Food and Co-administration of Acid Reducing Agents (ARAs) Have No Clinically Significant Effect on the Pharmacokinetics of Etrumadenant, a Novel Dual Adenosine Receptor Antagonist – Population Pharmacokinetic (PopPK) and Physiologically-Based (PBPK) Modeling Exploration

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BACKGROUND

- Etrumadenant (etruma), is an orally bioavailable, selective, A2a and A2b receptor antagonist that has demonstrated safety and clinical activity in solid tumors when combined with chemo/immunotherapy
- Etruma is a weak base with a pH-dependent solubility, potentially subject to absorption related drug interactions with acid reducing agents (ARAs)
- Many patients on chemotherapy take ARAs, and food restrictions limit patient adherence; a preliminary food effect study indicated the effect of food on etruma PK was minimal
- Across 11 studies, etruma has been co-administered with three types of ARAs: proton pump inhibitors (PPIs), histamine type 2 receptor antagonists (H2RAs), and antacids

OBJECTIVE

- Use PopPK and PBPK modeling to evaluate the effects of ARAs and food on the PK of etrumadenant

METHODS

- PopPK analysis was conducted using nonlinear mixed effects modeling with the NONMEM software, version 7.5
- PBPK analysis was conducted using Simcyp software
  - PBPK model was developed from physiochemical, in vitro experimental and clinical datasets
  - Predictive performance of the model was verified by comparing model PK predictions with the observed clinical PK data of etruma
- Graphical and all other statistical analyses, including evaluation of NONMEM outputs, were performed using R version 4.2.3 for Windows

Figure 1. PopPK Model Structure for Etrumadenant

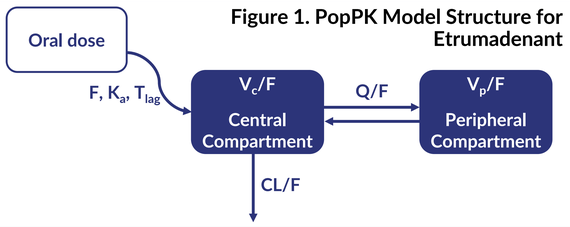


Table 1. Summary of Clinical Studies Evaluated

Study	ARC-1	ARC-2	ARC-3	ARC-4	ARC-5	ARC-6
Patient vs. Healthy	HV	Patient	Patient	Patient	Patient	Patient
N	65	35	44	46	48	111
Food Effect	11 (16.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	6 (5.4%)
pH Modulating Drugs						
Antacids	0 (0%)	15 (42.9%)	7 (15.9%)	22 (47.8%)	13 (27.1%)	31 (27.9%)
H2 Antagonists	0 (0%)	8 (22.9%)	6 (13.6%)	12 (26.1%)	2 (4.2%)	6 (5.4%)
PPI	0 (0%)	10 (28.6%)	15 (34.1%)	10 (21.7%)	13 (27.1%)	26 (23.4%)

Study	ARC-7	ARC-9	ARC-18	ARC-19	ARC-23	Total
Patient vs. Healthy	Patient	Patient	HV	HV	HV	
N	33	133	20	8	24	567
Food Effect	0 (0%)	0 (0%)	0 (0%)	0 (0%)	23 (95.8%)	40 (7.1%)
pH Modulating Drugs						
Antacids	11 (33.3%)	33 (24.8%)	0 (0%)	0 (0%)	1 (4.2%)	133 (23.5%)
H2 Antagonists	4 (12.1%)	28 (21.1%)	0 (0%)	0 (0%)	0 (0%)	66 (11.6%)
PPI	10 (30.3%)	31 (23.3%)	0 (0%)	0 (0%)	0 (0%)	115 (20.3%)

CONCLUSION: Supported by PopPK and PBPK modeling analyses

- **Acid reducing agents (PPIs, H2RAs, and Antacids)** can be co-administered **with etrumadenant**
- **Etrumadenant can be taken** with or without food

RESULTS: PopPK & PBPK Models adequately predict etrumadenant PK profiles for Fed State, or on PPI/other ARA agent

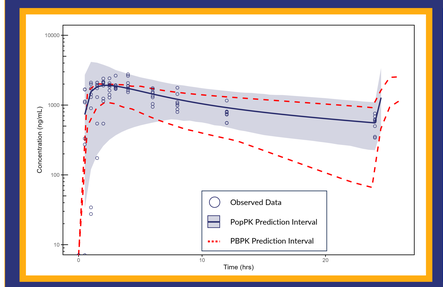


Figure 2. Fed State

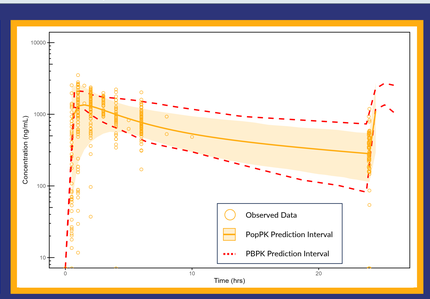


Figure 3. Use of PPI

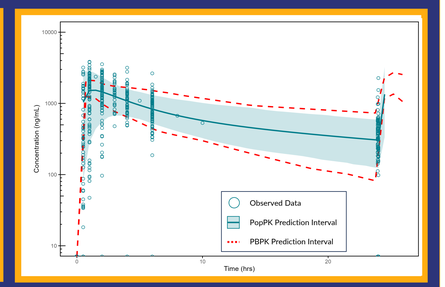


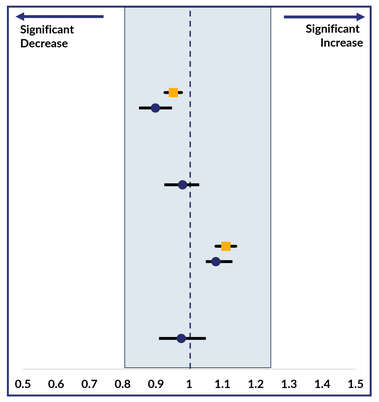
Figure 4. Use of Other ARA

RESULTS: Forest plot of predicted exposure and maximum concentration ratios at steady state based on PopPK/PBPK simulation

Table 2. Summary of PopPK and PBPK Simulation Results

Covariate (Scenario #)	Reference Scenario	PopPK Predicted AUC_{ss} Ratio [Median (90% CI)]	PBPK Predicted AUC_{ss} Ratio [Median (90% CI)]
Effect of PPI (1)	Fasted	**0.90** (0.85-0.95)	**0.95** (0.93-0.98)
Effect of H2RA/Other ARAs (2)	Fasted	**0.98** (0.93-1.03)	NA
Effect of Food (3)	Fasted	**1.08** (1.05-1.13)	**1.11** (1.08-1.14)
Effect of PPI & Food (4)	Fasted	**0.98** (0.91-1.05)	NA
		PopPK Sim.	PBPK Sim.

Figure 5. Steady-state AUC Ratio Relative to Reference



- Fasted patients with concomitant PPI use had a decreased etruma Cmax by 16.7% (90% confidence interval: 11.9-21.4%) and AUC by 10.2% (5.2-15.1%), compared to patients not using PPIs **(Table 2, Scenario 1)**
- Use of H2A or other ARAs decreased etruma Cmax by 6.8% (1.4-12.5%) with no effect on AUC **(Table 2, Scenario 2)**
- Fed condition decreased etruma Cmax by 10.6% (5-16.7%) and increased AUC by 8% (5-13%), compared to fasted patients **(Table 2, Scenario 3)**
- Patients with PPI use and in fed condition had no impact on AUC compared to patients not using PPIs while fasted **(Table 2, Scenario 4)**
- The AUC decrease in patients with PPI use is attenuated with use of food **(Table 2, Scenarios 1 to 4)**
- Effect of PPI and food estimated by PBPK modeling is consistent with PopPK results **(Figure 5, yellow vs. blue)**

Table 3. Parameter Estimates – PopPK Final Model

Parameter	Parameter Estimate [a]	Parameter	Parameter Estimate [a]
CL/F (L/h)	3.74 (3.4)	ARA1 on K_a	0.688 (23.7)
V_c/F (L)	47.1 (3.8)	ARA2 on K_a	0.897 (23.6)
Q/F (L/h)	6.63 (5.0)	ARA3 on K_a	1.46 (18.9)
V_p/F (L)	62.7 (4.7)	ARA1 on relative F[b]	0.584 (4.7)
K_a for fasted (1/h)	3.66 (17.4)	ARA2 on relative F[b]	0.637 (4.6)
TLAG (h)	0.326 (0.2)	ARA3 on relative F[b]	0.650 (3.8)
FED on KA	0.242 (17.8)	ARC-1 Form. on relative F[b]	0.586 (4.2)
FED on relative F[b]	1.109 (2.3)	ARC-1 Form. on ALAG	1.45 (2.7)
Unknown fasting condition on KA	0.389 (15.1)	ARC-19 on F	0.671 (8.9)
Unknown fasting condition on relative F[b]	0.963 (2.4)		
Weight on CL/F	0.366 (18.3)	$\eta_{CL/F}$	32.9 (3.5)
Weight on Vc/F	1.03 (7.0)	$\eta_{Vc/F}$	23.5 (8.0)
AGE on Vc/F	0.287 (15.4)	$\eta_{Vp/F}$	57.3 (7.0)
Weight on Vp/F	0.651 (29.6)	η_{Ka}	120 (5.7)
CP Proportional Error (%CV)	38.0 (1.9)	HV Proportional Error (%CV)	27.5 (2.8)

[a]Reported as typical value estimate (relative standard error); %CV: Coefficient of variation; [b] relative to healthy volunteers; ARA1: Patients with a PPI use; ARA2: Patients with antacid or H2RA and no PPI use; ARA3: Patients without ARA usage; FED: 0=no food effect, 1=food effect; UNK: 0=known fasting, 1=no food restriction; ARC-1 Form: alternative formulation used in study ARC-1; CP: cancer patients; HV: Healthy volunteers; CL/F is apparent clearance; V_c/F is apparent central volume; Q is intercompartmental clearance; V_p is peripheral volume; K_a is absorption rate constant; TLAG is absorption lag time; η is the between subject variability.

Figure 6. Goodness of Fit Plots – PopPK Model

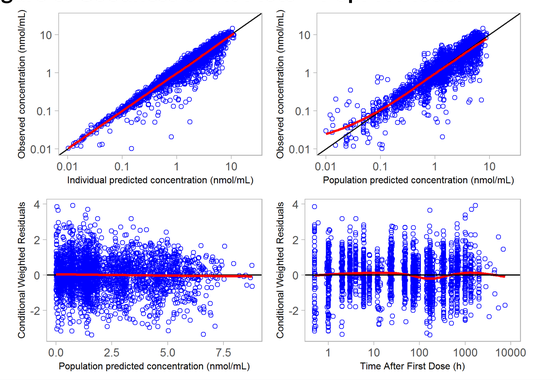


Table 4. Summary of PBPK Model Comparisons

	GMR (%) Observed/Predicted	
Population	Cmax	$AUC_{0\text{-}24h}$
Fed	89/90	108/110
PPI	83/94	90/95