ENABLE: A Phase 1 Study of ELVN-001, a selective active site inhibitor of BCR::ABL1, in patients with previously treated CML

Fabian Lang[1], Michael Mauro[2], Dong-Wook Kim[3], Dennis Dong Hwan Kim[4], Sebastian Kreil[5], Philipp le Coutre[6], Michael C. Heinrich[7], Sarah Altmeyer[8], Naranie Shanmuganathan[9], Elvira Mora Castera[10], Raquel de Paz Arias[11], Koji Sasaki[12], Franck E. Nicolini[13], Valerie Coiteux[14], Dragana Milojkovic[15], Gabriel Etienne[16], Yingsi Yang[17], Qi Wang[17], Brianna Hoffner[17], M. Damiette Smit[17], Andreas Hochhaus[18]

[1]Department of Hematology and Oncology, Goethe University Hospital Frankfurt, Frankfurt, Germany; [2]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [3]Uijeongbu Eulji Medical Center, Geumo-dong, Uijeongbu-si, South Korea; [4]Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, Canada; [5]Medizinische Fakultät Mannheim der Universität, Heidelberg, Germany; [6]Charité-Universitätsmedizin Berlin, Berlin, Germany; [7]Knight Cancer Institute, Portland, OR, USA; [8]Universitätsklinikum des Saarlandes, Homburg, Germany; [9]Royal Adelaide Hospital, Adelaide, South Australia, Australia; [10]Hospital Universitario y Politecnico La Fe, Valencia, Spain; [11]Hospital Universitario La Paz, Madrid, Spain; [12]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [13]Centre Léon Bérard & INSERM; U1052 CRCL, Lyon, France; [14]Service des Maladies du Sang Hôpital Huriez - CHRU de Lille, Lille, France; [15]Hammersmith Hospital, Imperial College NHS Trust, London, England; [16]Institut Bergonie - Centre Regional de Lutte Contre Le Cancer de Bordeaux et Sud Ouest, Bordeaux, France; [17]Enliven Therapeutics, Boulder, CO, USA; [18]Universitätsklinikum Jena, Jena, Germany

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Disclosures

Dr. Fabian Lang

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Why is There Still an Unmet Need in CML?

Off-Target Toxicity

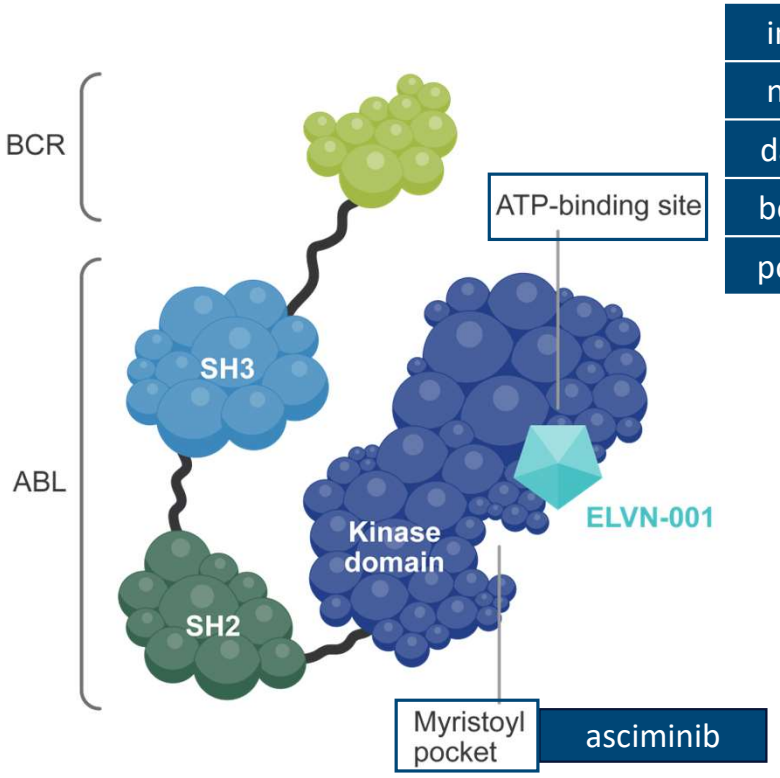
- Available ATP-competitive TKIs have poor kinase selectivity, resulting in off-target toxicity via KIT, FLT3, PDGFRB, VEGFR2 and/or SRC[1]

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]

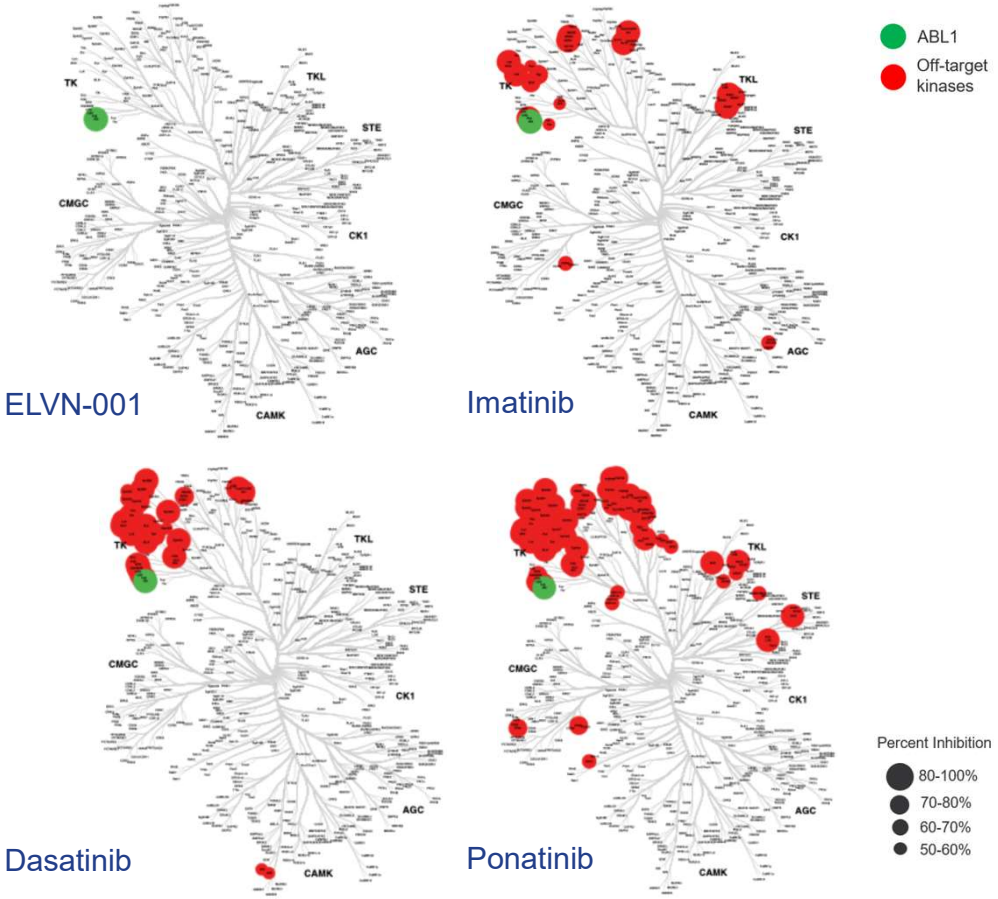


ATP, adenosine triphosphate; BCR::ABL1, breakpoint cluster region-Abelson leukemia virus 1; BCRP, breast cancer resistance protein; CML, chronic myeloid leukemia; P-gp, P-glycoprotein; TKI, tyrosine kinase inhibitor.

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[1], with potential for better tolerability
  - Creates a narrow tunnel allowing binding to T315I and other mutations
- Able to take with or without food, not a P-gp or BCRP substrate or inhibitor
- Not an inhibitor or substrate of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, and CYP3A5
- Maintains activity against T315I and emerging BCR::ABL1 mutations known to confer resistance to asciminib *in vitro*



1. Right panel: 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 mM ATP concentration in the screen (Reaction Biology). Metz, Kathleen S. et al. Cell Systems, Volume 7, Issue 3, 347 - 350.e1

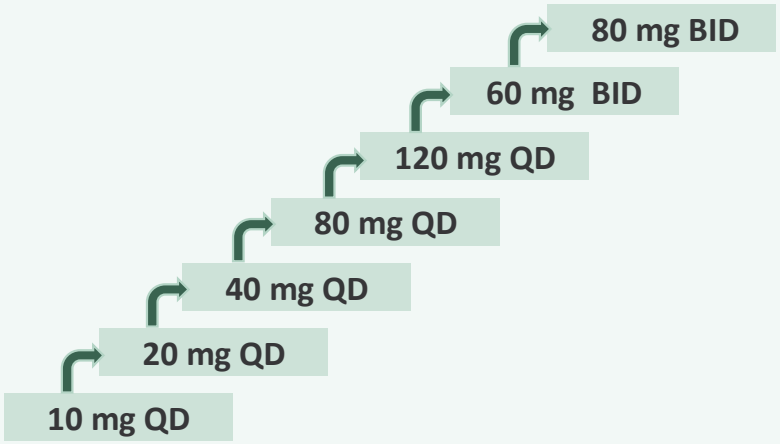
ELVN-001: Phase 1 Trial Design

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	**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

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Parameter	All Patients[a] (N = 90)
Age, years, median (range)	58 (19–79)
Male / female	58%/42%
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 mutation	9%[d]
Other mutations	7%
Not available	30%

[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 asciminib and/or ponatinib (any time)	
Asciminib[f]	58%
Ponatinib	43%
Last prior TKI asciminib or ponatinib	
Asciminib	31%
Asciminib + ATP-competitive TKI[g]	2%
Ponatinib	21%
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).
[f]Most (50/52 patients) received prior asciminib as third line treatment or later.
[g]Imatinib (n=1) and ponatinib (n=1)

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

Patient Disposition

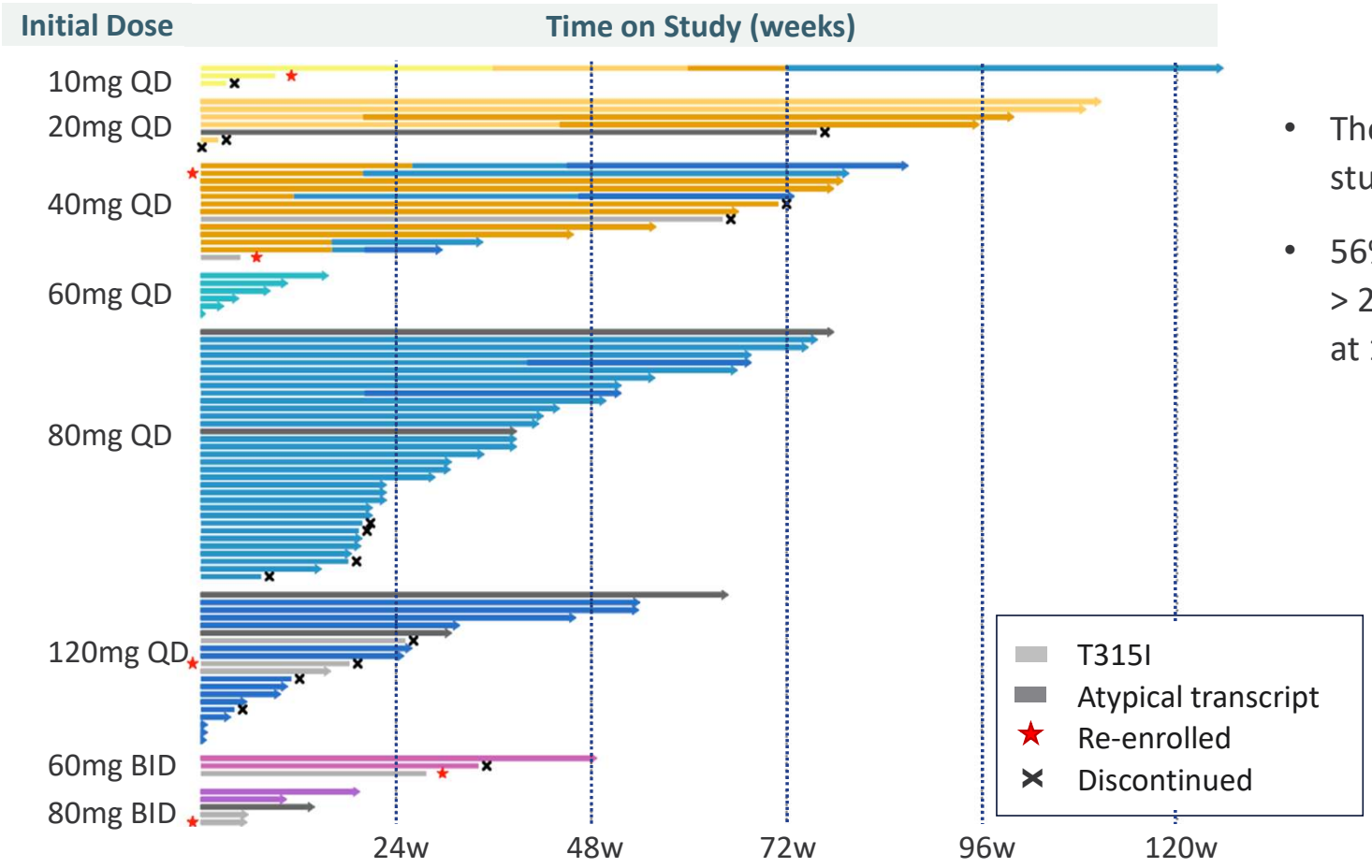
Disposition	Total (N = 90)
Median duration of exposure, weeks (range)	29 (0.1–126)
Ongoing, n (%)	72 (80.0%)
Discontinued, total n (%)	18 (20.0%)
Lack of efficacy	11 (12.2%)[a]
Adverse event	4 (4.4%)
Death	1 (1.1%)
Protocol violation	1 (1.1%)
Withdrawal of consent	1 (1.1%)

[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)

AE, adverse event.
Data cutoff: 28 Apr 2025.

Duration on Study Treatment



- The majority of patients remain on study (80% ongoing)
- 56% of patients have been on study > 24 weeks, with the longest ongoing at 126 weeks (~2.5 years)

NOTE: Study allows re-enrollment and intrasubject dose escalation, as shown by change in color.
Data cutoff: 28 Apr 2025.

ESH-iCMLf 2025: October 10-12, 2025; Estoril, Portugal

Safety Profile Consistent with ELVN-001's Selectivity for ABL1

Treatment Emergent Adverse Events (TEAEs) in ≥ 10% of Patients (any grade)

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)
Lipase increased	3 (13.0%)	0	7 (21.2%)	4 (20.0%)	2 (25.0%)	16 (18.4%)
Diarrhoea	3 (13.0%)	0	5 (15.2%)	4 (20.0%)	1 (12.5%)	13 (14.9%)
Thrombocytopenia[a]	4 (17.4%)	0	6 (18.2%)	0	2 (25.0%)	12 (13.8%)
Arthralgia	1 (4.3%)	1 (16.7%)	6 (18.2%)	3 (15.0%)	0	11 (12.6%)
Headache	4 (17.4%)	0	5 (15.2%)	2 (10.0%)	0	11 (12.6%)
Fatigue	0	1 (16.7%)	4 (12.1%)	2 (10.0%)	2 (25.0%)	9 (10.3%)
Myalgia	1 (4.3%)	0	3 (9.1%)	4 (20.0%)	1 (12.5%)	9 (10.3%)

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

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 had Favorable Safety and Tolerability

- **Well-tolerated** across all evaluated doses (10 mg QD to 80 mg BID)
- **The majority of treatment-emergent adverse events (TEAEs) were low grade**
  - Hematologic TEAE profile similar to or better than other TKIs
  - Low frequency of non-hematologic TEAEs
- **Low TEAE incidence rate leading to dose adjustment**
  - Dose interruptions: 14 (16.1%)
  - Dose reductions: 3 (3.4%)
  - Discontinuations: 4 (4.6%)
- **Maximum tolerated dose has not been identified**
- **No exposure-toxicity relationship observed**

Data cutoff: 28 Apr 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%)
Overall MMR for 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

MMR, major molecular response.
Data cutoff: 28 Apr 2025.
Overall MMR by 24 weeks when excluding patients with resistance to prior asciminib: 20/35 (57%), with MMR achieved by 13/28 (46%).
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.

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

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.

Tolerance and Response Achieved in Multi-Intolerant Patient

Patient Information

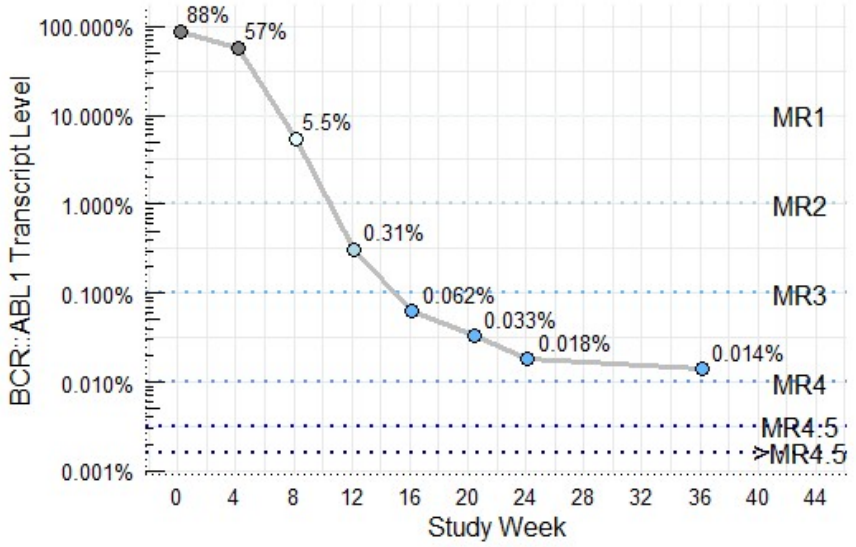
- 74-year-old male
- Primary diagnosis of CML in 2020
- Medical history notable for: pulmonary emphysema, diabetes mellitus, atrial fibrillation, hypertension, bilateral uveitis, chronic dry eye, osteoporosis and diverticular sigmoiditis

Prior TKI	Reason for Discontinuation	Time on Treatment
Imatinib	Acute renal insufficiency	139 days
Dasatinib	Pleural effusion	424 days
Asciminib	Pancreatitis	11 days
Bosutinib	Sepsis	374 days

Treatment-Emergent Adverse Events on ELVN-001 80 mg QD

- Grade 2 myalgia (R), Grade 2 bronchitis (NR), Grade 2 lower abdominal pain (NR), Grade 2 fungal skin infection (NR), Grade 1 peripheral edema (NR)

BCR::ABL1 Transcript on ELVN-001 80 mg QD



NR, not related to ELVN-001 per investigator; R, potentially related to ELVN-001 per investigator.
Data cutoff: 28 Apr 2025.

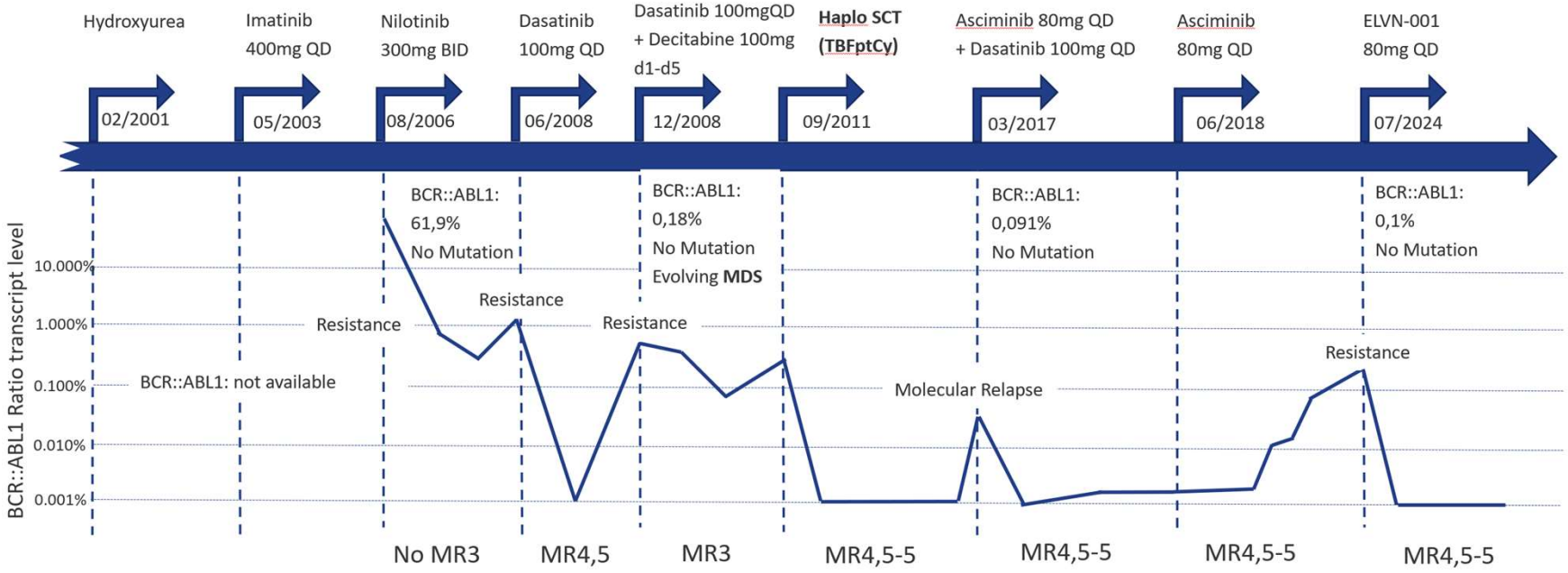
Anti-CML Activity in Patient with e13a3 Transcript

Patient Information

- 65-year-old female with primary diagnosis of CML in 2001
- Medical history: right bundle branch block, pulmonary emphysema, myelodysplastic syndrome, osteoporosis

Treatment-Emergent Adverse Events on ELVN-001

- None



d, day; Haplo-SCT, haploidentical stem cell transplantation; MDS, myelodysplastic syndrome; TBFptCY, thiotepa busulfan fludarabine with post transplant cyclophosphamide.
NOTE: Transcript analysis done by local laboratory, data on file at investigational site.
Graph represents illustrative timeline and is not according to scale.

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 with 47% MMR rate by 24 weeks**
  - 32% achieved MMR (not in MMR at baseline) and 52% achieved transcript ≤ 1% (> 1% at baseline)
  - Efficacy observed in patients exposed to prior asciminib or ponatinib
  - Anti-CML activity observed in a patient with an e13a3 transcript, which cannot be inhibited by allosteric TKIs
- **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**
- **Dose finding for patients with CML with T315I mutation is ongoing**
- **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.

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