (3.6)
Euphoric mood	1 (7.7)	0	1 (3.6)
Nausea	1 (7.7)	0	1 (3.6)

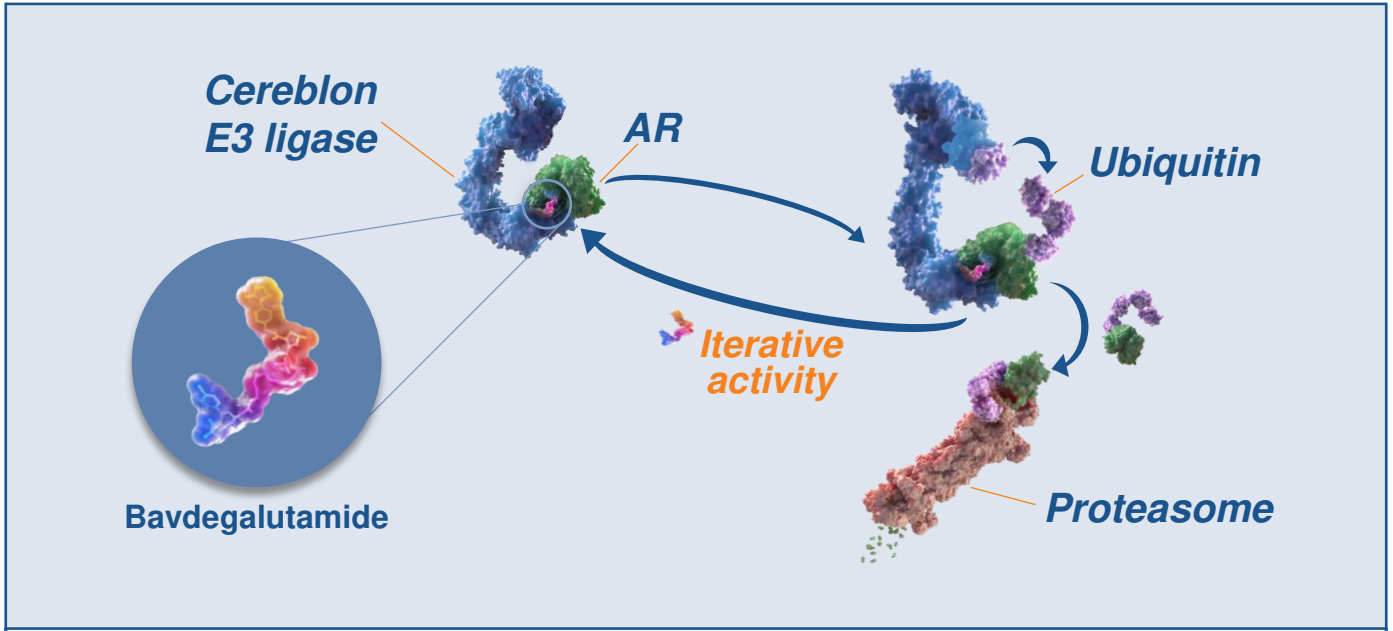
Data from safety analysis set, participants who received ≥1 dose of bavdegalutamide or itraconazole
[a]Data are shown as total number of events considered probably related to study drug, with incidence calculated as proportion of total number of TEAEs (bavdegalutamide 280 mg alone, 13; overall, 28)
TEAE=treatment-emergent adverse event; TRAE=treatment-related AE

Figure 3: Pairwise comparisons of itraconazole effects on bavdegalutamide 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
[a]Excluding participants whose %AUC_{tr-inf} was >20%
CV=coefficient of variation; LS=least square; PK=pharmacokinetics

Supplemental figure: Mechanism of action of bavdegalutamide[a]



Bavdegalutamide creates a trimer complex with AR and an E3 ubiquitin ligase to directly trigger ubiquitination of AR and its subsequent proteasomal degradation. Bavdegalutamide can then be recycled to target additional AR molecules

[a]General PROTAC protein degrader, cereblon E3 ligase, and AR target protein are shown
AR=androgen receptor; PROTAC=PROteolysis TArgeting Chimera
Békés M, et al. *Nat Rev Drug Discov*. 2022;21(3):181-200.

Supplemental table: Bavdegalutamide PK parameters with and without itraconazole

PK parameter	Bavdegalutamide 280 mg			Bavdegalutamide 280 mg + itraconazole 200 mg		
	n	Geometric mean	Interparticipant CV%	n	Geometric mean	Interparticipant CV%
AUC_{inf} (ng*h/mL)[a]	19	4358	60.2	13	9000	50.5
AUC_{last} (ng*h/mL)	19	3920	62.6	17	7171	55.7
C_{max} (ng/mL)	20	51.2	59.2	17	80.2	68.2
C_{last} (ng/mL)	19	3.0	38.1	17	6.5	44.8
T_{max} (h)[b]	20	6.0	4.0–24.0	17	8.0	6.0–12.0
T_{last} (h)[b]	20	312.0	24.0–312.1	17	312.0	312.0–312.1
λ_z (L/h)	19	0.007285	23.6	17	0.005153	29.1
$T_{1/2}$ (h)	19	95.1	23.6	17	134.5	29.1
CL/F (L/h)	19	64.2	60.2	17	32.8	52.3
V_z/F (L)	19	8818.0	52.4	17	6362.0	67.0

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

[a]Excluding participants whose $\%AUC_{tz\text{-}inf}$ was >20%. [b]T_{max} and T_{last} are presented as median (min–max)

$\%AUC_{tz\text{-}inf}$=percent of AUC_{inf} extrapolated; λ_z=apparent first-order terminal elimination rate constant; AUC_{inf}=area under the concentration-time curve from time 0 extrapolated to infinity; AUC_{last}=area under the curve from time 0 to time of the last measurable concentration of bavdegalutamide; CL/F=apparent total clearance after extravascular administration; C_{last}=observed concentration corresponding to T_{last}; C_{max}=maximum plasma concentration of bavdegalutamide; CV=coefficient of variation; PK=pharmacokinetics; $T_{1/2}$=apparent first-order terminal elimination half-life; T_{last}=time of last measurable observed concentration; T_{max}=time to reach C_{max}; V_z/F=apparent volume of distribution during the terminal elimination phase after extravascular administration