ASC4START: A Phase IIIb, Open-Label, Randomized Study of Tolerability and Efficacy of Asciminib Versus Nilotinib in Patients with Newly Diagnosed Philadelphia Chromosome-Positive Chronic Myelogenous Leukemia in Chronic Phase

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Introduction

• For patients with CML-CP, the use of TKIs have improved disease outcomes; however, 22%–40% of patients discontinue first-line treatment due to disease progression and adverse events

• Furthermore, more than 40% of patients receiving first-line ATP-competitive TKIs do not achieve MR by 5 years and sequential use of TKIs for disease control may lead to the emergence of new resistance mutations, resulting in limited sensitivity to other TKIs

• Asciminib is now approved in various countries/regions, including:
  - **US**: for adults with Ph+ CML-CP previously treated with ≥2 TKIs as well as Ph+ CML-CP with the T315I mutation
  - **EU**: for adults with Ph+ CML-CP previously treated with ≥2 TKIs

• Approval was based on the phase 3 ASCEMBL study comparing asciminib 40 mg BID with bosutinib 500 mg QD in patients with CML-CP after ≥2 prior ATP-competitive TKIs, where asciminib demonstrated greater efficacy vs bosutinib and an improved safety profile

• Asciminib improved HRQoL compared with baseline and bosutinib treatment

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Introduction

Ongoing clinical trials investigating asciminib in patients with Ph+ CML in chronic phase

• ASC4FIRST (NCT04971226) will primarily evaluate the efficacy and safety of asciminib versus an investigator-selected TKI (poster #3012 to be presented at 64th ASH Annual Meeting & Exposition, 2022)
• ASC4START (NCT05456191) will primarily assess the tolerability of asciminib versus nilotinib and the impact of treatment on HRQoL

CML, chronic myelogenous leukemia; HRQoL, health-related quality of life; Ph+, Philadelphia chromosome-positive; TKI, tyrosine kinase inhibitor.
• A multi-center, active-controlled, open-label randomized phase IIIb study with planned enrolment of ~541 patients randomized 1:1 to receive either asciminib 80 mg QD or nilotinib 300 mg BID

ASC4START Study Design

Newly diagnosed patients aged ≥18 years with Ph+ CML-CP and NO prior TKI treatment
Randomization stratified based on ELTS score at diagnosis (high/intermediate/low)

Asciminib
(80 mg PO QD)

Nilotinib
(300 mg PO BID)

R 1:1

N~541

End of study

Primary objective: To assess tolerability of asciminib vs nilotinib in the first-line setting as measured by the Time to Treatment Discontinuation due to AEs

A total of 64 events defined as Treatment Discontinuation due to an AE for the two arms will be needed to detect a difference of 5.73% between the arms by 96 weeks after the last patient had received their first treatment
## Eligibility Criteria

<table>
<thead>
<tr>
<th>Key inclusion criteria</th>
<th>Key exclusion criteria</th>
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<tbody>
<tr>
<td>• Patients ≥18 years of age with newly diagnosed Ph+ CML in chronic phase and ECOG PS of ≤1</td>
<td>• Previous treatment for CML with any other anticancer agents (except hydroxyurea and/or anagrelide) or prior stem cell transplant</td>
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<td>• CML in chronic phase (ELN 2020 criteria) with cytogenetic confirmation of the Ph chromosome</td>
<td>• Confirmed CNS infiltration</td>
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<td>• Cryptic Ph chromosome confirmed by metaphase FISH</td>
<td>• Impaired cardiac function or abnormalities in cardiac repolarization</td>
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<td>• A typical <em>BCR::ABL1</em> transcript (e14a2 and/or e13a2)</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>• History of acute pancreatitis within 1 year of study entry or medical history of chronic pancreatitis</td>
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<td>• Impaired GI function or GI disease that may significantly alter the absorption of study drug</td>
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CML, chronic myelogenous leukemia; CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; ELN, European LeukemiaNet; FISH, fluorescence in situ hybridization; GI, gastrointestinal; Ph, Philadelphia chromosome; Ph+, Philadelphia chromosome-positive.
### ASC4START Study Objectives and Endpoints

<table>
<thead>
<tr>
<th>Primary objective</th>
<th>Endpoint</th>
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<tbody>
<tr>
<td>To assess tolerability of asciminib versus nilotinib</td>
<td>Time to treatment discontinuation due to an AE</td>
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<tr>
<th>Secondary objectives for efficacy</th>
<th>Endpoints</th>
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<tr>
<td>To compare the efficacy of asciminib versus nilotinib at and by all scheduled data collection time points</td>
<td>MMR, MR(^4.0), MR(^4.5), CHR, BCR::ABL IS ≤1%; duration of MMR, MR(^4.0), and MR(^4.5); time to first MMR, MR(^4.0), and MR(^4.5); TTF; EFS; PFS; and overall survival</td>
</tr>
<tr>
<td>Time to treatment discontinuation for selected reasons</td>
<td>Time to treatment discontinuation due to a lack of efficacy, treatment failure, disease progression, suboptimal response, or death</td>
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<th>Secondary objective for PROs</th>
<th>Endpoint</th>
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<tbody>
<tr>
<td>To assess the effect of asciminib versus nilotinib on patient-reported disease-related symptoms, functioning, and HRQoL</td>
<td>Change from baseline in overall scores and individual scales of the EORTC QLQ-C30 and EORTC QLQ-CML24 questionnaires</td>
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<th>Secondary objective for safety</th>
<th>Endpoints</th>
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<tr>
<td>To characterize the safety and tolerability profile of asciminib versus nilotinib during the course of the study</td>
<td>AEs, dose modification due to AEs, changes in laboratory values that fall outside the pre-determined ranges, clinically notable ECG changes, and other safety data</td>
</tr>
</tbody>
</table>

AE, adverse event; CHR, complete hematologic response; ECG, electrocardiogram; EFS, event-free survival; EORTC, European Organisation for Research and Treatment of Cancer; HRQoL, health-related quality of life; MMR, major molecular response (BCR::ABL IS ≤0.1%); MR, molecular response; MR\(^4.5\), BCR::ABL IS ≤0.01%; MR\(^4.5\), BCR::ABL IS ≤0.0032%; PFS, progression-free survival; QLQ, quality of life questionnaire; TTF, time to treatment failure.
Current Status & Conclusions

- Newly diagnosed patients with Ph+ CML in chronic phase need novel safe and effective treatments to address unmet needs.

- ASC4START study will investigate the tolerability, further safety and efficacy, and HRQoL of asmitinib versus nilotinib.

- The study is recruiting as of November 2022.

- Patients will be recruited across multiple sites in the US, Europe, as well as Africa, the Asia-Pacific region, Canada, and the Middle East.

- The estimated study completion date is March 4, 2027.

CML, chronic myelogenous leukemia; HRQoL, health-related quality of life; Ph+, Philadelphia chromosome-positive.
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