Stephen Strickland | Stephen.Strickland@hcahealthcare.com

Poster CML-766

Primary Endpoint Results of the Phase 3b ASC4START Trial of Asciminib vs Nilotinib in Newly Diagnosed Chronic Phase Chronic Myeloid Leukemia (CML-CP): Time to Treatment Discontinuation Due to Adverse Events (TTDAE)

Stephen A. Strickland[1], Andreas Hochhaus[2], Susanne Saussele[3], Francois Xavier Mahon[4], Philipp le Coutre[5], Delphine Rea[6], Thomas Cluzeau[7], Francoise Huguet[8], Jiri Mayer[9], Viviane Dubruille[10], Dong-Wook Kim[11], Ilina Micheva[12], Gabrielle Roth-Guepin[13], Virginia Pilipovic[14], Jacqueline Ryan[15], Nabil Amirouchene Angelozzi[14], Nithya Agrawal[16], Ennan Gu[17], Tim H Brümmendorf[18], David J. Andorsky[19]

[1]SCRI at TriStar Centennial, Nashville, TN, USA; [2]Hematology and Medical Oncology, Universitätsklinikum Jena, Jena, Germany; [3]Universitätsmedizin Mannheim, III. Medizinische Klinik, Mannheim, Germany; [4]Institut Bergonié, Hematology Department, Bordeaux, France; [5]Department of Oncology and Hematology, Charité-Universitätsmedizin Berlin, Berlin, Germany; [6]Department of Hématologie, Hôpital Saint-Louis, Paris, France; [7]Université Cote d'Azur, CHU de Nice, Service d'hématologie, Nice, France; [8]Institut Universitaire du Cancer de Toulouse-Oncopole, Centre Hospitalier Universitaire, Toulouse, France; [9]Department of Internal Medicine, Hematology and Oncology, University Hospital Brno, Brno, Czech Republic; [10]CHU de Nantes, Nantes, France; [11]Jeonjongu Eulji Medical Center, Geumo-dong, Uijeongbu-si, Republic of Korea; [12]Medical University of Varna, Varna, Bulgaria; [13]Hematology Service, CHRU Nancy, Nancy, France; [14]Novartis Pharma AG, Basel, Switzerland; [15]Novartis Pharmaceuticals UK Ltd, London, UK; [16]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; [17]Novartis Pharmaceuticals Corporation, Cambridge, MA, USA; [18]Uniklinik RWTH Aachen, Medizinische Klinik IV, Center for Integrated Oncology (CIO), Aachen, Germany; [19]Rocky Mountain Cancer Centers, Boulder, CO, USA

KEY FINDINGS & CONCLUSIONS

- The ASC4START trial met its primary endpoint, and asciminib demonstrated significantly superior tolerability vs nilotinib based on TTDAE, with a cause-specific hazard ratio of 0.45 (95% CI, 0.25-0.81; *P*=.004)
- Significantly fewer patients discontinued treatment due to AEs (including deaths due to AEs) with asciminib (16/284 [5.6%]) vs nilotinib (34/282 [12.1%])*
- The safety profile of asciminib remained consistent with that seen in earlier trials,[1-4] and no new safety signals were identified
- Rates of *BCR::ABL1*[IS] ≤10%, *BCR::ABL1*[IS] ≤1%, and MMR by week 12 were higher with asciminib than nilotinib
- The study is ongoing, with analyses planned for longer-term tolerability, quality of life, efficacy, and TFR
- These findings, along with data from ASC4FIRST, further support the potential for asciminib to be standard of care for patients with newly diagnosed CML-CP, allowing more patients to meet their treatment goals without requiring treatment switch

* Asciminib: 14 discontinuations due to AEs and 2 deaths due to AEs (cardiac arrest and suicide; n=1 each); nilotinib: 33 discontinuations due to AEs and 1 death due to AE (cardiac arrest).

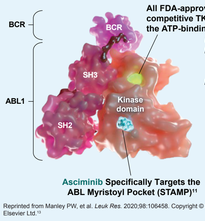
This study is sponsored by Novartis Pharma AG
Poster presented at SOHO 2025 Annual Meeting; September 3-6, 2025; Houston, TX.

INTRODUCTION

- CML requires prolonged treatment; therefore, an agent that is both highly efficacious and well tolerated is needed[5,6]
- Asciminib is a BCR::ABL1 inhibitor that Specifically Targets the ABL Myristoyl Pocket (STAMP; **Figure 1**) and has demonstrated superior efficacy and favorable safety and tolerability vs all IS-TKIs in newly diagnosed Ph+ CML-CP in the ASCAFIRST trial[1,2]
- Asciminib[a] is approved[7] for newly diagnosed Ph+ CML-CP in the United States, China, Japan, Switzerland, and other countries worldwide and is currently under review by the EMA[7,8]
- Compared with 2G TKIs, the high specificity of asciminib for BCR::ABL1 may reduce off-target effects and improve tolerability while maintaining efficacy[9-13]
- Here, we present the first results from the phase 3b ASC4START trial assessing the tolerability and efficacy of asciminib vs nilotinib in patients with newly diagnosed CML-CP

[a] At doses of 80 mg QD and 40 mg BID. [b] Based on MMR rate. Continued approval for this indication may be contingent on verification of clinical benefit in confirmatory trial(s).

Figure 1. Asciminib: Designed to Improve Efficacy and Reduce Off-Target Effects vs Current ATP-Competitive TKIs[11-13]

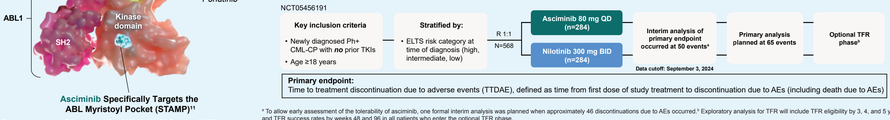


Reprinted from Manley PW, *et al. Leuk Res.* 2020;98:106458. Copyright © 2020 Elsevier Ltd.[13]

METHODS

- ASC4START is a phase 3b, open-label, global study comparing the tolerability of asciminib vs nilotinib in patients with newly diagnosed CML (**Figure 2**)
- The primary endpoint of TTDAE is defined as time from first dose of study treatment to discontinuation due to AEs, including death due to AEs (the events of interest)
  - To increase the TTDAE objectivity, protocol-required rules were applied to both arms equally, mandating dose modifications and discontinuations in patients who met specific criteria
- Adults with newly diagnosed CML-CP were randomized 1:1 to asciminib 80 mg QD (n=284) or nilotinib 300 mg BID (n=284), stratified by ELTS risk category
- An interim analysis was planned when 46 events of interest for the primary endpoint were observed to allow an earlier assessment of tolerability
  - At data cutoff (September 3, 2024), 50 events had occurred
- Secondary endpoints included type, frequency, and severity of AEs; dose modifications due to AEs; and molecular responses by week 12

Figure 2. Study Design



* To allow early assessment of the tolerability of asciminib, one formal interim analysis was planned when approximately 46 discontinuations due to AEs occurred.† Exploratory analysis for TFR will include TFR eligibility by 3, 4, and 5 years and TFR success rates by weeks 48 and 96 in all patients who enter the optional TFR phase.

RESULTS

- Baseline characteristics were balanced between asciminib and nilotinib arms (**Table 1**)
  - Efficacy analyses included the full analysis set of 568 patients (284 in each arm)
  - Safety analyses included 566 patients because 2 patients in the nilotinib arm were randomized but not treated due to an AE (grade 2 thrombocytopenia; n=1) and patient decision (n=1)

Table 1. Demographics and Baseline Characteristics

Variable	Asciminib (n=284)	Nilotinib (n=284)	All patients (N=568)
Age, median (range), years	49.0 (19-82)	50.0 (18-84)	50.0 (18-84)
Age group, n (%)			
18 to <65 years	237 (83.5)	247 (87.0)	484 (85.2)
65 to <75 years	38 (13.4)	24 (8.5)	62 (10.9)
≥75 years	9 (3.2)	13 (4.6)	22 (3.9)
Male, n (%)	177 (62.3)	158 (55.6)	335 (59.0)
ELTS risk category, n (%)[a]			
Low	171 (60.2)	172 (60.6)	343 (60.4)
Intermediate	75 (26.4)	75 (26.4)	150 (26.4)
High	38 (13.4)	37 (13.0)	75 (13.2)
Race, n (%)			
White	227 (79.9)	217 (76.4)	444 (78.2)
Asian	40 (14.1)	45 (15.8)	85 (15.0)
Black or African American	12 (4.2)	10 (3.5)	22 (3.9)
Other[b]	5 (1.8)	12 (4.2)	17 (3.0)
ECOG PS, n (%)			
0	226 (79.6)	235 (82.7)	461 (81.2)
1	57 (20.1)	49 (17.3)	106 (18.7)
2	1 (0.4)	0	1 (0.2)

[a] Based on randomization data. [b] American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, multiple, unknown, and not reported.

- By cutoff (September 3, 2024), 10.9% and 17.3% of patients discontinued asciminib and nilotinib, respectively (**Table 2**)
  - The main reasons for discontinuation in either arm were AEs and unsatisfactory therapeutic effect
  - Of the 4 patients who discontinued due to progressive disease, 3 entered blast phase, and 1 never achieved complete hematologic response and entered accelerated phase as defined by the study protocol
- By interim analysis data cutoff, 50 events of interest for the primary endpoint were observed, and the boundary for statistical significance was recalculated as .0062
  - TTDAE (primary endpoint) events of interest were discontinuations due to AEs (n=47) and deaths due to AEs (n=3)
- The median duration of follow-up was 9.7 months (range, 0-20.8 months) from randomization to data cutoff

Table 2. Patient Disposition at Data Cutoff

Randomized patients, n (%)	Asciminib (n=284)	Nilotinib (n=284)	All patients (N=568)
Treatment ongoing	253 (89.1)	233 (82.0)	486 (85.6)
Discontinued from treatment	31 (10.9)	49 (17.3)	80 (14.1)
AEs	14 (4.9)	33 (11.6)	47 (8.3)
Unsatisfactory therapeutic effect	7 (2.5)	8 (2.8)	15 (2.6)
Progressive disease	3 (1.1)	1 (0.4)	4 (0.7)
Physician decision	2 (0.7)	2 (0.7)	4 (0.7)
Patient decision	2 (0.7)	2 (0.7)	4 (0.7)
Death[a]	2 (0.7)	1 (0.4)	3 (0.5)
Protocol deviation	1 (0.4)	1 (0.4)	2 (0.4)
Pregnancy	0	1 (0.4)	1 (0.2)

[a] Deaths on treatment: with asciminib, cardiac arrest (n=1) and suicide (n=1); with nilotinib, cardiac arrest (n=1).

- Significantly fewer patients discontinued treatment due to AEs, including deaths due to AEs, with asciminib (5.6%) vs nilotinib (12.1%) (**Table 3**)
  - The primary endpoint was met, showing a statistically significant difference in TTDAE in favor of asciminib, with a cause-specific hazard ratio of 0.45 (95% CI, 0.25-0.81; *P*=.004)

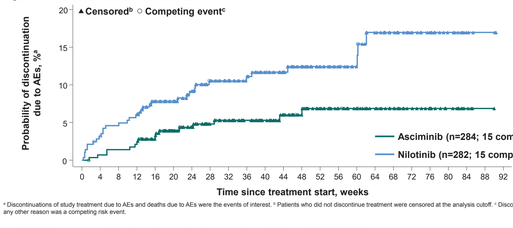
Table 3. Events of Interest

	Events of interest (discontinuations due to AEs and deaths due to AEs)[a]		
Treatment	**Events, n/N, (%)[b]**	**Hazard ratio (95% CI)[c]**	***P* value[d]**
Asciminib	16/284 (**5.6**)	0.45 (0.25-0.81)	**.004**
Nilotinib	34/282 (**12.1**)		

[a] Events counting toward primary endpoint from disposition: with asciminib, 14 discontinuations due to AEs and 2 deaths due to AEs; with nilotinib, 33 discontinuations due to AEs and 1 death due to an AE. [b] The safety set comprised 566 patients because 2 patients in the nilotinib arm were randomized but not treated due to AEs (grade 2 thrombocytopenia, n=1; patient decision, n=1). [c] Hazard ratio of asciminib vs nilotinib. The cause-specific hazard model is stratified by ELTS risk category. [d] Wald test *P* value.

- The risk of discontinuation due to AEs was 55% lower with asciminib than nilotinib at cutoff (**Figure 3**)

Figure 3. Cumulative Incidence of TTDAE



[a] Discontinuations of study treatment due to AEs and deaths due to AEs were the events of interest. [b] Patients who did not discontinue treatment were censored at the analysis cutoff. [c] Discontinuation of study treatment due to any other reason was a competing risk event.

- AEs leading to treatment discontinuation were less frequent with asciminib vs nilotinib (**Table 4**)
- Events counting toward the primary endpoint included 14 discontinuations due to AEs and 2 deaths due to AEs in patients on asciminib (16/284 [5.6%]) and 33 discontinuations due to AEs and 1 death due to an AE in patients on nilotinib (34/282 [12.1%])
- Protocol-required rules were applied to both arms equally, mandating discontinuations in patients who met specific criteria

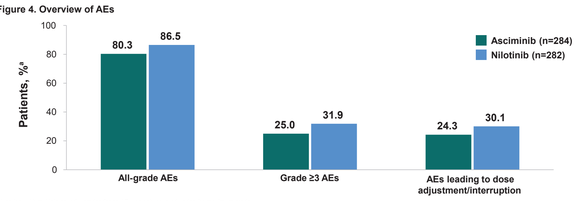
Table 4. AEs Leading to Treatment Discontinuation

	Asciminib[a] (n=284)		Nilotinib[a] (n=282)	
	All grades	Grade ≥3	All grades	Grade ≥3
AEs leading to discontinuation[a]	Patients, n (%)[a]			
Patients with ≥1 AE leading to discontinuation	**15 (5.3)**	**12 (4.2)**	**33 (11.7)**	**23 (8.2)**
AEs leading to discontinuation (≥2 patients in either arm)				
Thrombocytopenia[d]	4 (1.4)	4 (1.4)	1 (0.4)	1 (0.4)
Lipase increased[e]	2 (0.7)	0	6 (2.1)	4 (1.4)
ALT increased	1 (0.4)	1 (0.4)	2 (0.7)	2 (0.7)
Pancreatitis[e,f]	1 (0.4)	1 (0.4)	4 (1.4)	4 (1.4)
Amylase increased[e]	0	0	3 (1.1)	1 (0.4)
Asthenia	0	0	2 (0.7)	0
Atrial fibrillation	0	0	2 (0.7)	0
Blood bilirubin increased	0	0	3 (1.1)	1 (0.4)
Drug-induced liver injury	0	0	2 (0.7)	2 (0.7)

[a] Included AEs occurring during treatment or within 30 days of the last study treatment. A patient may have multiple AEs leading to treatment discontinuation. [b] 1 patient on asciminib had AE blast cell crisis and treatment discontinuation due to progressive disease (not contributing to primary endpoint). [c] 1 patient on nilotinib had death recorded as an AE and treatment discontinuation due to death (contributed to primary endpoint). 1 patient on nilotinib had treatment discontinuation due to an AE, but the AE (thrombocytopenia) leading to discontinuation occurred after 30 days of last dose (contributed to primary endpoint). [d] Thrombocytopenia included platelet count decreased and thrombocytopenia. [e] In the nilotinib arm, 1 discontinued due to increased amylase and pancreatitis, and 1 patient discontinued due to increased amylase and increased lipase. [f] Pancreatitis included acute pancreatitis and pancreatitis.

- Asciminib demonstrated lower rates of AEs leading to dose adjustment/interruption than nilotinib (**Figure 4**)
  - 15 patients (5.3%) in the asciminib arm and 29 (10.3%) in the nilotinib arm reported all-grade treatment-related AEs leading to dose reduction
  - A total of 55 patients (19.4%) in the asciminib arm and 68 (24.1%) in the nilotinib arm reported treatment-related AEs leading to dose interruption
  - Some patients who had dose adjustment or interruption later went on to discontinue treatment
- Median duration of exposure was 39.1 weeks with asciminib vs 38.0 weeks with nilotinib
- Mean relative dose intensity was 94.8% with asciminib vs 92.6% with nilotinib

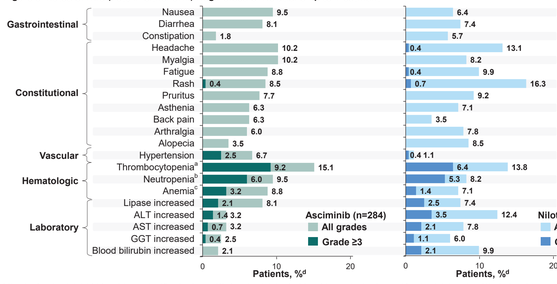
Figure 4. Overview of AEs



[a] A patient with multiple severity grades for an AE was only counted under the maximum grade.

- The most frequent (>10%) AEs in either treatment arm (asciminib vs nilotinib) were thrombocytopenia (15.1% vs 13.8%), myalgia (10.2% vs 8.2%), headache (10.2% vs 13.1%), rash (8.5% vs 16.3%), and alanine aminotransferase increased (3.2% vs 12.4%) (**Figure 5**)
  - Rates of rash and liver-related AEs were lower with asciminib than nilotinib
  - Asciminib was associated with increased cytopenias, consistent with safety profiles of ATP-competitive TKIs

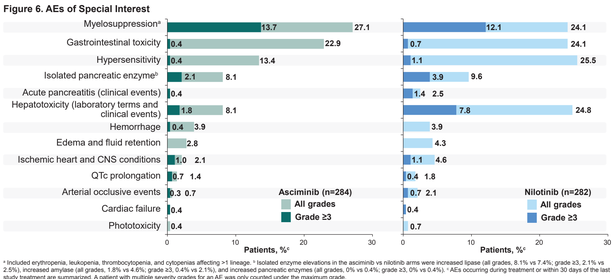
Figure 5. Rates of AEs (>5% in either arm) Regardless of Relationship to Treatment



[a] Thrombocytopenia included platelet count decreased and thrombocytopenia. [b] Neutropenia included neutrophil count decreased and neutropenia. [c] Anemia included anemia, red blood cell count decreased, and hematocrit decreased. [d] AEs occurring during treatment or within 30 days of the last study treatment are presented. A patient with multiple severity grades for an AE was only counted under the maximum grade.

- AEs of special interest were generally less frequent with asciminib than nilotinib (**Figure 6**)
  - Other AEs of special interest in the asciminib vs nilotinib arms were hepatotoxicity (clinical events; all grades, 2.1% vs 4.6%; grade ≥3, 1.1% vs 1.1%) and reproductive toxicity (all grades, 0.4% vs 1.1%)

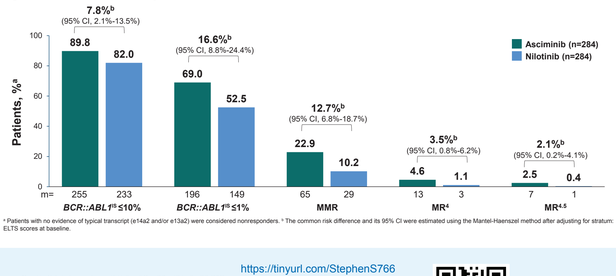
Figure 6. AEs of Special Interest



[a] Included erythropenia, leukopenia, thrombocytopenia, and cytopenias affecting >1 lineage. [b] Isolated enzyme elevations in the asciminib vs nilotinib arms were increased lipase (all grades, 8.1% vs 7.4%; grade ≥3, 2.1% vs 2.5%), increased amylase (all grades, 1.8% vs 4.6%; grade ≥3, 0.4% vs 2.1%), and increased pancreatic enzymes (all grades, 0% vs 0.4%; grade ≥3, 0% vs 0.4%). [c] AEs occurring during treatment or within 30 days of the last study treatment are summarized. A patient with multiple severity grades for an AE was only counted under the maximum grade.

- In the secondary efficacy endpoint analysis, all molecular response rates were 12 weeks higher with asciminib vs nilotinib (**Figure 7**)
  - *BCR::ABL1*[IS] ≤10% (89.8% vs 82.0%), *BCR::ABL1*[IS] ≤1% (69.0% vs 52.5%), MMR (22.9% vs 10.2%), MR[4] (4.6% vs 1.1%), and MR[4.5] (2.5% vs 0.4%) rates by week 12 were higher with asciminib vs nilotinib

Figure 7. Molecular Responses by Week 12



[a] Patients with no evidence of typical transcript (e14a2 and/or e13a2) were considered nonresponders. [b] The common risk difference and its 95% CI were estimated using the Mantel-Haenszel method after adjusting for stratum: ELTS scores at baseline.

References

1. Hochhaus A, *et al. N Engl J Med.* 2024;391:885-898.
2. Hochhaus A, *et al.* Abstract 4009-ASH Annual Meeting & Exposition; December 7-10, 2024; San Diego, CA. Abstract 673.
3. Mauro MJ, *et al. Blood Adv.* Published online May 7, 2025. doi:10.1182/bloodadvances.2025016042.
4. Hochhaus A, *et al. Leukemia.* 2025;39:1114-1123.
5. Efficace F, Cannella L. *Hematology Am Soc Hematol Educ Program.* 2016;1:170-179.
6. Garcia-Horton A, Lipton JH. *J Natl Compr Canc Netw.* 2020;18:1421-1428.
7. Scientific [prescribing information] East Hanover, NJ: Novartis Pharmaceuticals Corp.
8. Scientific [summary of product characteristics]. Dublin: Ireland: Novartis Europharm Limited.
9. Wylie AA, *et al. Nature.* 2017;543:733-737.
10. Lee H, *et al. Int J Hematol.* 2021;113:922-641.
11. Rea D, *et al. Blood.* 2021; 138:2031-2041.
12. Rea D, *et al.* Abstract 4-ASH Annual Meeting & Exposition; December 11-14, 2021; Atlanta, GA. Abstract 370.
13. Manley PW, *et al. Leuk Res.* 2020;98:106458.
14. Schwaller J, *et al. J Med Chem.* 2018;61:8120-8135.
15. Westerweel PE, *et al. Front Oncol.* 2019;9:665.
16. Hochhaus A, *et al. Leukemia.* 2020;34:966-984.

Acknowledgments

We thank all study participants and their families, the study investigators, the staff at the 120 participating study sites spanning 24 countries. Medical writing support was provided by Kenneth Maus, PhD, and Rohini Roy, PhD, CMMP, of Nucleus Global, an Inizio company, and was funded by Novartis Pharma AG. Data previously presented by Hochhaus A, *et al.* Presented at the 2025 ASCO Annual Meeting. Abstract 6501. Reprinted with permission from the author.

Abbreviations

2G, second generation; ABL1, ABL proto-oncogene 1, non-receptor tyrosine kinase; AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ATP, adenosine triphosphate; BCR, BCR activator of RhoGEF and GTPase; BCR::ABL1, breakpoint cluster region::ABL1 fusion protein; ECOG PS, Eastern Cooperative Oncology Group performance status; ELTS, EUTOS long-term survival; EMA, European Medicines Agency; EUTOS, European Treatment and Outcome Study; FDA, US Food and Drug Administration; GGT, gamma-glutamyltransferase; IS, international Scale; IS-TKI, investigator-selected tyrosine kinase inhibitor; n, number of patients within each subgroup with response; MMR, major molecular response; MR[4], *BCR::ABL1*[IS] ≤0.01%; MR[4.5], *BCR::ABL1*[IS] ≤0.0032%; Ph, Philadelphia chromosome; QD, once daily; QTc, corrected QT; R, randomized; TFR, treatment-free remission; TKI, tyrosine kinase inhibitor; TTDAE, time to treatment discontinuation due to adverse events.

https://tinyurl.com/StephenS766

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.

Scan to obtain:
- Poster