Trial in Progress: A Multicenter, Open-Label, Phase Ib/Ii Study to Determine the Dose and Safety of Asciminib in Pediatric Patients With Philadelphia Chromosome–Positive Chronic Myeloid Leukemia in Chronic Phase Treated With ≥1 Prior Tyrosine Kinase Inhibitor

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Background

- CML accounts for 2% to 3% of leukemias in children <15 years old and 9% in adolescents aged 15 to 19 years old\(^1\)
- TKIs are the standard of care in CML, with 3 out of 5 available TKIs approved in pediatric patients\(^1\)\(^-\)\(^3\)
- The longer life expectancy of pediatric patients likely necessitates longer exposure to TKIs, which could increase the risk of morbidities and decrease quality of life\(^2\)
- Asciminib was recently approved by the US FDA for the treatment of adults with Ph+ CML-CP, previously treated with ≥2 TKIs and in those with the T315I mutation\(^4\)
- Now we present the upcoming ASC4KIDS phase Ib/II trial evaluating asciminib monotherapy in pediatric patients (NCT04925479), which will characterize the PK and safety profile of asciminib in pediatric patients and identify a pediatric formulation dose

CML, chronic myeloid leukemia in chronic phase; CP, chronic phase; Ph+, Philadelphia chromosome positive; PK, pharmacokinetic; TKIs, tyrosine kinase inhibitors; US FDA, United States Food and Drug Administration.

Asciminib Specifically Targets the ABL Myristoyl Pocket (STAMP)

**Normal conditions**
- **Inactive ABL1** with N-terminus binding

**In CML**
- **Constitutively active BCR-ABL1** with loss of N-terminus

**In CML with Asciminib**
- **Inactive BCR-ABL1** with asciminib binding

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Native ABL1 is tightly regulated by the interaction of its N-terminus and the myristoyl pocket, which helps regulate and control cell proliferation in the bone marrow.

In the BCR-ABL1 fusion protein, the ABL1 N-terminal region is replaced with BCR, and this loss results in a constitutively open/active conformation leading to uncontrolled proliferation of immature abnormal blood cells.

Unlike ATP-competitive TKIs, by specifically targeting the ABL myristoyl pocket, asciminib restores inhibition of BCR-ABL1 preventing unregulated cell proliferation.

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.

ATP, adenosine triphosphate; CML, chronic myelogenous leukemia; SH, src homology; TKI, tyrosine kinase inhibitor.

Asciminib Efficacy and Safety in Adults
Phase III ASCEMBL Study

Efficacy

MMR at week 24
% of patients

Asciminib
(n=157)a
25.5%

Bosutinib
(n=76)a
13.2%

Cut-off-date 25-May-2020

MR4.5 rates at week 24:
- 8.9% with asciminib
- 1.3% with bosutinib

Safety

AEs leading to treatment discontinuation

<table>
<thead>
<tr>
<th>% of patients</th>
<th>Asciminib</th>
<th>Bosutinib</th>
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</thead>
<tbody>
<tr>
<td>All Grade</td>
<td>21.1</td>
<td>15.8</td>
</tr>
<tr>
<td>Grade ≥3c</td>
<td>5.1</td>
<td>5.8</td>
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</table>

AEs for asciminib and bosutinib:
- All grade: 89.7% vs 96.1%
- Grades ≥3c: 50.6% vs 60.5%

AE, adverse event; BID, twice daily; MCyR, major cytogenetic response; MMR, major molecular response; QD, once daily.

Median follow-up was 14.9 months. a Common treatment difference after adjusting for MCyR status at baseline with 95% CI (2.19%-22.3%) and 2-sided P=.029. b A patient with multiple severity grades for an AE is only counted under the maximum grade as determined by Medical Dictionary for Regulatory Activities version 23.0 and Common Terminology Criteria for Adverse Events version 4.03.

Study Design of ASC4KIDS
Phase Ib/II Pediatric Trial

**Adult formulation group**
14 to <18 years\(^a\)
Asciminib 40 mg BID under fasted conditions

**Pediatric formulation group**
Patients aged
1 to <12 years (n=15)
12 to <18 years (n=15)
Asciminib (mini-tablets) age- and body weight–adjusted dose taken with food

**Part 1**
Dose Determination
Evaluate PK from 4 patients

**Part 2**
Expansion Cohort
After last patient has completed day 28 in part 2
After last patient has completed week 52 in part 2
When all patients have completed ≥5 years of study treatment or discontinued earlier

Optional switch to pediatric formulation after pediatric formulation dose is confirmed on completion of part 1

Interim PK and safety analysis 1\(^b\)
Interim PK and safety analysis 2
Primary analysis
Final analysis

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PK, pharmacokinetics.
\(^a\) Patients must weigh ≥40 kg. \(^b\) Part 1 may be conducted multiple times to refine dose by exposure.

Poster presented at: the 63rd ASH Annual Meeting and Exposition in Atlanta, GA, held on December 11-14, 2021
Study Design of ASC4KIDS

Decision Tree for Parts 1 and 2

**Part 1: Dose Determination**
Recruitment with aim to have 4 to 6 evaluable patients at the initial dose for interim PK and safety analysis

- **2 DLTs in the first 2 patients**
  - No: Continue recruitment until ≥4 evaluable patients
  - Yes: Recruitment is halted

- **Interim PK and safety analysis 1**
  - PK comparable with 40 mg BID in adults using adult formulation
    - No: Refine the dose
    - Yes: Yes

**Part 2: Cohort Expansion**
Enroll remaining patients to have a total of ≥30 patients initiated on the pediatric formulation

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BID, twice daily; DLT, dose-limiting toxicity; PK, pharmacokinetics.

- a ≤6 patients, depending on the variability of the PK parameters.
- b Permitted safety does not warrant any dose adjustments.
## Study Objectives and Endpoints

### 1. Primary objective:
Identify the pediatric formulation dose (in a fed state) leading to asciminib exposure comparable to 40 mg BID in fasting adults

<table>
<thead>
<tr>
<th>Endpoints to achieve this goal</th>
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<tbody>
<tr>
<td>• Primary PK parameters of asciminib</td>
</tr>
<tr>
<td>• $\text{AUC}<em>{\text{last}}$ and $\text{AUC}</em>{\text{tau}}$</td>
</tr>
<tr>
<td>• Secondary PK parameters of asciminib</td>
</tr>
<tr>
<td>• $C_{\text{max}}$, $T_{\text{max}}$, and $C_{\text{trough}}$</td>
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</table>

### 2. Secondary objectives:
Assess long-term safety, tolerability, acceptability, palatability, and anti-leukemic activity of asciminib in pediatric patients

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<tr>
<td>• Assessments of TEAEs and other safety data, including growth and sexual maturation</td>
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<tr>
<td>• Hematologic and molecular responses</td>
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<tr>
<td>• Questionnaire on acceptability and palatability after first dose, 4 weeks, and 52 weeks</td>
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AUC, area under the curve; $\text{AUC}_{\text{last}}$, AUC from time zero to the time of the last measurable concentration; $\text{AUC}_{\text{tau}}$, AUC over the dosing interval; BID, twice daily; $C_{\text{max}}$, maximum concentration; $C_{\text{trough}}$, trough concentration; PK, pharmacokinetics; TEAE, treatment-emergent adverse event; $T_{\text{max}}$, time to reach $C_{\text{max}}$.  

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### Key Inclusion 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
- Prior treatment with ≥1 TKI
- Treatment failure (adapted from the 2020 ELN guidelines) or intolerance of the most recent TKI therapy at the time of screening
- Evidence of typical BCR-ABL1 transcript at screening
- Performance status
  - Karnofsky ≥50% for patients >10 years of age
  - Lansky ≥50 for patients ≤10 years of age

### Key Exclusion Criteria

- Known presence of the T315I mutation prior to study entry
- Known second CML-CP after previous progression to AP/BC
- Previous hematopoietic stem cell transplant
- Cardiac or cardiac repolarization abnormality
- 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

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AP, accelerated phase; BC, blast crisis; CML-CP, chronic myelogenous leukemia in chronic phase; ELN, European LeukemiaNet; GI, gastrointestinal; TKI, tyrosine kinase inhibitor.
Current Study Status

- ASC4KIDS is now open to enrollment
- The estimated primary completion date is November 2025, and the estimated study completion date is November 2029
- 36 study sites in the 14 countries shown below
Conclusions

- Recruitment to ASC4KIDS, a phase Ib/II study, is underway. This study will support development of asciminib in the pediatric population (1 to <18 years old) with Ph+ CML-CP previously treated with TKIs.
- The results of this study will be used to support extrapolation of asciminib data from adults to the pediatric setting.
- Asciminib is a potent and specific allosteric inhibitor of BCR-ABL1 that specifically targets the ABL myristoyl pocket (STAMP).
  - Asciminib’s specificity offers the potential to reduce off-target effects and thus improve safety and tolerability for pediatric pts vs approved TKIs.
  - By binding to the myristoyl pocket, asciminib may help overcome resistance mutations.
- Asciminib, through its novel mechanism of action offers a prospective new treatment option for pediatric patients with CML-CP.
Acknowledgments

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Disclosures