ASC4FIRST: A Phase III Study of Asciminib vs Investigator-Selected Tyrosine Kinase Inhibitor in Patients With Newly Diagnosed Chronic Myeloid Leukemia in Chronic Phase (CML-CP)

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• Asciminib is a first-in-class BCR::ABL1 inhibitor that works specifically targeting the ABL myristoyl pocket (STAMP)\textsuperscript{1–3}

• Asciminib is approved in various countries/regions, including:\textsuperscript{4–8}
  – US: for adults with Ph+ CML-CP previously treated with ≥2 TKIs as well as Ph+ CML-CP with the T315I mutation\textsuperscript{4}
  – EU: for adults with Ph+ CML-CP previously treated with ≥2 TKIs\textsuperscript{5}
  – Also approved in United Kingdom, Switzerland, Australia and others

• In the Phase III ASCEMBL study comparing asciminib 40 mg BID with bosutinib 500 mg QD in patients with CML-CP after ≥2 prior TKIs, asciminib demonstrated greater efficacy vs bosutinib, an improved safety profile, and favorable patient-reported HRQOL vs bosutinib\textsuperscript{9–11}

• The ongoing ASC4FIRST phase III trial evaluates the efficacy and safety of asciminib vs investigator-selected TKI as 1L therapy in CML.
ASC4FIRST - Study Design and Objective

• Multi-center, open-label, randomized, active-controlled, Phase III study

Objective: To compare the efficacy of asciminib versus investigator-selected 1G or 2G TKI in patients with newly diagnosed Ph+ CML-CP overall, as well as separately for asciminib vs investigator selected TKI within the imatinib stratum

• Newly diagnosed (as per ELN 2020 criteria) patients with Ph+ CML-CP with no prior TKIs
• ≥18 years of age

R 1:1
N = 402

Recruitment to 2K TKI Stratum has been completed

NCT04971226

MMR evaluation

Primary endpoint
Key secondary endpoint

Treatment duration 5 years

48 weeks
96 weeks

Asciminib 80 mg QD
Failure/Intolerance

Investigator-selected TKI[2]

• 1G TKI (imatinib)
• 2G TKI (bosutinib, dasatinib, or nilotinib)

Failure/Intolerance

[2]In the investigator-selected TKI group, patients will be assigned evenly to either 1G TKI or 2G TKI at their approved dose (imatinib 400 mg QD, bosutinib 400 mg QD, dasatinib 100 mg QD, nilotinib 300 mg BID).

1G, first generation; 2G, second generation; CML, chronic myeloid leukemia; CP, chronic phase; ECOG, Eastern Cooperative Oncology Group; ELN, European LeukemiaNet; ELTS, European Treatment Outcome Study long-term survival; MMR, major molecular response (BCR::ABL1 IS ≤0.1%); Ph+, Philadelphia chromosome-positive; QD, once daily; TKI, tyrosine kinase inhibitor.

[1]Hydroxyurea, anagrelide, or ≤2 weeks of imatinib, or nilotinib, or dasatinib, or bosutinib therapy;

1G, first generation; 2G, second generation; CML, chronic myeloid leukemia; CP, chronic phase; ECOG, Eastern Cooperative Oncology Group; ELN, European LeukemiaNet; ELTS, European Treatment Outcome Study long-term survival; MMR, major molecular response (BCR::ABL1 IS ≤0.1%); Ph+, Philadelphia chromosome-positive; QD, once daily; TKI, tyrosine kinase inhibitor.
### ASC4FIRST - Key Inclusion and Exclusion Criteria

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<thead>
<tr>
<th>Key inclusion criteria</th>
<th>Key exclusion criteria</th>
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<tr>
<td>• Patients ≥18 years of age with newly diagnosed Ph+ CML-CP (diagnosed within 3 months of study entry)</td>
<td>• Previous treatment for CML with any other anticancer agents (except hydroxyurea, anagrelide, or ≤2 weeks of imatinib, nilotinib, or dasatinib, or bosutinib therapy) or prior stem cell transplant</td>
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<td>• Diagnosis of CML-CP (ELN 2020 criteria) with cytogenetic confirmation of the Philadelphia chromosome</td>
<td>• Confirmed central nervous system infiltration</td>
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<td>• Evidence of typical BCR::ABL1 transcript (e14a2 and/or e13a2)</td>
<td>• Impaired cardiac function or abnormalities in cardiac repolarization</td>
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<td>• ECOG performance status ≤1</td>
<td>• Severe and/or uncontrolled concurrent disease that could cause unacceptable safety risks or compromise compliance with the protocol</td>
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<td>• No evidence of extramedullary leukemic involvement, with the exception of hepatosplenomegaly</td>
<td>• History of other active malignancy ≤3 years prior to study entry except for previous or concomitant basal cell skin cancer and previous carcinoma <em>in situ</em> treated curatively</td>
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<td>• Adequate organ function as well as laboratory values as per protocol</td>
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## ASC4FIRST - Study Endpoints

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<td>• MMR rate at Week 48</td>
<td>MMR at Week 48 within the stratum of patients with imatinib as pre-randomization selected TKI</td>
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<td>• Key secondary efficacy endpoint is MMR at Week 96</td>
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<td>• Other secondary endpoints include:</td>
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<td>– Time to discontinuation of study treatment due to AEs</td>
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<td>– BCR::ABL ≤1%, CHR, MMR, MR₄, and MR₄.₅ at and by all scheduled time points</td>
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<td>– FFS, EFS, PFS, and OS</td>
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<td>– Patient-reported outcomes</td>
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<td>– PK measures</td>
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ASC4FIRST - Current Status

- **Currently recruiting** (started in October 2021)
- Patients will be **recruited across 170 sites in 31 countries** including Australia, Asia, Europe, and North America
- As of November 2022, **worldwide 360 patients have been enrolled in the study**
- The 2G TKI stratum has completed enrollment; **1G TKI (imatinib) stratum is still open** for enrollment

### Participating countries

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*Russia was a participating country in the ASC4FIRST study, however, the recruitment currently stands cancelled.*

**ASC4FIRST study contact:**

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Clinical Development Medical Director  
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1G, first generation; 2G, second generation; TKI, tyrosine kinase inhibitor.
Outlook

• ASC4FIRST (NCT04971226) study will provide evidence on asciminib vs currently approved TKIs in adult patients with newly diagnosed Ph+ CML-CP.

• ASC4START (NCT05456191) is another asciminib phase IIIb trial in newly diagnosed patients with Ph+ CML-CP, which primarily assesses tolerability (as time to treatment discontinuation due to AEs) with asciminib vs nilotinib.
  – Recruitment for ASC4START has started in November 2022.

• Findings from these two trials will provide comprehensive evidence on the use of asciminib as 1L therapy for patients with Ph+ CML-CP.
• The authors would like to thank the patients enrolled in this study and their families, as well as all the participating investigators and their site teams

• They would also like to thank Venkatesh Taadla of Novartis Healthcare Pvt Ltd. Hyderabad, India, for providing medical writing support/editorial support, which was funded by Novartis Pharmaceuticals in accordance with Good Publication Practice (GPP) 2022 guidelines (www.ismpp.org/gpp-2022).

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References