CML-427

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AIM4CML Trial in Progress: A Phase IIIb Study of Asciminib Monotherapy in Patients With Chronic Myeloid Leukemia in Chronic Phase With and Without the T315I Mutation

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CONCLUSIONS

The phase IIIb AIM4CML trial is currently enrolling patients

AIM4CML is evaluating the efficacy and safety of asciminib 40 mg BID and 80 mg QD in patients with CML-CP without the T315I mutation treated with ≥2 prior TKIs and of asciminib 200 mg BID in patients with the T315I mutation treated with ≥1 prior TKI

Approximately 115 patients with CML-CP (without T315I, 90 patients; with T315I, 25 patients) will be recruited from multiple sites in the United States

This study aims to reinforce data for asciminib in the 3L+ setting reported in the phase III ASCEMBL study, strengthen efficacy and safety data from patients with CML-CP with the T315I mutation, and further assess a QD dosing regimen

Asciminib, via its novel mechanism of action as an ABL/BCR::ABL1 TKI that inhibits the BCR::ABL1 fusion protein by **Specifically Targeting the ABL Myristoyl Pocket (STAMP)**, has the potential to become the standard of care for later-line patients with CML-CP who were previously treated with ≥2 TKIs

This study is sponsored by Novartis Pharmaceuticals Corporation.
For more information, please refer to https://clinicaltrials.gov/ct2/show/NCT04666259.

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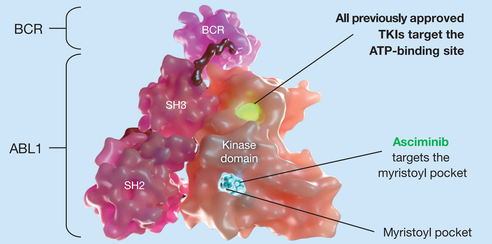
INTRODUCTION

- Tyrosine kinase inhibitors (TKIs) are the standard of care in the treatment and management of chronic myeloid leukemia (CML)[1,2]
- While most patients with CML receiving TKIs have life expectancies near that of the general population, many develop resistance to or intolerance of current therapies[3-7]
  - Patients with treatment failure with or intolerance of successive lines of TKI therapy, including those who develop resistance mutations, have few and often inadequate remaining treatment options[5,6]
  - Patients with the T315I mutation are resistant to all approved TKIs except ponatinib[5]
- Hence, there is a need to explore novel CML treatments, particularly for later-line patients who have cycled through multiple prior TKIs
- Asciminib is an ABL/BCR::ABL1 TKI that inhibits the ABL1 kinase activity of the BCR::ABL1 fusion protein by binding to the ABL myristoyl pocket (**Figure 1**)[8-11]
- Asciminib was recently approved in the United States for the treatment of[12]:
  - Adults with Philadelphia chromosome–positive (Ph+) CML in chronic phase (CP) previously treated with ≥2 TKIs (at 40 mg twice daily [BID] or 80 mg once daily [QD])
  - Adults with Ph+ CML-CP with the T315I mutation (at 200 mg BID)
- Here we describe the phase IIIb Asciminib in Monotherapy for CML-CP (AIM4CML) trial (NCT04666259), which was initiated to further evaluate the efficacy and safety of asciminib and to further explore a QD dosing regimen in patients with CML-CP

ASCIMINIB OVERVIEW

- Asciminib is an ABL/BCR::ABL1 TKI that inhibits the ABL1 kinase activity of the BCR::ABL1 fusion protein by binding to the ABL myristoyl pocket, contrasting with approved TKIs that bind to the ATP-binding site in BCR::ABL1 to block its kinase activity (**Figure 1**)[8-10]
- In a large phase I trial in heavily pretreated patients with CML, asciminib demonstrated efficacy and safety[11]
  - By 6 months, 37% and 25% of patients without and with the T315I mutation, respectively, achieved or maintained major molecular response (MMR)
  - The most frequent adverse events (AEs), most of which were grade 1 or 2, included fatigue, headache, and increased lipase level (occurring in ≥25% of patients)
- In the randomized, open-label, phase III ASCEMBL study comparing asciminib with bosutinib in patients with CML-CP after ≥2 prior ATP-competitive TKIs, asciminib demonstrated superior efficacy vs bosutinib and an improved safety profile[13-14]
  - The MMR rate at weeks 24 and 96 was 25.5% and 37.6%, respectively, with asciminib vs 13.2% and 15.8% with bosutinib, respectively
  - Fewer grade ≥3 AEs occurred with asciminib (56.4%) than bosutinib (68.4%), and fewer AEs leading to treatment discontinuation were reported with asciminib (7.7%) than bosutinib (26.3%) by the week 96 cutoff (Oct 6, 2021)

Figure 1. Asciminib Is an ABL/BCR::ABL1 TKI That Inhibits the ABL1 Kinase Activity of the BCR::ABL1 Fusion Protein by Binding to the ABL Myristoyl Pocket



STUDY DESIGN AND METHODS

- AIM4CML is a multicenter, phase IIIb, open-label, 3-cohort study of asciminib in patients with CML-CP without the T315I mutation after ≥2 prior TKIs and those with the T315I mutation after ≥1 prior TKI (**Figure 2**)
- The study comprises the following cohorts:
  - Asciminib 40 mg BID in patients with CML-CP without the T315I mutation (cohort A)
  - Asciminib 80 mg QD in patients with CML-CP without the T315I mutation (cohort B)
  - Asciminib 200 mg BID in patients with CML-CP with the T315I mutation (cohort C)
  - Baseline mutation testing to confirm historical T315I mutation status and ensure patients have not acquired new kinase domain mutations is required for all eligible patients
- Key eligibility criteria are summarized in **Table 1**
- Study objectives are described in **Table 2**

Figure 2A. Study Design

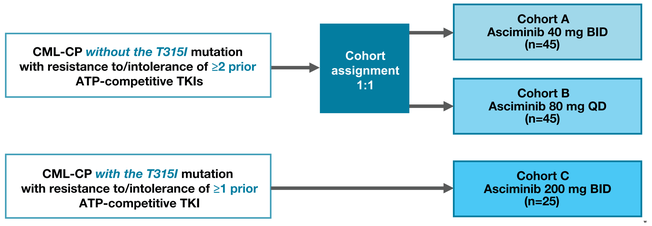
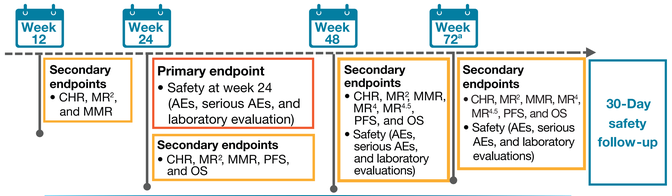


Figure 2B. Study Endpoints



[a]Patients will remain on study for 72 weeks after the last patient's first dose, unless they have discontinued early due to unacceptable toxicity, disease progression, and/or at the discretion of the investigator or the patient.

Table 1. Overview of Eligibility Criteria

Key inclusion criteria	Key exclusion criteria
Adults (≥18 years of age) with a diagnosis of CML-CP	Known second CML-CP after previous progression to CML-AP/BP
Prior treatment with ≥2 ATP-competitive TKIs in patients without the T315I mutation ***or*** ≥1 ATP-competitive TKI in patients with the T315I mutation	Previous hematopoietic stem cell transplant
Treatment failure (adapted from the 2020 ELN recommendations) with or intolerance of the most recent TKI at screening	Cardiac or cardiac repolarization abnormality
Evidence of typical *BCR::ABL1* transcripts at screening	Severe and/or uncontrolled concurrent disease that could cause unacceptable safety risks or compromise compliance with the protocol
ECOG performance status of 0, 1, or 2	History of acute pancreatitis within 1 year of study entry or medical history of chronic pancreatitis
Acceptable laboratory values at screening, including: – <15% blasts and <30% blasts + promyelocytes in peripheral blood and/or bone marrow and <20% basophils in peripheral blood – ≥50 × 10^9/L platelets – Transient prior therapy–related thrombocytopenia is acceptable – No evidence of extramedullary leukemic involvement (except hepatosplenomegaly)	Impaired GI function or GI disease that may significantly alter the absorption of study drug
Adequate end-organ function within 12 days of the first dose of asciminib (patients with renal and hepatic impairment being eligible if total bilirubin, serum lipase, and creatinine clearance criteria are met) and electrolytes within normal limits before the first dose of asciminib	
Mutation analysis testing performed 6 months before study entry	

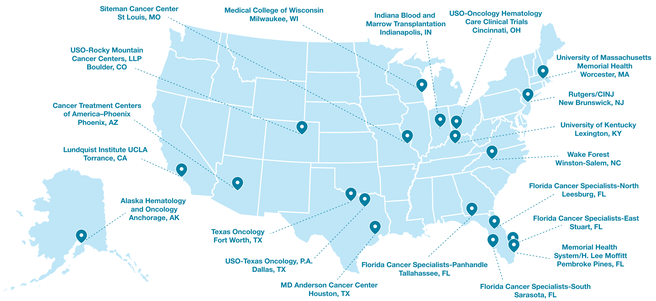
Table 2. Study Objectives

Primary objective	• Evaluate the safety profile of asciminib monotherapy in patients in the 3L and beyond (3L+) in cohorts A and B for 24 weeks
Secondary objectives	• Evaluate the safety profile of asciminib monotherapy in cohorts A, B, and C for 48 and 72 weeks • Estimate hematologic response and MR rates by specific time points • Estimate time to and duration of hematologic response and MR • Assess progression-free survival and overall survival during 72 weeks
Exploratory objectives	• Assess the pharmacokinetics profile of asciminib 40 mg BID, 80 mg QD, and 200 mg BID • Test for the presence of low-level mutations during asciminib treatment • Determine the impact of asciminib on patient symptom burden and quality of life during 72 weeks • Evaluate health care resource utilization during 72 weeks

CURRENT STATUS

- This study is currently enrolling patients in the United States (**Figure 3**)

Figure 3. Currently Enrolling Sites



Abbreviations

3L, third line; **ABL1,** Abelson tyrosine kinase 1; **AE,** adverse event; **AP,** accelerated phase; **ATP,** adenosine triphosphate; **BCR,** breakpoint cluster region; **BID,** twice daily; **BP,** blast phase; **CHR,** complete hematologic response; **CML-CP,** chronic myeloid leukemia in chronic phase; **ECOG,** Eastern Cooperative Oncology Group; **ELN,** European LeukemiaNet; **GI,** gastrointestinal; **IS,** International Scale; **MMR,** major molecular response (*BCR-ABL1*[IS] ≤0.1%); **MR**^{n}, molecular response; **MR**^{n}, (*BCR-ABL1*[IS] <1%; **MR**^{4}, *BCR-ABL1*[IS] ≤0.01%; **MR**$^{4.5}$, *BCR-ABL1*[IS] ≤0.0032%; **OS,** overall survival; **PFS,** progression-free survival; **QD,** once daily; **SH,** Src homology; **TKI,** tyrosine kinase inhibitor.

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References

1. Chopade P, Akard LP. *Clin Lymphoma Myeloma Leuk.* 2018;18:710-723. **2.** Sasaki K, et al. *Lancet Haematol.* 2015;2:e186-e193. **3.** Jabbour E, et al. *Hematol Oncol Clin North Am.* 2011;25:981-995. **4.** Patel AB, et al. *Hematol Oncol Clin North Am.* 2017;31:589-612. **5.** NCCN Clinical Practice Guidelines. Chronic Myeloid Leukemia. V2.2022. **6.** Jabbour E, et al. *Clin Lymphoma Myeloma Leuk.* 2015;15:323-334. **7.** Akard LP. *Clin Adv Hematol Oncol.* 2013;11:421-432. **8.** Schoepfer J, et al. *J Med Chem.* 2018;61:8120-8135. **9.** Wylie AA, et al. *Nature.* 2017;543:733-737. **10.** Manley P, et al. *Leuk Res.* 2020;98:106458. **11.** Hughes TP, et al. *N Engl J Med.* 2019;381:2315-2326. **12.** Scemblix [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2021. **13.** Réa D, et al. *Blood.* Published online August 18, 2021. doi:10.1182/blood.2020009884. **14.** Réa D, et al. Oral presentation at: 2022 ASCO Annual Meeting; June 3-7, 2022; Chicago, IL, and virtual. Abstract 7004. **15.** Réa D, et al. Oral presentation at: EHA 2022 Hybrid Congress; June 9-17, 2022; Vienna, Austria, and virtual. Abstract S155.