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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SOHO 2025: September 3-6, 2025; Houston, Texas

Disclosures

Dr. Michael Mauro

- Employment or leading position: n/a
- Advisory role: Bristol Myers Squibb, Enliven, Novartis, Pfizer, Takeda, Terns
- Share ownership: n/a
- Honoraria: n/a
- Research funding: Enliven, Novartis, Terns
- Other financial relationship: n/a

Why is There Still an Unmet Need in CML?

Off-Target Toxicity

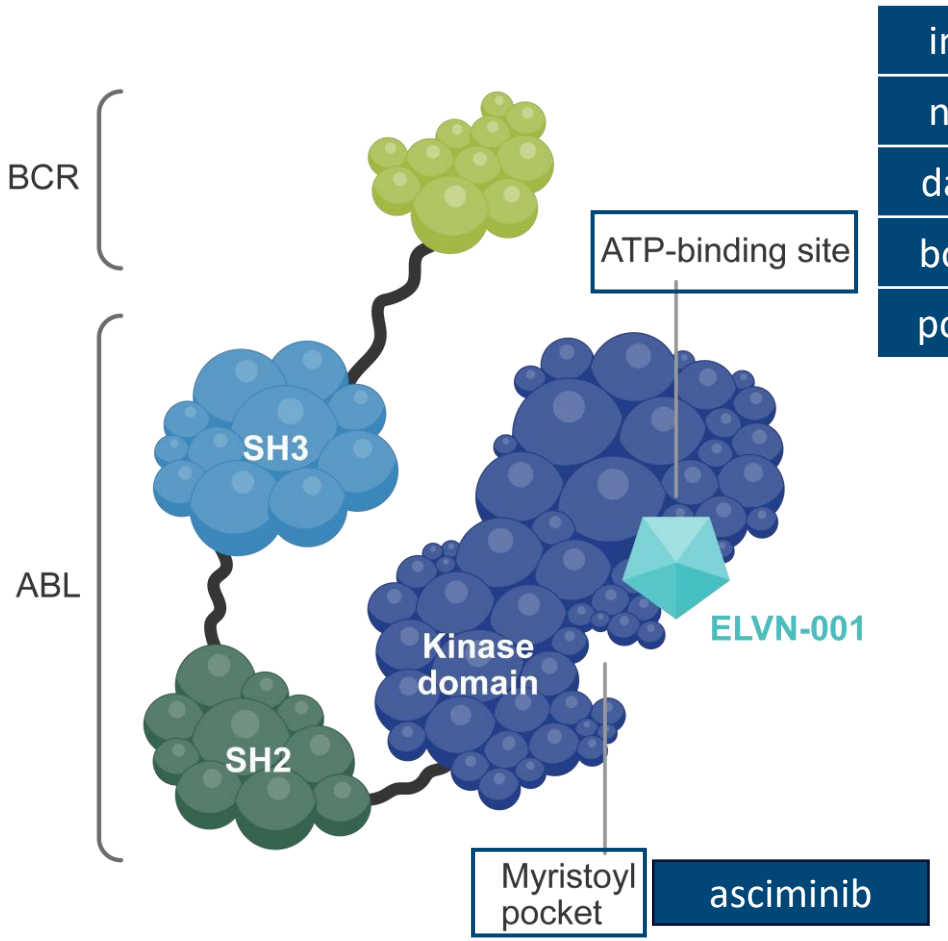
- Available ATP-competitive TKIs have poor kinase selectivity, resulting in off-target toxicity via KIT, FLT3, PDGFRB, VEGFR2 and/or SRC[1]

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 BCRP and P-gp[4]
- Existing and emerging BCR::ABL1 mutations of the ATP binding site or the myristoyl pocket[5]



ATP, adenosine triphosphate; BCR::ABL1, breakpoint cluster region-Abelson leukemia virus 1; BCRP, breast cancer resistant protein; P-gp, P-glycoprotein; TKI, tyrosine kinase inhibitor.

[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.

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[1]

ATP, adenosine triphosphate; BCRP, breast cancer resistant protein; IC_{50}, half-maximal inhibitory concentration; P-gp, P-glycoprotein.

1. Modified from Gross S, et al ASH 2022.

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)[1]

1. Gross SD, et al. AACR 2025; data on file.

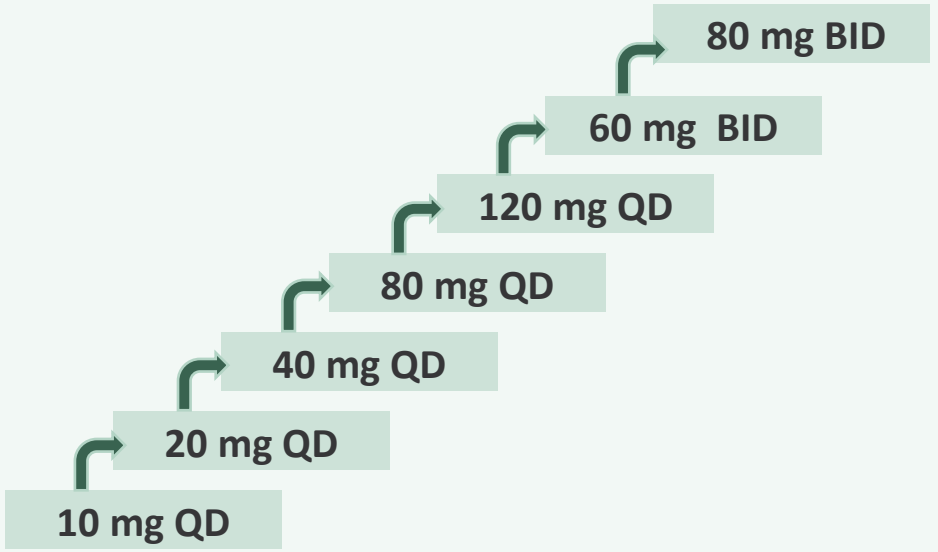
ELVN-001: Phase 1 Trial Design

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 Dose Expansion n = 20 each

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

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

Primary Endpoints

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

Key Secondary Endpoints

- Molecular response by central qPCR
- PK parameters

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

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]

[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).

Parameter	All Patients[a] (N = 90)
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%

[e]Median lines of prior TKIs is 4 (range 1-9).

Data cutoff: 28 Apr 2025.
ECOG PS, Eastern Cooperative Oncology Group performance status

Patient Disposition

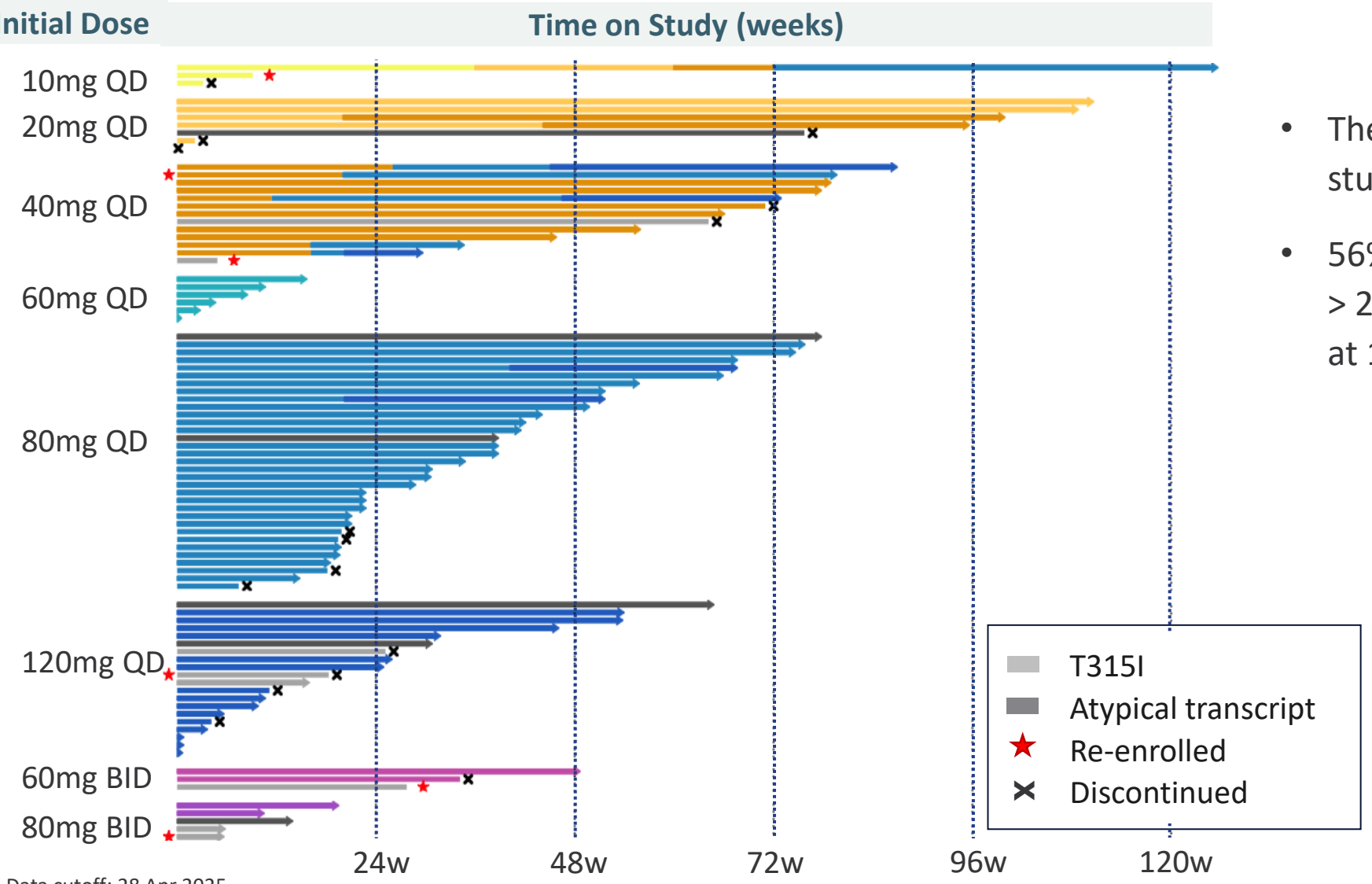
Disposition	Total (N = 90)
Median duration of exposure, weeks (range)	29 (0.1–126)
Ongoing, n (%)	72 (80.0%)
Discontinued, total n (%)	18 (20.0%)
Lack of efficacy	11 (12.2%)[a]
Adverse event	4 (4.4%)
Death	1 (1.1%)
Protocol violation	1 (1.1%)
Withdrawal of consent	1 (1.1%)

[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.

- 80% of patients remain on study with a median duration of exposure of 29 weeks
- 4 patients discontinued due to 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)

Data cutoff: 28 Apr 2025.

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)

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

Treatment Emergent Adverse Events (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

[a]Combined term: platelet count decreased/thrombocytopenia.

- No Maximum Tolerated Dose identified
- No dose-toxicity relationship observed
- 3 (3.4%) patients with dose reductions due to TEAEs
- 4 (4.6%) patients discontinued due to TEAEs

Data cutoff: 28 Apr 2025.

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

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%)

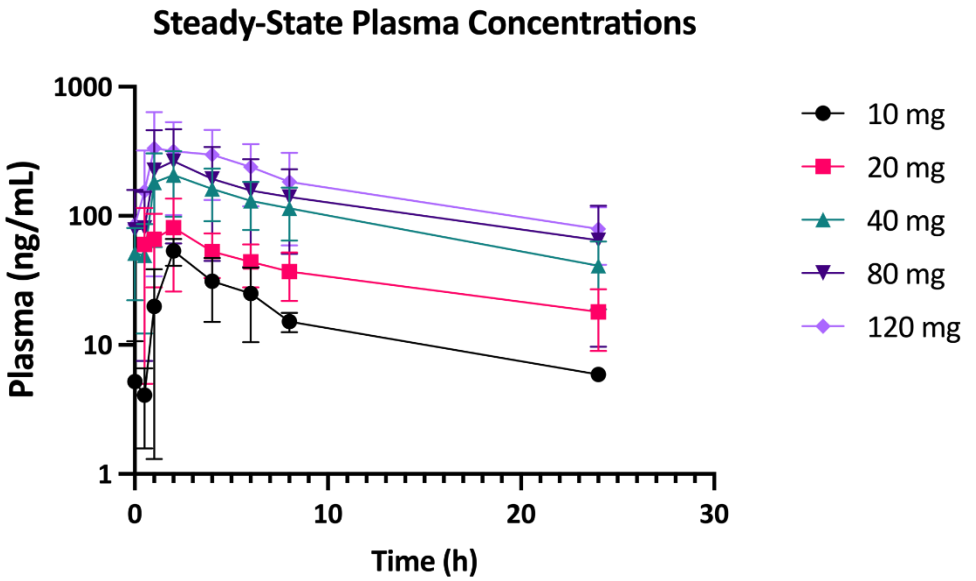
[a]Patients with intrasubject dose escalation were counted under their initial treatment group only. Re-enrolled patients were summarized at both dose levels with the corresponding data collected during each period, and once in the total column.
[b]Combined term: platelet count decreased/thrombocytopenia and neutrophil count decreased/neutropenia.

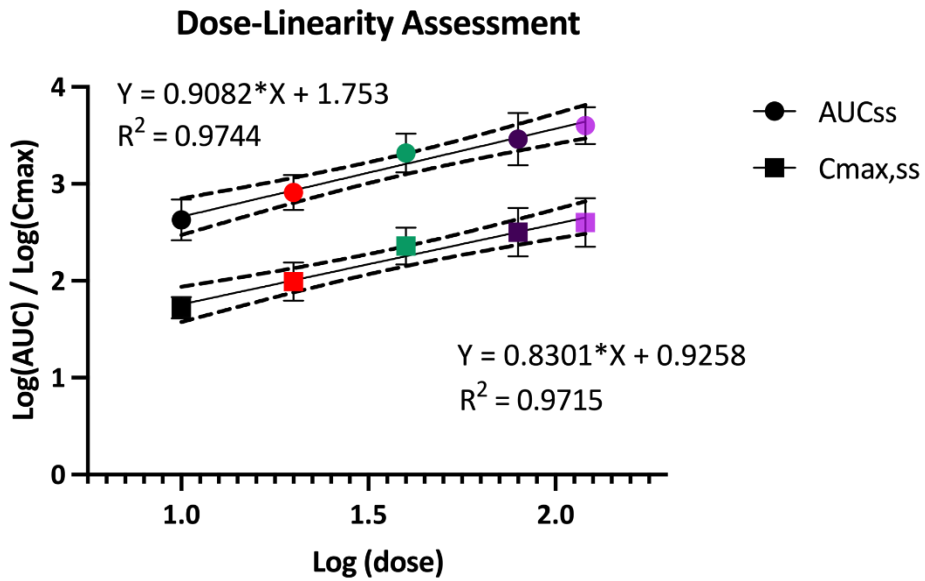
- 2 patients (2.3%) reported Grade 3 arterial occlusion events (AOEs)*; both had prior ponatinib and nilotinib, events were not related to ELVN-001 per investigator, and both patients remain on study

Data cutoff: 28 Apr 2025.
*Identified using Standardized MedDRA queries (SMQ)

ELVN-001 Pharmacokinetic Profile

- ELVN-001 PK profile showed a fast absorption followed by a monophasic decline
- ELVN-001 has linear PK, with both AUC 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





PK/PD modeling predicts biologically optimal dose for unmutated BCR::ABL1 in the 60–120 mg QD range[1]

Data cutoff: 28 Apr 2025.

AUC_{ss}, area under the curve at steady state; $C_{max,}$ maximum concentration; h, hours; QD, once daily; PK pharmacokinetic; $t_{1/2,}$ half-life.

1. Wang Q, et al, AACR 2025.

Encouraging Efficacy by 24 Weeks

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%)

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

Data cutoff: 28 Apr 2025.

MMR, major molecular response; TKI, tyrosine kinase inhibitor.

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

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

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

BCR::ABL1 = Breakpoint cluster region-Abelson leukemia virus 1. CML = Chronic myeloid leukemia. 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 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**
- **The phase 1 study is active and recruiting (NCT05304377)**

DDI, drug-drug interaction; MMR, major molecular response; MTD, maximum tolerated dose; TEAE, treatment-emergent adverse event; TKI, tyrosine kinase inhibitor.

Acknowledgments

Thank you

to all investigators and site staff, to the patients and their families for their participation in the study, to the Enliven medical team and to Ingrid Koo, PhD, who provided editorial support.

This study was funded by Enliven Therapeutics, Inc.