**Novel bifunctional inhibitors of xanthine oxidase and URAT1 induce profound hypouricemia in humans**

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**Abstract**

**Background:** We found that a prototype anticytotoxic drug (RLBN1001) induced marked hypouricemia in studies comprising > 350 human subjects. Previous anticytotoxic drugs have shown promise in reducing uric acid (UA) levels in vitro and ex vivo.

**Objectives:** To find that a prototype anticytotoxic drug (RLBN1001) induced marked hypouricemia in studies comprising > 350 human subjects.

**Methods:** We assessed RLBN1001, known human metabolites, and novel compounds developed via recursive syntheses based on iterative knowledge of structure-activity relationships (SARs). We initially assessed whether uric acid production and excretion.

**Results:** This drug was a potent inhibitor of URAT1 but not GLUT9a/b.

**Conclusions:** The prototype, RLBN1001, was a moderate inhibitor of URAT1 (~10-X more potent than lesinurad) and a (very) modest XO inhibitor. Metabolites and derivatives were developed by examining recursive SARs from in vitro assays.

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**Clinical Study**

**Serum Uric Acid (mg/dL)**

<table>
<thead>
<tr>
<th>Dose</th>
<th>Initial Value</th>
<th>Lowest Value</th>
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<tbody>
<tr>
<td>150</td>
<td>6.2</td>
<td>1.0</td>
</tr>
<tr>
<td>200</td>
<td>5.8</td>
<td>0.8</td>
</tr>
<tr>
<td>250</td>
<td>5.3</td>
<td>1.2</td>
</tr>
<tr>
<td>400</td>
<td>4.4</td>
<td>1.2</td>
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</table>

**Low Dose (150 mg/m²) URBN1001**

**High Dose (250 mg/m²) URBN1001**

**Profund hypouricemia (< 1.0 mg/dl) is associated with increased urinary excretion of both UA and oxypurines. This drug was a potent inhibitor of URAT1 but not GLUT9a/b,**

**Background:** We have developed a novel, potential first-line treatment for hyperuricemic patients with gout.

**Methods:** We iteratively synthesized a library of novel analogs and identified new series of unique compounds with strongly enhanced activities that both reduce compound are being optimized with the objective of developing a novel, UA production and enhance UA excretion. Pharmaceutical properties of a lead compound are being optimized with the objective of developing a novel, potential first-line treatment for hyperuricemic patients with gout.

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