Poster CML 590

Stephen Strickland, Stephen.Strickland@hcahealthcare.com

ASC4START: A phase 3b, open-label, randomized study of asciminib vs nilotinib in patients with newly diagnosed Ph+ chronic myelogenous leukemia in chronic phase (CML-CP)

Stephen Strickland,[1] David Andorsky,[2] Tim H. Brümmendorf,[3] Susanne Saussele,[4] Francois-Xavier Mahon,[5] Virginia Pilipovic,[6] Yifan Zhang,[7] Peter Schuld,[6] Andreas Hochhaus[8]

[1]Sarah Cannon Research Institute, Nashville, TN; [2]Rocky Mountain Cancer Center, Boulder, CO; [3]Medizinische Klinik IV, Uniklinik RWTHAachen, Aachen, Germany; [4]III. Medizinische Klinik für Hämatologie und Onkologie, Universitätsklinikum Mannheim, Ilvesheim, Germany; [5]Hematology Department, Institut Bergonié, Bordeaux, France; [6]Novartis Pharma AG, Basel, Switzerland; [7]Novartis Pharmaceuticals Corporation, East Hanover, NJ; [8]Univiersitätsklinikum Jena, Jena, Germany

Scan to obtain:
- Poster

http://bit.ly/StephenCML590

Copies of this poster obtained through Quick Response (QR) code are for personal use only and may not be reproduced without permission of the authors.

Conclusions

ASC4START is a clinical trial designed to evaluate the tolerability of oral asciminib (80 mg QD) versus the 2G TKI nilotinib (300 mg BID), in adult patients with newly diagnosed Ph+ CML-CP

Many patients discontinue first-line treatment using TKIs due to disease progression and/or adverse events

In the ASCEMBL study, asciminib demonstrated significantly superior efficacy and better safety and tolerability over bosutinib in patients treated with 2 or more prior TKIs

Asciminib is the first BCR::ABL1 inhibitor to Specifically Target the ABL Myristoyl Pocket (STAMP)

With this unique mechanism compared to 2G TKIs, asciminib maintains efficacy, safety, and tolerability while reducing off-target effects, which may improve tolerability and reduce probability of developing resistance

Recruitment for ASC4START began in November, 2022

As of August 23, 2023, 178 patients have been randomized and are receiving treatment while 13 more are being screened

This study is sponsored by Novartis Pharmaceuticals Corporation.

For more information, please refer to **https://clinicaltrials.gov/ct2/show/NCT05456191**

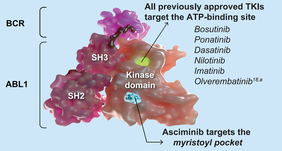
Poster presentation at: SOHO 2023 annual meeting; September 6-9, 2023; Houston, Texas, and Virtual.

Introduction

- TKIs have greatly improved treatment outcomes for newly diagnosed patients with CML-CP, which can now be managed as a chronic disease requiring long-term medication[1]
- However, 28.4%–63.7% of patients in major clinical trials discontinued 1L treatment; primary reasons for discontinuation included AEs (4.0%–31.7%), lack of efficacy (3.5%–16.3%), and disease progression (0.7%–11.0%)[2-8]
- Moreover, >40% of patients receiving 1L TKI therapy do not achieve MR$^{4.5}$ by 5 years[5,6]; treatment efficacy in earlier lines is key, as patients who do not achieve DMR may have increased risk of disease progression and inferior survival outcomes[9-12]
- Sequential use of TKIs due to inadequately controlled disease may lead to the emergence of new mutations, resulting in limited sensitivity to other TKIs[13]
- Hence, there is a need for a new treatment option that combines high efficacy with a favorable safety profile in earlier lines, improving over currently available options by enabling more patients to meet treatment goals and preserve HRQoL

- Asciminib is the first BCR::ABL1 inhibitor to **Specifically Target the ABL Myristoyl Pocket (STAMP)**
  - Unlike ATP-competitive TKIs, which target the same binding site shared by several kinases, asciminib has a unique MoA targeting the myristoyl binding pocket of ABL (**Figure 1**)[14-16]

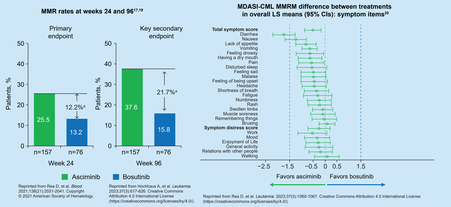
Figure 1. Asciminib is the first BCR::ABL1 inhibitor to Specifically Target the ABL Myristoyl Pocket (STAMP)[17]



[a] Approved in China.

- Asciminib specifically inhibits ABL kinases, being highly selective compared to imatinib, nilotinib, dasatinib, and bosutinib[14,16]
- This specificity can translate to reduced off-target effects, resulting in improved tolerability while maintaining efficacy and reducing the probability of developing resistance[16]
- In the ASCEMBL trial (NCT03106779), asciminib demonstrated significantly superior efficacy, improved safety and tolerability, and a trend for improvement of patient-reported outcomes vs bosutinib in patients with CML-CP after ≥2 prior TKIs and supported the approval of asciminib (**Figure 2**)[17,19-22]
- Two ongoing clinical trials, ASC4FIRST (NCT04971226) and ASC4START (NCT05456191), will assess whether asciminib can address the needs of patients with newly diagnosed Ph+ CML-CP
- Here we present the phase 3b ASC4START trial evaluating the tolerability of asciminib vs the 2G TKI nilotinib in adults with newly diagnosed Ph+ CML-CP, as measured by the time to treatment discontinuation due to an adverse event, safety, efficacy, and QoL outcomes

Figure 2. Asciminib showed superior efficacy, and a trend for improvement of PROs compared to baseline and relative to bosutinib in patients with CML-CP after ≥ 2 prior TKIs



Reprinted from Rea D, et al. *Blood*. 2021;138(21):2031-2041. Copyright © 2021 American Society of Hematology.

Reprinted from Hochhaus A, et al. *Leukemia*. 2023;37(3):617-626. Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by/4.0/).

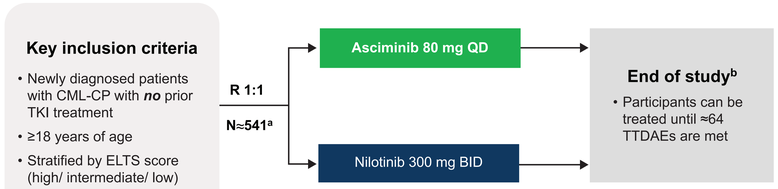
Reprinted from Rea D, et al. *Leukemia*. 2023;37(5):1060-1067. Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by/4.0/).

[b] The treatment difference after adjusting for baseline MCyR status was 12.2% (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.

Study design and methods

- ASC4START is a phase 3b, multi-center, active-controlled, open-label randomized study to evaluate tolerability of asciminib vs nilotinib in adults with newly diagnosed Ph+ CML-CP as measured by the TTDAE, safety, efficacy, and QoL outcomes
- The study is planned to randomize approximately 541 patients, which is the estimated number of patients needed to observe 64 treatment discontinuations due to AEs
- Patients will be randomized 1:1 to receive asciminib 80 mg QD or nilotinib 300 mg BID, both administered orally under fasting conditions, stratified by ELTS score at diagnosis (high vs intermediate vs low) (**Figure 3**)
- Study duration is approximately 4.5 to 5 years and treatment duration for an individual patient is expected to be 2 to 4.5 years
- Key eligibility criteria are summarized in **Table 1**
- Study objectives and endpoints are summarized in **Table 2**

Figure 3. Study design



[a] Participants can be treated in the study until approximately 64 discontinuations due to AEs are met. It has been estimated that a total of 64 events for the two arms will be needed to detect a difference between arms of 5.73% by 96 weeks after the last patient receives their first treatment.

[b] End of study is defined as when the necessary number of events has been reached and when end of treatment and the last assessments are completed.

Table 1. Overview of eligibility criteria

Key inclusion criteria	Key exclusion criteria
Patients ≥18 years of age with newly diagnosed Ph+ CML-CP (diagnosed within 3 months of study entry)	Previous treatment for CML with any other anticancer agents (except hydroxyurea and/or anagrelide) or prior stem cell transplant
Diagnosis of CML-CP (ELN 2020 criteria) with cytogenetic confirmation of the Philadelphia chromosome. A cryptic Philadelphia chromosome should be confirmed by metaphase FISH	Confirmed central nervous system infiltration
Evidence of typical *BCR::ABL1* transcript (e14a2 and/or e13a2)	Impaired cardiac function or abnormalities in cardiac repolarization
ECOG performance status ≤1	Severe and/or uncontrolled concurrent disease that could cause unacceptable safety risks or compromise compliance with the protocol
Adequate end organ function	History of acute pancreatitis within 1 year of study entry or medical history of chronic pancreatitis
Patients must have normal laboratory values, or corrected within normal limits, for potassium, total calcium corrected for serum albumin, and magnesium	Impaired GI function or GI disease that may significantly alter the absorption of study drug

Table 2. Study objectives and endpoints

	Endpoints to achieve this goal
Primary objective	
• To assess the tolerability of asciminib vs nilotinib in participants with newly diagnosed Ph+ CML-CP, with respect to TTDAE	• TTDAE, defined as the time from the date of first dose of study treatment to the date of discontinuation of study treatment due to an AE
Secondary objectives on efficacy	**Endpoints to achieve this goal**
• To compare the efficacy of asciminib vs nilotinib at and by all scheduled data collection time points	• MMR at all scheduled data collection time points • MMR by all scheduled data collection time points • MR$^{4.0}$ and MR$^{4.5}$ at and by all scheduled data collection time points • CHR at and by all scheduled data collection time points • *BCR::ABL1*^{IS} ≤1% at and by all data collection time points • Duration of MMR, MR$^{4.0}$ and MR$^{4.5}$ • Time to first MMR, first MR$^{4.0}$, first MR$^{4.5}$ • TTF • EFS • PFS • OS
• TTD for selected reasons of discontinuation	• TTD due to selected reasons (i.e., discontinuation due to lack of efficacy/ treatment failure/ disease progression/ suboptimal response/ death)
Secondary objective on PROs	**Endpoints to achieve this goal**
• To assess the effect of asciminib vs nilotinib on patient-reported disease-related symptoms, functioning, and HRQoL	• Change from baseline in overall scores and individual scales of the EORTC QLQ-C30 and EORTC QLQ-CML24 questionnaires
Secondary objective for safety	**Endpoints to achieve this goal**
• To characterize the safety and tolerability profile of asciminib vs nilotinib during the course of the study	• Type, frequency and severity of AEs, dose modification due to AEs, changes in laboratory values that fall outside the pre-determined ranges and clinically notable ECG changes, and other safety data (vital signs, physical examination)

Current status

- Recruitment began in November 2022.
- As of August 23, 2023, 178 patients have been randomized and are receiving treatment while 13 more are being screened
- The estimated primary completion date is February 15, 2027, while the estimated study completion date is March 15, 2027
- Patients are being recruited across multiple sites in Europe, as well as Africa, the Asia-Pacific region, Canada, and the Middle East

Abbreviations

1L, first line; 2G, second generation; 3L+, third line and beyond; AE, adverse event; BID, twice daily; CHR, complete hematologic response; CML-CP, chronic myelogenous leukemia in chronic phase; DMR, deep molecular response; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EFS, event-free survival; ELN, European LeukemiaNet; ELTS, European Treatment Outcome Study long-term survival; EORTC, European Organisation for Research and Treatment of Cancer; FISH, fluorescence in situ hybridization; GI, gastrointestinal; HRQoL, health-related quality of life; LS, least squares; MCyR, major cytogenetic response; MDASI-CML, M.D. Anderson Symptom Inventory – Chronic Myeloid Leukemia; MMR, major molecular response (BCR::ABL1^{IS} ≤0.1%); MoA, mechanism of action; MMRM, mixed-effects model for repeated measures; MR$^{4.5}$, BCR::ABL1^{IS} ≤0.01%; MR$^{4.0}$, BCR::ABL1^{IS} ≤0.0032%; OS, overall survival; PFS, progression-free survival; Ph+, Philadelphia chromosome-positive; PRO, patient-reported outcome; QD, once daily; QoL, quality of life; R, randomization; TKI, tyrosine kinase inhibitor; TTD, time to treatment discontinuation; TTDAE, time to treatment discontinuation due to an adverse event; TTF, time to treatment failure

Acknowledgements

We thank all study participants and their families, the study investigators, and staff participating at the study sites. Medical writing support was provided by Leah Maharaj (Nucleus Global, Inc) and was funded by Novartis Pharmaceuticals Corporation. This poster was developed in accordance with Good Publication Practice (GPP3) guidelines. Authors had full control of the content and made the final decision on all aspects of this publication.

References

1. Hochhaus A, et al. *Leukemia*. 2020;34(4):966-984. **2.** Hochhaus A, et al. *N Engl J Med*. 2017;376: 917-927. **3.** Kantarjian HM, et al. *Leukemia*. 2021;35:440–453. **4.** Druker BJ, et al. *N Engl J Med*. 2006;355:2408-2417. **5.** Hochhaus A, et al. *Leukemia*. 2016;30:1044-1054. **6.** Cortes JE, et al. *J Clin Oncol*. 2016;34:2333-2340. **7.** Brümmendorf TH, et al. *Br J Haematol*. 2015;168:69-81. **8.** Brümmendorf TH, et al. *Am J Hematol*. 2013;88:1024–1029. **9.** Falchi L, et al. *Am J Hematol*. 2014;89:458–464. **10.** Hehlmann R, et al. *J Clin Oncol*. 2014;32:415–423. **11.** Etienne G, et al. *Haematologica*. 2014;99:458–464. **12.** Kantarjian HM, et al. *Lancet Oncol*. 2011;12:841–851. **13.** Soverini S, et al. *Blood*. 2009;114:2168–2171. **14.** Wylie AA, et al. *Nature*. 2017;543:733– 737. **15.** Schoepfer J, et al. *J Med Chem*. 2018;61:8120–8135. **16.** Manley PW, et al. *Leuk Res*. 2020;98:106458. **17.** Réa D, et al. *Blood*. 2021;138(21):2031–2041. **18.** Dhillon S, *Drugs*. 2022;82:469–475. **19.** Hochhaus A, et al. *Leukemia*. 2023;37:617-626. **20.** Réa D, et al. *Leukemia*. 2023;37:1060-1067. **21.** Novartis Pharmaceuticals Corporation. Scemblix (asciminib) [package insert]. Novartis Pharmaceuticals Corporation: East Hanover, NJ; 2021. **22.** Scemblix [summary of product characteristics] Novartis Europharm Limited: Dublin, Ireland; 2022.