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Preliminary safety and efficacy of ELVN-001, a selective active site inhibitor of BCR::ABL1, in patients with CML driven by atypical fusion transcripts

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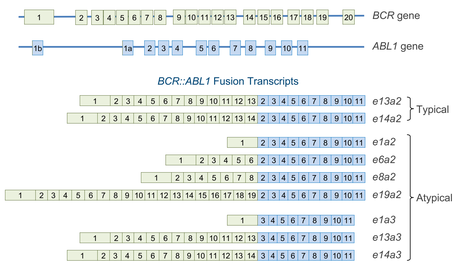
INTRODUCTION

- CML is characterized by a reciprocal translocation of t(9;22)(q34;q11), leading to the *BCR::ABL1* fusion gene[1]
- Most patients have a typical fusion transcript: e13a2 and/or e14a2. However, approximately 2% have an atypical fusion transcript for which there is limited data available about prognosis and response to tyrosine kinase inhibitors (TKIs)
- Emerging data show that atypical *BCR::ABL1* fusions lacking *ABL1* exon a2 (e.g., e13a3, e14a3, and e1a3) cannot be inhibited by allosteric TKIs targeting the myristoyl pocket (e.g., asciminib[2,3])
- In contrast, these translocations should be sensitive to active site TKIs

ELVN-001: Highly Selective ATP-competitive Inhibitor of BCR::ABL1

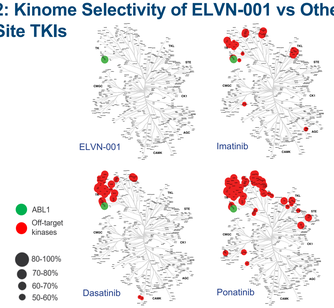
- ELVN-001 binds to a unique P-loop "folded-in" active conformation in the ATP-binding pocket, which:
  - Provides greater selectivity than available ATP inhibitors[4], with potential for better tolerability
  - Creates a narrow tunnel allowing binding to T315I and other mutations
- The ELVN-001 pharmacokinetic profile supports once daily dosing with or without food, which, in addition to low potential for DDIs, addresses key challenges with currently available TKIs
- In patients with typical transcripts, ELVN-001 demonstrated favorable safety and tolerability across a wide range of doses, and encouraging preliminary efficacy was observed

Figure 1: *BCR::ABL1* Genes



NOTE: Figure is for illustrative purposes and not drawn to scale. This is not a full list of all possible atypical transcripts/variants. There are other rare transcripts/variants which are not listed. This figure is adapted from Soverini et al, licensed under CC BY 4.0 (http://creativecommons.org/licenses/by/4.0/).[5]

Figure 2: Kinome Selectivity of ELVN-001 vs Other Active-Site TKIs



Each of these active site TKIs was profiled at 30x their respective ABL1 IC_{50} values against a panel of 377 protein kinases in biochemical assays with 100 nM ATP concentration in the screen (Reaction Biology).

OBJECTIVE

- Here, we first report tolerability and anti-CML activity of ELVN-001 in patients with atypical transcripts enrolled in ENABLE (NCT05304377), a phase 1 study of ELVN-001 in patients with previously treated CML

METHODS

- Patients with atypical transcript received ELVN-001 orally at doses from 20 mg to 160 mg daily in the dose escalation phase of the ENABLE study; intrasubject dose escalation was allowed if specific criteria were met
- Testing for molecular response is non-standardized for atypical transcripts and was therefore assessed locally by individual molecular response[6]; testing for *BCR::ABL1* mutations was done centrally at baseline by NGS

Figure 3: ELVN-001: Phase 1 Trial Design

Key Eligibility Criteria	Phase 1a Dose Escalation and Exploration	Phase 1b Dose Expansion	Key Primary & Secondary Endpoints
• Chronic phase CML • Failed, intolerant to, or not a candidate for available therapies known to be active for treatment of their CML • Typical or atypical transcripts	10 to 160 mg daily	60 to 120 mg daily	• Safety[a] • Molecular response by central qPCR (typical transcripts) • PK parameters **Key Exploratory Endpoint** • Post-treatment changes in *BCR::ABL1* transcript levels in patients with atypical transcripts

[a]Incidence of DLTs, AEs, clinically significant laboratory and ECG abnormalities.

CONCLUSIONS

- The safety of ELVN-001, a novel selective active-site inhibitor of BCR::ABL1, in patients with atypical transcripts was favorable and consistent with the safety profile of ELVN-001 previously reported in patients with typical transcripts[7]
- ELVN-001 demonstrated encouraging anti-CML activity in heavily pre-treated patients with atypical *BCR::ABL1* transcripts; this includes patients with atypical fusions lacking *ABL1* exon a2 (e.g., e1a3, e13a3), which are resistant to TKIs targeting the myristoyl pocket
- Although this is a limited sample size from the Phase 1a of the ENABLE study, these data support further evaluation of ELVN-001 in patients with CML with atypical transcripts
- The phase 1 ENABLE study is active and recruiting (NCT05304377)

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References:
1. Zhou X, et al. Oncol Rep. 2025.
2. Leske IB, et al. Leukemia. 2024.
3. Leyte-Vidal A, et al. Leukemia. 2024.
4. Metz KS. et al. Cell Systems. 2018.
5. Soverini et al. Mol Cancer. 2018.
6. Schäfer et al. J Cancer Res Clin Oncol. 2021.
7. Hochhaus A, et al. EHA 2025.

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RESULTS

Anti-CML Activity in Patient with e13a3 Transcript

Patient Information

- 65-year-old female with primary diagnosis of CML in 2001
- Medical history: right bundle branch block, vulvar carcinoma, pulmonary emphysema, osteoporosis, MDS
- BCR::ABL1 mutations at baseline: none

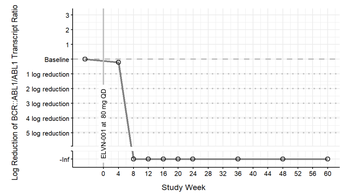
Prior Line of Therapy	Best Transcript Category	Reason for Discontinuation
Hydroxyurea	>10%	Completed
Imatinib	>10%	Lack of efficacy
Nilotinib	>0.1–1%	Lack of efficacy
Dasatinib	>0.01–0.1%	MDS diagnosis
Dasatinib+azacitidine[a]	n/a	SCT
SCT	n/a	n/a[b]
Asciminib+dasatinib	<0.001%	Lack of efficacy
Asciminib	unknown	Lack of efficacy

[a]For evolving MDS.
[b]Molecular relapse.

TEAEs on ELVN-001

- Grade 1 increased cholesterol (NR)

>1 Log Reduction of *BCR::ABL1/ABL1* Transcript Ratio



NOTE: A transcript level of zero indicates the result is below the limit of quantification.

Anti-CML Activity in Patient with e13a3 Transcript

Patient Information

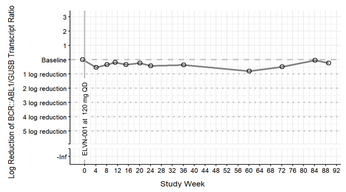
- 61-year-old female with primary diagnosis of CML in 2013
- Medical history: heart failure, stenosis of aortic valve, aortic insufficiency, hypertension, coronary 3-vessel disease, GGT increase, peripheral artery disease (Grade 1)
- BCR::ABL1 mutation at baseline: T315I (100%), S348L (34%)

Prior Line of Therapy	Best Transcript Category	Reason for Discontinuation
Nilotinib	>0.01–0.1%	Lack of efficacy
Ponatinib	>0.01–0.1%	Lack of efficacy
SCT	n/a	n/a
Ponatinib	>0.1–1%	Lack of efficacy
Asciminib	>10%	Lack of efficacy
Ponatinib	>0.001–0.01%	Hypertension
Asciminib	>0.1–1%	Lack of efficacy
Ponatinib	>0.001–0.01%	Cardiomyopathy

TEAEs on ELVN-001

- Grade 1 muscle spasms (R), Grade 2 peripheral arterial occlusive disease (NR), Grade 2 lipase increase (NR), Grade 2 chronic kidney disease (NR), Grade 1 diarrhea (NR)

Stable *BCR::ABL1/GUSB* Transcript Ratio in Patient with T315I Mutation



Anti-CML Activity in Patient with e19a2 Transcript

Patient Information

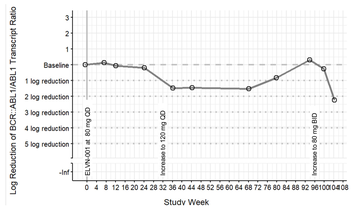
- 40-year-old male with primary diagnosis of CML in 2012
- Medical history: geographic tongue
- BCR::ABL1 mutation at baseline: T315I (100%)

Prior Line of Therapy	Best Transcript Category	Reason for Discontinuation
Nilotinib	>1%–10%	Lack of efficacy
Dasatinib	≤0.0032%	Lack of efficacy
Ponatinib	>0.1%–1%	Lack of efficacy
Asciminib	>0.1%–1%	Lack of efficacy
Asciminib+ponatinib	>0.1%–1%	Lack of efficacy

TEAEs on ELVN-001

- Grade 1 dry skin (R), Grade 2 speech disorder, (NR) Grade 1 vomiting (NR), Grade 1 diarrhea (NR), Grade 2 back pain (NR)

***BCR::ABL1/ABL1* Transcript Ratio in Patient with T315I Mutation**



Anti-CML Activity in Patient with e1a3 Transcript

Patient Information

- 63-year-old female with primary diagnosis of CML in 2020
- Medical history: history of tobacco use
- BCR::ABL1 mutation at baseline: none

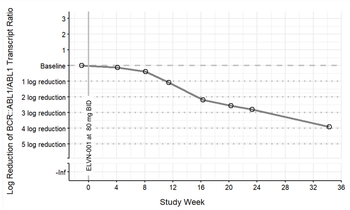
Prior Line of Therapy	Best Transcript Category	Reason for Discontinuation
Bosutinib	>10%	Hepatic toxicity
Dasatinib	>1%–10%	Lack of efficacy
Ponatinib	>1%–10%	Lack of efficacy
Asciminib	>1%–10%	Lack of efficacy
SCT	n/a	n/a[a]
DLI	n/a	n/a[b]
DLI	n/a	n/a[b]

[a]Lack of efficacy.
[b]Treatment failure.

TEAEs on ELVN-001

- Grade 2 bronchiolitis (NR), Grade 1 thrombo-cytopenia (R), Grade 2 vomiting (NR), Grade 2 diarrhea (NR), Grade 1 asthenia (R), Grade 2 viral bronchitis (NR), Grade 2 pulmonary mass (NR)

>1 Log Reduction in *BCR::ABL1/ABL1* Transcript Ratio



Anti-CML Activity in Patient with e1a2 Transcript

Patient Information

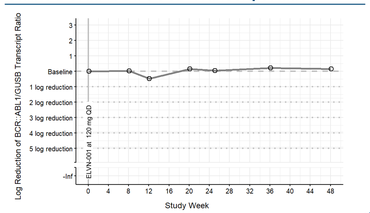
- 58-year-old female with primary diagnosis of CML in 2023
- Medical history: vitreous body detachment, hypertension, hypothyroidism, Hashimoto-thyroiditis, glaucoma, hypercholesterolemia
- BCR::ABL1 mutation at baseline: none

Prior Line of Therapy	Best Transcript Category	Reason for Discontinuation
Bosutinib	>10%	Lack of efficacy
Dasatinib	>10%	Lack of efficacy

TEAEs on ELVN-001

- Grade 1 COVID-19 (NR), Grade 1 pruritus (R), Grade 1 GFR decreased (R), Grade 1 dry skin (R)

Stable *BCR::ABL1/GUSB* Transcript Ratio



Anti-CML Activity in Patient with e1a2 Transcript

Patient Information

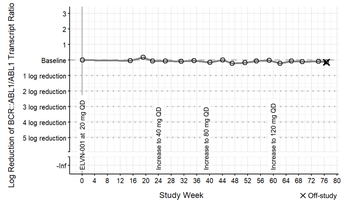
- 60-year-old female with primary diagnosis of CML in 2021
- Medical history: laparoscopic partial hysterectomy, spinal stenosis surgery, articularis inflammation both knees, onychomycosis, tinea pedis, thrombocytopenia, neutropenia, lipase elevation
- BCR::ABL1 mutation at baseline: none

Prior Line of Therapy	Best Transcript Category	Reason for Discontinuation
Imatinib	>10%	Lack of efficacy
Radotinib	>10%	Lack of efficacy
Dasatinib	>10%	Lack of efficacy

TEAEs on ELVN-001

- Grade 2 rash (R), Grade 1 pyrexia (NR)

Stable *BCR::ABL1/ABL1* Transcript Ratio



Abbreviations: AE, adverse event; ATP, adenosine triphosphate; BCR::ABL1, breakpoint cluster region-Abelson leukemia virus 1; BID, twice daily; CML, chronic myelogenous leukemia; DDI, drug-drug interaction; DLI, donor lymphocyte infusion; DLT, dose-limiting toxicity; ECG, electrocardiogram; GFR, glomerular filtration rate; GGT, gamma-glutamyl transferase; IC_{50}, half-maximal inhibitory concentration; MDS, myelodysplastic syndrome; NGS, next generation sequencing; NR, not related; PK, pharmacokinetics; QD, once daily; qPCR, quantitative reverse transcriptase polymerase chain; R, related; SCT, stem cell transplant; TEAE, treatment-emergent adverse event; TKI, tyrosine kinase inhibitor.

Data cutoff date: 06 Nov 2025