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632.CHRONIC MYELOID LEUKEMIA: CLINICAL AND EPIDEMIOLOGICAL

ASC4START and ASC4FIRST: Two Ongoing Phase 3 Trials Investigating Asciminib Monotherapy As First-Line Therapy Versus Tyrosine Kinase Inhibitors in Patients with Newly Diagnosed Philadelphia Chromosome-Positive Chronic Myeloid Leukemia in Chronic Phase

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Background: The current standard of care (SoC) for newly diagnosed patients (pts) with chronic myeloid leukemia in chronic phase (CML-CP) is treatment with 1 of the 4 tyrosine kinase inhibitors (TKIs) approved for this use (first generation [1G] imatinib [IMA] and second generation [2G] bosutinib [BOS], dasatinib [DAS], and nilotinib [NIL]). Although TKIs have vastly improved treatment outcomes, pts with newly diagnosed CML-CP experience lack of efficacy and intolerance to available treatments. A large number of pts treated with IMA do not achieve major molecular response (MMR) and even fewer pts achieve deep molecular response, a key requirement to attempt treatment-free remission. Treatment with 2G TKIs results in larger proportions of pts achieving deep responses albeit still with a sizeable minority not reaching this goal. Also, many pts are intolerant to 2G TKIs, resulting in therapy switching, frequently multiple times. For pts who remain on treatment, even low-grade adverse events (AEs) may significantly impact quality of life (QoL) given the long-term nature of treatment. Improved treatments with high efficacy and improved tolerability are needed to limit therapy switching, reduce treatment discontinuation, maintain, or improve pt QoL, and allow pts to remain on treatment at an optimal dose for longer duration to achieve deep responses.
Asciminib is the first and only approved BCR::ABL1 inhibitor that works by specifically targeting the ABL myristoyl pocket (STAMP). This unique mechanism of action (MoA) has no confirmed overlapping mutation-driven resistance profile with ATP-competitive TKIs. Asciminib shows better selectivity compared to other TKIs, with no known off-target kinase-mediated effects due to its MoA; this translates into improved tolerability. In clinical trials (Hughes et al. N Engl J Med. 2019; Rea et al. Blood 2021), asciminib has demonstrated sustained efficacy and a favorable safety profile over time in pts with Philadelphia chromosome positive (Ph+) CML-CP previously treated with ≥2 TKIs as well as in pts with T315I mutation.
Asciminib as monotherapy and in combination with ATP-competitive TKIs is being studied as first-line (1L) treatment in CML. The ongoing ASC4FIRST (NCT04971226) study is investigating the efficacy and safety of asciminib 80 mg once daily (QD) monotherapy vs investigator-selected 1G or 2G TKI in adults with newly diagnosed Ph+ CML-CP (**Table 1**). The primary endpoint of ASC4FIRST is MMR rate at 48 weeks. The ongoing ASC4START (NCT05456191) study is focused on pt-centric objectives, assessing the tolerability and efficacy of asciminib vs 2G TKI NIL in adults with newly diagnosed Ph+ CML-CP. The primary endpoint of ASC4START is time to treatment discontinuation due to an AE (**Table 1**).

Current Status:

As of December 20, 2022, the ASC4FIRST study completed recruitment, with 405 pts enrolled worldwide. The end of study (EOS) will occur 5 years from the last pt first treatment in the study. Pts will continue to receive the assigned treatment until the

EOS, or until premature discontinuation due to treatment failure, disease progression or intolerance, or due to investigator or participant decision.

Between 21 November 2022 and 25 July 2023, 180 pts have been screened for the ASC4START study, with 147 pts randomized to treatment (n=52 France, n=40 Germany, n=9 Bulgaria, n=7 Czechia, n=7 Hungary, n=6 Korea, n=6 Singapore, n=2 Slovakia, n=5 Argentina, n=3 Greece, n=2 each from Slovakia, Malaysia, and Oman, and n=1 each from the USA, Italy, Romania, UK, Jordan, and Canada). Recruitment is ongoing. Patients will be treated until approximately 64 discontinuations of either study treatment due to an AE have been recorded.

Conclusions:

With demonstrated efficacy and improved tolerability compared to ATP-binding TKIs, asciminib has the potential to become the therapy of choice for CML in 1L, enabling newly diagnosed patients to remain on therapy with improved QoL and overall survival, and reducing the need for therapy switching, ultimately allowing patients to achieve optimal milestone responses and reach treatment goals. Findings from these two trials will provide comprehensive evidenceon the use of asciminib as 1L therapy for newly diagnosed pts with Ph+ CML-CP.

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Table 1. Overview of the 1L Phase 3 Studies: ASC4FIRST versus ASC4START

	ASC4FIRST (N=405) (Completed recruitment)	**ASC4START (target N=541)** (Currently recruiting)
Purpose	Pivotal/registrational	Access, health technology assessment bodies decision-making
Arms	Asciminib 80 mg QD vs investigator-selected TKI (imatinib, nilotinib, dasatinib, bosutinib)	Asciminib 80 mg QD vs nilotinib
Randomization	1:1 to asciminib or investigator-selected TKI stratified by ELTS score at diagnosis (high vs intermediate vs low) and the control arm TKI selected by the investigator before randomization	1:1 to asciminib or nilotinib stratified by ELTS score at diagnosis (high vs intermediate vs low)
Key inclusion criteria	• Patients ≥18 years of age with newly diagnosed Ph+ CML-CP (diagnosed within 3 months of study entry) • Evidence of typical *BCR::ABL1* transcript (e14a2 and/or e13a2) • ECOG performance status ≤1	• Patients ≥18 years of age with newly diagnosed Ph+ CML-CP (diagnosed within 3 months of study entry) • Evidence of typical *BCR::ABL1* transcript (e14a2 and/or e13a2) • ECOG performance status ≤1
Key exclusion criteria	• Previous treatment for CML with any other anticancer agents (except hydroxyurea, anagrelide, or ≤2 weeks of imatinib, or nilotinib, or dasatinib, or bosutinib therapy) or prior stem cell transplant • Confirmed central nervous system infiltration • Impaired cardiac function or abnormalities in cardiac repolarization	• Previous treatment for CML with any other anticancer agents (except hydroxyurea, anagrelide, or ≤2 weeks of imatinib, or nilotinib, or dasatinib, or bosutinib therapy) or prior stem cell transplant • Confirmed central nervous system infiltration • Impaired cardiac function or abnormalities in cardiac repolarization
Geography	Worldwide	Worldwide
Primary endpoint	Efficacy: MMR at 48 weeks	Safety: Time to discontinuation due to an AE
Secondary endpoints	Key secondary – MMR at 96 weeks Other secondary: • Efficacy: MMR, $MR^{4.0}$, $MR^{4.5}$, CHR, *BCR::ABL1*^{IS} ≤1%, and CCyR at protocol-defined timepoints; time to and duration of responses, FFS, TTF, PFS, OS • Safety: type, frequency, and severity of AEs and dose modifications and time to discontinuation due to AEs • PK parameters • QOL PROs (EORTC QLQ-C30, EORTC-CML24)	• Efficacy: MMR, $MR^{4.0}$, $MR^{4.5}$, CHR, *BCR::ABL1*^{IS} ≤1%, and CCyR at protocol-defined timepoints; time to and duration of responses, TTF, PFS, OS • Time to treatment discontinuation (for any reason) • Safety: type, frequency, and severity of AEs and dose modifications due to AEs • QOL PROs (EORTC QLQ-C30, EORTC-CML24)
Exploratory endpoints	• QOL PROs (EQ-5D-5L, PRO-CTCAE, FACT GP5) • HCRU • Biomarkers (*BCR::ABL1* mutations and myeloid-associated mutations at baseline, loss of response, and EOT; correlations between expression profile changes from baseline and on treatment with response as an effect of asciminib; changes in immune markers and correlations responses; UGT2B genetic variants)	• QOL PROs (PRO-CTCAE, FACT GP5) • HCRU • *BCR::ABL1* gene mutations

1L, first-line; AE, adverse event; CCyR, complete cytogenetic response; CHR, complete hematologic response; CML-CP, chronic myeloid leukemia in chronic phase; ECOG, Eastern Cooperative Oncology Group; ELTS, European Treatment and Outcome Study Long-Term Survival; EORTC-CML24, European Organisation for Research and Treatment of Cancer quality of life questionnaire for chronic myeloid leukemia; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer quality of life core questionnaire; EOT, end of treatment; EQ-5D-5L, EuroQol 5-Dimension, 5-Level instrument; FACT GP5, Functional Assessment of Cancer Therapy – General item GP5; FFS, failure-free survival; HCRU, healthcare resource utilization; MMR, major molecular response; MR, molecular response; OS, overall survival; PFS, progression-free survival; Ph+, Philadelphia chromosome-positive; PK, pharmacokinetics; PRO, patient-reported outcome; PRO-CTCAE, patient-reported outcome of the Common Terminology Criteria for Adverse Events; QD, once daily; QOL, quality of life; TKI, tyrosine kinase inhibitor; TTF, time to treatment failure; UGT2B, UDP glycosyltransferase 2 family, polypeptide B.

Figure 1

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