Poster Number: CML-652

ENABLE: A Phase 1 Study of ELVN-001, a Novel, Selective ATP-Competitive Inhibitor of BCR::ABL1, in Patients with Previously Treated CP-CML

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Background

ELVN-001 is an oral, highly selective ATP-competitive tyrosine kinase inhibitor (TKI) of BCR::ABL1, with a unique binding mode enabling potent, targeted inhibition. ELVN-001's pharmacokinetic (PK) profile supports once daily (QD) dosing, with or without food, addressing key challenges of currently available TKIs. In the phase 1a dose-escalation part of the ENABLE study (NCT05304377), ELVN-001 showed encouraging safety/tolerability and anti-CML activity in patients with previously treated chronic phase (CP)-CML.

Objective

The primary objective was to evaluate the safety and tolerability of ELVN-001. Safety data are presented for all patients with CP-CML. Efficacy analyses included patients with non-T315I CP-CML in the phase 1b dose-expansion portion of ENABLE.

Conclusion

ELVN-001, an ATP-competitive BCR::ABL1 TKI with high selectivity for ABL1, demonstrated favorable safety and efficacy profile at biologically active doses.

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Background

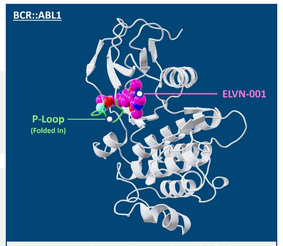
ELVN-001: A Highly Selective ATP-Competitive Inhibitor of BCR::ABL1

ELVN-001 was designed to address key unmet challenges in CML

Potency without Off-Target Toxicity[1]
- ELVN-001 delivers **potent** inhibition of BCR::ABL1 with **high ABL1 selectivity:** >100-fold selectivity against >99% of 370 kinases; no inhibition of KIT, VEGFR2, PDGFR, or SRC

Resistance[2,3]
- ELVN-001 showed activity against T315I and the emerging class of mutations associated with resistance to allosteric inhibition
- Not a P-gp or BCRP substrate or inhibitor

Administration Limitations[4,5]
- Once daily administration of ELVN-001 with or without food
- Potential for concomitant administration with CYP3A4 substrates or inhibitors and proton pump inhibitors

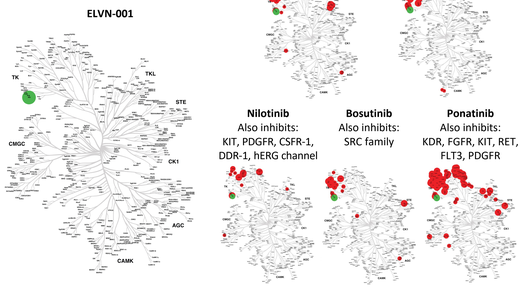


ELVN-001 has a unique P-loop folded-in binding mode

ATP, adenosine triphosphate; BCR::ABL1, breakpoint cluster region-Abelson leukemia virus 1; BCRP, breast cancer resistant protein; CML, chronic myeloid leukemia; P-gp, P-glycoprotein. [1]Lee H, et al. Int J Hematol. 2021; [2]Hegedus, et al. Clin Transl Sci. 2022; [3]Braun T, et al. Cancer Cell. 2020; [4]Osorio S, et al. Ann Hematol. 2018; [5]Cheng F, et al. Crit Rev Oncol Hematol. 2024.

ELVN-001: Differentiated by its Selective ABL1 Inhibition

ELVN-001 provides greater selectivity than available ATP inhibitors[a], with potential for better tolerability



[a]Each of these active site TKIs was profiled at 30x its respective ABL1 IC_{50} value against a panel of 377 protein kinases in biochemical assays with 100 mM ATP concentration in the screen (Reaction Biology) (Metz KS et al. Cell Systems. 2018).

Results: Safety & Efficacy

Most Patients Remain on Study

Overall, 146 person-years of exposure and 118 patients treated at doses ≥ 80 mg QD.

Disposition	All Patients (N = 161)	80 mg QD (Phase 1b) (N = 49)
Median duration of exposure, weeks (range)	35 (0.1–156)	16.1 (0.3–86.7)
Ongoing, n (%)	123 (76%)	40 (82%)
Discontinued, total n (%)	38 (24%)	9 (18%)
Lack of efficacy[a]	21 (13%)	1 (2.0%)
Adverse event	10 (6.2%)	3 (6.1%)
Death[b]	1 (0.6%)	1 (2.0%)
Other[c]	6 (3.7%)	4 (8.2%)

At 80 mg QD in phase 1b:
- 82% of patients remain on study
- Current median duration of exposure of 16 weeks (cohort actively enrolling)
- Low rate of discontinuation due to adverse events

[a] No patients progressed to blast phase.
[b] Death was due to post-operative complication (not related to ELVN-001).
[c] Protocol violation, investigator decision, and consent withdrawal.

ELVN-001 has Favorable Safety and Tolerability

Wide therapeutic window

80 mg BID determined to be MTD:
- 2 patients with DLT at 120 mg BID (one Grade 3 hallucination in patient with history of hallucinations and one Grade 3 myalgia)

Low incidence of AOEs*:
- 7 patients (4.4%) with any grade; 3 (1.9%) with Grade 3, all with CV disease/risk factors incl. prior nilotinib and/or ponatinib

Safety of 80 mg QD similar to overall safety; determination of optimal biological dose based on PK/PD modeling

Most Common TEAEs (by Preferred Term), n (%)	All Patients (N = 158 SAS)		80 mg QD (N = 62 SAS)	
	Any	≥ Grade 3	Any	≥ Grade 3
Any TEAE	142 (90%)	53 (34%)	51 (82%)	15 (24%)
Hematologic TEAEs ≥ 5%				
Thrombocytopenia[a]	23 (15%)	10 (6.3%)	10 (16%)	4 (6.5%)
Neutropenia[a]	11 (7.0%)	10 (6.3%)	1 (1.6%)	0
Non-hematologic TEAEs ≥ 10%				
Lipase increased	35 (22%)	9 (5.7%)[b]	13 (21%)	3 (4.8%)[b]
Fatigue	28 (18%)	2 (1.3%)[b]	7 (11%)	1 (1.6%)[b]
Headache	24 (15%)	1 (0.6%)[b]	11 (18%)	1 (1.6%)[b]
Arthralgia	22 (14%)	2 (1.3%)[b]	10 (16%)	1 (1.6%)[b]
Myalgia	22 (14%)	1 (0.6%)[b]	7 (11%)	0
Nausea	19 (12%)	0	8 (13%)	0
Diarrhea	18 (11%)	0	6 (9.7%)	0
Amylase increased	16 (10%)	0	5 (8.1%)	0

[a] Grouped terms: platelet count decreased/thrombocytopenia and neutrophil count decreased/neutropenia. [b] Grade 3 only.

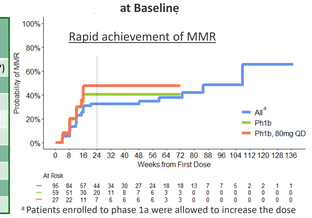
MTD, maximum tolerated dose; PD, pharmacodynamic(s); PK, pharmacokinetic(s); QD, once daily; SAS, safety analysis set; TEAE, treatment-emergent adverse event.
*AOEs (arterial occlusive events) identified by MedDRA. TEAE of hypertension, any grade, reported in 5.7% of patients,1.9% Grade 3.

Encouraging Anti-CML Activity in Phase 1b

Key Efficacy Milestones by Week 24 for Phase 1b

	Total QD (Phase 1b) (N = 90)	80 mg QD (Phase 1b) (N = 49)
Median exposure (weeks)	28.0 (0.3-86.7)	16.1 (0.3-86.7)
MMR (*BCR::ABL1* ≤ 0.1%)		
Overall MMR	37/69 (54%)	17/28 (61%)
MMR achieved	21/53 (40%)	10/21 (48%)
MMR maintained	16/16 (100%)	7/7 (100%)
MR2 (*BCR::ABL1* ≤ 1%)		
MR2 achieved	19/33 (58%)	9/13 (69%)
DMR (*BCR::ABL1* ≤ 0.01%)		
DMR achieved	14/64 (22%)	8/27 (30%)

Cumulative Incidence of MMR in Patients Not in MMR at Baseline

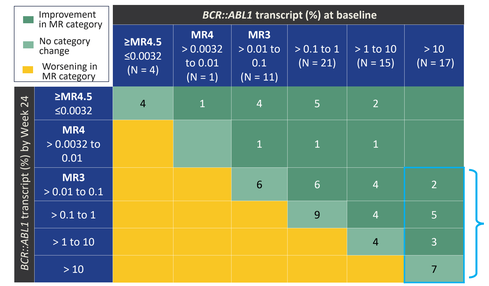


[a] Patients enrolled to phase 1a were allowed to increase the dose if certain criteria were met

DMR, deep molecular response; MMR, major molecular response; MR, molecular response; QD, once daily. NOTE: Patients were included if they had baseline typical *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.

All Patients in Phase 1b had Improved or Stable MR Category

Change in *BCR::ABL1* Transcript in Patients Evaluable for MMR by Week 24 (N = 69)



In the baseline transcript >10% subgroup: 59% (10/17) had improved MR category

MR, molecular response; MMR, major molecular response. NOTE: 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.

Encouraging MMR Rates Across Lines of Therapy and After Asciminib Failure

MMR, major molecular response; TKI, tyrosine kinase inhibitor; QD, once daily. NOTE: Analysis by number of prior TKIs done with prior *unique* TKIs. 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.

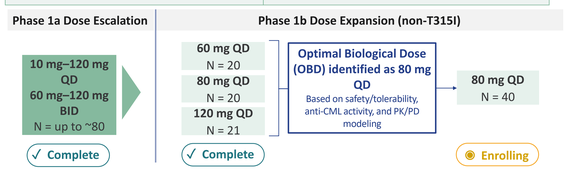
Trial Design & Demographics

ELVN-001: Phase 1 Trial Design and Status

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

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

Key Secondary Endpoints
- Molecular response by central qPCR
- PK parameters



Phase 1 is ongoing (NCT05304377). AE, adverse event; DLT, dose-limiting toxicity; ECG, electrocardiogram; BID, twice daily; OBD, optimal biological dose; CML, chronic myeloid leukemia; PD, pharmacodynamics; PK, pharmacokinetics; QD, once daily; qPCR, quantitative polymerase chain reaction.

Methodology

- Safety analyses included all treated patients with CP-CML.
- Efficacy analyses included patients with non-T315I CP-CML enrolled in the Phase 1b dose-expansion cohorts.
- Efficacy was assessed by molecular response based on BCR::ABL1 transcript levels.
- Data cutoff: 10 March 2026.

Patient Demographics and Baseline Characteristics

Most patients received ≥ 3 prior TKIs (70%) and prior ponatinib and/or asciminib (72%)

Parameter	All Patients (N = 161[a])	80 mg QD (Phase 1b) (N = 49)
Median age in years (range)	59 (19–82)	57 (19–82)
Typical BCR::ABL1 transcript (e13a2/e14a2), n (%)	150 (93%)	47 (96%)
Baseline BCR::ABL1 transcript[b] ≤0.1%	26 (17%)	8 (17%)
>0.1% – 1%	37 (25%)	11 (23%)
>1% – 10%	28 (19%)	10 (21%)
>10%	50 (33%)	10 (21%)
Baseline BCR::ABL1 mutation (Sanger), n (%)	39 (24%)	5 (10%)
T315I mutation	12 (7%)	n/a
Mutations associated with resistance to allosteric inhibition	13 (8%)	2 (4%)
Other mutations	9 (6%)	3 (6%)
Median **lines** of prior TKI therapy, n (range)	4 (1–10)	3 (1–9)
Median number of prior **unique** TKIs, n (range)	3 (1–7)	3 (1–6)
1–2 prior, n (%)	46 (29%)	19 (39%)
3 prior, n (%)	39 (24%)	11 (22%)
4 prior, n (%)	37 (23%)	11 (22%)
≥ 5 prior, n (%)	37 (23%)	7 (14%)
Prior asciminib or ponatinib at any time, n (%)		
Asciminib[b]	100 (62%)	27 (55%)
Ponatinib	60 (37%)	13 (27%)
Reason for discontinuation of last TKI, n (%)[c]		
Lack of efficacy	99 (61%)	25 (51%)
Lack of tolerability	51 (32%)	20 (41%)

[a]Includes 3 re-enrolled patients (158 individual patients). [b]Most received asciminib in late line and the majority discontinued asciminib due to lack of efficacy. [c]Unknown/other in 9 patients (all patients) and 3 patients (80 mg QD).

Conclusions

ELVN-001 showed favorable safety and tolerability with longer follow-up.
- Low rate of discontinuations due to TEAEs
- The safety profile is consistent with ELVN-001's selectivity for ABL1
- No evidence of increased cardiovascular toxicity to date

The Optimal Biological Dose (OBD) was determined to be 80 mg QD based on safety, efficacy, PK/PD.

Encouraging anti-CML activity continued to be observed.
- At the OBD of 80 mg QD in Phase 1b: 61% overall MMR with 48% achieving MMR by Week 24
- MR stable or improved in all patients enrolled in Phase 1b
- Encouraging MMR rates even in heavily pretreated patients and after asciminib failure

Phase 3 ENABLE-2 pivotal trial is expected to initiate in the 2nd half of 2026.

ELVN-001, an ATP-competitive BCR::ABL1 TKI with high selectivity for ABL1, demonstrated favorable safety and efficacy profile at biologically active doses.

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