CML-433

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ASC2ESCALATE Trial in Progress: A Phase II, Single-Arm, Dose-Escalation Study of Asciminib Monotherapy in Patients With Chronic Myeloid Leukemia in Chronic Phase Previously Treated With 1 Prior Tyrosine Kinase Inhibitor

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CONCLUSIONS

ASC2ESCALATE is the first clinical trial designed to evaluate the safety and efficacy of asciminib monotherapy in **patients with CML-CP who require a 2L therapy** after experiencing treatment failure with or intolerance of a prior ATP-competitive TKI

ASC2ESCALATE will investigate the safety and efficacy of **asciminib dose escalation** in patients who are not achieving treatment milestones responses at 6 and 12 months

An early switch to asciminib (the first BCR::ABL1 inhibitor to **S**pecifically **T**arget the **A**BL **M**yristoyl **P**ocket) for patients with CML-CP who are not meeting 1L treatment milestones could allow more patients to achieve molecular responses and provide another option for those with resistance to or intolerance of ATP-competitive TKIs

ASC2ESCALATE is planned to begin recruitment in Q3 2022
- FPFV is anticipated in **Q3 2022**
- The anticipated enrollment is approximately **92 patients** with CML-CP at approximately **40 sites** in the United States

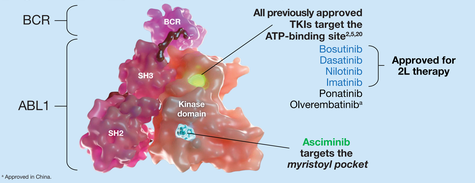
This study is sponsored by Novartis Pharmaceuticals Corporation.
For more information, please refer to https://clinicaltrials.gov/ct2/show/NCT05384587.

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INTRODUCTION

- ATP-competitive tyrosine kinase inhibitors (TKIs), such as imatinib and second-generation TKIs, are the standard of care for first-line (1L) treatment of chronic myeloid leukemia in chronic phase (CML-CP), with most patients receiving TKI therapy demonstrating normal life expectancy[1-4]
- However, a subset of patients with resistance to or intolerance of 1L TKI therapy need to switch to a second-line (2L) therapy[2,5]
- Approved 2L therapies are limited to ATP-competitive TKIs with the same mechanism of action and similar safety and tolerability profiles.[2,5] Roughly 28% to 40% of patients discontinue their 1L therapy by 5 years,[6-9] and 20% to 30% discontinue 2L therapy due to disease progression[10-12]
- Asciminib is the first BCR::ABL1 inhibitor to **S**pecifically **T**arget the **A**BL **M**yristoyl **P**ocket (**STAMP**) (**Figure 1**), allowing asciminib to have activity against most *BCR::ABL1* mutations that are resistant to ATP-competitive TKIs.[13-16] Additionally, asciminib specifically targets BCR::ABL1, ABL1, and ABL2, with limited off-target activity, unlike approved ATP-competitive TKIs, which have a broad kinase target spectrum[17,18]
- Here we present the upcoming **phase II ASC2ESCALATE** trial (NCT05384587) evaluating **asciminib** monotherapy with dose escalation for 2L treatment of **CML-CP**[19]
  - This study will assess safety and efficacy of asciminib in the 2L setting for patients with CML-CP, including those whose initial dose does not lead to the achievement of treatment milestones at 6 and 12 months

Figure 1. Asciminib Is the First BCR::ABL1 Inhibitor to Specifically Target the ABL Myristoyl Pocket (STAMP)[13]

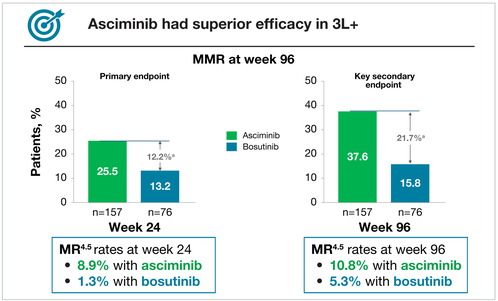


[a] Approved in China.

ASCIMINIB OVERVIEW

- Asciminib was first **approved** in the **United States** for the treatment of adults with Philadelphia chromosome–positive (Ph+) CML-CP previously treated with ≥2 TKIs and Ph+ CML-CP with the T315I mutation, based on data from 2 pivotal trials[13,21,22]
  - In **X2101**, a phase **I**, dose-escalation study, asciminib demonstrated **favorable safety across doses of 80 to 200 mg once daily** (QD) and **10 to 200 mg twice daily** (BID) in patients with CML-CP without the T315I mutation who had ≥2 prior lines of TKI therapy[22]
  - In the phase III **ASCEMBL** study, **asciminib** demonstrated **superior efficacy** and **better safety and tolerability** than bosutinib in adult patients with CML-CP treated with ≥2 prior TKIs (**Figure 2**)[13,23,24]
    - » Major molecular response (MMR, *BCR::ABL1*^{IS} ≤0.1%) rates continued to increase over time and remained higher with asciminib than bosutinib; deep molecular response rates were also higher with asciminib than bosutinib
    - » After longer follow-up, there were no new or worsening safety findings with asciminib, and its safety and tolerability continued to be better than those of bosutinib

Figure 2. Efficacy and Safety Results From the Phase III ASCEMBL Study



* The treatment difference after adjusting for baseline major cytogenetic response status was 12.24% (95% CI, 2.19%-22.30%; 2-sided P=.029) at week 24 and 21.74% (95% CI, 10.53%-32.95%; 2-sided P<.001) at week 96.

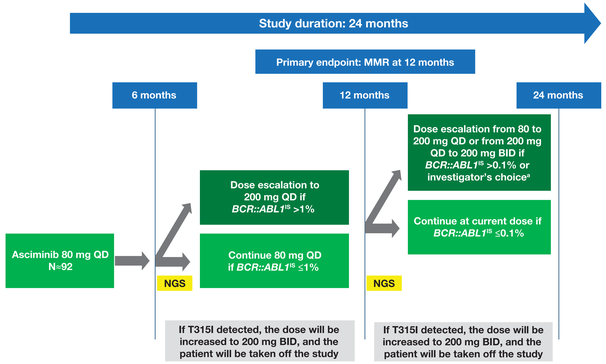
STUDY RATIONALE

- Although there are several currently available options for the treatment of patients who are **newly diagnosed** with CML-CP, some patients exhibit treatment **resistance** or **intolerance**, necessitating a **switch to 2L therapy**[2,5]
- The purpose of this study is to evaluate the **efficacy** and **safety** of **asciminib monotherapy** as a **2L treatment**
- The study will also evaluate whether patients with CML-CP with ***BCR::ABL1***^{IS} **levels >1%** and **>0.1% at 6 and 12 months**, respectively, could benefit from asciminib **dose escalation**
- This study aims to provide valuable **practical guidance** for the **use of asciminib** in patients with CML-CP who require a treatment switch due to intolerance of or resistance to 1L therapy

STUDY DESIGN AND METHODS

- ASC2ESCALATE is a single-arm, multicenter, phase II, open-label, **dose-escalation** study of **asciminib** in **patients with CML-CP without the T315I mutation** who received **1 prior** ATP-competitive **TKI** and discontinued due to treatment failure or intolerance (**Figure 3**)
- The purpose of this study is to evaluate the **efficacy** and **safety** of **asciminib** as a **2L therapy**
- Patients will be randomized to receive **asciminib 80 mg QD** with possible dose escalation at 6 months (to **200 mg QD**) if *BCR::ABL1*^{IS} levels remain >1% and at 12 months (to **200 mg QD** or **200 mg BID**) if patients have not achieved MMR
- Patients who achieve MMR at 12 months will continue asciminib at their current dose
- Patients may discontinue at any time due to unacceptable toxicity or disease progression or at investigator or patient discretion
- The study goal and endpoints are summarized in **Table 1**
- Key eligibility criteria are shown in **Table 2**

Figure 3. Study Design of the Single-Arm, Multicenter, Phase II, Open-Label, Dose-Escalation Study of Asciminib



[a] Patients switching to investigator's choice will be taken off study.

Table 1. Study Endpoints

The goal for this study is to determine efficacy of asciminib in patients with CML-CP in the 2L setting
Primary endpoint
Proportion of patients achieving MMR (*BCR::ABL1*^{IS} ≤0.1%) at 12 months
Secondary endpoints
Proportion of patients achieving MR$^{4.5}$ at 24 months
MMR rate by all scheduled data collection time points (3, 6, 18, and 24 months)
Time to and duration of MMR
Time to treatment failure
Time from first dose of study treatment to earliest occurrence of documented disease progression to CML-AP/BC or date of death from any cause, before cutoff date
Time from first dose of study treatment to death due to any cause during the study
Type, frequency, and severity of adverse events, changes in laboratory values that fall outside the predetermined ranges, and clinically notable ECG and other safety data (vital signs, physical examination findings)
Exploratory endpoint
BCR::ABL1 gene mutations on confirmed loss of response (per ELN 2013)

Table 2. Key Eligibility Criteria

Key inclusion criteria
Adults (≥18 years of age) with CML-CP with no previous CML-AP/BC
For patients with CML-CP with treatment failure with or resistance to 1L TKI:
a. *BCR::ABL1*^{IS} >10% at screening if 1L treatment duration between 6 and 12 months
b. *BCR::ABL1*^{IS} >1% at screening if 1L treatment longer than 12 months
For patients with CML-CP with treatment intolerance to 1L TKI, *BCR::ABL1*^{IS} >0.1% at screening
Previously treated with 1 ATP-competitive TKI for ≥6 months of therapy
Intolerance of TKI therapy and/or resistance to TKI therapy per ELN 2020
Adequate end-organ function within 12 days before the first dose of asciminib treatment (patients with mild to moderate renal and hepatic impairment being eligible if total bilirubin, AST, ALT, serum lipase, alkaline phosphatase, and creatinine clearance criteria are met)

Key exclusion criteria
Previous treatment with ≥2 ATP-competitive TKIs or asciminib
Known presence of the T315I mutation at any time prior to study entry
Known second CML-CP after previous progression to CML-AP/BC
Previous treatment with an HSCT or plans to undergo allogeneic HSCT
Cardiac or cardiac repolarization abnormality
History of acute pancreatitis within 1 year of study entry or medical history of chronic pancreatitis
Treatment with strong inducers of CYP3A (for patients receiving the asciminib dose of 80 or 200 mg QD) or strong inducers and inhibitors of CYP3A (for patients receiving the asciminib dose of 200 mg BID)

CURRENT STATUS

- ASC2ESCALATE is planned to begin recruitment in Q3 2022; it will enroll approximately 92 participants at approximately 40 sites in the United States
- The study will only be recruiting in the United States
- First patient's first visit (FPFV) is anticipated in Q3 2022
- The estimated primary completion date is February 2025, and estimated study completion date is February 2026

Abbreviations

1L, first line; **2L**, second line; **3L**, third line; **ABL**, Abelson tyrosine kinase; **AE**, adverse event; **ALT**, alanine aminotransferase; **AP**, accelerated phase; **AST**, aspartate aminotransferase; **ATP**, adenosine triphosphate; **BC**, blast crisis; **BCR**, breakpoint cluster region; **BID**, twice daily; **CML-CP**, chronic myeloid leukemia in chronic phase; **CYP3A**, cytochrome P450 3A; **ECG**, electrocardiogram; **ELN**, European LeukemiaNet; **FPFV**, first patient's first visit; **HSCT**, hematopoietic stem cell transplant; **IS**, International Scale; **MMR**, major molecular response (*BCR::ABL1*^{IS} ≤0.1%); **MR$^{4.5}$**, *BCR::ABL1*^{IS} ≤0.0032%; **NGS**, next-generation sequencing; **Ph**, Philadelphia chromosome; **Q**, quarter; **QD**, once daily; **SH**, Src homology; **STAMP**, Specifically Target the ABL Myristoyl Pocket; **TKI**, tyrosine kinase inhibitor.

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