CML-395

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Efficacy and Safety Results From ASCEMBL, a Phase III Study of Asciminib vs Bosutinib in Patients With Chronic Myeloid Leukemia in Chronic Phase After ≥2 Prior Tyrosine Kinase Inhibitors: Week 96 Update

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CONCLUSIONS

After over 2 years of follow-up in ASCEMBL, asciminib continued to demonstrate superior efficacy vs bosutinib, with more patients achieving responses over time

- The MMR rate at week 96 **was more than double with asciminib (37.6%; 95% CI, 29.99%-45.65%)** than with **bosutinib (15.8%; 95% CI, 8.43%-25.96%)**, meeting the key secondary objective and supporting the long-term efficacy of asciminib
- Responses were highly durable with asciminib, and median time to treatment failure was substantially longer with **asciminib (24 months)** than with **bosutinib (6 months)**
- The MMR rate at week 96 was **higher with asciminib** than with **bosutinib** across all demographic and prognostic subgroups, including in patients who discontinued their last TKI due to either resistance or intolerance
- The rate of *BCR::ABL1*^{IS} ≤1% at week 96 was **more than double** with **asciminib (45.1%)** than with **bosutinib (19.4%)**, a milestone response associated with improved long-term outcomes[6]

Regardless of asciminib's longer duration of exposure, its safety and tolerability continued to be better than those of bosutinib, with no new or worsening safety findings

Overall, more patients receiving **asciminib (53.5%)** than with **bosutinib (19.7%)** remained on treatment and continued to benefit from therapy over time, reinforcing the efficacy and tolerability of asciminib as a new CML therapy, with the potential to transform standard of care

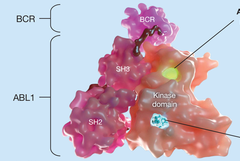
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INTRODUCTION

- Asciminib is the first BCR::ABL1 inhibitor to **Specifically Target the ABL Myristoyl Pocket (STAMP)**[1] (**Figure 1**)
- Asciminib is **approved by the US Food and Drug Administration** for the treatment of adults with Philadelphia chromosome–positive (Ph+) chronic myeloid leukemia in chronic phase (CML-CP) previously treated with ≥2 tyrosine kinase inhibitors (TKIs) and in those with the T315I mutation[2,3]
- In the primary (week 24) analysis from the pivotal ASCEMBL trial, **asciminib** demonstrated **superior efficacy** and **better safety** and **tolerability** than **bosutinib** in patients with CML-CP after ≥2 prior TKIs[1]
- After longer follow-up in ASCEMBL, major molecular response (MMR) rate at week 48 remained consistently higher with **asciminib** than **bosutinib (29.3%** vs **13.2%)** and the safety profile of asciminib remained favorable[4]
- **We report key secondary efficacy and safety results after a median follow-up of 2.3 years (16.5 months[†] additional follow-up since primary analysis)**

Figure 1. Asciminib Is The First BCR::ABL1 Inhibitor To Specifically Target the ABL Myristoyl Pocket (STAMP)[1]

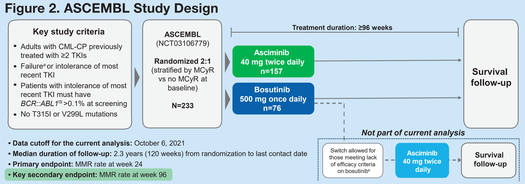


[a]Approved in China.

STUDY DESIGN

- This is a phase III, multicenter, open-label, randomized study of oral asciminib vs bosutinib in patients with CML-CP previously treated with ≥2 TKIs (**Figure 2**)
- Study methods can be found in the supplementary slides

Figure 2. ASCEMBL Study Design



[a]Must meet lack of efficacy criteria based on 2013 ELN recommendations for 2L TKI therapy.[5]
[b]Patients who discontinued bosutinib treatment due to intolerance or any reason other than lack of efficacy were *not* allowed to switch to asciminib.

RESULTS

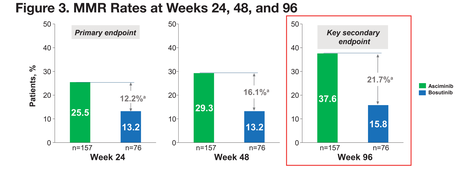
Table 1. Patient Disposition

Variable, n (%)	Asciminib 40 mg twice daily (n=157)	Bosutinib 500 mg once daily (n=76)
Patients randomized		
Treated	156 (99.4)[a]	76 (100.0)
Treatment ongoing[b]	**84 (53.5)**	**15 (19.7)**
Discontinued treatment	**72 (45.9)**	**61 (80.3)**
Before week 24	26 (16.6)	25 (32.9)
Week 24 to before week 48	25 (15.9)	29 (38.2)
Week 48 to before week 96	17 (10.8)	3 (3.9)
After week 96	4 (2.5)	4 (5.3)
Reason for discontinuation		
Lack of efficacy	**38 (24.2)**	**27 (35.5)**
Adverse event	**11 (7.0)**	**19 (25.0)**
Physician decision	14 (8.9)	6 (7.9)
Patient decision	5 (3.2)	4 (5.3)
Death	1 (0.6)	0
Lost to follow-up	1 (0.6)	2 (2.6)
Progressive disease	1 (0.6)	3 (3.9)
Protocol deviation	1 (0.6)	0
Switched to receive asciminib	NA	24 (31.6)

[a]1 patient developed cytopenia after randomization and was not treated per investigator's decision.
[b]Ongoing at the time of data cutoff: October 6, 2021.

- The rate of discontinuations due to adverse events (AEs) continued to be low with asciminib, with minimal increase since the primary analysis (**Table 1**)

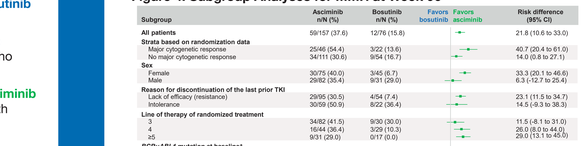
Figure 3. MMR Rates at Weeks 24, 48, and 96



[a]The treatment difference after adjusting for baseline MCyR status was 12.24% (95% CI, 2.19%-22.30%; 2-sided *P*=.029) at week 24, 16.09% (95% CI, 5.69%-26.49%; 2-sided *P*=.007) at week 48, and 21.74% (95% CI, 10.53%-32.95%; 2-sided *P*<.001) at week 96.

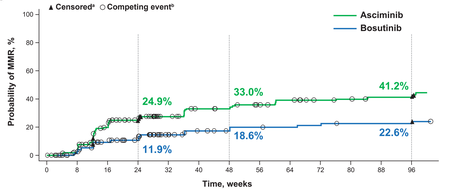
- The MMR rate with asciminib increased consistently over time, suggesting the long-term benefit of continuing treatment with asciminib (**Figure 3**)
- The MMR rate was **consistently higher** with asciminib than with bosutinib in **all demographic** and **prognostic subgroups** (**Figure 4**)

Figure 4. Subgroup Analyses for MMR at Week 96



[a]Patients with T315I and V299L *BCR::ABL1* mutations or a nonevaluable mutation assessment were excluded from the subgroup analysis.

Figure 5. Cumulative Incidence of MMR



Number of patients still at risk																									
Asciminib	157	152	145	129	108	94	89	73	64	60	51	51	49	44	42	39	35	32	30	29	28	26	24	24	24
Bosutinib	76	72	66	60	52	47	41	33	22	19	15	13	11	10	10	9	9	8	8	7	6	6	6	6	6
Cumulative number of competing events																									
Asciminib	0	5	8	14	17	23	27	35	44	47	49	49	51	52	54	56	56	59	61	62	62	64	64	64	64
Bosutinib	0	4	8	11	16	20	25	31	42	45	47	49	50	50	50	51	51	51	51	52	52	52	52	52	52

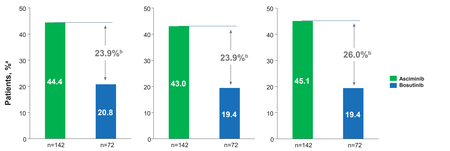
[a]Nonresponders were censored at their last molecular assessment date.
[b]Discontinuation from treatment for any reason without prior achievement of MMR is considered a competing event.

- The cumulative incidence of MMR, adjusted by competing risks, was higher with asciminib than bosutinib (**Figure 5**)

Duration of MMR

- The probability (95% CI) of maintaining MMR for ≥72 weeks was **96.7%** (87.4%-99.2%) with **asciminib** and **92.9%** (59.1%-99.0%) with **bosutinib**
- Of the **69** and **18** patients who achieved MMR with **asciminib** and **bosutinib**, respectively, **67** and **17** had maintained response at the time of their last assessment
  - At data cutoff, median duration of MMR was not reached in either treatment arm

Figure 6. Rates of *BCR::ABL1*^{IS} ≤1% at Weeks 24, 48, and 96



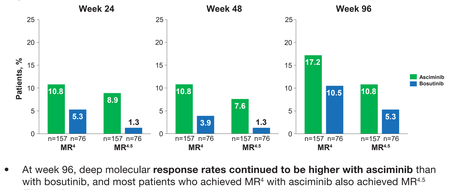
[a]Based on 142 of 157 patients (90.4%) receiving asciminib and 72 of 76 (94.7%) receiving bosutinib with *BCR::ABL1*^{IS} >1% at baseline.
[b]The treatment difference after adjusting for baseline MCyR status was 23.92% (95% CI, 11.36%-36.49%; 2-sided *P*<.000) at week 24, 23.85% (95% CI, 11.36%-36.33%; 2-sided *P*<.000) at week 24, and 26.02% (95% CI, 13.48%-38.56%; 2-sided *P*=.000) at week 96.

- At week 96, the rate of *BCR::ABL1*^{IS} ≤1% (in patients with *BCR::ABL1*^{IS} >1% at baseline) continued to be **more than double with asciminib** than bosutinib (**Figure 6**)

Duration of *BCR::ABL1*^{IS} ≤1%

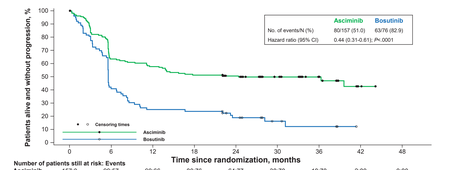
- The probability (95% CI) of maintaining *BCR::ABL1*^{IS} ≤1% for ≥72 weeks was **94.6%** (86.2%-97.9%) with **asciminib** and **95.0%** (69.5%-99.3%) with **bosutinib**
- Of the **78** and **24** patients who achieved *BCR::ABL1*^{IS} ≤1% with **asciminib** and **bosutinib**, respectively, **74** and **23** had maintained response at the time of their last assessment
  - At data cutoff, median duration of *BCR::ABL1*^{IS} ≤1% was not reached in either treatment arm

Figure 7. MR[4] and MR[4.5] Rates at Weeks 24, 48, and 96



- At week 96, deep molecular **response rates continued to be higher with asciminib** than with bosutinib, and most patients who achieved MR[4] with asciminib also achieved MR[4.5] (**Figure 7**)

Figure 8. Time to Treatment Failure[a]

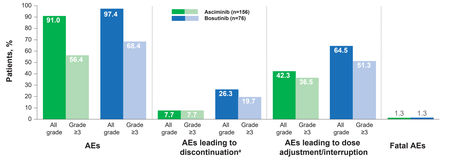


Number of patients still at risk: Events								
Asciminib	157:0	99:57	90:66	80:76	64:77	38:78	18:78	2:80	0:80
Bosutinib	76:0	31:45	19:57	18:58	11:61	5:62	3:63	0:63	0:63

[a]Treatment failure was defined as lack of efficacy (per 2013 ELN recommendations for 2L patients[5]) or discontinuation for any reason. To meet the definition of failure per ELN 2013 recommendations, patients must meet ≥1 of the following criteria: no complete hematologic response (CHR) or >95% Ph+ metaphases 3 months after initiation of therapy; *BCR::ABL1*^{IS} >10% and/or >65% Ph+ metaphases 6 months after initiation of therapy; *BCR::ABL1*^{IS} >10% and/or >35% Ph+ metaphases 12 months after initiation of therapy; loss of CHR, complete cytogenetic response, or partial cytogenetic response at any time after initiation of therapy; the development of new *BCR::ABL1* mutations which potentially cause resistance to study treatment at any time after initiation of therapy; confirmed loss of MMR in 2 consecutive tests, of which one must have a *BCR::ABL1*^{IS} ≥1% at any time after initiation of therapy; new clonal chromosome abnormalities in Ph+ cells at any time after initiation of therapy.

- The proportion of patients without treatment failure by **2 years** was **50.6%** (95% CI, 42.5%-58.2%) with **asciminib** vs **18.9%** (95% CI, 10.8%-28.6%) with **bosutinib** (**Figure 8**)
- Median time to treatment failure was substantially longer with **asciminib (24 months)** than with **bosutinib (6 months)**

Figure 9. Overview of AEs

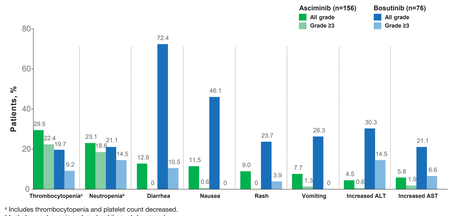


[a]Grade 1/2 AEs leading to discontinuation with bosutinib (n=5) included ALT/AST level increased, blood creatinine level increased, diarrhea, drug eruption, and pleural effusion.

- The median duration of exposure was **23.7 months** (range, 0.0-46.2 months) for **asciminib** and **7.0 months** (range, 0.2-43.3 months) for **bosutinib**
- The safety and tolerability of asciminib continued to be better than with bosutinib, with no new or worsening safety findings and no on-treatment deaths in either arm since the primary analysis cutoff (**Figure 9**)

- The most common AEs leading to treatment discontinuation did not change since the primary analysis and included thrombocytopenia (**3.2%**) and neutropenia (**2.6%**) with **asciminib** and increased ALT (**5.3%**) and neutropenia (**3.9%**) with **bosutinib**
- **Most hematologic AEs** with asciminib initially **presented within the first 6 months** of treatment

Figure 10. Most Frequent All-Grade AEs (in ≥20% of Patients in Any Arm)



[a]Includes thrombocytopenia and platelet count decreased.
[b]Includes neutropenia and neutrophil count decreased.

- Regardless of the longer duration of exposure, safety and tolerability of asciminib remained consistent with that at the time of the primary analysis and continued to be better than with bosutinib with longer follow-up (**Figure 10**)

Table 2. AOEs

AOE, n (%)	Asciminib 40 mg twice daily (n=156)	Bosutinib 500 mg once daily (n=76)
Patients with AOEs, n (%)	8 (5.1)	1 (1.3)
Patients with events observed by the cutoff for primary analysis (week 24)		
Myocardial ischemia[a]	2 (1.3)*,†	0
Acute coronary syndrome	0	1 (1.3)
Coronary artery disease[a]	1 (0.6)	0
Ischemic stroke	1 (0.6)*	0
Mesenteric artery embolism/thrombosis[b]	1 (0.6)*,†	0
Additional patients with events by week 96 cutoff since the week 24 cutoff		
Cerebral infarction	1 (0.6)*,†	0
Myocardial infarction	1 (0.6)*	0
Troponin increased	1 (0.6)*	0
Exposure-adjusted AOE rate (per 100 patient-years)		
Primary analysis (week 24)	3.3	2.0
Week 96 analysis	3.0	1.4

*Myocardial ischemia (n=2) and coronary artery disease (n=1) in patients receiving asciminib occurred without clinical manifestations and was identified based on ECG performed per protocol after dosing and coronary arteriography performed due to medical history, respectively.
†Mesenteric artery embolism/thrombosis occurred 15 days after asciminib discontinuation and following ponatinib treatment for 7 days.

- There was no increase in risk of arterial occlusive events (AOEs) with asciminib over time (**Table 2**)
  - Exposure-adjusted AOE rate (per 100 patient-years) in the week 96 analysis (**3.0**) was comparable to that in the primary analysis (**3.3**)
  - Of the 8 with AOEs in the **asciminib** arm, *7 had prior exposure to nilotinib, †6 to dasatinib, and ‡3 to ponatinib
  - The patient with an AOE in the **bosutinib** arm had prior exposure to nilotinib and ponatinib

Abbreviations

2L, second line; **ABL1**, Abelson tyrosine kinase 1; **AE**, adverse event; **ALT**, alanine aminotransferase; **AOE**, arterial occlusive event; **AST**, aspartate aminotransferase; **ATP**, adenosine triphosphate; **BCR**, breakpoint cluster region; **CML-CP**, chronic myeloid leukemia in chronic phase; **ECG**, electrocardiogram; **ELN**, European LeukemiaNet; **IS**, International Scale; **MCyR**, major cytogenetic response; **MMR**, major molecular response; **MR^{4}**, *BCR::ABL1*^{IS} ≤0.01%; **MR$^{4.5}$**, *BCR::ABL1*^{IS} ≤0.0032%; **NA**, not applicable; **Ph**, Philadelphia chromosome; **SH**, Src homology; **STAMP**, Specifically Target the ABL Myristoyl Pocket; **TKI**, tyrosine kinase inhibitor.

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