Poster 166

The Effect of Food and the Proton Pump Inhibitor Esomeprazole on the Single-Dose Pharmacokinetics and Safety of ARV-766, a PROteolysis TArgeting Chimera (PROTAC) Androgen Receptor Degrader, in Healthy Volunteers

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Objectives

- To evaluate the effect of food and the proton pump inhibitor (PPI) esomeprazole on single-dose ARV-766 pharmacokinetics (PK) in healthy male participants
- To evaluate the safety of ARV-766 with and without food and esomeprazole

Key Findings

- Administration of a single dose of ARV-766 in the fed vs fasted state increased C_{max} and AUC_{inf} by 3.9-fold and 3.1-fold, respectively, and delayed the median T_{max} by ≈4 hours (12.0 vs 7.8 hours)
- Co-administration of ARV-766 with esomeprazole in the fed state slightly reduced C_{max} and AUC_{inf} of ARV-766 (≈20% and 11%, respectively) and delayed the median T_{max} by 3 hours (10.0 vs 7.0 hours)
- Treatment-related adverse events (TRAEs) occurred in 3 (21.4%) participants in the fed/fasted cohort and 2 (12.5%) in the PPI cohort; TRAEs were primarily grade 1

Conclusions

- ARV-766 as a single oral dose administered in the fasted state, fed state, or in combination with esomeprazole was generally well tolerated by healthy male participants
- Based on these findings, ARV-766 will be administered with food, and use of PPIs will not be restricted but will be monitored closely in clinical studies

References

1. Békés M, et al. *Nat Rev Drug Discov*. 2022;21(3):181-200.
2. Petrylak DP, et al. Presented at ASCO GU; Feb 16-18, 2023; San Francisco, CA.
3. Nexium capsules. Prescribing information. AstraZeneca; 2022.
4. FDA. Accessed July 24, 2023. https://www.fda.gov/media/166156/download.
5. FDA. Accessed July 24, 2023. https://www.fda.gov/media/121313/download.

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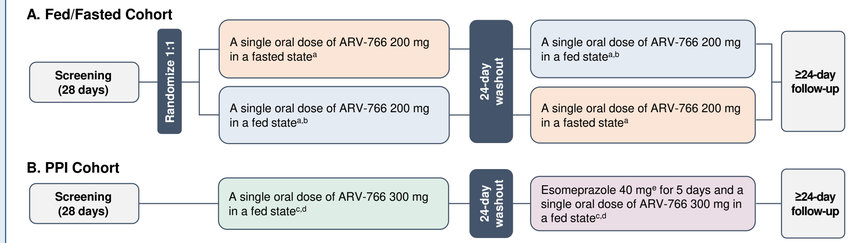
Background

- ARV-766 is a small molecule, orally bioavailable PROTAC androgen receptor (AR) degrader that is being evaluated as a potential treatment for men with prostate cancer[1,2]
- ARV-766 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 preclinical studies, ARV-766 exposure was increased with food and decreased with an acid-reducing agent
- Esomeprazole, a commonly used gastroesophageal reflux disease treatment, is a PPI that raises gastric pH and is used for evaluating pH-dependent drug interactions, as it is expected to provide near-maximum effect on pH elevation[3,4]

Methods

- This phase 1, open-label study included a crossover fed/fasted cohort and a fixed-sequence PPI cohort (**Figure 1**)
- Blood samples were collected at predetermined time points for PK analyses (**Figure 1**)
- Plasma concentrations of ARV-766 were determined by liquid chromatography-tandem mass spectrometry (LC-MS/MS) at the bioanalytical laboratory of Q2 Solutions (Ithaca, NY) with lower limit of quantification of 1 ng/mL
- Primary PK endpoints were AUC_{inf} and C_{max}, and secondary PK endpoints included AUC_{last} and other PK parameters[a]; safety was also evaluated
  - Safety evaluation included assessment of type, frequency, and severity of adverse events (AEs) and laboratory abnormalities
- Plasma PK parameters for the study drugs were estimated using noncompartmental methods with Phoenix® WinNonlin®
- Descriptive statistics were used to summarize PK and safety by treatment
- The natural log–transformed PK parameters AUC_{last}, AUC_{inf}, and C_{max} of ARV-766 were analyzed using a mixed-effects model with treatment as the fixed effect and subject as the random effect
- Geometric least squares means, geometric mean ratios, and 90% CIs are presented

Figure 1: Study design



PK samples for ARV-766 were collected at predose and 1, 3, 5, 6, 6.5, 7, 7.5, 8, 12, 24, 36, 48, 60, 72, 96, 144, 168, 216, 264, and 312 hours post ARV-766 dose

[a]Administered as two 100 mg tablets
[b]Participants received a high-fat meal of 800–1000 calories[5]
[c]Administered as three 100 mg tablets
[d]Participants received a moderate-fat meal of ≈700 calories
[e]Administered as one 40 mg capsule
PK=pharmacokinetics; PPI=proton pump inhibitor

[a]$T_{1/2}$, CL/F, T_{max}, V_z/F, λz, T_{last}, C_{last}, and T_{lag} (fed/fasted cohort only)
λz=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 ARV-766; CL/F=apparent total clearance after extravascular administration; C_{last}=observed concentration corresponding to T_{last}; C_{max}=maximum plasma concentration of ARV-766; $T_{1/2}$=terminal elimination half-life; T_{lag}= delay in achieving T_{max}; 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

- 14 healthy male volunteers were enrolled in the fed/fasted cohort and 16 healthy male volunteers in the PPI cohort (**Table 1**)
- Analysis sets were PK analysis population (N=30; fed/fasted cohort [n=14] and PPI cohort [n=16]) and safety population (N=30)

Plasma Concentration-Time Profiles

- Plasma concentration-time profiles of ARV-766 were similarly shaped for all treatments (**Figure 2**)

Food Effect

- ARV-766 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 3.9-fold and 3.1-fold, respectively, indicating an increase in ARV-766 exposure when administered with food
  - Median T_{max} was delayed by ≈4 hours in the fed state (12.0 vs 7.8 hours)
  - Geometric mean $T_{1/2}$ was ≈6.6 hours shorter (65.3 vs 58.7 hours), and geometric mean CL/F and V_z/F were decreased 3.0-fold and 3.4-fold, respectively, in the fed state
- Interindividual variability in PK parameters was generally lower under fed vs fasted conditions

PPI Effect (Fed State)

- PK parameters of ARV-766 alone vs in combination with esomeprazole are summarized in **Table 3** and the **Supplemental Table** and displayed in **Figure 3**
  - C_{max} and AUC_{inf} were slightly reduced (≈20% and 11%, respectively) in combination with esomeprazole
  - Median T_{max} was delayed by 3 hours (10.0 vs 7.0 hours) in combination with esomeprazole
  - Co-administration of esomeprazole shortened geometric mean $T_{1/2}$ by ≈7 hours (58.4 vs 65.5 hours) and increased geometric mean CL/F and V_z/F slightly (12.1% and 25.7%, respectively)
- Interindividual variability in PK parameters was similar for ARV-766 alone vs co-administration with PPI (**Figure 3**)

Safety

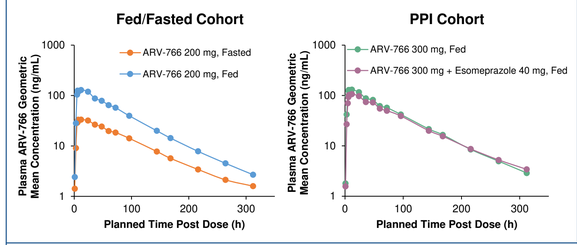
- Treatment-emergent AEs occurred in 5 (35.7%) participants in the food effect cohort and 8 (50.0%) in the PPI effect cohort; all were grade 1/2
- In both cohorts, TRAEs were mostly grade 1 (**Table 4**)
- No participants discontinued due to an AE

Table 1: Healthy male participant demographics and baseline characteristics

Characteristic	Fed/fasted cohort (n=14)	PPI cohort (n=16)
Age, median (range), y	37.0 (23–62)	43.5 (25–56)
Race, n (%)		
White	6 (42.9)[a]	13 (81.3)
Black	7 (50.0)[b]	2 (12.5)
Asian	1 (7.1)	1 (6.3)
Ethnicity, n (%)		
Hispanic or Latino	0	1 (6.3)
Not Hispanic or Latino	14 (100)	15 (93.8)
BMI, median (range), kg/m²	25.2 (20.1–29.6)	25.5 (20.0–29.3)
Weight, median (range), kg	79.5 (57.1–91.0)	77.8 (53.1–99.2)

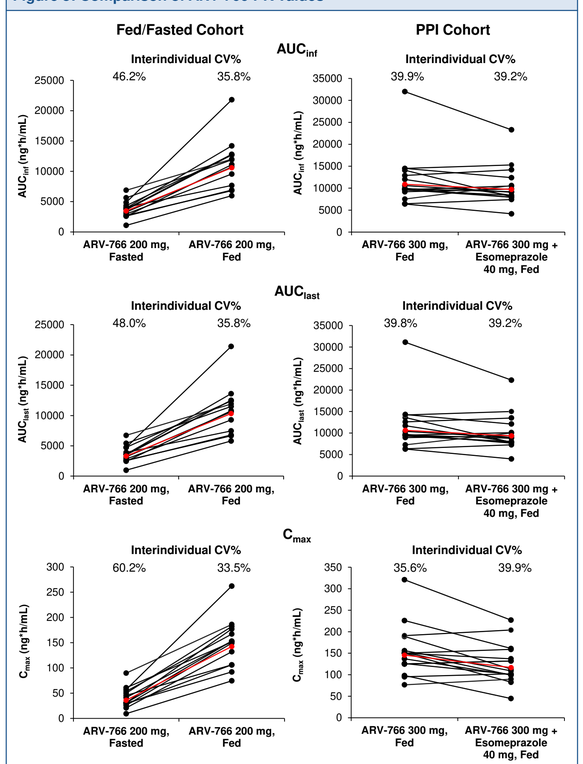
[a]2 (14.3%) participants identified as more than one race
[b]2 (14.3%) participants identified as more than one race
BMI=body mass index; PPI=proton pump inhibitor

Figure 2: ARV-766 plasma concentration vs time on a semi-log scale



Data from PK analysis set, treated participants who have sufficient PK data to provide ≥1 PK endpoint that was defined as primary (AUC_{inf} and C_{max}) and was not excluded due to a protocol deviation relevant to the evaluation of PK or due to PK non-evaluability
PK=pharmacokinetics; PPI=proton pump inhibitor

Figure 3: Comparison of ARV-766 PK values



Data from PK analysis set, treated participants who have sufficient PK data to provide ≥1 PK endpoint that was defined as primary (AUC_{inf} and C_{max}) and was not excluded due to a protocol deviation relevant to the evaluation of PK or due to PK non-evaluability. Red dots/lines indicate geometric mean for each treatment and parameter. Black dots/lines indicate individual values
CV=coefficient of variation; PK=pharmacokinetics; PPI=proton pump inhibitor

Table 2: Food effects on ARV-766 PK

PK parameter	ARV-766 200 mg, fasted (reference) n	ARV-766 200 mg, fasted (reference) Adjusted geometric LS mean	ARV-766 200 mg, fed (test) n	ARV-766 200 mg, fed (test) Adjusted geometric LS mean	Adjusted geometric LS mean ratio (test/reference) Estimate (%)	90% CI	Intra-participant CV%
AUC_{inf} (ng*h/mL)	14	3457	14	10590	306.3	260.1–360.8	24.7
AUC_{last} (ng*h/mL)	14	3302	14	10340	313.0	264.2–370.9	25.6
C_{max} (ng/mL)	14	36	14	142	394.5	323.0–481.7	30.3

Data from PK analysis set, treated participants who have sufficient PK data to provide ≥1 PK endpoint that was defined as primary (AUC_{inf} and C_{max}) and was not excluded due to a protocol deviation relevant to the evaluation of PK or due to PK non-evaluability
CV=coefficient of variation; LS=least squares; PK=pharmacokinetics

Table 3: PPI effects on ARV-766 PK

PK parameter	ARV-766 300 mg, fed (reference) n	ARV-766 300 mg, fed (reference) Adjusted geometric LS mean	ARV-766 300 mg + esomeprazole 40 mg, fed (test) n	ARV-766 300 mg + esomeprazole 40 mg, fed (test) Adjusted geometric LS mean	Adjusted geometric LS mean ratio (test/reference) Estimate (%)	90% CI	Intra-participant CV%
AUC_{inf} (ng*h/mL)	16	10890	16	9716	89.2	80.4–99.0	16.9
AUC_{last} (ng*h/mL)	16	10630	16	9369	88.1	79.5–97.7	16.8
C_{max} (ng/mL)	16	146	16	117	80.2	70.8–90.8	20.3

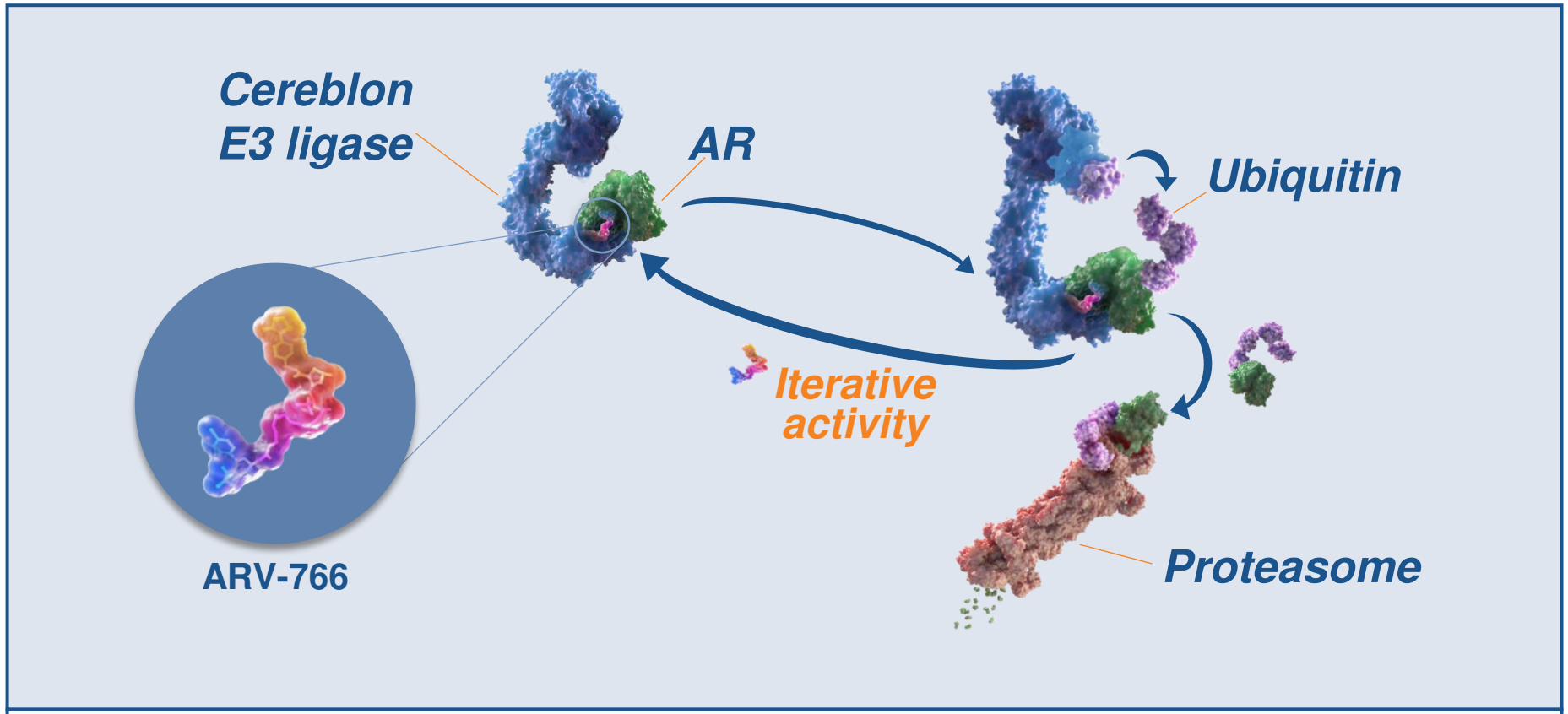
Data from PK analysis set, treated participants who have sufficient PK data to provide ≥1 PK endpoint that was defined as primary (AUC_{inf} and C_{max}) and was not excluded due to a protocol deviation relevant to the evaluation of PK or due to PK non-evaluability
CV=coefficient of variation; LS=least squares; PK=pharmacokinetics; PPI=proton pump inhibitor

Table 4: Summary of TRAEs

Category, n (%)	Fed/fasted cohort ARV-766 200 mg, fasted (n=14)	Fed/fasted cohort ARV-766 200 mg, fed (n=14)	Fed/fasted cohort Overall (n=14)	PPI cohort ARV-766 300 mg, fed (n=16)	PPI cohort ARV-766 300 mg + esomeprazole 40 mg, fed (n=16)	PPI cohort Overall (n=16)
Any grade TRAE	3 (21.4)	0	3 (21.4)	0	2 (12.5)	2 (12.5)
Headache	2 (14.3)	0	2 (14.3)	0	1 (6.3)	1 (6.3)
Dizziness	1 (7.1)	0	1 (7.1)	0	0	0
Fatigue	1 (7.1)	0	1 (7.1)	0	0	0
Increased CRP	0	0	0	0	1 (6.3)[a]	1 (6.3)
Oral hypoesthesia	0	0	0	0	1 (6.3)	1 (6.3)
Oral discomfort	0	0	0	0	1 (6.3)	1 (6.3)

Data from safety analysis set, treated participants who received ≥1 dose of ARV-766 or esomeprazole
TRAEs were grade 1 unless indicated otherwise
[a]Grade 2; was considered by the investigator also to be possibly related to esomeprazole
CRP=C-reactive protein; PPI=proton pump inhibitor; TRAE=treatment-related adverse event

Supplemental figure: Mechanism of action of ARV-766[a]



ARV-766 creates a trimer complex with AR and an E3 ubiquitin ligase to directly trigger ubiquitination of AR and its subsequent proteasomal degradation. ARV-766 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: ARV-766 PK parameters

PK parameter	ARV-766 200 mg, fasted			ARV-766 200 mg, fed			ARV-766 300 mg, fed			ARV-766 300 mg + esomeprazole 40 mg, fed		
	n	Geometric mean	Interparticipant CV%	n	Geometric mean	Interparticipant CV%	n	Geometric mean	Interparticipant CV%	n	Geometric mean	Interparticipant CV%
AUC_{last} (ng*h/mL)	14	3302	48.0	14	10340	35.8	16	10630	39.8	16	9369	39.2
AUC_{inf} (ng*h/mL)	14	3457	46.2	14	10590	35.8	16	10890	39.9	16	9716	39.2
C_{max} (ng/mL)	14	36	60.2	14	142	33.5	16	146	35.6	16	117	39.9
C_{last} (ng/mL)	14	1.5	23.7	14	2.7	54.1	16	2.9	51.5	16	3.4	51.0
T_{max} (h)[a]	14	7.8	5.00–24.03	14	12.0	5.99–24.13	16	7.0	5.97–24.00	16	10.0	6.00–24.00
T_{last} (h)[a]	14	312.0	216.00–312.03	14	312.0	311.98–312.10	16	312.1	311.98–313.13	16	312.0	312.00–312.12
T_{lag} (h)[a]	14	0	0.00–1.01	14	1.0	0.00–1.01	-	-	-	-	-	-
λ_z (1/h)	14	0.01062	12.1	14	0.01182	12.7	16	0.01187	10.7	16	0.01059	11.5
$T_{1/2}$ (h)	14	65.3	12.1	14	58.7	12.7	16	58.4	10.7	16	65.5	11.5
CL/F (L/h)	14	57.9	46.2	14	18.9	35.8	16	27.5	39.9	16	30.9	39.2
V_z/F (L)	14	5450	46.7	14	1598	40.3	16	2320	40.0	16	2916	41.6

Data from PK analysis set, treated participants who have sufficient PK data to provide ≥1 PK endpoint that was defined as primary (AUC_{inf} and C_{max}) and was not excluded due to a protocol deviation relevant to the evaluation of PK or due to PK non-evaluability

[a]T_{max}, T_{last}, and T_{lag} 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 ARV-766; CL/F=apparent total clearance after extravascular administration; C_{last}=observed concentration corresponding to T_{last}; C_{max}=maximum plasma concentration of ARV-766; CV=coefficient of variation; PK=pharmacokinetics; $T_{1/2}$=terminal elimination half-life; T_{lag}= delay in achieving T_{max}; 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