Trial in Progress: First-in-human study of ELVN-001, a highly selective BCR::ABL1 tyrosine kinase inhibitor, in patients with chronic myeloid leukemia who failed previous TKI therapies

Authors: Timothy P. Hughes, Michael Mercer, Dong-Wha Kim, Susan Gardner, Wei Deng, Yi Rong, Jeremy Colls, Andrea Heitkamp

1 South Australian Health and Medical Research Institute, University of Adelaide, Adelaide, SA, Australia
2 Enliven Therapeutics, Boulder, Colorado, USA
3 Memorial Sloan Kettering Cancer Center, New York, New York, USA
4 South Australian Health and Medical Research Institute, University of Adelaide, Adelaide, SA, Australia
5 Memorial Sloan Kettering Cancer Center, New York, New York, USA
6 Enliven Therapeutics, Boulder, Colorado, USA

INTRODUCTION

Chronic Myeloid Leukemia (CML):
- CML is a myeloproliferative neoplasm characterized by the deregulated production and uncontrolled proliferation of maturing myeloid cells with relatively normal differentiation.

- The BCR::ABL1 oncogene encodes an enzyme, BCR::ABL1 kinase, with constitutive tyrosine kinase activity that activates downstream signaling pathways, leading to abnormal differentiation, growth, and survival of leukemic cells.

Current state of the disease:
- The development of tyrosine kinase inhibitors (TKIs) targeting the BCR::ABL1 kinase have improved the outcomes for patients with CML.
- Life expectancy for newly diagnosed patients with chronic phase (CP) CML now approaches the age-matched general population.

- Less off-target activity may improve safety and tolerability, which may result in a wider therapeutic index for patients with or without the T315I mutation.

Unmet medical needs and challenges to standard of care:
- Approximately 1 in 5 patients switches therapies within the first year and ~40% of patients switch in the first 5 years.

- Therapeutic outcomes and quality of life of patients are affected by adverse events (AEs) or intolerance to existing TKIs, at least in part, due to off-target effects on other tyrosine kinases, such as SRC, PDGFR, c-KIT, PDGFRα (VEGFR2), and CSF-1R.

- Loss of efficacy in patients with CML may be due to point mutations in the BCR::ABL1 kinase which impair TKI binding.

- ELVN-001 is a first-in-human study to evaluate the safety, tolerability, and preliminary anti-CML activity of ELVN-001 in patients with CP-CML with and without T315I mutations.

BACKGROUND AND PRECLINICAL DATA

ELVN-001 binds to the ATP-binding site in the kinase domain of activated BCR::ABL1 (Figure 1). As shown in Figure 2, ELVN-001 is a type 1 binder with the p-loops of BCR::ABL1 protein adopting a very unique “folded-in” conformation. Unlike approved TKIs, ELVN-001 is a highly selective small-molecule inhibitor of BCR::ABL1, which may avoid various AEs associated with approved TKIs due to off-target activity (Table 1). Through this design, ELVN-001 has the potential to be a drug with a wider therapeutic index and provide better efficacy and quality of life to patients. In addition to native BCR::ABL1, ELVN-001 also inhibits many mutations of BCR::ABL1, including the prevalent mutation T315I.

ELVN-001 has a favorable and distinctive pharmacokinetic (PK) profile, which warrants its clinical development. ELVN-001 has a low risk of QTc prolongation and a favorable in vitro drug-drug interaction (DDI) profile. ELVN-001 has a low risk of QTc prolongation as a victim or perpetrator, particularly CYP enzyme-mediated interactions. ELVN-001 is a first-in-human study to evaluate the safety, tolerability, and preliminary anti-CML activity of ELVN-001 in patients with CP-CML with and without T315I mutations.

ELVN-001 is a Selective Active-Site, Active-Form Inhibitor of BCR::ABL1

In vitro

Figure 1. Site of action of ELVN-001 and other BCR::ABL1 protein inhibitors.

ELVN-001 binds to the ATP-binding site in the kinase domain of activated BCR::ABL1 (Figure 1). As shown in Figure 2, ELVN-001 is a type 1 binder with the p-loops of BCR::ABL1 protein adopting a very unique “folded-in” conformation. Unlike approved TKIs, ELVN-001 is a highly selective small-molecule inhibitor of BCR::ABL1, which may avoid various AEs associated with approved TKIs due to off-target activity (Table 1). Through this design, ELVN-001 has the potential to be a drug with a wider therapeutic index and provide better efficacy and quality of life to patients. In addition to native BCR::ABL1, ELVN-001 also inhibits many mutations of BCR::ABL1, including the prevalent mutation T315I.

ELVN-001 has a favorable and distinctive pharmacokinetic (PK) profile, which warrants its clinical development. ELVN-001 has a low risk of QTc prolongation and a favorable in vitro drug-drug interaction (DDI) profile. ELVN-001 has a low risk of QTc prolongation as a victim or perpetrator, particularly CYP enzyme-mediated interactions. ELVN-001 is a first-in-human study to evaluate the safety, tolerability, and preliminary anti-CML activity of ELVN-001 in patients with CP-CML with and without T315I mutations.

TRIAL DESIGN

ELVN-001-101: A Phase 1, Open-label, Multicenter, Dose-escalation, and Expansion Study

Primary Trial Objective:

- To assess the PK profile of ELVN-001 and preliminary efficacy

Secondary Trial Objective:

- Determine the recommended doses for expansion (RDE) and to evaluate the safety and tolerability of ELVN-001

Table 1. ELVN-001 in vitro Profile

<table>
<thead>
<tr>
<th>Drug</th>
<th>IC50 (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELVN-001</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Table 2. Cellular Phosphorylation IC50 (nM)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Primaries</th>
<th>Minors</th>
<th>MLL-AF4/8</th>
<th>c-KIT</th>
<th>FGFR1</th>
<th>FGFR2</th>
<th>FGFR3</th>
<th>FGFR4</th>
<th>PDGFRα</th>
<th>PDGFRβ</th>
<th>SRC</th>
<th>CSF-1R</th>
<th>Src-GRK</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELVN-001</td>
<td>0.3</td>
<td>4.9</td>
<td>24.6</td>
<td>300</td>
<td>300</td>
<td>300</td>
<td>300</td>
<td>300</td>
<td>300</td>
<td>300</td>
<td>300</td>
<td>300</td>
<td>300</td>
</tr>
</tbody>
</table>

Table 3. Kinase Selectivity (100 μM ATP)

<table>
<thead>
<tr>
<th>Drug</th>
<th>BCR::ABL1</th>
<th>c-KIT</th>
<th>PDGFRα</th>
<th>PDGFRβ</th>
<th>FGFR1</th>
<th>FGFR2</th>
<th>FGFR3</th>
<th>FGFR4</th>
<th>SRC</th>
<th>CSF-1R</th>
<th>c-SRC</th>
<th>c-TK</th>
<th>KDR (VEGFR2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELVN-001</td>
<td>0.3</td>
<td>4.9</td>
<td>24.6</td>
<td>300</td>
<td>300</td>
<td>300</td>
<td>300</td>
<td>300</td>
<td>300</td>
<td>300</td>
<td>300</td>
<td>300</td>
<td>300</td>
</tr>
</tbody>
</table>

SUMMARY

- Highly selective small-molecule inhibitor of BCR::ABL1

- Low risk of QTc prolongation and no preclinical cardiotoxicity

- Potentially avoid drug-drug interactions, particularly mediated by CYP enzymes

- NCT05304377

- This study is sponsored by Enliven Therapeutics.