**Background**

Castration resistant prostate cancer (CRPC) is characterized by high androgen receptor (AR) expression and persistent activation of AR signaling axis by residual tissue androgens (1, 2). Synthesis of testosterone (T) requires a battery of enzymes, the key enzyme being CYP17A1. Inhibiting AR and androgen biosynthesis together may be more effective than inhibiting either alone to treat CRPC (3).

ODM204 is a potent, orally administered investigational nonsteroidal dual inhibitor of CYP17A1 and AR. In vitro, ODM204 shows potential balanced activity both of the targets AR and CYP17. In vivo, ODM204 shows favourable pharmacokinetic/pharmacodynamic (PK/PD) properties in intact male mature monkeys and strong antitumor activity in intact mouse VCaP xenograft model.

**Methods**

**Inhibition of CYP17A1 in vitro:** Conversion of 3α-labeled 17α-hydroxyprogrenolone into dehydroepiandrosterone (DHEA) was studied with a human adrenal cortex cell line (NCI-H295R). Formation of 17α-hydroxyprogesterone from progesterone was tested using human, monkey and rat testicular microsomes.

**AR binding affinity:** The binding affinity to wild type (wt) AR was determined in cytosolic lysates obtained from ventral prostates of castrated rats using a competition binding assay.

**Primate PK/PD:** PK relationships were evaluated in intact male mature monkeys (Macaca fascicularis) of Mauritian origin after single and multiple oral doses of ODM-204 (10, 20, 30 and 60 mg/kg/day) by measuring plasma PK after several time points (1, 2.5, 5, 10, 15 and 24 h). For hormonal analysis, 3 days baseline plasma samples were collected. During the study daily plasma samples (at 5 and 10 h) timepoints for testosterone (T), dehydroepiandrosterone (DHEA), luteinizing hormone (LH), progesterone, aldosterone, and cortisol analysis were collected.

**Pharmacokinetics:** The pharmacokinetic evaluation was performed by using WinNonLin Phoenix version 6.2 methodology.

**Hormonal analysis:** Plasma T, DHEA, progesterone and cortisol were analyzed by RIA (Radio Immune Assay) method provided by Beckmann coulter. Plasma LH and aldosterone were analyzed by in house assays.

**VCaP xenograft:** Tumors were established by subcutaneous injection of VCaP cells into male nude mice. Oral treatment of Abiraterone acetate (Abi) (56.2 mg/kg/day), Enzalutamide (Enza) 20 mg/kg/day, combination of Enza+Abi and ODM-204 60 mg/kg/day was started when the average tumor volume reached ~200 mm³ and was continued for 21-28 days. Data collected from three different experiments, n-number in control group 29, and in treatment groups 9-12.

**Results**

1. **ODM-204 has unique chemical structure**

![ODM-204 structure](image1)

2. **ODM-204 binds to AR and inhibits CYP17A**

![Inhibition of CYP17A1 in H295R cells](image2)

3. **ODM-204 inhibits CYP17A1 in testicular microsomes in vitro**

<table>
<thead>
<tr>
<th>Compound</th>
<th>IC50 (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Human</td>
</tr>
<tr>
<td>ODM-204</td>
<td>22</td>
</tr>
<tr>
<td>Abiraterone</td>
<td>1.3</td>
</tr>
<tr>
<td>Galetamide</td>
<td>9</td>
</tr>
</tbody>
</table>

4. **ODM-204 has favourable PK/PD properties in primates**

- **PK curves (Day 1)**
  - Monkey PK
  - ODM-204 10 mg/kg, ODM-204 20 mg/kg, ODM-204 30 mg/kg
  - Cmax (µM): 3.1, 3.7, 10.2
  - Tmax (h): 2.0, 6.0, 3.5
  - T1/2 (h): 4.05, 6.25, 5.54
  - AUC (0-1h) (µM): 17, 36, 110

- **Hormonal changes in intact male monkey plasma after single doses: fold from baseline**

<table>
<thead>
<tr>
<th>Hormone</th>
<th>ODM-204 10 mg/kg</th>
<th>ODM-204 20 mg/kg</th>
<th>ODM-204 30 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5 h</td>
<td>10 h</td>
<td>5 h</td>
</tr>
<tr>
<td>Testosterone</td>
<td>0.25</td>
<td>0.57</td>
<td>0.32</td>
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<tr>
<td>DHEA</td>
<td>0.74</td>
<td>0.88</td>
<td>0.67</td>
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<tr>
<td>Cortisol</td>
<td>0.96</td>
<td>0.87</td>
<td>0.95</td>
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<tr>
<td>Aldosterone</td>
<td>0.7</td>
<td>0.4</td>
<td>0.4</td>
</tr>
<tr>
<td>LH</td>
<td>2.2</td>
<td>2.1</td>
<td>3.4</td>
</tr>
</tbody>
</table>

**Conclusions**

ODM-204 is a potent, nonsteroidal, orally active, single agent that is a dual inhibitor of CYP17A1 and AR:

- Species specific inhibition of CYP17A1 seen in testicular microsomes.
- Favorable in vivo PK properties in primates (BA %, T %)
- Well tolerated.
- Dose dependent inhibition of T and DHEA after single and multiple oral doses of ODM-204 in intact mature male primates. Only slight changes in cortisol and aldosterone plasma levels.
- Dose dependent increase in LH and progesterone, as expected in intact animals.
- In VCaP xenograft model overexpressing AR, ODM-204 shows prominent and better antitumor activity than enzalutamide, abiraterone, or their combination

Phase I/2 clinical trial (NCT 02344017) is ongoing in Europe.

**References**

1. Chen CD. et al., Nat Med, 2004