CML-575

ENABLE: A Phase 1A/1B Study of ELVN-001, a Selective Active Site Inhibitor of BCR::ABL1, in Patients with Previously Treated CML

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BACKGROUND

Why is There Still an Unmet Need in Chronic Myeloid Leukemia (CML)?

Off-Target Toxicity

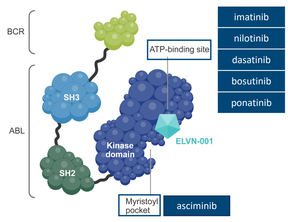
- Available ATP-competitive tyrosine kinase inhibitors (TKIs) have poor kinase selectivity, resulting in off-target toxicity via KIT, FLT3, PDGFRB, VEGFR2 and/or SRC[1]

Administration Limitations

- Concomitant medication restrictions: moderate/strong CYP inhibitors/inducers may alter TKI exposure, potentially leading to toxicity or decreased efficacy[2,3]
- Food alters the absorption of some TKIs making drug administration inconvenient

Resistance

- Potential resistance through breast cancer resistance protein (BCRP) and P-glycoprotein (P-gp)[4]
- Existing and emerging BCR::ABL1 mutations of the ATP binding site or the myristoyl pocket[5]



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:
  - Provides greater selectivity than available ATP inhibitors, with potential for better tolerability
  - Creates a narrow tunnel allowing binding to T315I and other mutations
- Able to take with or without food
- Not an inhibitor or substrate of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, and CYP3A5
- Not a P-gp or BCRP substrate or inhibitor

	KIT	FLT3	PDGFRB	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	2,900	>10,000
Dasatinib	0.6	>1,000	7.1	>1,000	10
Bosutinib	1,000	4,700	7,900	>10,000	16

Fold-Shift in *In Vitro* Cellular Phosphorylation IC_{50} vs. pCRKL in a Panel of Receptor Tyrosine Kinases[6]

ELVN-001: Broad Activity Against BCR::ABL1 Mutations

- ELVN-001 maintains activity against T315I and emerging BCR::ABL1 mutations known to confer resistance to asciminib
- Emerging BCR::ABL1 mutations are predicted to require concentrations in a similar range to native BCR::ABL1

	T315I	M244V	A337T	E355G	F359C	F359V	P465S
Asciminib	96	611	173	>2380	>2380	>2380	>2380
ELVN-001	4	2	1	4	3	2	2
Dasatinib	2935	2	1	3	4	2	2
Bosutinib	113	3	1	4	5	5	4
Ponatinib	3	2	1	3	5	5	2
Imatinib	>20	3	1	8	18	10	4
Nilotinib	>341	2	1	5	33	21	3

Fold-Shift Inhibitory Activity vs. Unmutated BCR::ABL1 in a Panel of BCR::ABL1 Resistance Mutants *In Vitro* (BA/F3 Cells)[7]

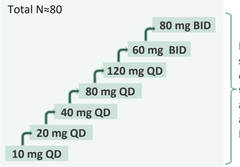
ELVN-001: Phase 1 Trial Design

Key eligibility criteria:

- 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

Phase 1a Dose Escalation[a]: 3+3

Total N≈80



Up to 10 additional patients per dose level (max n=50)

Phase 1b doses selected based on safety, tolerability, anti-CML activity, and PK/PD

Phase 1b Dose Expansion n=20 each

80 mg QD Non-T315I	Completed Enrollment
60 mg QD Non-T315I	Randomized (Enrolling)
120 mg QD Non-T315I	
Dose TBD CP-CML with T315I mutations	

Primary Endpoints

- Incidence of DLTs, AEs, clinically significant laboratory and ECG abnormalities

Key Secondary Endpoints

- Molecular response (MR) by central qPCR
- PK parameters

AE, adverse event; BID, twice daily; CML, chronic myeloid leukemia; DLT, dose-limiting toxicity; ECG, electrocardiogram; PD, pharmacodynamic; PK, pharmacokinetic; QD, once daily; qPCR, quantitative reverse transcriptase polymerase chain reaction; TBD, to be determined; TKI, tyrosine kinase inhibitor.
[a]Re-enrollment and intrasubject dose escalation allowed if meeting specific criteria.

RESULTS

Patient Demographics and Baseline Characteristics

Parameter	All Patients[a] (N = 90)
Age, years, median (range)	58 (19–79)
Male / female	58% / 42%
White / Asian / Black or African American / not reported / other	70% / 18% / 1% / 9% / 2%
ECOG PS 0 / 1	74%/26%
Median time since diagnosis, months (range)	58.1 (2.6–281.9)
Typical *BCR::ABL1* transcript (e13a2/e14a2)	93%
Baseline *BCR::ABL1* transcript level[b]	
≤ 0.1%	18%
> 0.1%– ≤1.0%	23%
> 1.0%	52%
Baseline *BCR::ABL1* mutation (central)[c]	
No mutation	54%
T315I or other mutation or not available	46%[d]
Median number of prior unique TKIs, n (range)[e]	3 (1–7)
1–2 prior	32%
3–4 prior	41%
≥ 5 prior	26%
Prior TKI	
Dasatinib	73%
Imatinib	67%
Asciminib	58%
Nilotinib	54%
Ponatinib	43%
Bosutinib	38%
Reason for discontinuation of last TKI	
Lack of efficacy	72%
Lack of tolerability	23%
Other	3%

ECOG PS, Eastern Cooperative Oncology Group Performance Status; TKI, tyrosine kinase inhibitor.
Data cutoff: 28 Apr 2025.
[a]Includes 3 re-enrolled patients (87 individual patients).
[b]Percentages based on 84 patients with typical transcript.
[c]Only available for patients with typical transcripts.
[d]Includes 2 re-enrolled patients (6 individual patients with T315I).
[e]Median lines of prior TKIs is 4 (range 1-9).

Patient Disposition

- 80% of patients remain on study with a median duration of exposure of 29 weeks
- 4 patients discontinued due to adverse events (AEs):
  - Alcoholic pancreatitis (10 mg QD)
  - Thrombocytopenia (20 mg QD and 80 mg QD)
  - Dyspnea (80 mg QD; confounded by pulmonary comorbidities)
- 1 patient died of a post-operative complication (after hip surgery; not related to study drug)

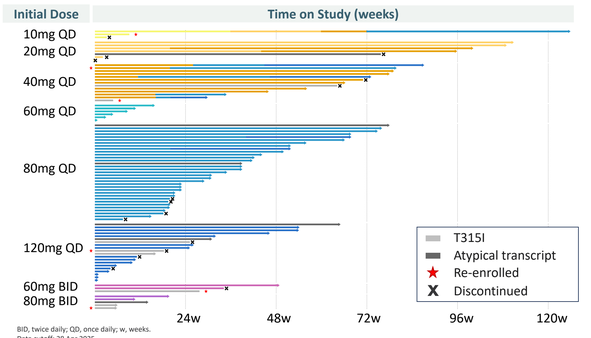
Disposition	Total (N = 90)
Median duration of exposure, weeks (range)	29 (0.1–126)
Ongoing, n (%)	72 (80.0%)
Discontinued, total n (%)	18 (20.0%)
Lack of efficacy	11 (12.2%)[a]
Adverse event	4 (4.4%)
Death	1 (1.1%)
Protocol violation	1 (1.1%)
Withdrawal of consent	1 (1.1%)

Data cutoff: 28 Apr 2025.
[a]3 of 11 patients discontinued at lower doses, subsequently re-enrolled at higher dose levels; no patients progressed to blast crisis or acute leukemia.

RESULTS (cont.)

Duration on Study Treatment

- The majority of patients remain on study
- 56% of patients have been on study > 24 weeks, with the longest ongoing at 126 weeks (~2.5 years)



BID, twice daily; QD, once daily; w, weeks.
Data cutoff: 28 Apr 2025.
NOTE: Study allows re-enrollment and intrasubject dose escalation, as shown by change in color.

ELVN-001 had Favorable Safety and Tolerability Across Dose Levels

- No maximum tolerated dose (MTD) identified
- No dose-toxicity relationship observed
- 3 (3.4%) patients with dose reductions due to treatment-emergent adverse events (TEAEs)
- 4 (4.6%) patients discontinued due to TEAEs

TEAEs in ≥ 10% of Patients

Preferred term n (%)	Total (N = 87)	
	Any	Grade 3/4
Lipase increased	16 (18.4%)	1 (1.1%)
Diarrhea	13 (14.9%)	0
Thrombocytopenia[a]	12 (13.8%)	6 (6.9%)
Arthralgia	11 (12.6%)	1 (1.1%)
Headache	11 (12.6%)	0
Fatigue	9 (10.3%)	0
Myalgia	9 (10.3%)	0

Data cutoff: 28 Apr 2025.
[a]Combined term: platelet count decreased/thrombocytopenia.

Grade 3/4 TEAEs Were Uncommon and Not Dose-Dependent

- 2 patients (2.3%) reported Grade 3 arterial occlusion events (AOEs)*; both had prior ponatinib and nilotinib, events were not related to ELVN-001 per investigator, and both patients remain on study

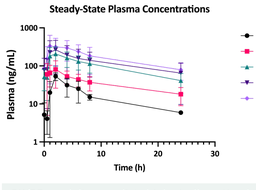
Grade 3/4 TEAEs Reported in ≥ 5% of Patients by Dose Level

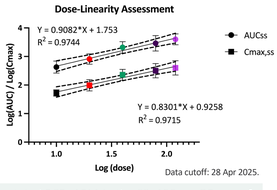
Preferred term n (%)	10–40 mg QD (n = 23)	60 mg QD (n = 6)	80 mg QD (n = 33)	120 mg QD (n = 20)	60–80 mg BID (n = 8)	Total (N = 87[a])
Any Grade 3/4 event	5 (21.7%)	1 (16.7%)	8 (24.2%)	4 (20.0%)	2 (25.0%)	20 (23.0%)
Thrombocytopenia[b]	2 (8.7%)	0	3 (9.1%)	0	1 (12.5%)	6 (6.9%)
Neutropenia[b]	4 (17.4%)	0	0	0	1 (12.5%)	5 (5.7%)

BID, twice daily; QD, once daily.
Data cutoff: 28 Apr 2025.
[a]Identified using Standardized MedDRA queries (SMQ).
[a]Patients with intrasubject dose escalation were counted under their initial treatment group only. Re-enrolled patients were summarized at both dose levels with the corresponding data collected during each period, and once in the total column.
[b]Combined term: platelet count decreased/thrombocytopenia and neutrophil count decreased/neutropenia.

ELVN-001 Pharmacokinetic (PK) Profile

- ELVN-001 PK profile showed a fast absorption followed by a monophasic decline
- ELVN-001 has linear PK, with both AUC at steady state (AUC_{ss}) and C_{max} increasing approximately dose-proportionally from 10–120 mg
- Half-life ($t_{1/2}$ range 10–20 hours) in patients supports the QD regimen





Data cutoff: 28 Apr 2025.

PK/PD modeling predicts biologically optimal dose for unmutated BCR::ABL1 in the 60–120 mg QD range[8]

Encouraging Efficacy by 24 Weeks

- Robust anti-CML activity despite heavily pretreated patient population, including in patients exposed to prior asciminib or ponatinib

BCR::ABL1 ≤ 0.1% (MMR) by 24 weeks	
Overall MMR by 24 weeks	25/53 (47%)
Achieved (not in MMR at baseline)	13/41 (32%)
Maintained (in MMR at baseline)	12/12 (100%)
Key subgroups	
Post asciminib	9/28 (32%)
Post ponatinib	7/20 (35%)
Lack of efficacy to last TKI	14/34 (41%)
Intolerant to last TKI	9/17 (53%)

BCR::ABL1 ≤ 1% by 24 weeks	
Overall ≤ 1% by 24 weeks	43/56 (77%)
Achieved (not ≤ 1% at baseline)	14/27 (52%)
Maintained (≤ 1% at baseline)	29/29 (100%)

MMR, major molecular response; TKI, tyrosine kinase inhibitor.
Data cutoff: 28 Apr 2025.
NOTE: Patients were included if they had baseline BCR::ABL1 transcript, and postbaseline assessment of BCR::ABL1 transcript at 24 weeks or achieved MMR/≤1% within 24 weeks or discontinued treatment before 24 weeks without achieving MMR /≤1%. For patients with MMR /≤1% at baseline, only postbaseline assessments beyond 70 days were included in the analysis.

98% (52/53) Patients with Improved or Stable MR Category

- Improvement in transcript category was observed in patients independent of baseline transcript

Change in BCR::ABL1 Transcript in Patients Evaluable for MMR by 24 Weeks (n=53)

Improvement in MR Category
No Category Change
Worsening in MR Category

BCR::ABL1 transcript by 24 weeks	Baseline *BCR::ABL1* transcript: >MR4.5 ≤ 0.0016 (n = 1)	MR4.5 > 0.0016 to 0.0032 (n = 0)	MR4 > 0.0032 to 0.01 (n = 3)	MR3 > 0.01 to 0.1 (n = 8)	> 0.1 to 1 (n = 16)	> 1 to 10 (n = 9)	> 10 (n = 16)
>MR4.5 ≤ 0.0016	1		1	2			
MR4.5 > 0.0016 to 0.0032							
MR4 > 0.0032 to 0.01			2		1	1	
MR3 > 0.01 to 0.1				6	5	4	2
> 0.1 to 1					10	3	2
> 1 to 10							1
> 10						1[a]	11

MMR, major molecular response; MR, molecular response.
Data cutoff: 28 Apr 2025.
[a]Worsening of transcript level from 6.3% at baseline to 13% after 4 weeks in patient with E255V mutation who previously discontinued asciminib and ponatinib due to lack of efficacy.
Notes: >MR4.5 category assigned based on transcript level < limit of quantitation. Evaluable patients had baseline typical BCR::ABL1 transcript without T315I mutation and post-baseline assessment of BCR::ABL1 transcript at 24 weeks or achieved MMR within 24 weeks or discontinued treatment before 24 weeks without achieving MMR. For patients with MMR at baseline, only post-baseline assessments beyond 70 days were included in the analysis.

CONCLUSIONS

- ELVN-001, a novel active-site inhibitor of BCR::ABL1, had a favorable safety and tolerability profile in this phase 1 study
  - No MTD identified and no dose-toxicity relationship observed
  - Most TEAEs were low grade, with low rates of dose reductions and discontinuations due to TEAEs
  - No evidence to date of increased cardiovascular toxicity
- Encouraging anti-CML activity in a heavily pretreated patient population
  - 47% MMR rate by 24 weeks, with 32% achieving MMR (not in MMR at baseline)
  - 52% of those with a transcript > 1% at baseline, achieved ≤ 1% by 24 weeks
  - Efficacy observed in patients exposed to prior asciminib or ponatinib
- The ELVN-001 PK profile supports once daily dosing with or without food, which, in addition to low potential for drug-drug interactions (DDIs), addresses key challenges with currently available TKIs
- The phase 1 study is active and recruiting (NCT05304377)

Abbreviations: AE, adverse event; AOE, arterial occlusion event ; ATP, adenosine triphosphate; AUC, area under the curve; AUC_{ss}, area under the curve at steady state; BCR::ABL1, breakpoint cluster region-Abelson leukemia virus 1; BCRP, breast cancer resistant protein; BID, twice daily; C_{max}, maximum concentration; CML, chronic myeloid leukemia; DLT, dose-limiting toxicity; ECG, electrocardiogram; ECOG PS, Eastern Cooperative Oncology Group performance status; h, hours; IC_{50}, half-maximal inhibitory concentration; MMR, major molecular response; MR, molecular response; PD, pharmacodynamic; PK, pharmacokinetic; QD, once daily; qPCR, quantitative reverse transcriptase polymerase chain reaction; P-gp, P-glycoprotein; $t_{1/2}$, half-life; TBD, to be determined; TKI, tyrosine kinase inhibitor.

References: 1. Lee H, et al. Int J Hematol. 2021; 2. Osorio S, et al. Ann Hematol. 2018; 3. Cheng F, et al. Crit Rev Oncol Hematol. 2024; 4. Hegedus, et al. Clin Transl Sci. 2022; 5. Braun T, et al. Cancer Cell. 2020; 6. Modified from Gross S, et al ASH 2022; 7. Gross SD, et al. AACR 2025; data on file; 8. Wang Q, et al, AACR 2025.

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