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# First-in-Human Phase I Study of ELVN-001, an Oral, Selective BCR::ABL1 Tyrosine Kinase Inhibitor, in Patients With Chronic Myeloid Leukemia Who Failed Prior Tyrosine Kinase Inhibitors

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## KEY POINTS

- ELVN-001 is a highly selective, small-molecule inhibitor of the active form of BCR::ABL1 that can also target the T315I mutation as well as other clinically relevant mutations conferring TKI resistance
- ELVN-001 is designed to provide a meaningful therapeutic option with a wide therapeutic index and better quality of life to patients with CP-CML with and without the T315I mutation
- ELVN-001-101 is a first-in-human, multicenter, open-label, phase 1a/1b study to evaluate the dosing, safety, tolerability, PK profile, and preliminary efficacy of ELVN-001 in CP-CML patients with and without T315I mutation

## BACKGROUND

- The development of tyrosine kinase inhibitors (TKIs) targeting the BCR::ABL1 kinase has improved outcomes for patients with chronic myeloid leukemia (CML); life expectancy for newly diagnosed patients with chronic phase (CP) CML now approaches the aged-match general population[1]
- Resistance, due in part to point mutations in the BCR::ABL1 kinase that impair TKI binding, or drug efflux transporters, such as breast cancer resistance protein (BCRP), remains a significant challenge[2-4]
  - One of the most frequent mutations is the T315I mutation, which occurs in approximately 20% of patients with resistant CML[5]
- Furthermore, 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[6]

### ELVN-001

- A potent, highly selective, active-form inhibitor of BCR::ABL1 that potentially affords an improved therapeutic index for patients with or without the T315I mutation (**Figure 1**)
- Nonclinical data show that ELVN-001 targets native and T315I-mutant BCR::ABL1 while having favorable pharmacologic and pharmacokinetic (PK) profiles (**Table 1**)
  - ELVN-001 exhibits potent antiproliferative and biomarker (phosphorylated CRKL) inhibition in native BCR::ABL1 and T315I-mutant cell lines in the presence of human serum, which models the attenuating effects of serum protein binding *in vivo*
  - The low hepatic extraction ratio of ELVN-001 predicts good human PK to enable maximum target engagement over the dosing interval
  - *In vitro* CYP isoform inhibition data predict low risk of clinically meaningful drug-drug interactions (DDIs)
- Highly selective vs key off-target kinases KIT, FLT3, PDGFRβ, VEGFR2, and SRC[7] (**Table 2**)
- Preclinical data demonstrate that ELVN-001 exhibits broad activity against a number of clinically relevant BCR::ABL1 resistance mutants (**Table 3**)
  - Importantly, ELVN-001 retains potency versus the myristoyl-pocket mutations A344P and P465S that exhibit marked insensitivity to asciminib and is active against the M244V P-loop mutation and the F359V C-loop mutation, which are clinically relevant asciminib resistance mutations[8,9]

## STUDY DESIGN

- ELVN-001-101 (NCT05304377) is a first-in-human study to determine the safety, PK, and preliminary anti-CML activity of ELVN-001 for patients with CML with and without a T315I mutation (**Figure 2**)
- ELVN-001-101 is currently enrolling at 19 sites globally (**Figure 3**)

### Phase 1a Dose Escalation

- Dose escalation will follow a standard 3+3 design at a starting dose of continuous, oral ELVN-001 at 10 mg/day and escalate to the maximum predicted biologically effective dose in 28-day cycles until treatment failure, disease progression, or unacceptable toxicity
- Up to an additional 30 patients may be enrolled at any dose level that has cleared the 28-day dose-limiting toxicity (DLT) window

### Phase 1b Dose Expansion

- Phase 1b will evaluate ELVN-001 in up to 3 cohorts (n=20 patients each) at the recommended doses for expansion (RDE)

## OBJECTIVES AND ENDPOINTS

### Phase 1a Dose Escalation

**Primary Objectives**
- Determine the RDE of ELVN-001 in patients with CML and patients with T315I-mutated CML
- Evaluate the safety and tolerability of treatment with ELVN-001

**Secondary Objectives**
- Assess PK profile of ELVN-001 in plasma
- Assess preliminary anti-CML activity associated with ELVN-001

**Primary Endpoints**
- DLTs
- Incidence of AEs, laboratory abnormalities, and electrocardiogram (ECG) abnormalities

**Secondary Endpoints**
- PK parameters
- Molecular response, measured by quantitative polymerase chain reaction (qPCR) using the International System of Units

### Phase 1b Dose Expansion

**Primary Objective**
- Evaluate the safety and tolerability of ELVN-001 in patients with CML treated at RDE-1 and RDE-2 and T315I-mutated CML treated at RDE-3

**Secondary Objectives**
- Evaluate the clinical benefit of ELVN-001 in patients with CML (RDE-1 and -2) and T315I-mutated CML (RDE-3)
- Assess PK profile of ELVN-001 in plasma

**Primary Endpoint**
- Incidence of AEs, clinical laboratory abnormalities, and ECG abnormalities in patients with CML treated at RDE-1 and RDE-2, and patients with T315I-mutated CML treated at RDE-3

**Secondary Endpoints**
- Molecular response, measured by qPCR using the International System of Units
- Duration of molecular response
- BCR::ABL1 qPCR ≤1%
- Complete hematologic response
- PK parameters

## INCLUSION/EXCLUSION CRITERIA

### Inclusion Criteria

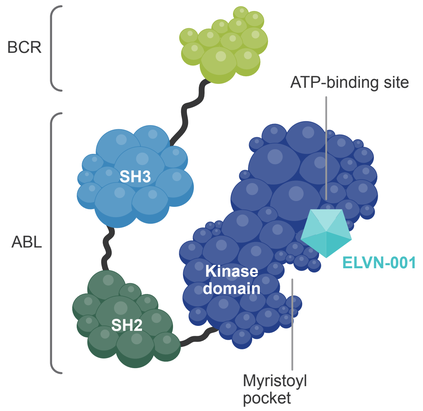
- Aged ≥18 years (patients in Korea must be aged ≥19 years)
- BCR::ABL1 positive CP-CML patients who are intolerant to or have failed (per 2020 European LeukemiaNet Recommendations[10]) available TKIs known to be active for treatment of their CML
- ECOG performance status 0-2
- Prior marrow transplant is allowed
- Adequate hematologic, hepatic, renal, and pancreatic function
- All mutations, including T315I. Patients with E255, Y253H, G250, F317L, or Q252 mutations[a] may enroll with sponsor approval

[a]Less than 10% of patients in the late-line setting.[11]

### Exclusion Criteria

- Treatment with anticancer or anti-CML therapy within 7 days or 5 half-lives, whichever is longer
- Corrected QT interval of >470 ms on baseline ECG

## Figure 1: ELVN-001 Mechanism of Action (MOA)




**Targeted MOA**
- Type 1 small molecule inhibitor of BCR::ABL1 targeting the ATP-binding site of the ABL1 kinase domain that binds to a unique P-loop "folded-in" active conformation of ABL1
- Broad activity against multiple clinically important BCR::ABL1 mutations including T315I

**Kinase specificity**
- Highly specific ABL1 kinase inhibitor with >100× selectivity versus key receptor tyrosine kinase targets KIT, FLT3, PDGFRβ, VEGFR2 and SRC in cells
- Broadly selective against a panel of >370 protein kinases

**Preclinical antitumor activity**
- Demonstrated antiproliferative activity and biomarker suppression in both native and T315I-mutant cell lines
- Potential to overcome resistance mechanisms related to drug efflux transporters such as BCRP
- Low potential for DDIs, allowing for safe and flexible use in combination

## Table 1: ELVN-001 *In Vitro* Profile

| | Asciminib | Ponatinib | Nilotinib | ELVN-001 | |
|---|---|---|---|---|---|
| KCL-22 (BCR::ABL1$^{Native}$) cytotoxicity $IC_{50}$ (50% human serum) [nM] | 7 | 1 | 90 | 19 | *In vitro* activity against both native BCR::ABL1 and T315I cell lines |
| KCL-22 (BCR::ABL1$^{T315I}$) cytotoxicity $IC_{50}$ (50% human serum) [nM] | >1150 | 14 | >10,000 | 131 | |
| K-562 (BCR::ABL1$^{Native}$) cytotoxicity $IC_{50}$ (50% human serum) [nM] | 85 | 4 | 228 | 65 | |
| **K-562 pCRKL $IC_{50}$ (100% human serum) [nM]** | **NA** | **36** | **1080** | **112** | Potential correlation to major molecular response in humans |
| Human hepatocyte stability, extraction ratio | 64[12] | 62 | 62 | 0 | |
| Plasma protein binding (% unbound) | ~2 | <1 | <1 | 40 | |
| Cytochromes P450 (CYPs) (% inhibition at 10 µM) | All <50% | All <50% | 2C8, 2C9, 3A4, 2C19 >50% | All <50% | |
| Human ether-à-go-go-related gene (hERG) $IC_{50}$ [µM] | 25 | 2.3 | 0.13 | >30 | |
| BCRP substrate | Yes | Yes | Yes | **No** | BCRP may play a role in off-target resistance |

**Table 1**: **ELVN-001 *In Vitro* Profile.** KCL-22 and K-562 cells expressing native BCR::ABL1 or BCR::ABL1$^{T315I}$ were used to evaluate *in vitro* activity of ELVN-001. Cytotoxicity $IC_{50}$ values were determined via Cell Titer Glo® after compound treatment for 3 days. pCRKL $IC_{50}$ was measured by an electrochemiluminescence assay (Meso Scale Discovery). All $IC_{50}$ values represent average values from multiple experiments. Hepatocyte stability, plasma protein binding, CYP inhibition, and BCRP substrate assays represent a subset of our absorption, disposition, metabolism, and excretion screening assays.

## Table 2: Off-Target Activity of Approved ABL TKIs vs ELVN-001

| | KIT | FLT3 | PDGFRβ | VEGFR2 | SRC |
|---|---|---|---|---|---|
| **ELVN-001** | >10,000 | >10,000 | >10,000 | >10,000 | >10,000 |
| **Ponatinib** | 30 | 3.8 | 89 | 4.8 | 630 |
| **Nilotinib** | 200 | >10,000 | 720 | 2900 | >10,000 |
| **Dasatinib** | 0.6 | >1000 | 7.1 | >1,000 | 10 |
| **Bosutinib** | 1000 | 4700 | 7900 | >10,000 | 16 |
| **Imatinib** | 82 | >10,000 | 230 | 9600 | >10,000 |

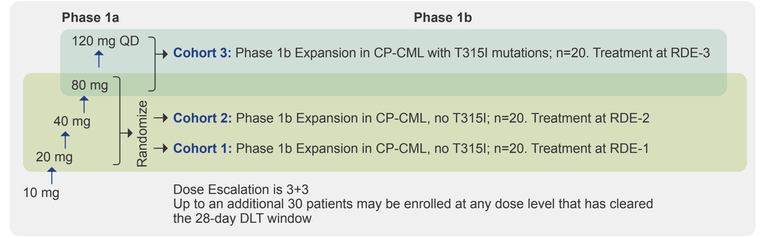
**Table 2: Off-Target Activity of Approved ABL TKIs vs ELVN-001.** ELVN-001 and 5 currently approved ABL TKIs were compared in cell-based assays using relevant cell lines and specific ligands of KIT, VEGFR2, FLT3, and PDGFRβ as well as an engineered line overexpressing exogenously expressed SRC. Inhibition of autophosphorylation of each of these targets was determined by enzyme-linked immunosorbent assay.

## Table 3: ELVN-001 and Asciminib Preclinical Efficacy Against Clinically Relevant BCR::ABL Mutations

| BCR::ABL1 Mutant Ba/F3 Cell Line | Asciminib Fold-Shift vs Native BCR::ABL1 | ELVN-001 Fold-Shift vs Native BCR::ABL1 | |
|---|---|---|---|
| **Native** | 1 (4 nM) | 1 (35 nM) | |
| **M244V** | 1 | 1 | P-loop |
| **G250E** | 0.2 | >10 | |
| **Y253F** | 3 | 8 | |
| **Y253H** | 2 | >10 | |
| **E255K** | 2 | >10 | |
| **T315A** | 2 | 0.5 | ATP pocket |
| **T315I** | 2 | 8 | |
| **F317L** | >10 | >10 | |
| **F317V** | 7 | 0.7 | |
| **M351T** | 7 | 1 | SH2 contact |
| **F359V** | >10 | 1 | |
| **H396P** | >10 | 0.6 | A-loop |
| **A344P** | >10 | 4 | Myristoyl pocket |
| **P465S** | >10 | 4 | |

**Table 3: ELVN-001 and Asciminib Preclinical Efficacy Against Clinically Relevant BCR::ABL1 Mutations.** Ba/F3 cells expressing select BCR::ABL1 mutations were grown in the absence of IL-3 and subjected to a concentration range of either ELVN-001 or asciminib. After 3 days, the antiproliferative activity of these agents was determined employing an MTS-based assay.

## Figure 2: ELVN-001-101 Study Design




## Figure 3: Clinical Trial Sites

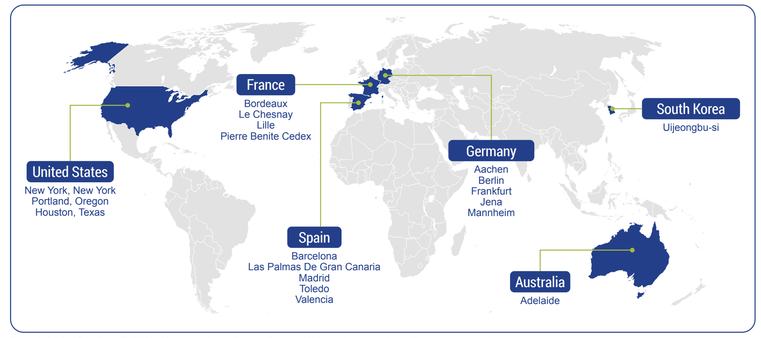



**Figure 3**: **Clinical Trial Sites.** ELVN-001-101 opened for enrollment in February 2022. Locations currently enrolling patients are marked.

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