ASC4OPT Study: High Efficacy and Favorable Tolerability of Asciminib Once or Twice Daily in CML Patients with Suboptimal Response, Resistance or Intolerance of 2 or More Tyrosine Kinase Inhibitors

Supplementary slides

Andreas Hochhaus[1], Philipp le Coutre[2], Dragana Milojkovic[3, 4], Dennis Kim[5], Soo Min Lim[6], Carolina Pavlovsky[7], Thanh Nguyen[8], Franck Emmanuel Nicolini[9], Elena Moiraghi[10], Sebastian Grosicki[11], Chi Dung Phu[12], Gabriel Etienne[13], Fernando Marco de Lucas[14], Rosa María Ayala Díaz[15, 16], Massimo Breccia[17], Charles Chuah[18], Roberto Abi Rached[19], Braja Gopal Sahoo[20], Peter Schuld[19], Virginia Pilipovic[19], Carla Maria Boquimpani[21]

[1]Klinik für Innere Medizin II, Hematology/Oncology, Universitätsklinikum Jena and Comprehensive Cancer Center Central Germany, Campus Jena, Jena, Germany; [2]Department of Oncology and Hematology, Charité-Universitätsmedizin Berlin, Berlin, Germany; [3]Centre for Haematology, Department of Immunology and Inflammation, Imperial College London, London, UK; [4]Department of Clinical Haematology, Imperial College Healthcare NHS Trust, London, UK; [5]Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, Canada; [6]Sultanah Aminah Hospital, Johor Bahru, Malaysia; [7]FUNDALEU, Buenos Aires, Argentina; [8]National Institute of Hematology and Blood Transfusion, Hanoi, Vietnam; [9]Department of Hematology & INSERM U1052, Centre Léon Bérard and CRCL, Lyon, France; [10]Hospital Jose Maria Ramos Mejia, Buenos Aires, Argentina; [11]Department of Hematology and Cancer Prevention, Faculty of Health Sciences in Bytom, Medical University of Silesia, Katowice, Poland; [12]Blood Transfusion Hematology Hospital, Ho Chi Minh City, Vietnam; [13]Hematology Department, Institut Bergonié, Bordeaux, France; [14]Servicio de Hematología, Hospital Universitario Basurto, Osakidetza, Bilbao, Spain; [15]Haematological Malignancies Clinical Research Unit, Hospital 12 de Octubre Universidad Complutense, CNIO, CIBERONC, Madrid, Spain; [16]Spanish National Cancer Research Center (CNIO), Madrid, Spain; [17]Hematology, Department of Translational and Precision Medicine, Sapienza University of Rome, Rome, Italy; [18]Singapore General Hospital, Duke-NUS Medical School, Singapore, Singapore; [19]Novartis Pharma AG, Basel, Switzerland; [20]Novartis Healthcare Pvt. Ltd., Salarpuria-Sattva Knowledge City, Hyderabad, India; [21]HEMORIO, State Institute of Hematology Arthur de Siquiera Cavalcanti, Rio de Janeiro, Brazil

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Supplementary Methods: Warning, failure and intolerance criteria used in ASC4OPT

- Warning criteria used were *BCR::ABL1*^{IS} >10% after 3 months; or *BCR::ABL1*^{IS} >1–10% after 6 months; or *BCR::ABL1*^{IS} >0.1–1% after 12 months; or *BCR::ABL1*^{IS} >0.1–1%, loss of MMR (>0.1% with 5-fold increase of *BCR::ABL1* transcripts) at any time after the initiation of therapy
- Failure criteria used were *BCR::ABL1*^{IS} >10% if confirmed within 1–3 months; or *BCR::ABL1*^{IS} >10% after 6 months; or *BCR::ABL1*^{IS} >1% after 12 months; or at any time *BCR::ABL1*^{IS} >1%, emergence of resistance mutations, presence of high-risk additional chromosomal abnormalities
- Non-hematologic intolerance was defined as patients with grade 3 or 4 toxicity while on therapy, or with persistent grade 2 toxicity, unresponsive to optimal management, including dose adjustments (unless dose reduction was not considered in the best interest of the patient if response was already suboptimal). Hematologic intolerance was defined as patients with grade 3 or 4 toxicity (absolute neutrophil count or platelets) while on therapy that is recurrent after dose reduction to the lowest doses recommended by manufacturer

IS, international scale; MMR, major molecular response (*BCR::ABL1*^{IS} ≤0.1%).

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Supplementary Methods: Propensity Scores Indirect Comparison

- Propensity score weighting is a statistical technique that addresses confounding in observational studies to estimate causal treatment effects. This approach is invaluable in indirect treatment comparisons where direct head-to-head comparisons are not feasible due to variations across different studies or populations
- The propensity score e(X) is defined as the conditional probability of receiving a particular treatment given the vector of observed covariates X: e(X) = P(T = 1|X), where T denotes the treatment indicator (1 for treated, 0 for control)
- To create a pseudo-population in which the distribution of covariates is independent of the treatment assignment, weights are computed as follows:
  - For treated individuals: w_i=1/e(Xi)
  - For control individuals: w_i=1/(1-e(Xi))
- These weights adjust for the imbalance in baseline covariates between treatment groups. When comparing multiple treatments across different datasets, propensity score weighting helps to adjust for baseline differences, making the treatment groups comparable
- The effective sample size (ESS) can be used to quantify how well the matching worked. It is given by

$$ESS = \frac{(\sum_i w_i)^2}{\sum_i w_i^2}$$

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Supplementary Methods: PROs

- Patient-reported outcomes and quality of life were assessed using the MD Anderson Symptom Inventory – Chronic Myelogenous Leukemia [MDASI-CML] questionnaire

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MMR rate over time – Main cohort

This analysis included all patients, even those in whom the T315I mutation was detected after screening.

MMR rate, n (%)	Asciminib 40 mg BID n=85	Asciminib 80 mg QD n=84	All patients N=169
At Week 12	26 (30.6)	20 (23.8)	46 (27.2)
At Week 24	30 (35.3)	25 (29.8)	55 (32.5)
At Week 36	35 (41.2)	30 (35.7)	65 (38.5)
At Week 48	**36 (42.35)**	**29 (34.52)**	**65 (38.46)**

A propensity score weighting analysis to investigate the significance of the numerical differences in MMR rates between the two dosing schedules revealed no significant differences (p=0.681)

Pearson-Clopper 95% 2-sided CI for response rate. Patients without RT-qPCR assessment at a time point are considered as non-responders at that time point.
BID, twice daily; IS, international scale; MMR, major molecular response (*BCR::ABL1*^{IS} ≤0.1%); QD, once daily; RT-qPCR, real-time quantitative polymerase chain reaction.

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MMR rate over time – Main cohort

This analysis excluded patients in whom the T315I mutation was detected after screening.

MMR rate, n (%)	Asciminib 40 mg BID n=83	Asciminib 80 mg QD n=82	All patients N=165
At Week 12	26 (31.3)	20 (24.4)	46 (27.9)
At Week 24	30 (36.1)	25 (30.5)	55 (33.3)
At Week 36	35 (42.2)	30 (36.6)	65 (39.4)
At Week 48	**36 (43.4)**	**29 (35.4)**	**65 (39.4)**

A propensity score weighting analysis to investigate the significance of the numerical differences in MMR rates between the two dosing schedules revealed no significant differences (p=0.763)

Pearson-Clopper 95% 2-sided CI for response rate. Patients without RT-qPCR assessment at a time point are considered as non-responders at that time point.
BID, twice daily; IS, international scale; MMR, major molecular response (*BCR::ABL1*^{IS} ≤0.1%); QD, once daily; RT-qPCR, real-time quantitative polymerase chain reaction.

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MMR rate over time – Exploratory cohort

MMR rate, n (%)	Asciminib 40 mg BID n=14	Asciminib 80 mg QD n=16	All patients N=30
at Week 12[a]	11 (78.6)	14 (87.5)	25 (83.3)
at Week 24[a]	13 (92.9)	14 (87.5)	27 (90.0)
at Week 36[a]	13 (92.9)	14 (87.5)	27 (90.0)
at Week 48[a]	**14 (100)**	**14 (87.5)**	**28 (93.3)**

Pearson-Clopper 95% 2-sided CI for response rate. [a] Before week 12, two patients in the 80 mg QD arm discontinued from the study due to adverse events and were considered as non-responders. Patients without RT-qPCR assessment at a time point are considered as non-responders at that time point.
BID, twice daily; IS, international scale; MMR, major molecular response (*BCR::ABL1*^{IS} ≤0.1%); QD, once daily; RT-qPCR, real-time quantitative polymerase chain reaction.

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ASC4OPT 40 mg BID vs ASC4OPT 80 mg QD
Comparison of baseline prognostic factors

Demographic Variable, n (%)		ASC4OPT 40 mg BID N = 85	ASC4OPT 80 mg QD N = 84
Age Group	<65 years	64 (75.3)	59 (70.2)
	≥65 years	21 (24.7)	25 (29.8)
Sex	Female	37 (43.5)	27 (32.1)
	Male	48 (56.5)	57 (67.9)
Cytogenetic response at baseline	Major cytogenetic response	30 (35.3)	26 (31.0)
	No major cytogenetic response	55 (64.7)	58 (69.0)
Number of prior TKI therapies	2	47 (55.5)	42 (50.0)
	≥3	38 (44.7)	42 (50.0)
Mutation	Mutant	5 (5.9)	12 (14.3)
	Wild-type	68 (80.0)	62 (73.8)
	Unknown	12 (14.1)	10 (11.9)

BID, twice daily; QD, once daily; TKI, tyrosine kinase inhibitor.

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ASC4OPT 40 mg BID vs ASC4OPT 80 mg QD
Propensity score weighting analysis

Study	N	MMR	Difference	CI	P value
ASC4OPT 80 mg QD	84	34.52			
ASC4OPT 40 mg BID adjusted	66*	37.77	3.24	(-12.23, 18.71)	0.681**
ASC4OPT 40 mg BID unadjusted	85	42.35			

*Effective sample size = square of the summed weights / sum of squared weights. ** Computed only for the ad hoc analysis.

BID, twice daily; CI, confidence interval; MMR, major molecular response; QD, once daily.

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ASC4OPT 40 mg BID vs ASC4OPT 80 mg QD
Comparison of baseline prognostic factors – Excluding patients with T315I

Demographic Variable, n (%)		ASC4OPT 40 mg BID N = 83	ASC4OPT 80 mg QD N = 82
Age Group	<65 years	62 (74.7%)	57 (69.5%)
	≥65 years	21 (25.3%)	25 (30.5%)
Sex	Female	37 (44.6%)	26 (31.7%)
	Male	46 (55.4%)	56 (68.3%)
Cytogenetic response at baseline	Major cytogenetic response	30 (36.1%)	26 (31.7%)
	No major cytogenetic response	53 (63.9%)	56 (68.3%)
Number of prior TKI therapies	2	46 (55.4%)	41 (50%)
	≥3	37 (44.6%)	41 (50%)
Mutation	Mutant	5 (6%)	11 (13.4%)
	Wild-type	66 (79.5%)	61 (74.4%)
	Unknown	12 (14.5%)	10 (12.2%)

BID, twice daily; QD, once daily; TKI, tyrosine kinase inhibitor.

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ASC4OPT 40 mg BID vs ASC4OPT 80 mg QD

Propensity score weighting analysis – Excluding patients with T315I

Study	N	MMR	Difference	CI	P value
ASC4OPT 80 mg QD	82	35.37			
ASC4OPT 40 mg BID adjusted	68*	37.75	2.38	(-13.09, 17.85)	0.763**
ASC4OPT 40 mg BID unadjusted	83	43.37			

*Effective sample size = square of the summed weights / sum of squared weights. ** Computed only for the ad hoc analysis.

BID, twice daily; CI, confidence interval; MMR, major molecular response; QD, once daily.

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MR^4 at scheduled times

	Asciminib 40 mg BID N=83		Asciminib 80 mg QD N=82		All patients N=165	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
MR^4						
at Week 12	52 (62.7)	(51.34, 73.03)	45 (54.9)	(43.49, 65.90)	97 (58.8)	(50.87, 66.38)
at Week 24	55 (66.3)	(55.05, 76.28)	49 (59.8)	(48.34, 70.44)	104 (63.0)	(55.18, 70.40)
at Week 36	54 (65.1)	(53.81, 75.20)	54 (65.9)	(54.55, 75.97)	108 (65.5)	(57.67, 72.67)
at Week 48	55 (66.3)	(55.05, 76.28)	50 (61.0)	(49.57, 71.56)	105 (63.6)	(55.80, 70.97)

Pearson-Clopper 95% 2-sided CI for response rate.
BID, twice daily; CI, confidence interval; MR, molecular response; QD, once daily.

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$MR^{4.5}$ at scheduled times

	Asciminib 40 mg BID N=83		Asciminib 80 mg QD N=82		All patients N=165	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
$MR^{4.5}$						
at Week 12	1 (1.2)	(0.03, 6.53)	1 (1.2)	(0.03, 6.61)	2 (1.2)	(0.15, 4.31)
at Week 24	10 (12.0)	(5.93, 21.04)	4 (4.9)	(1.34, 12.02)	14 (8.5)	(4.72, 13.83)
at Week 36	12 (14.5)	(7.70, 23.89)	6 (7.3)	(2.73, 15.25)	18 (10.9)	(6.59, 16.69)
at Week 48	10 (12.0)	(5.93, 21.04)	7 (8.5)	(3.50, 16.80)	17 (10.3)	(6.12, 15.98)

Pearson-Clopper 95% 2-sided CI for response rate.
BID, twice daily; CI, confidence interval; MR, molecular response; QD, once daily.

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BCR::ABL1^{IS} ≤1% at scheduled times

	Asciminib 40 mg BID N=83		Asciminib 80 mg QD N=82		All patients N=165	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
BCR::ABL1^{IS} ≤1%						
at Week 12	30 (36.1)	(25.88, 47.43)	26 (31.7)	(21.87, 42.92)	56 (33.9)	(26.76, 41.71)
at Week 24	52 (62.7)	(51.34, 73.03)	45 (54.9)	(43.49, 65.90)	97 (58.8)	(50.87, 66.38)
at Week 36	55 (66.3)	(55.05, 76.28)	49 (59.8)	(48.34, 70.44)	104 (63.0)	(55.18, 70.40)
at Week 48	54 (65.1)	(53.81, 75.20)	54 (65.9)	(54.55, 75.97)	108 (65.5)	(57.67, 72.67)

Pearson-Clopper 95% 2-sided CI for response rate.
BID, twice daily; CI, confidence interval; MR, molecular response; QD, once daily.

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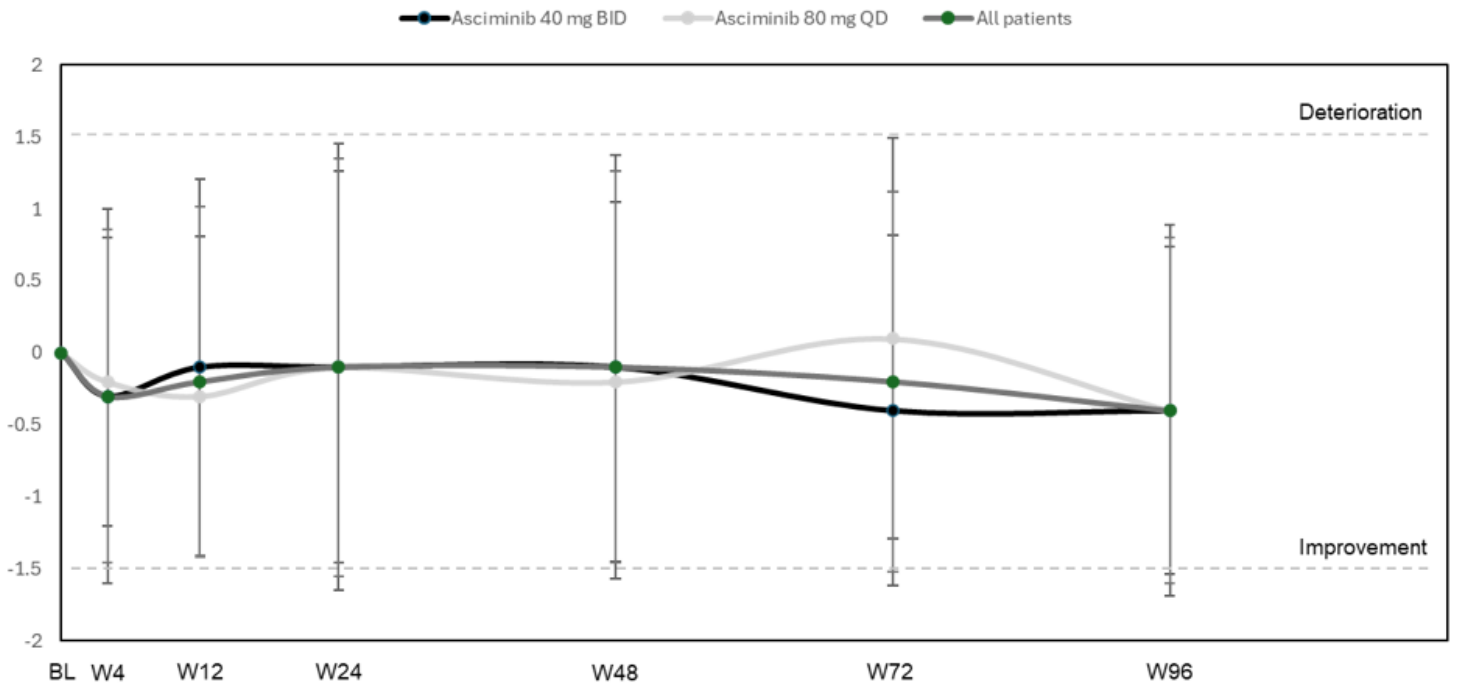
MDASI-CML Symptom Total Score Derived scores – Main cohort



Asciminib 40 mg BID	84	83	77	74	72	37	17
Asciminib 80 mg QD	84	81	79	78	71	37	15
All patients	168	164	156	152	143	74	32

BID, twice daily; QD, once daily.

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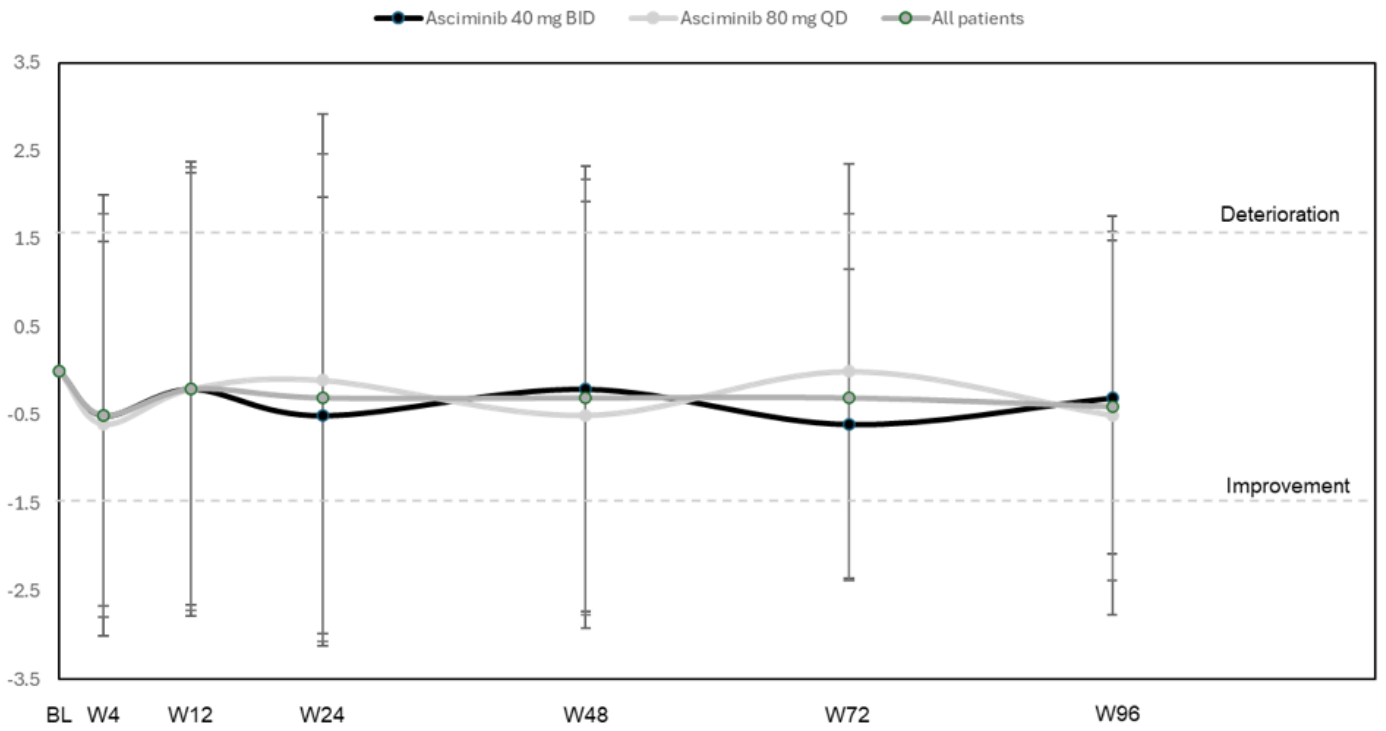
MDASI-CML Interference Total Score Derived scores – Main cohort



Asciminib 40 mg BID	84	81	76	73	69	36	17
Asciminib 80 mg QD	83	79	77	77	69	36	15
All patients	167	160	153	150	138	72	32

BID, twice daily; QD, once daily.

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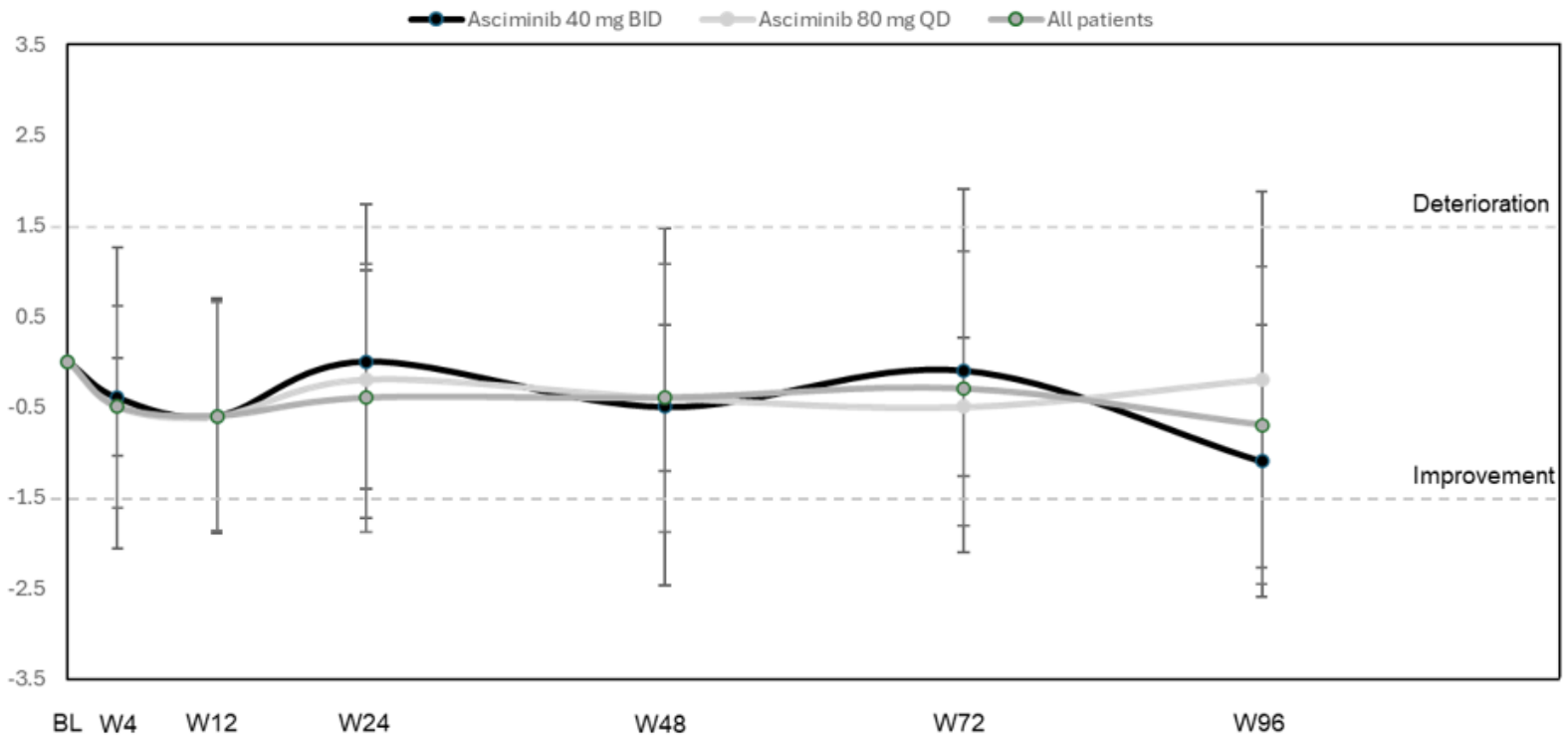
MDASI-CML Symptom Total Score Derived scores – Exploratory cohort



	BL	W4	W12	W24	W48	W72	W96
Asciminib 40 mg BID	13	10	12	13	13	9	6
Asciminib 80 mg QD	15	14	13	13	13	8	5
All patients	28	24	25	26	26	18	11

BID, twice daily; QD, once daily.

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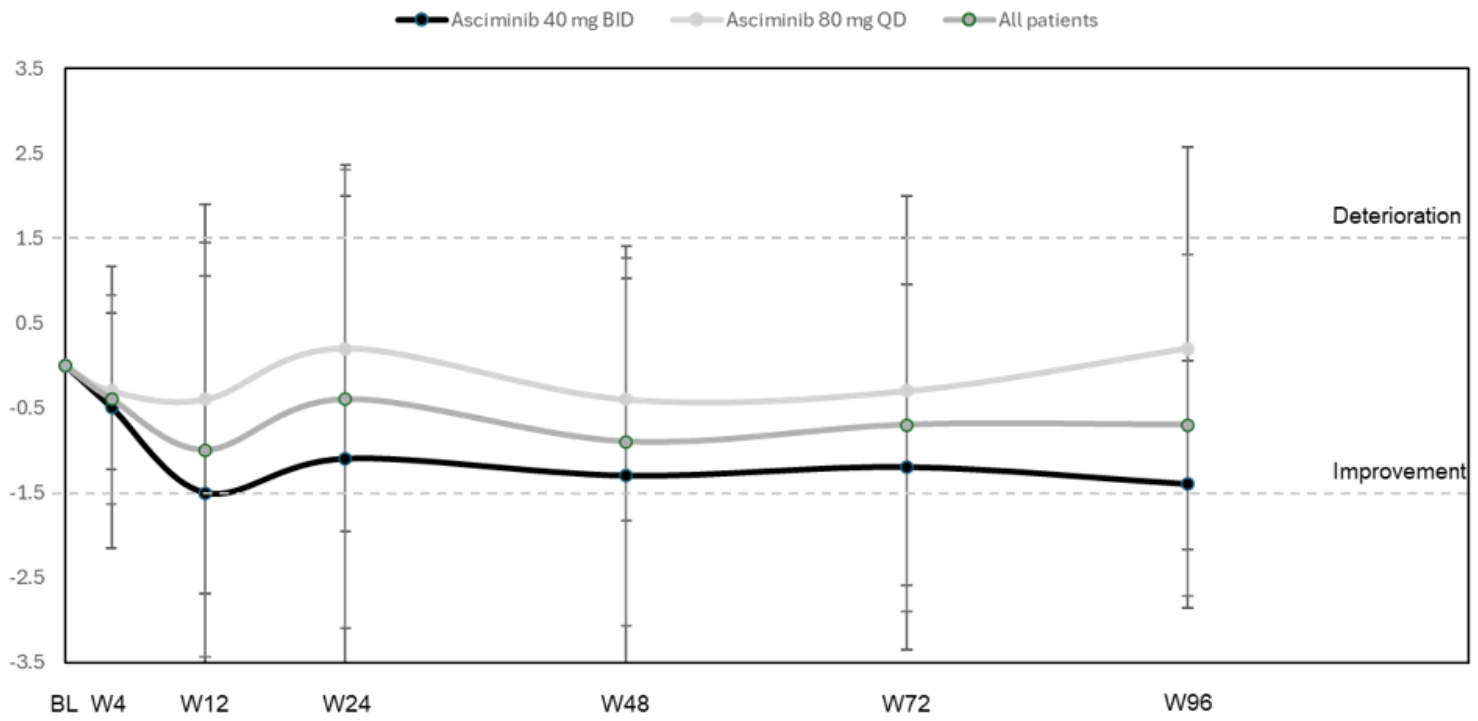
MDASI-CML Interference Total Score Derived scores – Exploratory cohort



	BL	W4	W12	W24	W48	W72	W96
Asciminib 40 mg BID	13	9	12	13	13	9	6
Asciminib 80 mg QD	15	14	13	13	13	8	5
All patients	28	23	25	26	26	17	11

BID, twice daily; QD, once daily.

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Most frequent AEs (reported in ≥10% of patients in any group) - Main cohort

Preferred term, n (%)	Asciminib 40 mg BID n=84		Asciminib 80 mg QD n=84		All patients N=168	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Number of patients with at least one event	76 (90.5)	21 (25.0)	74 (88.1)	29 (34.5)	150 (89.3)	50 (29.8)
Thrombocytopenia[a]	11 (13.1)	7 (8.3)	15 (17.9)	10 (11.9)	26 (15.5)	17 (10.1)
Arthralgia	10 (11.9)	2 (2.4)	13 (15.5)	0	23 (13.7)	2 (1.2)
COVID-19	11 (13.1)	0	9 (10.7)	0	20 (11.9)	0
Pruritus	12 (14.3)	0	5 (6.0)	0	17 (10.1)	0
Headache	8 (9.5)	0	8 (9.5)	0	16 (9.5)	0
Fatigue	3 (3.6)	0	12 (14.3)	1 (1.2)	15 (8.9)	1 (0.6)
ALT increased	9 (10.7)	2 (2.4)	2 (2.4)	0	11 (6.5)	2 (1.2)

[a]Includes thrombocytopenia and platelet count decreased. Numbers (n) represent counts of patients. A patient with multiple severity grades for an AE is only counted under the maximum grade. AEs occurring during treatment or within 30 days of last study medication are summarized. MedDRA version 26.1, CTCAE version 5.0.

BID, twice daily; COVID-19, coronavirus disease of 2019; QD, once daily.

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Most frequent AEs (reported in ≥25% of patients in any group) - Exploratory cohort

Preferred term, n (%)	Asciminib 40 mg BID n=14		Asciminib 80 mg QD n=16		All patients N=30	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Number of patients with at least one event	13 (92.9)	6 (42.9)	16 (100)	6 (37.5)	29 (96.7)	12 (40.0)
Pruritus	3 (21.4)	0	5 (31.3)	0	8 (26.7)	0
Arthralgia	3 (21.4)	0	4 (25.0)	0	7 (23.3)	0
Myalgia	2 (14.3)	0	4 (25.0)	1 (6.3)	6 (20.0)	1 (3.3)
COVID-19	3 (21.4)	0	3 (18.8)	0	6 (20.0)	0
Headache	2 (14.3)	0	4 (25.0)	0	6 (20.0)	0
Diarrhea	1 (7.1)	0	4 (25.0)	0	5 (16.7)	0

Numbers (n) represent counts of patients. A patient with multiple severity grades for an AE is only counted under the maximum grade. AEs occurring during treatment or within 30 days of last study medication are summarized. MedDRA version 26.1, CTCAE version 5.0.

BID, twice daily; COVID-19, coronavirus disease of 2019; QD, once daily.

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