**ELVN-001, a Next-Generation, ATP-Competitive ABL1 Tyrosine Kinase Inhibitor for the Treatment of Chronic Myeloid Leukemia**

**INTRODUCTION**

Chronic Myeloid Leukemia (CML) is a myeloproliferative disease that manifests an uncontrolled granulocyte proliferation with a relatively normal differentiation from 80% of patients with CML harboring a reciprocal translocation between chromosomes 9 and 22 within the breakpoint cluster region (BCR) and the abelson tyrosine kinase (ABL) gene.

The result of BCR-ABL1 expression is a fusion protein, BCR-ABL1, which carries tyrosine kinase activity that leads to abnormal activation of downstream signaling pathways, driving abnormal differentiation, growth, and survival of myeloid cells.

**Current state of the disease**

The development of specific tyrosine kinase inhibitors (TKIs) targeting the BCR-ABL1 kinase has improved the outcome for patients with CML. Specifically, 3 TKIs have been approved to treat this disease: imatinib, dasatinib, and nilotinib.

**ELVN-001**

- ELVN-001 is a next-generation, ATP-competitive ABL1 tyrosine kinase inhibitor.
- It shows highly selective kinase profile in vitro and in cells.
- It has a unique binding mode that confers selectivity for activated BCR::ABL1 (and T315I).
- It has low turnover by human hepatocytes and in vitro CYP isoform inhibition data predicting low risk of clinically meaningful drug-drug interactions (DDIs).
- It has marked anti-tumor activity at both 50 mg/kg QD and BID in a BCR::ABL1 WT xenograft.
- It has potential to overcome acquired resistance mutations.

**RESULTS**

**Table 1: ELVN-001 in vitro Profile**

<table>
<thead>
<tr>
<th>Compound</th>
<th>IC50 (nM)</th>
<th>Selectivity (IC50 aminopeptidase/IC50 ABL1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELVN-001</td>
<td>0.04</td>
<td>10000</td>
</tr>
<tr>
<td>Imatinib</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Dasatinib</td>
<td>10</td>
<td>100</td>
</tr>
<tr>
<td>Nilotinib</td>
<td>1</td>
<td>100</td>
</tr>
</tbody>
</table>

**Table 2: ELVN-001 and Asciminib Have Complementary Mutant Profiles**

<table>
<thead>
<tr>
<th>Compound</th>
<th>T415L</th>
<th>T584A</th>
<th>T585P</th>
<th>M287T</th>
<th>M452V</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELVN-001</td>
<td>&lt;1</td>
<td>&gt;100</td>
<td>&gt;100</td>
<td>&gt;100</td>
<td>&gt;100</td>
</tr>
<tr>
<td>Asciminib</td>
<td>&gt;100</td>
<td>&lt;1</td>
<td>&gt;100</td>
<td>&gt;100</td>
<td>&gt;100</td>
</tr>
</tbody>
</table>

**TARGETING CYTOKINES**

- ELVN-001 is effective against both the WT and the T315I mutant BCR::ABL1 both in vitro and in vivo.
- It is highly active against both the WT and the T315I mutant BCR::ABL1 both in vitro and in vivo.
- It has profound selectivity vs the broad kinome in biochemical assays.
- It has high activity against both the WT and the T315I mutant BCR::ABL1 both in vitro and in vivo.
- It has good human clinical PK with a clean safety profile and minimal risk for DDIs.
- It represents a potential best-in-class therapeutic option for patients with CML.

**SUMMARY AND CONCLUSIONS**

ELVN-001 is a next-generation, ATP-competitive ABL1 tyrosine kinase inhibitor that shows highly selective kinase profile in vitro and in cells.

- It has marked anti-tumor activity at both 50 mg/kg QD and BID in a BCR::ABL1 WT xenograft.
- It has potential to overcome acquired resistance mutations.

- It is a promising therapeutic option for patients with CML.

**REPRESENTATIVE REFERENCES**

4. Ba/F3 cells expressing the indicated BCR::ABL1 mutations were grown in the absence of IL-3 and subjected to a MTS-based assay to determine cellular proliferation. The exposures of ELVN-001 at 1 mg/kg (+ABT) vs 50 mg/kg (-ABT) reveal that despite markedly lower C trough at the 1 mg/kg dose, ELVN-001 retains activity.

**Click here to watch the presentation poster**