Multiple Elimination Pathways are Responsible for the Elimination of Etrumadenant after Oral Administration of [14C]-Etrumadenant to Humans

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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

OBJECTIVE

- To determine the overall pathways of metabolism and excretion of etruma
- To identify circulating metabolites and assess the pharmacokinetics (PK) of [14C]-etruma

METHODS

Clinical Study Design

- This was a non-randomized, open label study
- Eight healthy subjects received a single oral dose of [14C]-etruma 150 mg containing 3.7 MBq (0.1 mCi) of radioactivity in fasted state on day 1 and remained on site for 12 – 14 days until discharge criteria were met

Metabolic Profiling

- Radioactivity and metabolite identification were performed using liquid chromatography (LC)-fraction collection-radiometric detection and LC-high resolution tandem mass spectrometry, respectively
- For each subject, fecal, urine and plasma samples were pooled for total radioactivity (TRA) analysis and metabolite identification

Physiologically-based Pharmacokinetic (PBPK) Model

- PBPK model for etruma 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

RESULTS

- Eight healthy male subjects with a mean age of 29 years (range: 20 – 40) and mean weight of 79.8 kg (range: 61.2 – 102.9) were enrolled
- Etruma was safe and well tolerated; no clinically significant adverse events, clinical lab findings or changes in vital signs were observed
- [14C]-etruma was quickly absorbed in plasma with a Tmax of 1.5 hours and completely eliminated with T1/2 of 26.6 hours (**Figure 1, Table 1**)

CONCLUSION

- **Etruma is eliminated through multiple metabolic pathways, including CYP3A4-mediated oxidation and glucuronidation; renal excretion is a minor elimination pathway (Table 2)**
- **Etruma, etruma glucuronide (M2, 8.8-fold less potent than etruma), and N-dealkylated etruma (M1, inactive) are the major circulating drug-related compounds (Figure 1, Table 1)**

RESULTS (Continued)

Figure 1: Mean Concentration of Etruma, M1, M2 and Total Radioactivity in Plasma Following a Single 150-mg Dose of [14C]-etruma

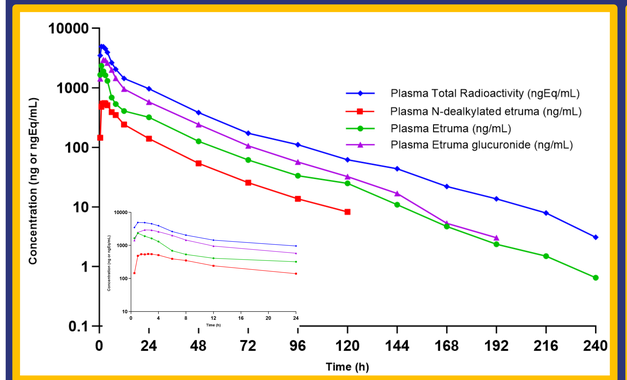
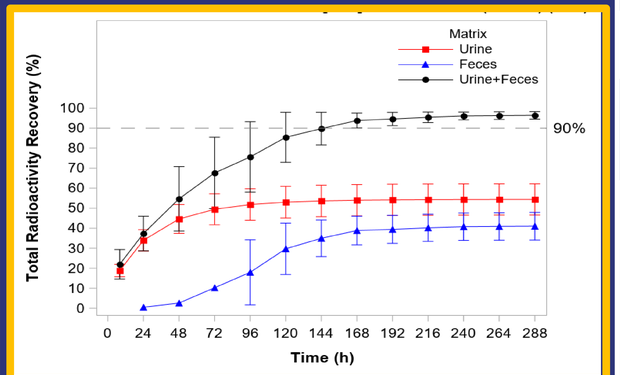
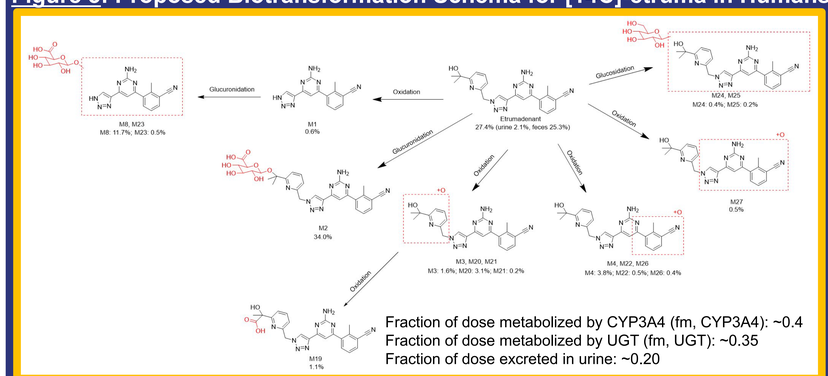


Figure 2: Mean Total Radioactivity Excretion in Urine, Feces and Total Following a Single 150-mg Dose of [14C]-etruma



- Over 90% TRA was recovered in urine and feces combined by 168 hrs (**Figure 2**), with >80% identified (**Figure 3**); the most abundant compound in urine was M2 (33.8%); the most abundant in feces was etruma (25.3%)
- Etruma in feces could come from unabsorbed etruma or de-glucuronidation of M2; M2 at a concentration of 13.69 ug/mL in fecal homogenate was found to be completely converted to parent after 4 hours of incubation at 37°C, indicating that part of fecal etruma could be from M2 de-glucuronidation

Figure 3: Proposed Biotransformation Schema for [14C]-etruma in Humans



- Without enterohepatic recirculation of metabolites, observed data is well captured by PBPK model (**Figure 4**)
- Etruma was eliminated predominantly by metabolism via CYP3A4 and multiple UGT enzymes (**Figure 3**), suggesting a low likelihood of strong drug-drug interaction of etruma with CYPs and other metabolic enzymes

RESULTS (Continued)

Table 1: Summary PK of Etruma, M1, M2 and TRA in Plasma Following a Single 150-mg dose of [14C]-etruma

Parameter	Plasma etruma	Plasma etruma-glucuronide	Plasma N-dealkylated etruma	Plasma TRA
T1/2 (hr)	20.5 (29)	20.8 (33)	27.2 (9)	26.6 (41)
Tmax (hr)	1.0 (0.5-2.0)	2.1 (1.0-3.0)	2.5 (1.0-3.0)	1.5 (1.0-2.1)
Cmax (ng Eq/mL)	2,355 (21)	2,961 (23)	536 (43)	5,051 (11)
AUC0-24 (hr.ng Eq/mL)	16,122 (41)	31,478 (26)	6,460 (41)	49,096 (23)
AUC0-inf (hr.ng Eq/mL)	23,935 (41)	47,138 (25)	10,700 (25)	77,077 (23)

Table 2: Distribution of Etruma and its Metabolites (>5%) in Plasma, Urine and Feces

Compound Code	Identification	% Total Radioactivity in $AUC_{0\text{-}48h}$ Pooled Plasma	Mean % Dose in Urine	Mean % Dose in Feces
Etruma	Parent	31.4	2.1	25.3
M1	N-dealkylated etruma	15.4	-	0.6
M2	Etruma glucuronide	43.2	33.8	0.2
M3	Mono-oxygenated etruma	0.1	1.6	3.8
M8	Glucuronide of N-dealkylated etruma	0.4	11.7	
Total[a,b]		**90.9**	**50.4**	**35.3**

[a]Includes all drug-related compounds regardless of %

[b]A small amount of radioactivity remains unidentified but is accounted for in the overall recovery

Figure 4: Simulated and Observed Plasma Concentration-Time Profile of Single Dose [14C]-etruma 150 mg Oral Solution with LC/MC detection