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,[1] Michael Mauro,[2] Dong-Wook Kim,[3] Susan Branford,[1] Wei Deng,[4] Qi Wang,[4] Helen Collins,[4] Andreas Hochhaus[5]
[1] South Australian Health and Medical Research Institute, University of Adelaide, Adelaide, SA, Australia;
[2] Memorial Sloan Kettering Cancer Center, New York, New York, USA;
[3] Uijeongbu Eulji Medical Center & Leukemia Omics Research Institute, Eulji Universit. Republic of Korea;
[4] Enliven Therapeutics, Boulder, Colorado, USA;
[5] Universitätsklinikum Jena, Germany

INTRODUCTION

Chronic Myeloid Leukemia (CML):

- CML is a myeloproliferative neoplasm characterized by the dysregulated production and uncontrolled proliferation of maturing granulocytes with relatively normal differentiation[1]
- 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 outcome for patients with CML
- Life expectancy for newly diagnosed patients with chronic phase (CP) CML now approaches the aged-match general population[2]

Unmet medical needs and challenges to standard of care:

- Approximately 1 in 5 patients switches therapy within the first year and ~40% of patients switch in the first 5 years[3]
- 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, KDR (VEGFR2), and CSF-1R[4]
- Loss of efficacy in patients with CML may be due to point mutations in the BCR::ABL1 kinase which impair TKI binding[5]
- One of the most frequent mutations is the T315I mutation, which occurs in approximately 20% of patients with resistant CML[6]

Solution:

- ELVN-001 is 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

BACKGROUND AND PRECLINICAL DATA

ELVN-001 binds to the ATP-binding sites 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-loop 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.

A comprehensive nonclinical program has been conducted for ELVN-001. Nonclinical data suggest that ELVN-001 has a favorable absorption, distribution, metabolism, elimination, and 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 DDI as a victim or perpetuator, particularly CYP enzyme–mediated interactions. ELVN-001-101 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

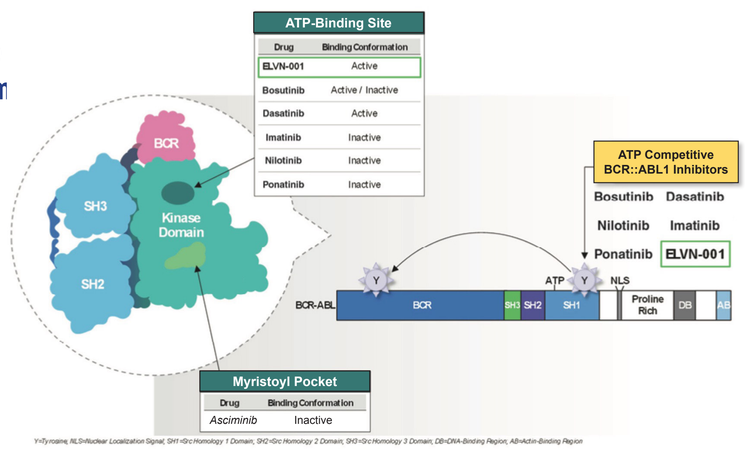


Figure 1. Site of action of ELVN-001 and other BCR::ABL1 inhibitors. All approved small-molecule BCR::ABL1 TKIs (imatinib, bosutinib, nilotinib, dasatinib, and ponatinib) work through interacting with the ATP-binding site, which in turn inhibits the kinase activity. In contrast, asciminib, a fourth-generation TKI, is designed to allosterically inhibit BCR::ABL1 by binding to the myristoyl pocket, which is distal to the active site.

Unique Type 1 Binding Mode Confers Selectivity for Activated BCR::ABL1 (and T315I)

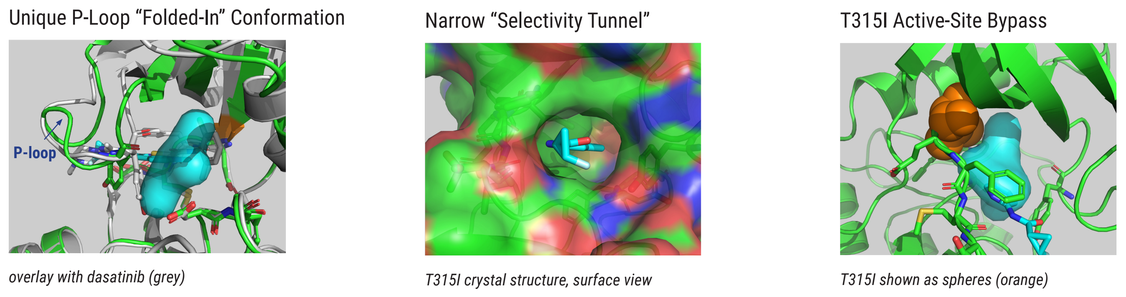


Figure 2. Unique Type 1 Binding Mode to Activated BCR::ABL1. The X-ray structure illustrates that ELVN-001 is a type 1 binder (DFG-in) with the p-loop of the ABL protein adopting a very unique "folded-in" conformation, while accommodating T315I. This is in contrast to promiscuous type 1 inhibitors such as dasatinib which bind the ABL protein in the more common p-loop "extended" conformation, and also clash with T315I.

Table 1. ELVN-001 *in vitro* Profile

	Asciminib	Ponatinib	Nilotinib	ELVN-001
KCL-22 (BCR::ABL1^{wt}) cytotox IC_{50} (50% human serum)	7 nM	1 nM	90 nM	19 nM
KCL-22 (BCR::ABL1^{T315I}) cytotox IC_{50} (50% human serum)	>1,150 nM	14 nM	>10,000 nM	131 nM
K-562 (BCR::ABL1^{wt}) cytotox IC_{50} (50% human serum)	101 nM	4 nM	228 nM	65 nM
K-562 pCRKL IC_{50} (100% human serum)	**NA**	**36 nM**	**1,080 nM**	**112 nM**
HL-60 cytotox IC_{50} (10% FBS)	12,200 nM	366 nM	5,050 nM	3,550 nM
Human hepatocyte stability, extraction ratio	60	62	62	**0**
Plasma protein binding (% unbound)	~2	<1	<1	40
CYPs (% inhibition @ 10 µM)	All <50%	All <50%	2C8, 2C9, 3A4, 2C19 >50%	All <50%
hERG IC_{50}	25 µM	2.3 µM	0.13 µM	>30 µM
Breast Cancer Receptor Protein (BCRP) substrate	Yes	Yes	Yes	**No**

} Potential correlation to MMR in humans

} BCRP may play a role in off-target resistance

- *In vitro* activity against both native BCR::ABL1 and T315I cell lines
- Low hepatic extraction ratio suggests the potential for good human PK, which would enable maximum target coverage over the full 24-hour dosing period
- *In vitro* data suggest low likelihood of clinically meaningful DDI

Table 2. Cellular Phosphorylation IC_{50} (nM)

	cKIT	FLT3wt	PDGFRb	VEGFR2	cSRC
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	2,900	>10,000
Dasatinib	0.6	>1,000	7.1	>1,000	10
Bosutinib	1,000	4,700	7,900	>10,000	16

- ELVN-001 has a selective kinase profile
- 372 kinases screened at 1 µM compound (100 µM ATP)
- Kinases with >50% inhibition selected for IC_{50} determination
- >100x window vs all but 2 kinases profiled
- ELVN-001 is also clean (>10 µM) in an *in vitro* safety panel of >130 receptors

Table 3. Kinase Selectivity (100 µM ATP)

Kinase	IC_{50} (nM)
ABL1	**1**
ABL2/ARG	31
TRKC	41
TNIK	110
LOK/STK10	183
LRRK2	486
FGR	550
ACK1	698
FYN	725
HGK/MAP4K4	973
LCK	>1,000

} Window for ABL2/ARG may result in less toxicity[7]

TRIAL DESIGN

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

Primary Trial Objective:

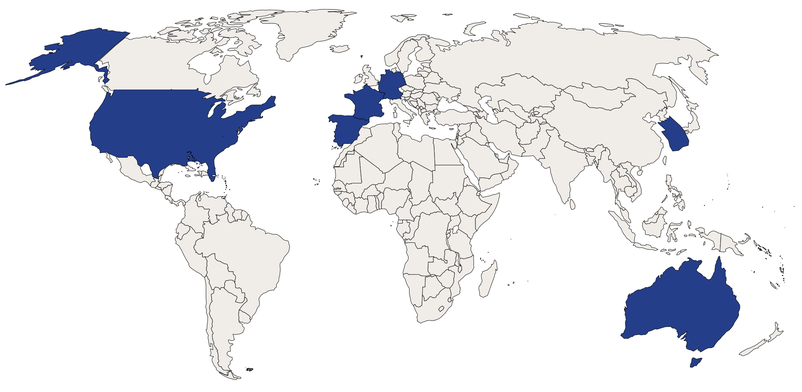
Determine the recommended doses for expansion (RDE) and to evaluate the safety and tolerability of ELVN-001

Secondary Trial Objective:

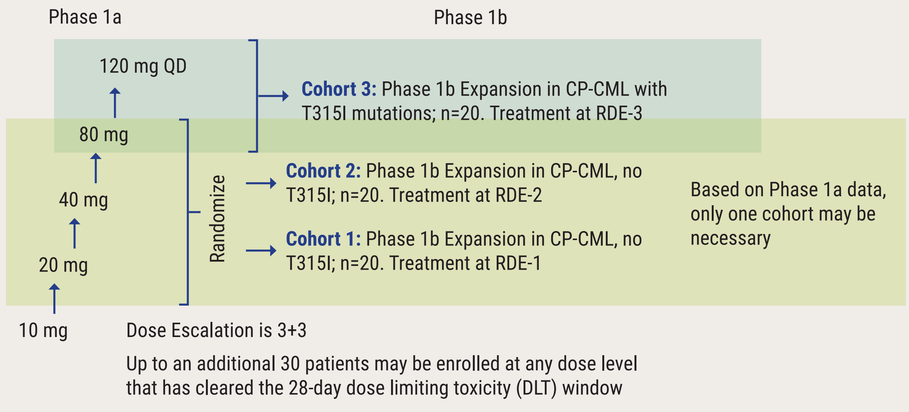
To assess the PK profile of ELVN-001 and preliminary efficacy

Clinical Trial Sites:

- US
- Korea
- Australia
- Spain
- France
- Germany



Study Schema:



Key Inclusion Criteria:

- Adults with CP-CML who are intolerant or have failed (as per European LeukemiaNet 2020 Recommendations)[8] available TKIs known to be active for treatment of their CML TKI therapy
- Eastern Cooperative Oncology Group performance status 0-2
- Adequate bone marrow, renal, and liver function, and resolved adverse effects of prior therapy
- Prior marrow transplant is allowed
- All mutations, including T315I. Patients with E255, Y253H, G250, F317L, or Q252 mutations* may enroll with Sponsor approval

* Less than 10% of patients in the late line setting[9]

Primary Endpoints:

- Incidence of DLT, AEs, electrocardiogram, and lab abnormalities

Secondary Endpoints:

- Molecular response
- PK parameters

SUMMARY

- Highly selective small-molecule inhibitor of BCR::ABL1
- Can target the most common CML mutation, T315I
- Favorable absorption, distribution, metabolism, excretion, and toxicity (ADMET) profile
- Less off-target activity may improve safety and tolerability, which may result in a wider therapeutic index and provide better quality of life to patients
- Low risk of QTc prolongation and no preclinical cardiotoxicity
- Potentially avoid drug-drug interactions, particularly mediated by CYP enzymes

Conclusion:

- Nonclinical data support this first-in-human study, which is evaluating dosing, safety, tolerability, PK profile, and preliminary efficacy of ELVN-001 in CP-CML patients with and without T315I mutation

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