Poster CML 532

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ASC4KIDS: A multicenter, open-label, phase 1b/2 study to determine the dose and safety of asciminib in pediatric patients with chronic myeloid leukemia in chronic phase (CML-CP)

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Conclusions

The ongoing ASC4KIDS study will support the development of asciminib for pediatric patients (≥1 to <18 years old) with Ph+ CML-CP (without T315I) and resistant to or intolerant of ≥1 prior TKI

The PK profile of asciminib in pediatric patients will be characterized with the goal of identifying the pediatric formulation dose in a fed state that leads to asciminib exposure comparable to 40 mg BID in adult patients (in a fasted state)

The results of this study will be used to support extrapolation of asciminib data from adults to the pediatric setting

Asciminib, the first BCR::ABL1 inhibitor to work by **S**pecifically **T**argeting the **A**BL **M**yristoyl **P**ocket (**STAMP**), has the potential to overcome resistance to TKIs and minimize AEs as a prospective new treatment option for pediatric patients with CML-CP

This study is sponsored by Novartis Pharmaceuticals Corporation.

For more information, please refer to **https://clinicaltrials.gov/ct2/show/NCT04925479**

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Introduction

- TKIs that inhibit BCR::ABL1 are the standard of care for adult and pediatric patients with CML-CP[1-3]
  - 6 TKIs are approved in Europe for adults: imatinib, dasatinib, nilotinib, bosutinib, ponatinib, and asciminib[4-6]
  - 3 TKIs are approved in Europe for pediatric patients: imatinib, dasatinib, and nilotinib[7-9]
- CML accounts for 2% to 3% of leukemias in children <15 years old and 9% in adolescents aged 15 to 19 years old[†]
- Growth retardation in the pediatric population has been reported with imatinib, dasatinib, and nilotinib[10-12]
- The longer life expectancy of pediatric patients likely necessitates longer exposure to TKIs, which can increase the risk of morbidities and decrease quality of life[1,2,10]
- Here, we present the ongoing ASC4KIDS phase 1b/2 trial (NCT04925479) evaluating the PK and safety profile of asciminib in pediatric patients to identify a safe pediatric formulation dose

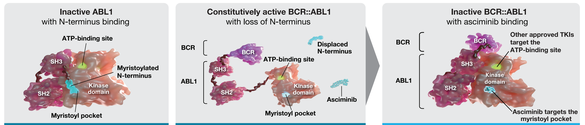
Asciminib overview

- Asciminib is approved in the following countries/regions:
  - In the US, for the treatment of adults with Ph+ CML-CP previously treated with ≥2 TKIs (at 40 mg BID or 80 mg QD), as well as those with Ph+ CML-CP and the T315I mutation (at 200 mg BID)[13]
  - In the EU, for the treatment of adults with Ph+ CML-CP previously treated with ≥2 TKIs (at 40 mg BID)[5,14]
  - In other countries including the United Kingdom and Switzerland (see local prescribing information for specific indications)[5,15]

Novel mechanism of action

- Asciminib is a potent and specific allosteric inhibitor of BCR::ABL1 that works by **S**pecifically **T**argeting the **A**BL **M**yristoyl **P**ocket (**STAMP**) (**Figure 1**)[16-18]
  - Asciminib's specificity is intended to avoid off-target effects from inhibition of other kinases, potentially leading to reduced toxicity
  - Targeting this novel site may help overcome resistance to approved TKIs

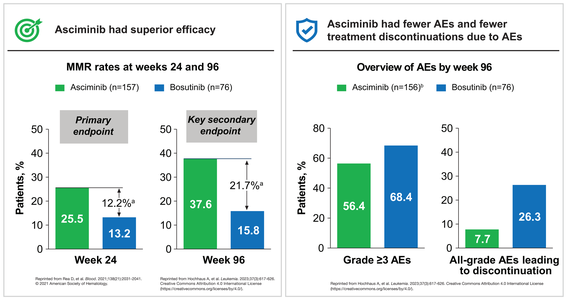
Figure 1. Asciminib Specifically Targets the ABL Myristoyl Pocket (STAMP)



Asciminib efficacy and safety in adults with CML-CP after ≥2 prior TKIs

- In the phase 3 ASCEMBL study, asciminib 40 mg BID demonstrated significantly superior efficacy and better safety and tolerability compared to bosutinib 500 mg QD in adults with CML-CP after ≥2 prior TKIs (**Figure 2**)[23,24]
- Asciminib was administered in the fasted state (defined as without food for 2 h before and 1 h after taking asciminib)[13]

Figure 2. Efficacy and safety results from the phase 3 ASCEMBL study[23,24]

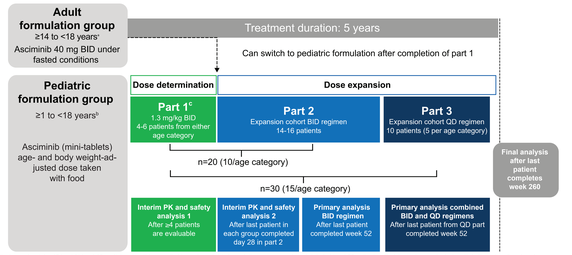


[a] The treatment difference after adjusting for baseline MC$_4$R status was 12.24% (95% CI, 2.19%-22.30%; 2-sided P=.029) at week 24 and 21.74% (95% CI, 10.53%-32.95%; 2-sided P=.001) at week 96; [b] 1 patient developed cytopenia after randomization and was not treated per investigator's decision.

Study design and methods

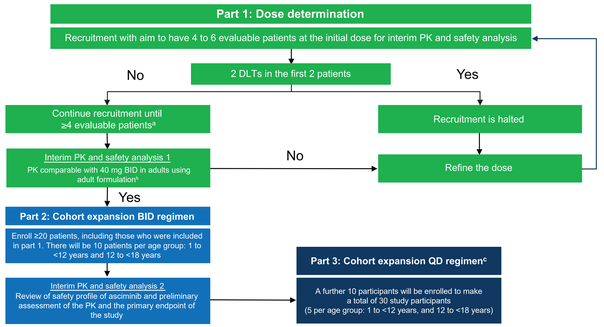
- ASC4KIDS is a phase 1b/2 multicenter, open-label, single-arm study to determine the appropriate dose of asciminib (pediatric formulation) in pediatric patients aged ≥1 to <18 years with Ph+ CML-CP, who are resistant to or intolerant of ≥1 prior TKI (**Figures 3a and 3b**)
- In the adult formulation group, adolescent patients, weighing ≥40kg, will receive asciminib 40 mg BID under fasting conditions and can switch to the pediatric formulation once part 1 is complete
- In the pediatric formulation group, patients will receive body weight–adjusted pediatric asciminib BID (in parts 1 and 2) or QD (in part 3) doses with food
  - In part 1 (dose determination), 4–6 participants will be enrolled to determine the dose of asciminib comparable to adults taking asciminib 40 mg BID under fasting conditions. The initial starting dose will be based on body weight and administered BID with food
  - In part 2 (cohort-expansion BID), 20 participants will be enrolled including participants from part 1. Participants will receive the dose determined in part 1 BID
  - In part 3 (cohort-expansion QD), 10 patients will be enrolled to receive the same total daily asciminib dose as in part 2 but given QD

Figure 3a. ASC4KIDS study design



[a] Patients must weigh ≥40 kg; [b] At least 15 participants will be enrolled in each pediatric formulation age group, for a total of at least 30 patients; [c] Part 1 may be conducted multiple times to refine dose by exposure.

Figure 3b. Decision tree for parts 1, 2, and 3



[a] ≤6 patients, depending on the variability of the PK parameters; [b] Permitted safety does not warrant any dose adjustments; [c] In part 2 and part 3 the same total daily dose will be administered but may be adjusted depending on the results of Interim PK and Safety Analysis 2.

- Study objectives and endpoints are summarized in **Figure 4**
- Key eligibility criteria are summarized in **Table 1**

Figure 4. Study objectives and endpoints

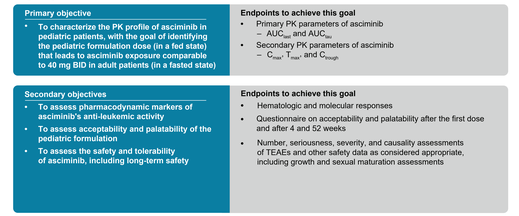


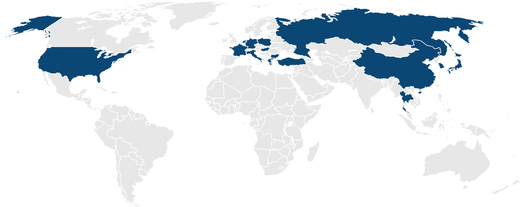
Table 1. Overview of eligibility criteria

Key inclusion criteria	Key exclusion criteria
• Pediatric formulation group: ≥1 and <18 years of age • Adult formulation group: ≥14 and <18 years of age and body weight of ≥40 kg at study entry	• Known presence of the T315I mutation prior to study entry
• Prior treatment with ≥1 TKI	• Known second CML-CP after previous progression to AP/BC
• Treatment failure (adapted from the 2020 ELN guidelines) or intolerance of the most recent TKI therapy at the time of screening[a]	• Previous or planned intention to undergo hematopoietic stem cell transplantation
• Evidence of typical *BCR::ABL1* transcripts at screening	• Cardiac or cardiac repolarization abnormality
• Performance status at screening: – Karnofsky ≥50% for patients ≥16 years of age – Lansky ≥50 for patients <16 years of age	• History of acute pancreatitis within 1 year of study entry or medical history of chronic pancreatitis • Impaired GI function or GI disease that may significantly alter the absorption of study drug

Current status

- Enrollment into ASC4KIDS is ongoing for parts 1-3
- As of 22 May 2023, 4 and 6 patients, respectively, have been enrolled in the adult and part 1-pediatric formulation groups
- The estimated primary completion date is September 14, 2026, and the estimated study completion date is October 4, 2030
- 30 study sites in the 14 countries shown in **Figure 5** are participating

Figure 5. Participating countries



Abbreviations

AE, adverse event; **AP**, accelerated phase; **AUC**, area under the curve; **AUC$_{inf}$**, AUC from time zero to the time of the last measurable concentration; **AUC$_{tau}$**, AUC over the dosing interval; **BC**, blast crisis; **BID**, twice daily; **C$_{max}$**, maximum plasma concentration; **C$_{trough}$**, trough plasma concentration; **DLT**, dose-limiting toxicity; **ELN**, European LeukemiaNet; **GI**, gastrointestinal; **MCyR**, major cytogenetic response; **MMR**, major molecular response; **Ph**, Philadelphia chromosome; **PK**, pharmacokinetic; **SH**, src homology; **QD**, once daily; **TEAE**, treatment-emergent adverse event; **T$_{max}$**, time to reach C$_{max}$; **TKI**, tyrosine kinase inhibitor.

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