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

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Objectives

- To evaluate the effect of food and the proton pump inhibitor (PPI) esomeprazole on the single-dose pharmacokinetics (PK) of bavdegalutamide (ARV-110) in healthy male participants
- To evaluate the safety of bavdegalutamide with and without food and esomeprazole

Key Findings

- Administration of a single dose of bavdegalutamide in the fed state increased C_{max} and AUC_{inf} by 9.7-fold and 6.5-fold, respectively, and delayed the median T_{max} by 4 hours (10 vs 6 hours) compared with the fasted state
- In combination with esomeprazole in the fed state, bavdegalutamide C_{max} and AUC_{inf} were reduced 4.8-fold and 4.1-fold, respectively, vs bavdegalutamide alone, and the median T_{max} was reduced by 2 hours (8 vs 10 hours)
- Treatment-related adverse events (TRAEs) occurred in 6 (33.3%) participants in the fasted cohort, 8 (47.1%) in the fed cohort, and 3 (18.8%) in the esomeprazole cohort, respectively; all were grade 1/2

Conclusions

- Based on these findings, in clinical studies, bavdegalutamide should be administered with food, and concomitant use of PPIs is not recommended
- A single oral dose of bavdegalutamide 280 mg was generally well tolerated by healthy male participants

References

1. Békés M, et al. *Nat Rev Drug Discov.* 2022;21(3):181-200.
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Please scan this QR code to **download a copy of the poster** and **supplementary material**

For additional information on bavdegalutamide PK, see 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" presented by J Alicea et al

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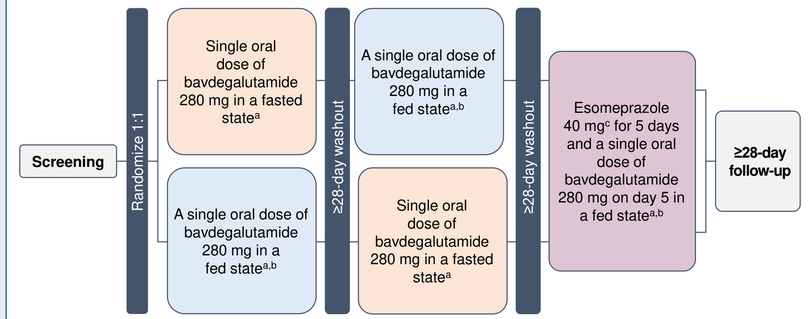
Background

- The small molecule, orally bioavailable PROTAC androgen receptor (AR) degrader bavdegalutamide (ARV-110) is 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 preclinical studies, food increased bavdegalutamide exposure, whereas H_2 blockers decreased exposure
- Esomeprazole (commonly taken for gastroesophageal reflux disease) is a PPI that is used to evaluate gastric pH-dependent drug interactions, as it is expected to provide a near-maximum effect on pH elevation[4,5]

Methods

- This was a phase 1, open-label, 3-treatment, crossover 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 selected to provide an adequate safety margin in healthy participants to mitigate the risk of first administration in this population and the risk of increased bavdegalutamide exposure expected with food
- Plasma concentrations of bavdegalutamide were determined by liquid chromatography-tandem mass spectrometry (LC-MS/MS) performed at the bioanalytical laboratory of Pyxant Labs Inc. (Colorado Springs, CO) with lower limit of quantification of 1 ng/mL
- Primary PK endpoints were AUC_{inf} and C_{max}, and secondary PK endpoints were AUC_{last} and other PK parameters[a]; safety was also evaluated
  - Safety evaluation included assessment of type, frequency, and severity of AEs and laboratory abnormalities
- Plasma PK parameters of the study drugs were estimated using noncompartmental methods with Phoenix® WinNonlin®
- Descriptive statistics were used for safety and PK assessment by treatment
- The effect of food and the effect of the PPI esomeprazole on the AUC_{inf}, C_{max}, and AUC_{last} values of bavdegalutamide were evaluated using a linear mixed-effect model of logarithmically transformed PK parameters
- Geometric least squares means, geometric mean ratios, and 90% CIs are presented

Figure 1: Study design



PK samples for bavdegalutamide were collected at predose and 1, 2, 4, 6, 8, 12, 24, 36, 48, 60, 72, 96, 120, 144, 288, 312, 456, 480, and 648 hours post bavdegalutamide dose

[a]Administered as two 140 mg tablets
[b]Participants received a high-fat meal of 800–1000 calories[6]
[c]Administered as one 40 mg capsule
PK=pharmacokinetics

[a]$T_{1/2}$, CL/F, T_{max}, V_z/F, λ_z, C_{last}, and T_{last}
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 the time of dosing to the 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; $T_{1/2}$=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

- 18 healthy men participated in the study (**Table 1**)
- Analysis sets were PK food effects (n=16), PK PPI effects (n=15), and safety (N=18)
  - 3 participants were additionally excluded from the primary PK analysis due to emesis

Plasma Concentration-Time Profiles

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

Food Effect

- Bavdegalutamide PK parameters for fed vs fasted states are summarized in **Table 2** and the **Supplemental Table** and displayed in **Figure 3**
  - C_{max} and AUC_{inf} increased 9.7-fold and 6.5-fold, respectively, in the fed state compared with fasted state, indicating a notable increase of bavdegalutamide exposure when administered with food
  - Median T_{max} was delayed by 4 hours in the fed state (10 vs 6 hours)
  - Geometric mean $T_{1/2}$ was 9 hours shorter (89 vs 98 hours), and geometric mean CL/F and V_z/F were decreased 7-fold and 7.5-fold, respectively, in the fed state
- Interindividual variability in PK parameters was generally lower under fed vs fasting conditions

PPI Effect (Fed State)

- PK parameters for bavdegalutamide with or without esomeprazole in the fed state are summarized in **Table 3** and **Supplemental Table** and displayed in **Figure 3**
  - C_{max} and AUC_{inf} were reduced 4.8-fold and 4.1-fold, respectively, in combination with esomeprazole
  - Median T_{max} was reduced by 2 hours in combination with esomeprazole (8 vs 10 hours)
  - Geometric mean $T_{1/2}$ was 87 hours with esomeprazole vs 89 hours without esomeprazole, and geometric mean CL/F and V_z/F were increased each by 4-fold
- Interindividual variability in PK parameters was higher with esomeprazole vs without esomeprazole

Safety

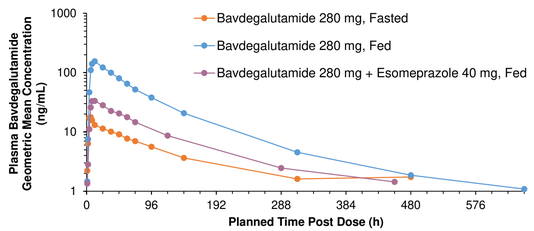
- Overall, 16 (88.9%) participants experienced treatment-emergent AEs; all were grade 1/2
- TRAEs were reported in 11 (61.1%) participants, with nausea being most common; however, the incidence rate was low (**Table 4**)
- 3 participants discontinued the study; 2 participants discontinued due to an AE (grade 2 abscess in the jaw that was investigator assessed as possibly related to the study drugs and grade 1 COVID-19), and 1 participant was lost to follow-up

Table 1: Healthy male participant demographics and baseline characteristics

Characteristic	Total (N=18)
Age, median (range), y	27.5 (23–51)
Race, n (%)	
White	16 (88.9)
Asian	1 (5.6)
Other	1 (5.6)
Ethnicity, n (%)	
Hispanic or Latino	5 (27.8)
Not Hispanic or Latino	13 (72.2)
BMI, median (range), kg/m²	26.3 (19.4–29.9)
Weight, median (range), kg	79.3 (56.4–98.5)

BMI=body mass index

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



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

Table 2: Food effects on bavdegalutamide PK

PK parameter	Bavdegalutamide 280 mg, fasted (reference) n	Bavdegalutamide 280 mg, fasted (reference) Adjusted geometric LS mean	Bavdegalutamide 280 mg, fed (test) n	Bavdegalutamide 280 mg, fed (test) Adjusted geometric LS mean	Adjusted geometric LS mean ratio (test/reference) Estimate (%)	Adjusted geometric LS mean ratio (test/reference) 90% CI	Intra-participant CV%
AUC_{inf} (ng*h/mL)	12	2093.8	14	13563.0	647.8	526.0–797.7	31.3
AUC_{last} (ng*h/mL)	16	1458.2	14	13326.5	913.9	684.3–1220.4	48.9
C_{max} (ng/mL)	16	19.8	14	192.2	972.6	721.7–1310.7	50.7

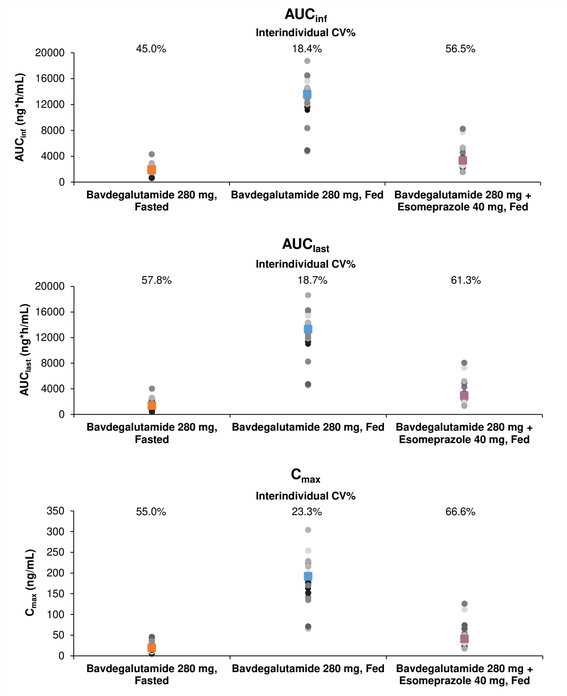
Data from PK analysis set for food effects, treated participants in the PK set who received study drug in fed and fasted treatments and who had sufficient PK data to determine the effects of food on bavdegalutamide PK
CV=coefficient of variation; LS=least squares; PK=pharmacokinetics

Table 3: PPI effects on bavdegalutamide PK

PK parameter	Bavdegalutamide 280 mg, fed (reference) n	Bavdegalutamide 280 mg, fed (reference) Adjusted geometric LS mean	Bavdegalutamide 280 mg + esomeprazole 40 mg, fed (test) n	Bavdegalutamide 280 mg + esomeprazole 40 mg, fed (test) Adjusted geometric LS mean	Adjusted geometric LS mean ratio (test/reference) Estimate (%)	Adjusted geometric LS mean ratio (test/reference) 90% CI	Intra-participant CV%
AUC_{inf} (ng*h/mL)	13	13609.4	14	3333.6	24.5	18.6–32.2	43.4
AUC_{last} (ng*h/mL)	13	13389.8	15	2952.5	22.1	16.6–29.4	46.5
C_{max} (ng/mL)	13	197.4	15	41.2	20.9	15.2–28.6	49.1

Data from PK analysis set for PPI effects, treated participants in the PK set who received bavdegalutamide with and without a PPI under fed condition and who had sufficient PK data to determine the effects of a PPI on bavdegalutamide PK
CV=coefficient of variation; LS=least squares; PK=pharmacokinetics; PPI=proton pump inhibitor

Figure 3: Comparison of bavdegalutamide PK values



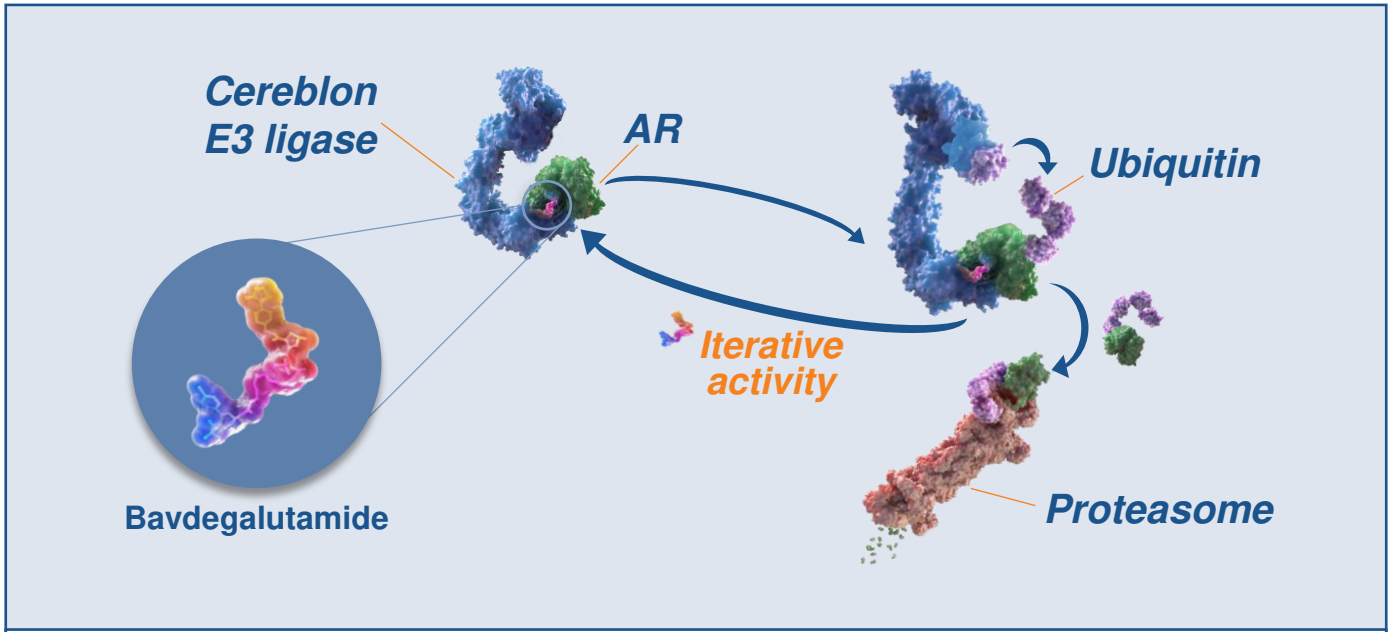
Data from PK analysis set, treated participants who received ≥1 dose of the study drug and had sufficient concentration-time data to reliably determine the primary PK parameters. Colored squares indicate geometric mean for each treatment and parameter. Grey circles indicate individual values
CV=coefficient of variation; PK=pharmacokinetics

Table 4: TRAEs in ≥10% participants overall

Category, n (%)	Bavdegalutamide 280 mg, fasted (N=18)	Bavdegalutamide 280 mg, fed (n=17)	Bavdegalutamide 280 mg + esomeprazole 40 mg, fed (n=16)	Overall (N=18)
Any grade TRAE	6 (33.3)	8 (47.1)	3 (18.8)	11 (61.1)
Nausea	4 (22.2)	5 (29.4)	2 (12.5)	6 (33.3)
Vomiting	1 (5.6)	3 (17.6)	1 (6.3)	3 (16.7)
Headache	1 (5.6)	2 (11.8)	0	3 (16.7)
Dizziness	1 (5.6)	2 (11.8)	0	2 (11.1)

Data from safety analysis set, treated participants who received ≥1 dose of bavdegalutamide or esomeprazole in each treatment period
TRAE=treatment-related adverse event

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

PK parameter	Bavdegalutamide 280 mg, fasted			Bavdegalutamide 280 mg, fed			Bavdegalutamide 280 mg + esomeprazole 40 mg, fed		
	n	Geometric mean	Interparticipant CV%	n	Geometric mean	Interparticipant CV%	n	Geometric mean	Interparticipant CV%
AUC_{inf} (ng*h/mL)	13	1919	45.0	14	13563	18.4	14	3334	56.5
C_{max} (ng/mL)	17	19.4	55.0	14	192.0	23.3	15	41.2	66.6
T_{max} (h)[a]	17	6.0	2.0–8.0	14	10.0	6.0–12.1	15	8.0	6.0–24.0
AUC_{last} (ng*h/mL)	17	1378	57.8	14	13327	18.7	15	2952	61.3
$T_{1/2}$ (h)	11	97.9	14.6	14	89.1	21.5	14	86.9	16.3
CL/F (L/h)	13	146	58.0	14	20.6	21.2	14	84.0	49.9
V_z/F (L)	13	20021	50.4	14	2654	26.3	14	10531	62.0
C_{last} (ng/mL)	17	1.60	36.4	14	1.74	37.2	15	2.14	68.7
T_{last} (h)[a]	17	312	144–482	14	479	437–649	15	292	121–465

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

[a] T_{max} and T_{last} are presented as median (min–max)

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 the time of dosing to the 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; $T_{1/2}$=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