S155 EFFICACY AND SAFETY RESULTS FROM ASCEMBL, A PHASE 3 STUDY OF ASCIMINIB VS BOSUTINIB IN PATIENTS WITH CHRONIC MYELOID LEUKEMIA IN CHRONIC PHASE AFTER ≥2 PRIOR TYROSINE KINASE INHIBITORS: WK 96 UPDATE Topic: 08. Chronic myeloid leukemia – Clinical**.** Delphine Rea1, Andreas Hochhaus2, Michael J Mauro3, Yosuke Minami4, Elza Lomaia5, Sergey Voloshin6, Anna Turkina7, Dong-Wook Kim8, Jane F Apperley9, Jorge E Cortes10, Andre Abdo11, Laura Marie Fogliatto12, Dennis Dong Hwan Kim13, Philipp le Coutre14, Susanne Saussele15, Mario Annunziata16, Timothy P Hughes17, Naeem Chaudhri18, Lynette Chee19, ***Valentin García-Gutiérrez20***, Koji Sasaki21, Shruti Kapoor22, Alex Allepuz23, Sara Quenet23, Véronique Bédoucha23, Carla Boquimpani24 1 *Hôpital Saint-Louis, Paris, France;*2 *Universitätsklinikum Jena, Jena, Germany;*3 *Memorial Sloan Kettering Cancer Center, New York, United States;*4 *National Cancer Center Hospital East, Kashiwa, Japan;*5 *Almazov National Medical Research Centre, St. Petersburg, Russian Federation;*6 *Russian Research Institute of Hematology and Transfusiology, St. Petersburg, Russian Federation;*7 *National Medical Research Center for Hematology, Moscow, Russian Federation;*8 *Uijeongbu Eulji Medical Center, Geumo-dong, Uijeongbu-si, Korea, Republic Of;*9 *Centre for Haematology Imperial College London, London, United Kingdom;*10 *Georgia Cancer Center, Augusta, United States;*11 *Instituto do Câncer do Estado de São Paulo (ICESPSP), São Paulo, Brazil;*12 *Hospital de Clínicas de Porto Alegre (HCPA), Porto Alegre, Brazil;*13 *Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, Canada;*14 *Charité–Universitätsmedizin Berlin, Berlin, Germany;*15 *III. Medizinische Klinik, Medizinische Fakultät Mannheim der Universität Heidelberg, Mannheim, Germany;*16 *Division of Hematology, AORN Cardarelli, Naples, Italy;*17 *South Australian Health and Medical Research Institute and University of Adelaide, Adelaide, Australia;*18 *King Faisal Specialist Hospital & Research Center, Riyadh, Saudi Arabia;*19 *Peter MacCallum Cancer Center and The Royal Melbourne Hospital, Victoria, Australia;* ***20 Servicio de Hematología, Hospital Universitario Ramón y Cajal (IRYCIS)****, Madrid, Spain;*21 *The University of Texas MD Anderson Cancer Center, Houston, United States;*22 *Novartis Pharmaceuticals Corporation, East Hanover, United States;*23 *Novartis Pharma AG, Basel, Switzerland;*24 *HEMORIO, State Institute of Hematology Arthur de Siquiera Cavalcanti, Rio de Janeiro, Brazil Oncoclínica Centro de Tratamento Oncológico, Rio de Janeiro, Brazil*

Background: Asciminib is the 1st BCR::ABL1 inhibitor to Specifically Target the ABL Myristoyl Pocket (STAMP). In the ASCEMBL primary analysis, asciminib had superior efficacy and better safety/tolerability vs bosutinib (BOS) in patients (pts) with chronic myeloid leukemia in chronic phase (CML-CP) after ≥2 prior tyrosine kinase inhibitors (TKIs). Major molecular response (MMR) rate at wk 24 was 25.5% on asciminib vs 13.2% on BOS; the difference in MMR rates after adjusting for baseline major cytogenetic response (MCyR) was 12.2% (95% CI, 2.19%-22.30%; 2- sided P=.029). Fewer grade ≥3 adverse events (AEs) and AEs leading to treatment discontinuation occurred on asciminib vs BOS. After a median follow-up of 2.3 years (16.5 months' additional follow-up since the primary analysis), we report updated efficacy and safety results (cutoff: October 6, 2021).

Aims: The key secondary objective was to compare MMR rate at wk 96 on asciminib vs BOS.

Methods: Eligible pts provided informed consent, were adults with CML-CP after ≥2 prior TKIs, with intolerance or lack of efficacy per 2013 European LeukemiaNet recommendations. They

were randomized 2:1 to asciminib 40 mg twice daily or BOS 500 mg once daily, stratified by baseline MCyR status (Ph+ metaphases ≤35%).

Results: 233 pts were randomized to asciminib (n=157) or BOS (n=76). At cutoff, treatment was ongoing in 84 (53.5%) and 15 (19.7%) pts, respectively; the most common reason for discontinuation was lack of efficacy in 38 (24.2%) and 27 (35.5%) pts, respectively. MMR rate at wk 96 (per ITT) was 37.6% on asciminib and 15.8% on BOS, meeting the key secondary objective. The difference after adjusting for baseline MCyR was 21.7% (95% CI, 10.5%-33.0%; 2-sided P=.001). Preplanned subgroup analyses showed that MMR rate at wk 96 was consistently higher with asciminib than BOS in all demographic and prognostic subgroups, including all prior lines of TKI therapy, and regardless of the reason for discontinuation of the last TKI (Figure). At wk 96, more pts on asciminib than BOS had BCR: ABL1IS ≤1% (45.1% vs 19.4%) (Table). Responses were durable, with a probability (95% CI) of maintaining MMR and BCR::ABL1IS ≤1% for ≥72 wk of 96.7% (87.4%- 99.2%) and 94.6% (86.2%-97.9%), respectively, on asciminib and 92.9% (59.1%-99.0%) and 95.0% (69.5%- 99.3%), respectively, on BOS. Median time to treatment failure was 24 months on asciminib and 6 months on BOS. Median duration (range) of exposure was 103.1 (0.1-201.1) wk on asciminib and 30.5 (1.0-188.3) wk on BOS. Despite asciminib’ s longer duration of exposure, its safety/tolerability continued to be better than that of BOS (Table). Fewer pts on asciminib than BOS had AEs leading to treatment discontinuation (7.7% vs 26.3%). No new on-treatment deaths were reported since the primary analysis. Most frequent (>10%) grade ≥3 AEs on asciminib vs BOS were thrombocytopenia (22.4%, 9.2%), neutropenia (18.6%, 14.5%), diarrhea (0%, 10.5%), and increased alanine aminotransferase (0.6%, 14.5%).

Figure. Risk Difference (95% CI) for MMR at wk 96 From Subgroup Analyses

Subgroup	Asciminib n/N (%)	Bosutinib n/N (%)	Risk difference (95% CI)
All patients	59/157 (37.6)	12/76 (15.8)	21.8 (10.6 to 33.0)
Strata based on randomization data			
Major cytogenetic response	25/46 (54.4)	3/22 (13.6)	40.7 (20.4 to 61.0)
No major cytogenetic response	34/111 (30.6)	9/54 (16.7)	14.0 (0.8 to 27.1)
Sex			
Female	30/75 (40.0)	3/45 (6.7)	33.3 (20.1 to 46.6)
Male	29/82 (35.4)	9/31 (29.0)	6.3 (-12.7 to 25.4)
Reason for discontinuation of the last prior TKI			
Lack of efficacy	29/95 (30.5)	4/54 (7.4)	23.1 (11.5 to 34.7)
Intolerance	30/59 (50.9)	8/22 (36.4)	14.5 (-9.3 to 38.3)
Line of therapy of randomized treatment			
3	34/82 (41.5)	9/30 (30.0)	11.5 (-8.1 to 31.0)
4	16/44 (36.4)	3/29 (10.3)	26.0 (8.0 to 44.0)
≥5	9/31 (29.0)	0/17 (0.0)	29.0 (13.1 to 45.0)
BCR::ABL1* mutation at baseline			
Unmutated	47/125 (37.6)	10/63 (15.9)	21.7 (9.3 to 34.1)
Mutated	7/17 (41.2)	2/8 (25.0)	16.2 (-21.9 to 54.2)

IS, International Scale; MMR, *BCR::ABL1*^{IS} ≤0.1%.
* Patients with T315I and V299L *BCR::ABL1* mutations or a nonevaluable mutation assessment were excluded from the subgroup analysis.

Table. Efficacy and Safety Results From ASCEMBL: A Comparison of wk 24 (Primary Analysis) With wk 96 (Current Analysis)

	Wk 24 (primary analysis)		Wk 96 (current analysis)	
	Asciminib (n=157)	Bosutinib (n=76)	Asciminib (n=157)	Bosutinib (n=76)
Efficacy, %	At wk 24		At wk 96	
MMR	25.5	13.2	37.6	15.8
CCyR[a]	40.8	24.2	39.8	16.1
BCR::ABL1^{IS} ≤1%[b]	44.4	20.8	45.1	19.4
MR^4	10.8	5.3	17.2	10.5
MR$^{4.5}$	8.9	1.3	10.8	5.3
	By wk 24		By wk 96	
Cumulative incidence of MMR[c]	24.9	11.9	41.2	22.6
Cumulative incidence of *BCR::ABL1*^{IS} ≤1%[b,d]	41.5	25.2	53.7	33.7
	≥ 24 wk		≥ 72 wk	
Probability of maintaining MMR, % (95% CI)[e]	98.4 (89.3-99.8)	100.0 (NA)	96.7 (87.4-99.2)	92.9 (59.1-99.0)
Probability of maintaining *BCR::ABL1*^{IS} ≤1%, % (95% CI)[f]	94.6 (86.2-97.9)	95.0 (69.5-99.3)	94.6 (86.2-97.9)	95.0 (69.5-99.3)
	Long-term outcomes (by 1 y)		Long-term outcomes (by 2 y)	
Estimated rate of PFS	95.1	88.6	94.4	91.1
Estimated rate of OS	97.5	98.6	97.3	98.6

	Asciminib (n=156)[g]		Bosutinib (n=76)		Asciminib (n=156)[g]		Bosutinib (n=76)	
Safety, n (%)	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
AEs	140 (89.7)	79 (50.6)	73 (96.1)	46 (60.5)	142 (91.0)	88 (56.4)	74 (97.4)	52 (68.4)
AEs leading to discontinuation	9 (5.8)	8 (5.1)	16 (21.1)	12 (15.8)	12 (7.7)	12 (7.7)	20 (26.3)	15 (19.7)
AEs leading to dose adjustment/interruption	59 (37.8)	53 (34.0)	46 (60.5)	37 (48.7)	66 (42.3)	57 (36.5)	49 (64.5)	39 (51.3)
AEs requiring additional therapy	103 (66.0)	44 (28.2)	67 (88.2)	31 (40.8)	112 (71.8)	52 (33.3)	68 (89.5)	35 (46.1)

CCyR, complete cytogenetic response; MR^4, *BCR::ABL1*^{IS} ≤0.01%; MR$^{4.5}$, *BCR::ABL1*^{IS} ≤0.0032%; NA, not applicable; OS, overall survival; PFS, progression-free survival.
[a] In pts without CCyR at baseline (asciminib, n=103; bosutinib, n=62).
[b] In pts with *BCR::ABL1*^{IS} >1% at baseline (asciminib, n=142; bosutinib, n=72).
[c] Adjusted by competing risks, including discontinuation from treatment for any reason without prior achievement of MMR.
[d] Adjusted by competing risks, including discontinuation from treatment for any reason without prior achievement of *BCR::ABL1*^{IS} ≤1%.
[e] In pts who achieved MMR (asciminib, n=69; bosutinib, n=18).
[f] In pts who achieved *BCR::ABL1*^{IS} ≤1% (asciminib, n=78; bosutinib, n=24)
[g] 1 pt on asciminib developed cytopenia after randomization and was not treated per investigator's decision.

Summary/Conclusion: After >2 years of follow-up, asciminib continued to show clinically and statistically significant, superior efficacy and better safety/tolerability vs BOS. Responses were durable, and MMR was more than double on asciminib than BOS. The difference in MMR rates

between the 2 arms increased from 12.2% at wk 24 to 21.7% at wk 96. A higher proportion of pts had BCR: ABL1IS ≤1%, a milestone response in later lines that is associated with improved long-term survival. These results further support the use of asciminib as a new CML therapy, with the potential to transform standard of care.