Pre-clinical and clinical pharmacology of EPI-7386, an androgen receptor N-terminal domain inhibitor for castration-resistant prostate cancer

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EPI-7386-CS-001: A phase 1, open-label study to evaluate the safety, PK and anti-tumor activity of oral EPI-7386 in patients with mCRPC

All current anti-androgens function through the ligand-binding domain of the androgen receptor (AR)

- Anti-androgen resistance mechanisms generally develop at the ligand binding domain (LBD)

Anitens are small molecules capable of targeting the AR N-terminal domain

- Anitens are active against multiple forms of AR: Wild-type AR, LBD-mutant AR, and splice-variant AR

EPI-7386 is a novel aniten which exhibits high potency, low metabolism, on-target specificity, ease of manufacturing, shelf-life stability and a viable commercial formulation

- EPI-7386 is currently in a Phase 1 First in Human clinical trial

### Part 1a

**Primary objective**
- To evaluate the safety and tolerability of EPI-7386

**Secondary objectives**
- To determine the maximum tolerated dose of EPI-7386
- To define the recommended phase 2 dose of EPI-7386
- To evaluate the PK of EPI-7386 following single- and multiple-dose oral administration
- To assess EPI-7386’s potential for drug-drug interactions
  - By measuring 4β hydroxycholesterol and total cholesterol levels (by LCMS) as an endogenous marker for cytochrome P450 3A induction

### Phase 1, multi-center, open-label, ascending multiple-dose study

First in-human, 2-part study
- Part 1a (dose escalation) and Part 1b (dose expansion)

Patients with metastatic castration-resistant prostate cancer (CRPC) resistant to standard of care treatment:

- Progression on at least 2 approved systemic therapies for mCRPC, including at least one second generation anti-androgen drug

### Part 1a – Dose escalation

- Planned dose levels
  - n = up to 30 patients
  - > 3 months follow up

Now enrolling

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EPI-7386 is a novel aniten which exhibits high potency, low metabolism, on-target specificity, ease of manufacturing, shelf-life stability and a viable commercial formulation

- EPI-7386 is currently in a Phase 1 First in Human clinical trial
EPI-7386 is predicted to achieve high human exposures and a long half-life based upon preclinical projections

### In Vitro Hepatocyte Stability

<table>
<thead>
<tr>
<th>Compound</th>
<th>Human T1/2 (min)</th>
<th>Mouse T1/2 (min)</th>
<th>Rat T1/2 (min)</th>
<th>Dog T1/2 (min)</th>
<th>Monkey T1/2 (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPI-7386</td>
<td>&gt;480</td>
<td>&gt;480</td>
<td>&gt;360</td>
<td>&gt;360</td>
<td>&gt;360</td>
</tr>
</tbody>
</table>

### Animal PK parameter after a single IV dose

<table>
<thead>
<tr>
<th>Species</th>
<th>Sex</th>
<th>Dose (mg/kg)</th>
<th>CL (mL/min/kg)</th>
<th>Vss (L/kg)</th>
<th>t½ (h)</th>
<th>AUC0–24h (ng*h/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD-1 mouse</td>
<td>M</td>
<td>0.5</td>
<td>0.58</td>
<td>0.29</td>
<td>5.86</td>
<td>13,518</td>
</tr>
<tr>
<td>SD rat</td>
<td>M</td>
<td>0.5</td>
<td>1.1</td>
<td>0.446</td>
<td>4.85</td>
<td>7,421</td>
</tr>
<tr>
<td>Beagle dog</td>
<td>M</td>
<td>0.5</td>
<td>0.668</td>
<td>0.74</td>
<td>13.4</td>
<td>13,028</td>
</tr>
</tbody>
</table>

### Estimated human PK parameters

<table>
<thead>
<tr>
<th>Method</th>
<th>IVIVC (hepatocytes)</th>
<th>Allometric scaling</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human clearance (mL/min/kg)</td>
<td>0.28</td>
<td>0.30</td>
</tr>
<tr>
<td>Volume of distribution (L/kg)</td>
<td>0.87</td>
<td>0.8</td>
</tr>
<tr>
<td>Half-life (hrs)</td>
<td>36.50</td>
<td>33.60</td>
</tr>
<tr>
<td>Bioavailability (%)</td>
<td>NA</td>
<td>79.4</td>
</tr>
</tbody>
</table>

### Projection of human PK parameters at steady state based on preclinical data

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</th>
<th>AUC&lt;sub&gt;0–24&lt;/sub&gt; (ng*hr/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>200</td>
<td>6,915</td>
<td>137,278</td>
</tr>
<tr>
<td>400</td>
<td>13,830</td>
<td>274,556</td>
</tr>
<tr>
<td>600</td>
<td>20,748</td>
<td>411,834</td>
</tr>
<tr>
<td>800</td>
<td>27,659</td>
<td>549,113</td>
</tr>
<tr>
<td>1000</td>
<td>34,580</td>
<td>686,390</td>
</tr>
</tbody>
</table>

- Projection of human PK parameters predicts low clearance and a long half-life
- Doses ≥ 600 mg are predicted to achieve an AUC that exceed the AUC needed for anti-tumor activity in mouse xenograft studies
Human PK parameters measured in the 200 mg cohort correlate well with preclinical projections

- Drug accumulation observed with repeat QD dosing; steady state reached after day 8
  - Confirmed EPI-7386 long half life (~24 hrs) in humans, supporting QD dosing
- Average Day 28 AUC ~ 147K is similar to preclinical projections for the AUC (137K) in patients at the 200 mg dose
- Doses ≥ 600 mg of EPI-7386 are projected to achieve the AUC goal of >300K, corresponding to drug exposures in mouse xenograft studies showing antitumor activity
- No signs of CYP3A induction at the 200 mg level, as measured by 4β-OH cholesterol / total cholesterol ratios

Measured PK parameters at 200 mg cohort

<table>
<thead>
<tr>
<th>Dose (mg/day)</th>
<th>Day</th>
<th>N</th>
<th>t1/2 (hr)</th>
<th>T_max (hr)</th>
<th>C_max (ng/mL)</th>
<th>C_last (ng/mL)</th>
<th>AUC_0-24 (ng*h/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>200</td>
<td>1</td>
<td>4</td>
<td>22.0</td>
<td>6.5</td>
<td>3,295</td>
<td>1,808</td>
<td>53,850</td>
</tr>
<tr>
<td></td>
<td>28</td>
<td>3</td>
<td>24.8</td>
<td>6.7</td>
<td>8,020</td>
<td>4,593</td>
<td>146,833</td>
</tr>
</tbody>
</table>

EPI-7386 human PK
EPI-7386-CS-001: Patient treatment history, duration of therapy and safety profile of the 200mg cohort

- Four patients enrolled into cohort
- Three patients evaluable for DLT assessment
  - One patient discontinued before D28 due to disease progression
- Prior lines of treatment for mCRPC: 2 to 7
  - 2 patients received both abiraterone and enzalutamide
  - 3 patients received prior chemotherapy (taxanes)
- 2 patients had high levels of neuroendocrine markers
  - Neuron-specific enolase (NSE) used as a marker

### Safety Assessment

- No DLTs observed
- Possible related adverse events (AEs):

<table>
<thead>
<tr>
<th>Patient</th>
<th>Grade</th>
<th>AE</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>01-001</td>
<td>1</td>
<td>Anemia</td>
<td>Ongoing at time of death</td>
</tr>
<tr>
<td>01-002</td>
<td>2</td>
<td>Hot flashes</td>
<td>Ongoing</td>
</tr>
<tr>
<td>02-001</td>
<td>2</td>
<td>Neutropenia</td>
<td>Resolved</td>
</tr>
<tr>
<td>02-001</td>
<td>1</td>
<td>Hyperkalemia</td>
<td>Resolved</td>
</tr>
<tr>
<td>09-001</td>
<td>1</td>
<td>Weight loss</td>
<td>Ongoing at time of PD</td>
</tr>
</tbody>
</table>
EPI-7386-CS-001: Patient PSA level changes in the 200 mg cohort

- At 200 mg, EPI-7386 levels are still below the optimal target exposures for antitumor efficacy observed in animal models
- PSA response first observed at the end of Cycle 3. Radiologic assessment at 12 weeks showed SD (bone and pelvic lymph nodes)
- Patient 01-002 is scheduled for intra-patient escalation to 400 mg when starting cycle 7
Conclusions

• Human PK parameters projected from preclinical species predicted a low clearance and a long half-life for EPI-7386 i.e. good pharmaceutical properties

• PK parameters at 200 mg confirm the preclinical projections
  o $T_1/2 \sim 24$ hrs with drug accumulation noted through Day 8

• The exposure achieved at 200 mg in the clinic is still below optimal target exposures associated with anti-tumor activity in animal models
  o Serum PSA level decline $> 50\%$ was observed in one patient after 3 cycles (12 weeks) and is ongoing (Cycle 6)

• EPI-7386 was well tolerated at 200 mg with no SAEs observed

• Following the recent 400 mg cohort for safety and tolerability, the 600 mg cohort dosing has been initiated