Poster CML-282

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Asciminib Once-Daily Dosing Demonstrates Comparable Tolerability and Efficacy to Twice-Daily Dosing: Updated Results From the AIM4CML Study in Patients With Chronic Myeloid Leukemia in Chronic Phase With Prior Tyrosine Kinase Inhibitor Treatment

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KEY FINDINGS & CONCLUSIONS

- This primary analysis of AIM4CML supports the favorable safety and tolerability and efficacy of asciminib 40 mg BID (cohort A) and 80 mg QD (cohort B)
  - The favorable safety and tolerability profile of asciminib at both doses was consistent with those described in previous publications[7,9-11]
  - Safety was comparable between cohorts, with similar rates of AEs and AEs leading to treatment discontinuation and dose adjustment/interruption
  - In cohort B, the proportion of patients with molecular responses increased from weeks 12 to 24
  - Most patients achieved *BCR::ABL1*^{IS} ≤1% by week 12, which is associated with improved long-term outcomes in CML[3]
  - Patients receiving asciminib at both doses achieved MMR and deeper molecular responses
  - A higher proportion of patients in cohort B achieved MMR; patients had a relatively shorter time to MR4 in cohort A
- The primary analysis of AIM4CML is among the first clinical reports on QD dosing of asciminib in patients with CML-CP and supports the flexibility of either asciminib 40 mg BID or 80 mg QD dosing

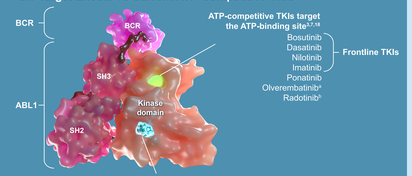
This study is sponsored by Novartis Pharmaceuticals Corporation. For more information, please refer to https://clinicaltrials.gov/study/NCT04666259.

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BACKGROUND

- Patients with CML-CP who require successive lines of therapy due to failure with or intolerance of prior TKIs do not have clearly defined treatment options and often have poor outcomes[1-3]
- An unmet need remains for treatments that improve efficacy without compromising safety and tolerability[3-6]
- Asciminib is a *BCR::ABL1* inhibitor that inhibits ABL1 kinase activity by binding to the ABL myristoyl pocket[7] (**Figure 1**)
  - The phase 3 ASCEMBL and phase 1 X2101 trials led to the approval of asciminib 40 mg BID and 80 mg QD in the US for the treatment of adults with Ph+ CML-CP after ≥2 prior TKIs,[7,10] and the latter X2101 trial also resulted in the approval of asciminib 200 mg BID for adults with Ph+ CML-CP with the T315I mutation[8,10]
  - Long-term follow-up of the ASCEMBL and X2101 trials further supported the strong efficacy and enduring safety of asciminib[9,11-13]
- Similar efficacy and safety were observed with asciminib 40 mg BID and 80 mg QD in the phase 1 X2101 trial; however, a QD dosing regimen could be more convenient and improve patient adherence, outcomes, and QoL[13-15]
- Here we present the primary analysis from the phase 3b AIM4CML trial (NCT04666259) to further evaluate the safety and efficacy of asciminib monotherapy, including QD dosing, in patients with CML-CP after ≥2 TKIs

Figure 1. Asciminib: Designed to Improve Efficacy and Reduce Off-Target Effects vs Current ATP-Competitive TKIs[7,16,17]



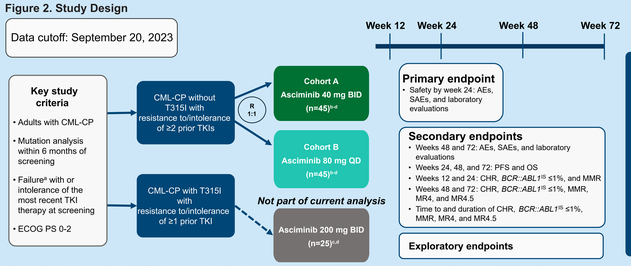
[a] Approved in China. [b] Approved in South Korea.

METHODS

Study Design

- AIM4CML is a multicenter, phase 3b, open-label study of asciminib in patients with CML-CP without the T315I mutation who have received ≥2 prior TKIs and patients with CML-CP with the T315I mutation after ≥1 prior TKI (**Figure 2**)
- The study consisted of the following cohorts:
  - Cohort A: patients without the T315I mutation randomized to receive asciminib 40 mg BID
  - Cohort B: patients without the T315I mutation randomized to receive asciminib 80 mg QD
  - Cohort C: patients with the T315I mutation assigned to receive asciminib 200 mg BID (not presented in the current analysis)
- The study was not powered to detect statistical differences between cohorts
- The primary objective was to evaluate the safety profile of asciminib in patients with CML-CP without the T315I mutation

Figure 2. Study Design



[a] Must meet failure criteria adapted from the 2020 ELN recommendations. [b] The study was not powered to detect statistical differences between cohorts. [c] By the data cutoff, 26, 27, and 3 patients were enrolled in cohorts A, B, and C, respectively. [d] The study closed enrollment before reaching 115 patients as the enrollment rate was considered unexpectedly slow. Slow enrollment was attributed to the availability of asciminib on the US market since October 2021, which was approved for the same indications.

RESULTS

- By the data cutoff for the primary analysis (week 24), 26 and 27 patients were enrolled in cohorts A and B, respectively
- Baseline characteristics were mostly well balanced between cohorts (**Table 1**)
  - Most patients were <65 years old and female
- The median time since diagnosis of CML in cohorts A and B was 3.3 and 5.0 years, respectively

Table 1. Baseline Characteristics

Characteristic	Cohort A 40 mg BID (n=26)	Cohort B 80 mg QD (n=27)
Age, median (range), years	58.5 (24.0-81.0)	57.0 (22.0-84.0)
Female, n (%)	16 (61.5)	14 (51.9)
Race, n (%)		
Asian	0	2 (7.4)
Black/African American	4 (15.4)	2 (7.4)
White	21 (80.8)	22 (81.5)
Unknown	1 (3.8)	1 (3.7)
ECOG PS, n (%)		
0	12 (46.2)	13 (48.1)
1	12 (46.2)	13 (48.1)
2	1 (3.8)	1 (3.7)
Missing	1 (3.8)	0
Time since initial diagnosis, median (range), years[a]	3.3 (0.7-17.6)	5.0 (1.2-17.5)
No. of prior therapies, n (%)		
1	1 (3.8)	0
2	10 (38.5)	13 (48.1)
3	10 (38.5)	10 (37.0)
≥4	5 (19.2)	4 (14.8)

[a] Time (years) since initial diagnosis of CML = (treatment start date – diagnosis date + 1)/365.25.

- At data cutoff, 6 (23.1%) and 14 (51.9%) patients were ongoing treatment, 6 (23.1%) and 6 (22.2%) had completed treatment, and 15 (57.7%) and 9 (33.3%) had enrolled in the safety follow-up in cohorts A and B, respectively (**Table 2**)
- 13 patients (50.0%) in cohort A and 7 (25.9%) in cohort B discontinued treatment
  - Common reasons for discontinuation in both cohorts (A and B, respectively) were physician decision due to lack of efficacy (15.4% and 11.1%), AEs (11.5% and 3.7%), and patient decision (3.8% and 7.4%)

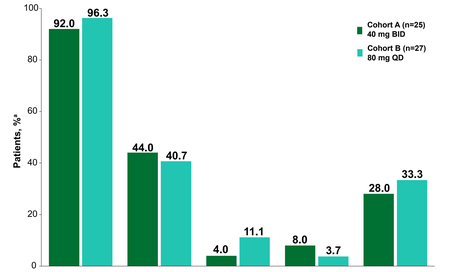
Table 2. Patient Disposition

Variable, n (%)[a]	Cohort A 40 mg BID (n=26)	Cohort B 80 mg QD (n=27)
Treated	25 (96.2)[b]	27 (100)
Ongoing treatment	6 (23.1)	14 (51.9)
Completed treatment	6 (23.1)	6 (22.2)
Discontinued treatment	13 (50.0)	7 (25.9)
Primary reason for discontinuation		
Physician decision	9 (34.6)	3 (11.1)
Lack of efficacy[c]	4 (15.4)	3 (11.1)
Early discontinuation	1 (3.8)	0
Non-compliance	1 (3.8)	0
Non-compliance with taking prescription	1 (3.8)	0
Switched to bosutinib	1 (3.8)	0
Terminated	1 (3.8)	0
AE	3 (11.5)	1 (3.7)
Patient decision	1 (3.8)	2 (7.4)
Progressive disease	0	1 (3.7)
Enrolled in safety follow-up	15 (57.7)	9 (33.3)
Discontinued safety follow-up	3 (11.5)	1 (3.7)
Primary reason for discontinuation of safety follow-up		
Physician decision	2 (7.7)	0
Patient decision	1 (3.8)	0
Death	0	1 (3.7)

[a] At the data cutoff of September 20, 2023. [b] One patient was not treated in cohort A due to patient decision. [c] Lack of efficacy includes patients who did not achieve MMR, had treatment failure, had treatment failure per protocol, or had treatment failure per investigator.

- The safety profile of asciminib was comparable in both cohorts (**Figure 3**)
  - The incidence of any-grade and grade ≥3 AEs was similar between cohorts despite a longer median (range) duration of exposure in cohort B (55.4 [1.3-80.6] weeks) than cohort A (48.9 [2.7-73.4] weeks)
  - SAEs were reported in 4.0% of patients in cohort A and 11.1% in cohort B
  - AEs leading to treatment discontinuation occurred in 2 patients (8.0%) in cohort A (neutropenia [includes neutropenia and neutrophil count decreased] and thrombocytopenia [includes thrombocytopenia and platelet count decreased], n=1; abdominal pain, n=1) and 1 (3.7%) in cohort B (myocardial infarction, n=1)
- In cohort B, on-treatment deaths were reported in 2 patients (7.4%) due to disease progression and an SAE (sepsis)
  - Both deaths were not thought to be related to the study drug by investigators
- No new safety signals were observed compared with prior asciminib trials and the approved label[7,11]

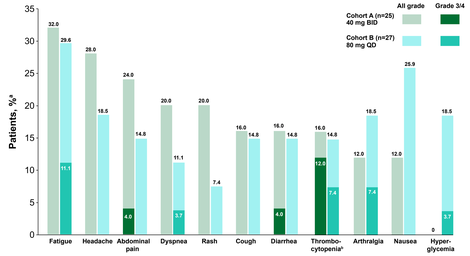
Figure 3. Overview of AEs



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

- Similar AEs were reported in both cohorts and were mostly low grade (**Figure 4**)
  - The most common grade ≥3 AEs (in ≥5% of patients) were thrombocytopenia and neutropenia (12.0% each) and increased lipase (8.0%) in cohort A and fatigue and hypertension (11.1% each) and thrombocytopenia, hypokalemia, and arthralgia (7.4% each) in cohort B
  - In cohort B, 1 patient (3.7%) had grade 4 AOEs (acute coronary syndrome and myocardial infarction)

Figure 4. Most Frequent All-Grade AEs (in ≥15% of Patients in Any Cohort)



[a] A patient with multiple severity grades for an AE is only counted under the maximum grade. [a] Thrombocytopenia includes thrombocytopenia and platelet count decreased.

- Dose adjustments and discontinuations occurred in 68.0% of patients in cohort A and 48.1% in cohort B (**Table 3**)
- AEs were the primary reason for adjustments and discontinuations in both cohorts
  - The most frequently reported all-grade AEs leading to dose interruption were thrombocytopenia (n=3) and neutropenia (n=2) in cohort A and thrombocytopenia, arthralgia, and cough (n=2 each) in cohort B
  - The most frequently reported AEs leading to dose reduction were neutropenia (n=2) in cohort A and fatigue (n=2) in cohort B
- Treatment was permanently discontinued in 4 patients in cohort A (AE, n=2; physician decision, n=1; patient decision, n=1) and 2 in cohort B (AE, n=1; per protocol, n=1)

Table 3. Dose Adjustments and Discontinuations

Adjustments and discontinuations/reasons, n (%)[a]	Cohort A 40 mg BID (n=25)	Cohort B 80 mg QD (n=27)
Patients without dose reduction, interruption, or permanent discontinuation	8 (32.0)	14 (51.9)
Patients with dose reduction, interruption, or permanent discontinuation	17 (68.0)	13 (48.1)
Reason for dose reduction		
AE	4 (16.0)	6 (22.2)
Per protocol	1 (4.0)	0
Dispensing error	1 (4.0)	0
Dosing error	0	1 (3.7)
Physician decision	2 (8.0)	2 (7.4)
Reason for dose interruption		
AE	8 (32.0)	10 (37.0)
Per protocol	2 (8.0)	0
Dosing error	2 (8.0)	1 (3.7)
Physician decision	2 (8.0)	1 (3.7)
Patient decision	1 (4.0)	2 (7.4)
Technical problems	0	1 (3.7)
Reasons for permanent discontinuation		
AE	2 (8.0)	1 (3.7)
Per protocol	0	1 (3.7)
Physician decision	1 (4.0)	0
Patient decision	1 (4.0)	0

[a] A patient with ≥1 dose reduction or interruption within a category was only counted once in that category.

- Of the 9 evaluable patients in cohort A with *BCR::ABL1*^{IS} >10% at baseline, 4 (44.4%) achieved *BCR::ABL1*^{IS} ≤10% by 6 months; of the 13 evaluable patients with *BCR::ABL1*^{IS} ≤10% at baseline, 4 (30.8%) achieved deeper responses by 6 months (**Table 4**)
- Of the 10 evaluable patients in cohort B with *BCR::ABL1*^{IS} >10% at baseline, 8 (80.0%) achieved *BCR::ABL1*^{IS} ≤10% by 6 months; of the 14 evaluable patients with *BCR::ABL1*^{IS} ≤10% at baseline, 6 (42.9%) achieved deeper responses by 6 months (**Table 4**)
- Most patients in both cohorts had molecular responses by week 12 (**Figure 5**)
  - By week 12, a total of 60.9% and 78.3% of patients in cohorts A and B, respectively, achieved *BCR::ABL1*^{IS} ≤1%
- By week 24 in cohorts A and B, respectively:
  - *BCR::ABL1*^{IS} ≤1% was achieved by 62.5% and 91.7% of patients
  - MMR was achieved by 45.8% and 66.7% of patients
  - MR4 was achieved by 33.3% and 29.2% of patients
  - MR4.5 was achieved by 29.2% and 16.7% of patients
- The median time to first MMR was similar in cohorts A (24.0 weeks) and B (23.1 weeks)
- A relatively shorter median time to first MR4 was observed in cohort A (36.1 weeks) than cohort B (58.6 weeks)

Figure 5. Molecular Responses by Weeks 12 and 24



* n = number of patients who achieved a response by scheduled visits; M = number of patients with ≥1 nonmissing response assessment by that visit.

Table 4. Categorical Response Shift from Baseline

Posttreatment *BCR::ABL1*^{IS}, n (%)[a]	Cohort A (40 mg BID) Baseline *BCR::ABL1*^{IS}[b,c]					Cohort B (80 mg QD) Baseline *BCR::ABL1*^{IS}[b,c]				
	≤0.01% (n=5)	>0.01% to ≤0.1% (n=2)	>0.1% to ≤1% (n=4)	>1% to ≤10% (n=2)	>10% (n=10)	≤0.01% (n=3)	>0.01% to ≤0.1% (n=4)	>0.1% to ≤1% (n=4)	>1% to ≤10% (n=4)	>10% (n=12)
By 3 months										
Patients who could be evaluated[c]	**5**	**2**	**4**	**2**	**8**	**2**	**3**	**4**	**4**	**10**
≤0.01%	5 (100)	1 (50.0)	0	1 (50.0)	0	2 (100)	0	1 (25.0)	0	0
>0.01% to ≤0.1%	0	1 (50.0)	1 (25.0)	0	0	0	3 (100)	2 (50.0)	2 (50.0)	1 (10.0)
>0.1% to ≤1%	0	0	3 (75.0)	0	1 (12.5)	0	0	1 (25.0)	1 (25.0)	4 (40.0)
>1% to ≤10%	0	0	0	1 (50.0)	2 (25.0)	0	0	0	0	3 (30.0)
>10%	0	0	0	0	5 (62.5)	0	0	0	1 (25.0)	2 (20.0)
By 6 months										
Patients who could be evaluated[c]	**5**	**2**	**4**	**2**	**9**	**2**	**4**	**4**	**4**	**10**
≤0.01%	5 (100)	1 (50.0)	0	1 (50.0)	0	2 (100)	0	2 (50.0)	1 (25.0)	1 (10.0)
>0.01% to ≤0.1%	0	1 (50.0)	2 (50.0)	0	0	0	3 (75.0)	1 (25.0)	1 (25.0)	4 (40.0)
>0.1% to ≤1%	0	0	2 (50.0)	0	2 (22.2)	0	1 (25.0)	1 (25.0)	1 (25.0)	3 (30.0)
>1% to ≤10%	0	0	0	1 (50.0)	2 (22.2)	0	0	0	0	0
>10%	0	0	0	0	5 (55.6)	0	0	0	1 (25.0)	2 (20.0)

[a] Percentages were calculated on the basis of the number of patients who could be evaluated. A total of 2 patients with CML-CP had a missing *BCR::ABL1*^{IS} value at baseline. [b] The number of patients is the number who received ≥1 dose of asciminib in each category of *BCR::ABL1* transcript level at baseline. [c] The number of patients who could be evaluated in each category of baseline *BCR::ABL1* transcript level who had undergone assessment of molecular response at 3 or 6 months after treatment or who had a MMR within 3 or 6 months.

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Abbreviations

ABL1, Abelson tyrosine kinase 1; AE, adverse event; AOE, arterial occlusive event; ATP, adenosine triphosphate; BCR, breakpoint cluster region; BID, twice daily; CHR, complete hematologic response; CML, chronic myeloid leukemia; CP, chronic phase; ECOG, Eastern Cooperative Oncology Group; ELN, European LeukemiaNet; IS, International Scale; MMR, major molecular response (*BCR::ABL1*^{IS} ≤0.1%); MR4, *BCR::ABL1*^{IS} ≤0.01%; MR4.5, *BCR::ABL1*^{IS} ≤0.0032%; OS, overall survival; PFS, progression-free survival; Ph, Philadelphia chromosome; PS, performance status; QD, once daily; QoL, quality of life; R, randomized; SAE, serious adverse event; SH, Src homology; TKI, tyrosine kinase inhibitor.