Limited Drug Interaction Supported by a Clinical Drug Interaction Study and Physiologically Based Pharmacokinetic Modeling of Etrumadenant (AB928), a Novel Dual Adenosine Receptor Antagonist, Under Coadministration with a Strong CYP3A4 and P-glycoprotein Inhibitor (Itraconazole) in Healthy Participants

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BACKGROUND
- Etrumadenant (AB928) is an orally bioavailable selective dual antagonist of the adenosine 2a receptor (A₂aR) and the adenosine 2b receptor (A₂bR) being developed for cancer therapy (Figure 1).
- Most tumors contain high extracellular levels of adenosine, leading to activation of A₂aR on T lymphocytes and A₂bR on myeloid cells and impaired T-cell activation and proliferation.
- Inhibition of ligand-dependent signaling by etrumadenant reverses these immunosuppressive effects without causing any immune activation effects.

METHODS
- PBPK Modelling
- The PBPK model was developed from physicochemical, in vitro data suggesting etrumadenant metabolism is mediated by CYP3A4 (to the dealkylated metabolite) and by CYP2C8 and UDP-glucuronosyltransferase (UGT) to the glucuronide metabolites.
- The model was also in vitro substrates of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) (Figure 1).

OBJECTIVES
- To evaluate the effect of iraconazole (a strong CYP3A4/P-gp inhibitor) on the pharmacokinetics (PK) of etrumadenant by conducting a direct drug-drug interaction (DDI) study in healthy participants.
- To assess the CYP3A4 contribution to overall metabolism and to predict DDI using a physiologically based pharmacokinetic (PBPK) model.

RESULTS
- Following multiple doses of iraconazole:
  - Etrumadenant area under the curve (AUC) and maximum concentration (Cₘₚₙ) increased approximately 82% and 18%, respectively, compared to etrumadenant given alone (Table 1, Figure A).
  - AUCs and Cₘₚₙ of the dealkylated metabolite (metabolism mediated by CYP3A4) increased 5.6- to 7.6-fold respectively, compared to etrumadenant given alone (Figure B).
  - AUCs of the glucuronide metabolite (metabolism mediated by UDP-glucuronosyltransferase) increased 1.5- to 1.7-fold whereas the Cₘₚₙ increased 1.3-fold, compared to etrumadenant given alone (Figure C).

Table 1. Summary of Statistical Comparisons of Plasma Etrumadenant PK Parameters With and Without Itraconazole

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Etrumadenant Alone</th>
<th>Etrumadenant + Itraconazole</th>
<th>GMR (%)</th>
<th>90% Confidence Interval</th>
<th>Intrasubject CV%</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUCₘₚₙ (ng*h/mL)</td>
<td>59,500 / 36,500</td>
<td>118/112 143/140 163/172</td>
<td>144.83-176.40</td>
<td>162.58</td>
<td>19.36</td>
</tr>
<tr>
<td>Cₘₚₙ (ng/mL)</td>
<td>62,400 / 36,800</td>
<td>118/112 143/140 163/172</td>
<td>144.83-176.40</td>
<td>161.61</td>
<td>18.70</td>
</tr>
<tr>
<td>CLR (L/h)</td>
<td>3540 / 3000</td>
<td>118/112 143/140 163/172</td>
<td>144.83-176.40</td>
<td>117.87</td>
<td>13.71</td>
</tr>
<tr>
<td>GMR (%)</td>
<td>1.90</td>
<td>1.90 1.90 1.90</td>
<td>1.90-1.90</td>
<td>1.90</td>
<td></td>
</tr>
</tbody>
</table>

The PBPK model predicted a similar level of interaction as the observed values. The model was then used to simulate changes in exposures with other CYP3A4 inhibitors (Table 2).

Table 2. Summary of PBPK Modeling Comparisons of Plasma Etrumadenant Pharmacokinetic Parameters With and Without Various CYP3A4 Inhibitors

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Geometric LSMAs</th>
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</table>

CONCLUSIONS
- The limited increase (62% increase in AUC) when co-administered with iraconazole indicates that CYP3A4 is partially responsible for the elimination of etrumadenant.
- The minimal increase (18%) in etrumadenant Cₘₚₙ suggests coadministration of a P-gp inhibitor (itraconazole) does not cause meaningful differences in etrumadenant PK.

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Figure 1. Critical Role of the Adenosine Pathway in the Immunosuppressive Tumor Microenvironment

Figure 2. ARC-18 Study Design

Figure 3. (A) Advanced Dissolution, Absorption, and Metabolism Model and (B) Full PBPK Distribution Model

Figure 4. Mean (SD) Plasma Concentration of (A) Etrumadenant 150 mg, (B) Dealkylated Etrumadenant, and (C) Glucuronide Etrumadenant Over Time With and Without Itraconazole

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