Preliminary safety and efficacy of ELVN-001, a selective active site inhibitor of BCR::ABL1 in CML

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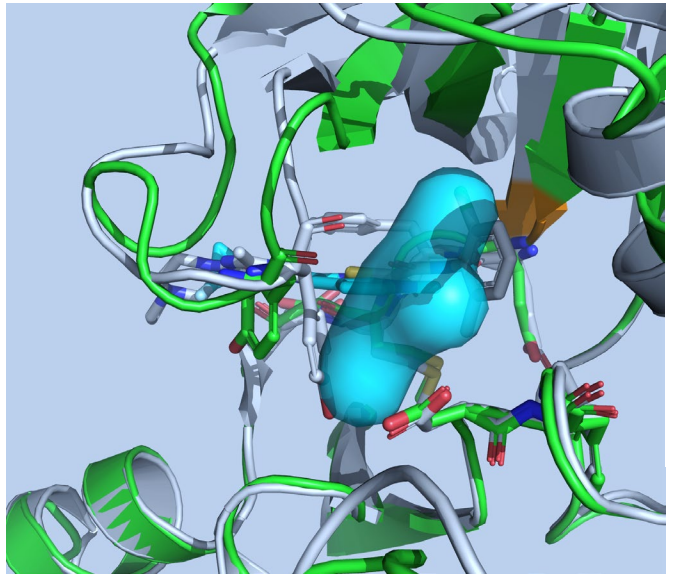
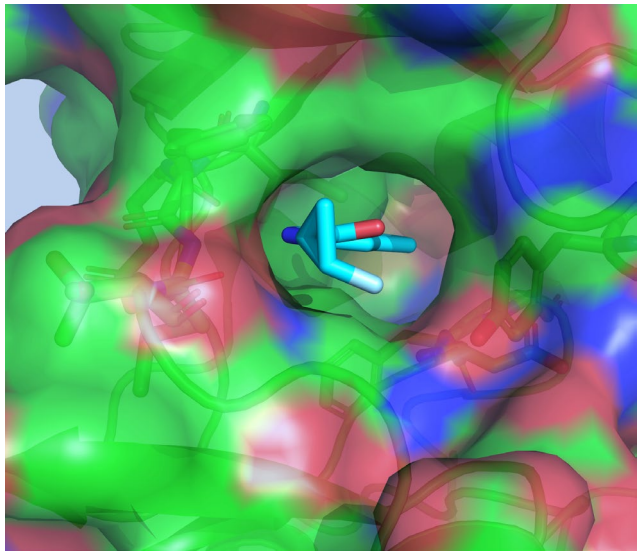
ELVN-001: Background

ELVN-001 is a novel small molecule inhibitor of BCR::ABL1 with:

- **Kinase specificity**
  - >100x selectivity vs. key receptor tyrosine kinase targets KIT, FLT3, PDGFRβ, VEGFR2, and SRC in cells
- **Broad activity**
  - Against multiple clinically important BCR::ABL1 mutations including T315I
- **Preclinical antitumor activity**
  - Antiproliferative activity and biomarker suppression in both native and T315I-mutant cell lines
- **Other key properties**
  - Able to take with or without food[1]
  - Low potential for DDI[1]
  - Not a BCRP/P-gp substrate (drug efflux transporters associated with resistance[2])



ELVN-001 binds to a unique P-loop "folded-in" active conformation in the ATP binding pocket creating a narrow selectivity tunnel



BCR::ABL1 = breakpoint cluster region-Abelson leukemia virus 1. DDI = drug-drug interaction. BCRP = breast cancer resistance protein. P-gp = P-glycoprotein.

1. Data on file; 2. Qiang W et al. Mechanisms of Resistance to the BCR-ABL1 Allosteric Inhibitor Asciminib. *Leukemia.* 2017;31:2844-2847; Hussaarts KGAM et al. Clinically relevant drug interactions with multikinase inhibitors: a review. Ther Adv Med Oncol. 2019;11:1758835918818347. Hegedus C et al. Interaction of nilotinib, dasatinib and bosutinib with ABCB1 and ABCG2: implications for altered anti-cancer effects and pharmacological properties. Br J Pharmacol. 2009;158(4):1153–64.

ELVN-001: Key Properties

ELVN-001 selectively inhibits ABL with low off-target activity against other kinases[1]

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
Imatinib	82	>10,000	230	9,600	>10,000
Asciminib	>10,000	>10,000	>10,000	>10,000	>10,000

Off-target kinase inhibition (IC50) by ELVN-001 vs. approved ABL TKIs in cell-based assays

ELVN-001 maintains activity against T315I and other BCR::ABL1 mutations known to confer resistance to asciminib[1-3]

Fold-Shift from 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
Vodobatinib	445	2	1	3	10	7	2
Olverembatinib	5	2	1	3	6	6	2

Antiproliferative activity of ELVN-001 vs. approved ABL TKIs in Ba/F3 cells harboring various BCR::ABL1 mutations

A337T and M244V were the most frequent emergent mutations to asciminib and F359C/V were the most frequent mutations at baseline in patients resistant to asciminib in ASCEMBL[4]

ASCEMBL = phase 3 study of asciminib vs bosutinib in CML after 2 or more prior TKIs. BCR::ABL1 = breakpoint cluster region-Abelson leukemia virus 1. IC_{50} = half-maximal inhibitory concentration. nM = nanomolar. TKI = tyrosine kinase inhibitor. WT = wildtype.
Cell viability measured with Cell titer glo luminescent assay. Values expressed as fold-shift in IC_{50} from $BCR::ABL1^{WT}$.

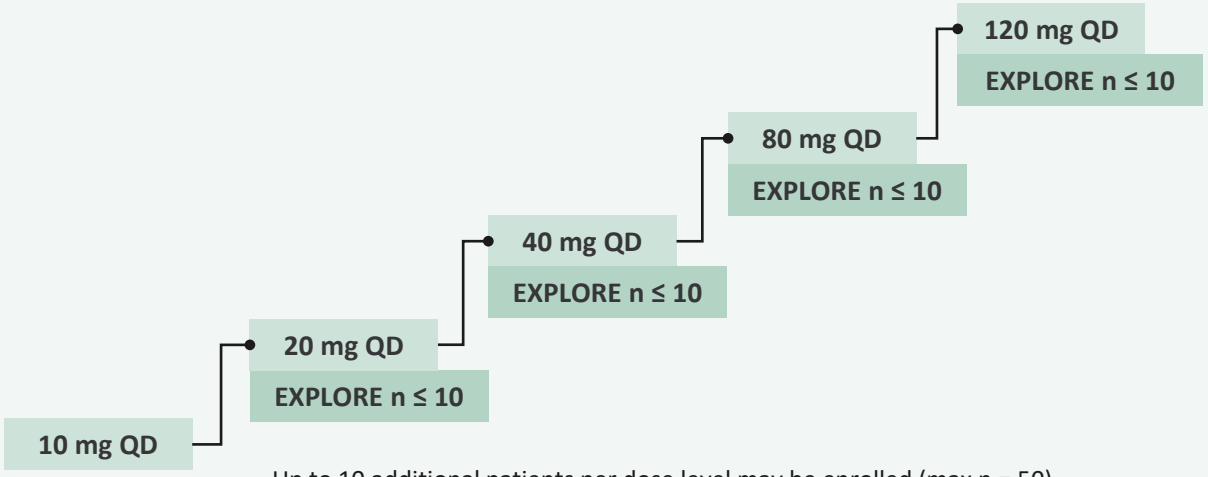
References: 1. Enliven data on file; 2. Réa D and Hughes TP. Development of asciminib, a novel allosteric inhibitor of BCR-ABL1. Crit Rev Oncol Hematol. 2022;171:103580.; 3. Qiang W et al. Mechanisms of Resistance to the BCR-ABL1 Allosteric inhibitor Asciminib. Leukemia. 2017;31(12):2844-2847.; 4. Réa D et al. A phase 3, open-label, randomized study of asciminib, a STAMP inhibitor, vs bosutinib in CML after 2 or more prior TKIs. Blood. 2021;138:2031-2041.

ENABLE (ELVN-001-101): Trial Design

Key eligibility criteria:

- Chronic Phase CML (CP-CML)
- Failed, intolerant to, or not a candidate for, available therapies known to be active for treatment of their CML[a]

Phase 1a: Dose Escalation[b]



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

Phase 1b: Dose Expansion

Dose level 1 Phase 1b expansion in CP-CML no T315I mutations; n=20	**Dose level 2** Phase 1b expansion in CP-CML no T315I mutations; n=20	**T315I** Phase 1b expansion in CP-CML with T315I mutations; n=20

Additional expansion cohorts may be opened for patients based on emerging data

Primary endpoints:

- Incidence of dose limiting toxicities, adverse events, clinically significant laboratory abnormalities and ECG abnormalities

Secondary endpoints (Phase 1a[d]):

- Pharmacokinetics parameters[c]
- Molecular response (MR) by central qPCR using the International System (measured every 4 weeks x 6, then every 12 weeks)

Clinicaltrials.gov Identifier: NCT05304377.
CML = Chronic myeloid leukemia. CP = Chronic phase. QD = Once daily. qPCR = Quantitative reverse transcriptase polymerase chain reaction. [a] In the United States, S. Korea, Australia, EU; at least 2 prior therapies known to be active for treatment of their CML are required in Canada. [b] Re-enrollment and intra-subject dose escalation allowed if meeting specific criteria; BID (twice daily) dosing may be explored [c] area under the curve (AUC), maximum concentration (C_{max}), time at which C_{max} is observed (T_{max}), minimum concentration (C_{min}), terminal half-life ($t_{1/2}$) [d] Phase 1b additional secondary endpoints: duration of MR, BCR::ABL1 qPCR ≤ 1%, complete hematological response.

Patient Demographics and Baseline Characteristics

Parameter	All Patients (N = 39)
Age, years, median (range)	60 (29–76)
Male / female, n (%)	26/13 (66.7%/33.3%)
Race	
White	26 (66.7%)
Asian	9 (23.1%)
Black or African American	1 (2.6%)
Other or not reported	3 (7.7%)
ECOG performance status, n (%)	
0	32 (82.1%)
1	7 (17.9%)
Median time since diagnosis, months (range)	72.7 (5.2–240.6)
Typical *BCR::ABL1* transcript	36 (92.3%)[a]
BCR::ABL1 mutation at baseline (central)[b]	
T315I mutation, n (%)	4 (10.3%)[c]
E255V, n (%)	1 (2.6%)

[a] e13a2 and e14a2.
[b] Only available for patients with typical transcripts. Notable local testing in 1 patient with transcript level below the threshold for central mutational testing: A337T/V506M.
[c] Includes one re-enrolled patient, hence 3 individual patients with T315I.

Parameter	All Patients (N = 39)
Median number of prior TKIs, n (range)	3 (0–6)[d]
2 prior TKIs, n (%)	10 (25.6%)
3 prior TKIs, n (%)	11 (28.2%)
4 prior TKIs, n (%)	6 (15.4%)
≥ 5 prior TKIs, n (%)	10 (25.6%)
Prior TKI, n (%)	
Dasatinib	30 (76.9%)
Imatinib	28 (71.8%)
Asciminib	21 (53.8%)
Ponatinib	20 (51.3%)
Nilotinib	19 (48.7%)
Bosutinib	10 (25.6%)
Reason for discontinuation of last TKI, n (%)[e]	
Lack of efficacy	27 (69.2%)
Lack of tolerability	11 (28.2%)

[d] Number reflects individual TKIs. Median lines of prior TKIs is 4 (range 0-9). Range includes recently enrolled patient whose prior history had not been entered yet and one patient with 1 prior TKI who discontinued ELVN-001 after 1 dose due to protocol violation.
[e] One patient had no prior history entered.

Data cutoff date: 25 June 2024.
BCR::ABL1 = breakpoint cluster region-Abelson leukemia virus 1. ECOG = Eastern Cooperative Oncology Group. TKI = tyrosine kinase inhibitor.
NOTE: Patients who had gone through intra-patient dose escalation as per protocol were counted under their initial treatment group only. Patients who were re-enrolled were counted under their initial treatment group and their re-enrolled treatment group.

Patient Disposition

	ELVN-001 Dose Group					Total[a] (N = 39)
	10 mg QD (n = 3)	20 mg QD (n = 7)	40 mg QD (n = 11)	80 mg QD (n = 11)	120 mg QD (n = 7)	
Median Duration of Exposure, weeks (range)	10 (4–80)	53 (0.1–64)	31 (0.3–45)	20 (0.3–32)	8 (0.3–20)	20 (0.1–80)
Ongoing, n (%)	1 (33.3%)[a]	5 (71.4%)	10 (90.9%)[a]	11 (100%)	5 (71.4%)	32 (82.1%)
Discontinued, n (%)	2 (66.7%)	2 (28.6%)	1 (9.1%)		2 (28.6%)	7 (17.9%)[b]
Due to AE	1 (33.3%)	1 (14.3%)				2 (5.1%)
Due to lack of efficacy	1 (33.3%)[c]		1 (9.1%)[c]		2 (28.6%)[d]	4 (10.3%)
Due to protocol violation		1 (14.3%)				1 (2.6%)

[a] Includes 2 re-enrolled patients (number of individuals enrolled was 37); [b] Includes 2 re-enrolled patients who discontinued at initial enrolled dose level. [c] Both patients who discontinued due to lack of efficacy at 10 mg and 40 mg were re-enrolled at higher dose levels (40 mg and 120 mg, respectively). [d] The 2 patients who discontinued at 120mg QD both discontinued prior asciminib and ponatinib for lack of efficacy; one had CML with T315I mutation and was the same patient who discontinued 40 mg, the other had CML with E255V mutation.

Data cutoff: 25 June 2024.
AE = adverse event. QD = once daily.
NOTE: Patients who had gone through intra-patient dose escalation as per protocol were counted under their initial treatment group only. Patients who were re-enrolled were counted under their initial treatment group and their re-enrolled treatment group.

Hematologic Treatment Emergent Adverse Events

Hematologic TEAEs

Preferred term n (%)	ELVN-001 Dose Group										Total (N = 37)	
	10 mg QD (n = 3)		20 mg QD (n = 7)		40 mg QD (n = 11)		80 mg QD (n = 11)		120 mg QD (n = 7)			
	Any Gr	Gr 3/4	Any Gr	Gr 3/4	Any Gr	Gr 3/4	Any Gr	Gr 3/4	Any Gr	Gr 3/4	Any Gr	Gr 3/4
Neutropenia[a]	2 (66.7%)	2 (66.7%)	2 (28.6%)	2 (28.6%)	0	0	0	0	0	0	4 (10.8%)	4 (10.8%)
Thrombocytopenia[b]	0	0	2 (28.6%)	2 (28.6%)	0	0	2 (18.2%)	0	0	0	4 (10.8%)	2 (5.4%)
Leukopenia[c]	0	0	0	0	0	0	1 (9.1%)	0	0	0	1 (2.7%)	0
Pancytopenia	0	0	1 (14.3%)	1 (14.3%)	0	0	0	0	0	0	1 (2.7%)	1 (2.7%)
Anemia	1 (33.3%)	0	1 (14.3)	0	0	0	0	0	0	0	2 (5.4%)	0

[a] Grouped term for neutropenia includes neutrophil count decreased; [b] Grouped term for thrombocytopenia includes platelet count decreased; [c] Grouped term for leukopenia includes white blood cell count decreased;

- Most Grade 3/4 TEAEs were hematologic, all occurring within the first 8 weeks
- No dose reductions due to cytopenias
- One patient discontinued ELVN-001 in the setting of Gr 3/4 cytopenias (at 20 mg QD; DLT)
- No exposure-toxicity relationship identified to date

Data cutoff date: 25 June 2024.. DLT = dose-limiting toxicity. Gr = Grade. QD = once daily. TEAE = treatment-emergent adverse event. TKI = Tyrosine Kinase Inhibitor.
NOTE: Severity grades were defined by CTCAE (Common Terminology Criteria for Adverse Events) Version 5.0. Patients who had gone through intra-patient dose escalation as per protocol were counted under their initial treatment group only. Patients who were re-enrolled were counted under their initial treatment group and their re-enrolled treatment group but counted as one patient in the total column

Low Incidence of Non-Hematologic Adverse Events Consistent with Selective Kinase Profile

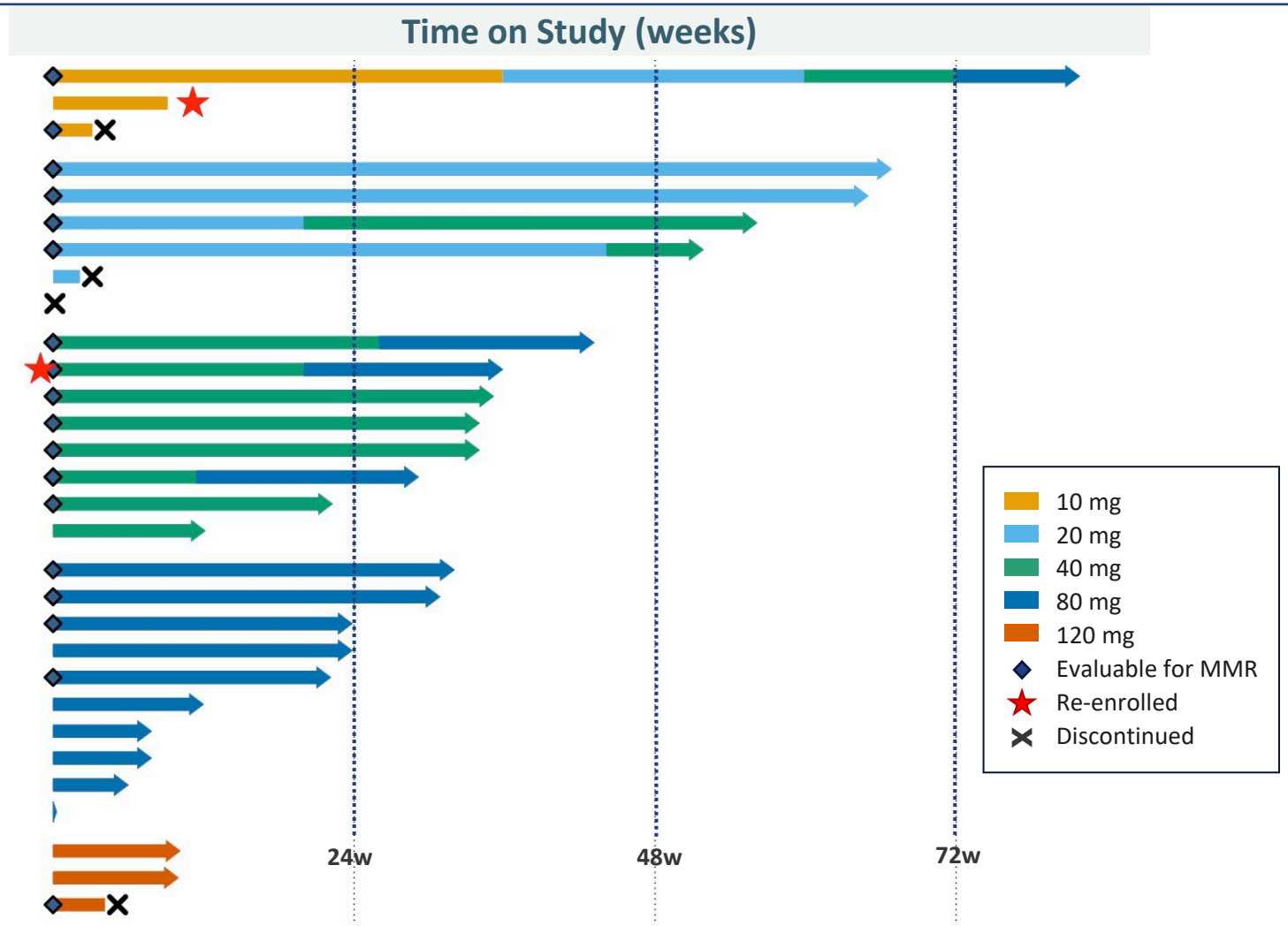
Non-Hematologic TEAEs in ≥ 10% of Patients

Preferred term n (%)	ELVN-001 Dose Group										Total (N = 37)	
	10 mg QD (n = 3)		20 mg QD (n = 7)		40 mg QD (n = 11)		80 mg QD (n = 11)		120 mg QD (n = 7)			
	Any Gr	Gr 3/4	Any Gr	Gr 3/4	Any Gr	Gr 3/4	Any Gr	Gr 3/4	Any Gr	Gr 3/4	Any Gr	Gr 3/4
Headache	2 (66.7%)	0	2 (28.6%)	0	0	0	1 (9.1%)	0	0	0	5 (13.5%)	0
Lipase increased	1 (33.3%)	0	1 (14.3%)	0	1 (9.1%)	0	2 (18.2%)	0	0	0	5 (13.5%)	0
Arthralgia	0	0	1 (14.3%)	0	0	0	1 (9.1%)	0	2 (28.6%)	0	4 (10.8%)	0
Diarrhea	1 (33.3%)	0	1 (14.3%)	0	0	0	2 (18.2%)	0	0	0	4 (10.8%)	0
Nausea	0	0	1 (14.3%)	0	0	0	2 (18.2%)	0	1 (14.3%)	0	4 (10.8%)	0

- Almost all non-hematologic TEAEs were low grade; two patients had Gr 3 TEAEs* (one with Gr 3 hypertriglyceridemia; one with Gr 3 proctitis and Gr 3 appendicitis)
- No dose reductions due to non-hematologic TEAEs
- One patient discontinued ELVN-001 due to SAE of Gr 2 pancreatitis (at 10 mg QD); no additional TEAEs of pancreatitis reported
- No exposure-toxicity relationship identified to date

Data cutoff date: 25 June 2024. Gr= Grade. QD = once daily. SAE = serious adverse event. TEAE = treatment-emergent adverse event; *assessed as not related by investigator
NOTE: Severity grades were defined by CTCAE (Common Terminology Criteria for Adverse Events) Version 5.0. Patients who had gone through intra-patient dose escalation as per protocol were counted under their initial treatment group only. Patients who were re-enrolled were counted under their initial treatment group and their re-enrolled treatment group but counted as one patient in the total column.

MMR Rate in CML without T315I Mutation by 24 weeks



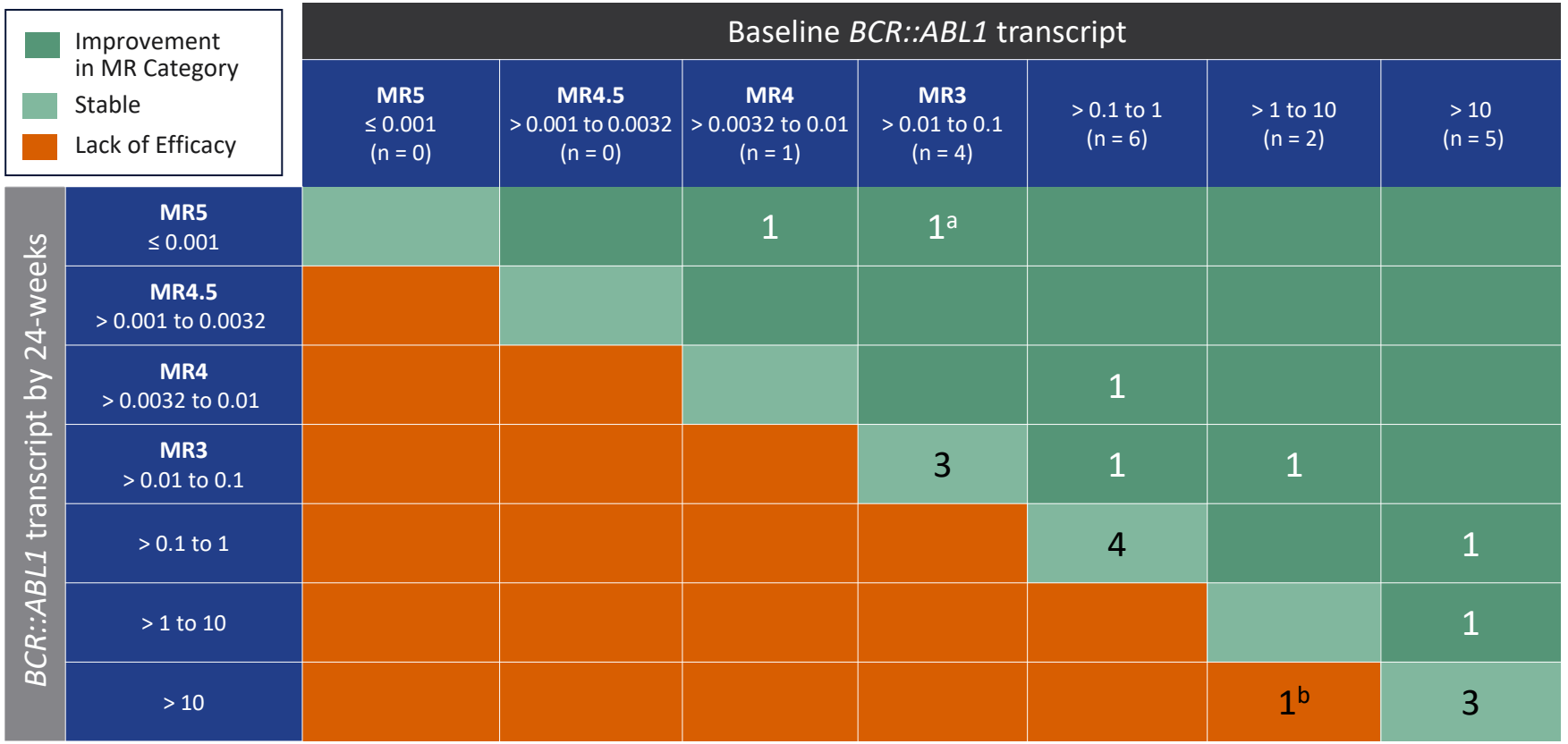
Cumulative MMR[a] by 24 weeks

	MMR, n/N (%)
All evaluable patients[b]	8/18 (44.4%[c])
Achieved MMR	3/13 (23.1%)
Maintained MMR	5/5 (100.0%)
TKI-resistant	5/12 (41.7%)
TKI-intolerant	3/6 (50.0%)
Post-asciminib	4/10 (40.0%)

NOTE: Swimmer plot includes all patients treated who had typical *BCR::ABL1* transcripts without T315I mutation.

Data cutoff date: 25 June 2024. BCR::ABL1 = breakpoint cluster region-Abelson leukemia virus 1. CML = chronic myeloid leukemia. MMR = major molecular response. qPCR = quantitative reverse transcriptase polymerase chain reaction. TKI = tyrosine kinase inhibitor. [a] Molecular response was assessed by central qPCR measured every 4 weeks x 6, then every 12 weeks. MMR is defined as BCR::ABL1 <0.1%; b Evaluable patients had baseline typical *BCR::ABL1* transcript without T315I mutation and postbaseline 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.
[c] 95% CI (21.5%, 69.2%)

Change in *BCR::ABL1* Transcript in CML without T315I mutation by 24 Weeks



Within 24 weeks of treatment:

7 patients with improved MR category

- 2 improved by 1 category
- 4 improved by 2 categories
- 1 improved by 3 categories

[a] Deep response (MR3 → MR5) in patient with lack of efficacy to prior asciminib and A337T mutation by local lab (below the threshold for central mutation testing).

[b] 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.

Data cutoff date: 25 June 2024. BCR::ABL1 = breakpoint cluster region-Abelson leukemia virus 1. CML = Chronic myeloid leukemia. MR = molecular response. Stable = transcript levels remain within listed category.
NOTE: MR5 category assigned based on transcript level; < limit of quantitation. Evaluable patients had baseline typical BCR::ABL1 transcript without T315I mutation and postbaseline 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 postbaseline assessments beyond 70 days were included in the analysis.

Summary

- **ELVN-001, a novel active-site inhibitor of BCR::ABL1, has an emerging safety profile consistent with its kinase selectivity**
  - Low Incidence of Adverse Events Consistent with Selective Kinase Profile
    - Most TEAEs were Grade 1-2
    - Hematologic TEAE profile consistent with that observed in CML patients treated with TKIs
  - No dose reductions due to TEAEs and at ≥ 40mg, no discontinuations due to TEAEs
  - Early data support wide therapeutic window with no exposure-toxicity relationship identified to date

- **Despite a heavily pretreated population, early evidence of anti-CML activity**
  - Cumulative MMR rate of 44.4% by 24 weeks
  - Encouraging anti-CML activity in patients resistant to prior TKIs
  - Anti-CML activity in patients who received prior asciminib, including one patient with an A337T mutation
  - To date, no emerging mutations identified[a]

The phase 1 study is active and recruiting (NCT05304377)

BCR::ABL1 = breakpoint cluster region-Abelson leukemia virus 1. CML = chronic myeloid leukemia. MMR = major molecular response. TEAE = treatment emergent adverse event. TKI = tyrosine kinase inhibitor

[a] Data on file

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