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Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Nilotinib

Trial Indication(s)

Chronic myeloid leukemia

Protocol Number

CAMN107ADE23

Protocol Title

Nilotinib for patients with chronic myeloid leukemia in first line and any subsequent line – a non-interventional study on the assessment of deep molecular response in CML patients in daily routine.

Clinical Trial Phase

Phase IV

Phase of Drug Development

Approval

Study Start/End Dates

Study Start Date: June 28, 2016 (Actual)
Primary Completion Date: September 08, 2022 (Actual)
Study Completion Date: September 08, 2022 (Actual)

Reason for Termination

Not applicable

Study Design/Methodology

This was a non-interventional observational study within the routine chronic myeloid leukemia (CML) treatment practice; no further tests were required apart from the assessments routinely performed for CML patients treated with nilotinib.

All patients were treated with nilotinib in accordance with the clinical routine at the respective institution and the summary of product characteristics (SmPC).

The observation interval were not fixed and should have been aligned with the regular treatment schedule and the clinical symptoms of each patient. The medical decision about the schedule as well as therapeutic and diagnostic measures was made solely by the responsible physician. Patients who discontinued treatment within two years of the observation period were followed until starting a new tyrosine kinase inhibitor therapy line, however with a maximum time period of six months. All other patients that reached the official end of treatment after completion of the 24-month observation period were followed up for 28 days.

Centers

Germany(78)

Objectives:

The aim of this NIS was to document the Deep molecular response (DMR) and the time to achieve a DMR in Philadelphia chromosome positive (Ph+) CML patients with prescribed nilotinib therapy in routine medical practice in the German population. To this end, the study captured both the proportion of patients in MMR, MR4.0 and MR4.5 at 24 months as well as the time to achievement and duration of an MR4.0 and MR4.5.

Additionally, the quality and frequency of molecular monitoring as well as the safety and efficacy of therapy with nilotinib in routine medical practice was documented. This NIS documented the proportion of patients whose molecular response was routinely analyzed by a MR4.5-certified laboratory as well as the proportion of patients analyzed in European Treatment and Outcome Study for CML (EUTOS)-qualified laboratories that perform qRT-PCR.

Using validated questionnaires, data on individual QoL and patient compliance were documented within this NIS. On this account, the EORTC QLQ-C30 questionnaire in conjunction with the EORTC QLQ-CML24 module was used to assess patient-reported QoL. Furthermore, patient adherence was documented using the MMAS-8 patient questionnaire. Overall safety and tolerability of nilotinib therapy were measured by frequency and severity of AEs. Moreover, the proportion of patients who discontinued tyrosine kinase inhibitor (TKI) therapy were documented. In particular, it was recorded whether therapy discontinuation was due to good or poor molecular response.

Test Product (s), Dose(s), and Mode(s) of Administration

Nilotinib, in any line of therapy and in accordance with the current version of the SmPC.

Statistical Methods

Statistical analyses were purely exploratory and descriptive. The study was not aimed to confirm or reject predefined hypotheses. The statistical evaluation was performed using the software package SAS release 9.4.
Variables, at least at the interval, level were tabulated with their sample characteristics (number of valid and missing values, minimum, maximum, fifth percentile, first quartile, third quartile, 95th percentile, median, mean, standard deviation).
For nominal and ordinal level variables, distributions of absolute and relative frequencies were given.
Data were analyzed for all patients, and separately for patients who were being treated with nilotinib in first-line treatment or in second- or subsequent-line at study inclusion visit. Results were summarized in total and by treatment line.

The main analysis set for this NIS was the Full Analysis Set (FAS). All tables, figures and listings (TFL) except for AEs were analyzed for the FAS. All tables for AEs were calculated for the Safety Analysis Set (SAF).

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:
- Adult patients diagnosed with Ph+ CML (or evidence of BCR-ABL transcript) treated with nilotinib under routine medical practice and the SmPC, as amended, in first or any subsequent line, if the current therapy with nilotinib has not been in place for more than twelve months. Retrospective documentation of patients for up to one year will be permitted.
- Patients who have already had an interruption/discontinuation of nilotinib therapy.

- Patients who have been informed about this NIS and have personally dated and signed their informed consent form.

Exclusion Criteria:
- There are no exclusion criteria, apart from the contraindications mentioned in the SmPC. Participating patients are not allowed to take part in a clinical trial in parallel,

Participant Flow Table

Table 10-2 Analysis sets

	N (%)
Number of patients screened	227 (100.0%)
Number of patients included into study database	224 (98.68%)
Number of patients included into SAF	222 (97.80%)
Number of patients excluded from SAF	5 (2.20%)
Reasons for exclusion from the SAF (multiple response)	
No informed consent	1 (0.44%)
No documentation of at least one intake of nilotinib	5 (2.20%)
No documentation of any follow-up information after initial visit nor any adverse event	4 (1.76%)

	N (%)
Number of patients included into FAS	192 (84.58%)
Number of patients excluded from FAS (multiple response)	35 (15.42%)
Reasons for exclusion from the FAS	
No informed consent signed	1 (0.44%)
Age<18 years	0 (0.00%)
Previous treatment with nilotinib more than 12 months (> 365 days) ago	1 (0.44%)
No documentation of at least one intake of nilotinib	5 (2.20%)
No documentation of any follow-up information after initial visit	4 (1.76%)
Major protocol deviation	31 (13.66%)

FAS: Full analysis set, N: Number of patients in analysis set, SAF: Safety analysis set.

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Baseline Characteristics

Table 10-5 Demographic characteristics, by treatment line – FAS

Parameter n (%)	Overall N=192	First-line N=144	Subsequent-line N=48
Demographics			
Sex, n (%)			
Female	103 (53.65%)	70 (48.61%)	33 (68.75%)
Male	89 (46.35%)	74 (51.39%)	15 (31.25%)
Age at baseline [years], mean (SD)	56.5 (14.46)	56.7 (13.78)	55.8 (16.48)
Weight at baseline [kg], mean (SD)	79.4 (17.37)	80.0 (16.82)	77.4 (19.27)
BMI at baseline [kg/m^2], mean (SD)	27.0 (5.40)	27.1 (5.17)	26.9 (6.25)
Smoking status			
Never smoked	75 (39.06%)	57 (39.58%)	18 (37.50%)
Past smoker	27 (14.06%)	21 (14.58%)	6 (12.50%)
Smoker	20 (10.42%)	16 (11.11%)	4 (8.33%)
Not collected	70 (36.46%)	50 (34.72%)	20 (41.67%)
Missing	0 (0.00%)	0 (0.00%)	0 (0.00%)
Spleen extension			
Ultrasound at baseline [cm], mean (SD)	13.8 (5.35)	14.0 (5.33)	11.1 (5.11)

BMI: Body Mass Index, FAS: Full analysis set, N: Number of patients in analysis set, n: Number of patients with observations; SD: Standard deviation.

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Table 10-6 Demographic characteristics, by age group – FAS

Parameter n (%)	Overall N=192	≤ 65 years N=139	> 65 years N=53
Demographics			
Sex, n (%)			
Female	103 (53.65%)	78 (56.12%)	25 (47.17%)
Male	89 (46.35%)	61 (43.88%)	28 (52.83%)
Age at baseline [years], mean (SD)	56.5 (14.46)	50.1(11.43)	73.2 (5.56)
Weight at baseline [kg], mean (SD)	79.4 (17.37)	79.5 (18.47)	79.2 (14.25)
BMI at baseline [kg/m^2], mean (SD)	27.0 (5.40)	26.9 (5.80)	27.4 (4.15)
Smoking status			
Never smoked	75 (39.06%)	54 (38.85%)	21 (39.62%)
Past smoker	27 (14.06%)	18 (12.95%)	9 (16.98%)
Smoker	20 (10.42%)	17 (12.23%)	3 (5.66%)
Not collected	70 (36.46%)	50 (35.97%)	20 (37.74%)
Missing	0 (0.00%)	0 (0.00%)	0 (0.00%)
Spleen extension			
Ultrasound at baseline [cm], mean (SD)	13.8 (5.35)	14.5 (5.31)	11.2 (4.82)

BMI: Body Mass Index, FAS: Full analysis set, N: Number of patients in analysis set, n: Number of patients with observations; SD: Standard deviation.

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Table 10-7 Demographic characteristics – SAF

Parameter n (%)	Overall N=222
Demographics	
Sex, n (%)	
Female	122 (54.95%)
Male	100 (45.05%)
Age at baseline [years], mean (SD)	58.0 (15.07)
Weight at baseline [kg], mean (SD)	79.5 (17.12)
BMI at baseline [kg/m^2], mean (SD)	27.1 (5.28)
Smoking status	
Never smoked	88 (39.64%)
Past smoker	31 (13.96%)
Smoker	23 (10.36%)
Not collected	80 (36.04%)
Missing	0 (0.00%)
Spleen extension	
Ultrasound at baseline [cm], mean (SD)	13.6 (5.19)

BMI: Body Mass Index, N: Number of patients in analysis set, n: Number of patients with observations, SAF: Safety Analysis Set, SD: Standard deviation.

Primary Outcome Result(s)

1. Proportion of patients in major molecular response (MMR), and Deep molecular response according to international standard (MR^4.0 and MR^4.5).

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Table 10-26 Molecular response. Subgroup of patients with performance of molecular examination, by treatment line – FAS

Visit n (%)	N	Missing	No MMR	MMR (MR3.0)	MR4.0	MR4.5	MR5.0	MMR or higher [1]	MR4.0 or higher [1]
Overall									
M3	154	2	89 (57.79%)	27 (17.53%)	14 (9.09%)	13 (8.44%)	9 (5.84%)	63 (40.91%)	36 (23.38%)
M6	153	0	50 (32.68%)	45 (29.41%)	23 (15.03%)	24 (15.69%)	11 (7.19%)	103 (67.32%)	58 (37.91%)
M9	148	0	33 (22.30%)	41 (27.70%)	18 (12.16%)	39 (26.35%)	17 (11.49%)	115 (77.70%)	74 (50.00%)
M12	140	1	26 (18.57%)	35 (25.00%)	30 (21.43%)	25 (17.86%)	23 (16.43%)	113 (80.71%)	78 (55.71%)
M18	137	0	15 (10.95%)	40 (29.20%)	18 (13.14%)	37 (27.01%)	27 (19.71%)	122 (89.05%)	82 (59.85%)
M24	128	0	11 (8.59%)	25 (19.53%)	28 (21.88%)	44 (34.38%)	20 (15.63%)	117 (91.41%)	92 (71.88%)
FU1	19	0	10 (52.63%)	1 (5.26%)	1 (5.26%)	6 (31.58%)	1 (5.26%)	9 (47.37%)	8 (42.11%)
FU2	3	0	1 (33.33%)	0 (0.00%)	1 (33.33%)	1 (33.33%)	0 (0.00%)	2 (66.67%)	2 (66.67%)
FU3	4	0	1 (25.00%)	2 (50.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	3 (75.00%)	1 (25.00%)
FU4	3	0	2 (66.67%)	0 (0.00%)	0 (0.00%)	1 (33.33%)	0 (0.00%)	1 (33.33%)	1 (33.33%)
FU5	1	0	1 (100.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
First-line [2]									
M3	112	2	77 (68.75%)	21 (18.75%)	7 (6.25%)	4 (3.57%)	1 (0.89%)	33 (29.46%)	12 (10.71%)
M6	115	0	43 (37.39%)	38 (33.04%)	14 (12.17%)	16 (13.91%)	4 (3.48%)	72 (62.61%)	34 (29.57%)
M9	110	0	26 (23.64%)	35 (31.82%)	13 (11.82%)	24 (21.82%)	12 (10.91%)	84 (76.36%)	49 (44.55%)
M12	105	0	19 (18.10%)	31 (29.52%)	23 (21.90%)	16 (15.24%)	16 (15.24%)	86 (81.90%)	55 (52.38%)
M18	103	0	11 (10.68%)	32 (31.07%)	16 (15.53%)	22 (21.36%)	22 (21.36%)	92 (89.32%)	60 (58.25%)
M24	97	0	8 (8.25%)	20 (20.62%)	21 (21.65%)	34 (35.05%)	14 (14.43%)	89 (91.75%)	69 (71.13%)
FU1	13	0	9 (69.23%)	1 (7.69%)	1 (7.69%)	1 (7.69%)	1 (7.69%)	4 (30.77%)	3 (23.08%)
FU2	1	0	0 (0.00%)	0 (0.00%)	1 (100.00%)	0 (0.00%)	0 (0.00%)	1 (100.00%)	1 (100.00%)
FU3	1	0	0 (0.00%)	1 (100.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (100.00%)	0 (0.00%)
FU4	1	0	1 (100.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

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Visit n (%)	N	Missing	No MMR	MMR (MR3.0)	MR4.0	MR4.5	MR5.0	MMR or higher [1]	MR4.0 or higher [1]
Subsequent-line									
M3	42	0	12 (28.57%)	6 (14.29%)	7 (16.67%)	9 (21.43%)	8 (19.05%)	30 (71.43%)	24 (57.14%)
M6	38	0	7 (18.42%)	7 (18.42%)	9 (23.68%)	8 (21.05%)	7 (18.42%)	31 (81.58%)	24 (63.16%)
M9	38	0	7 (18.42%)	6 (15.79%)	5 (13.16%)	15 (39.47%)	5 (13.16%)	31 (81.58%)	25 (65.79%)
M12	35	1	7 (20.00%)	4 (11.43%)	7 (20.00%)	9 (25.71%)	7 (20.00%)	27 (77.14%)	23 (65.71%)
M18	34	0	4 (11.76%)	8 (23.53%)	2 (5.88%)	15 (44.12%)	5 (14.71%)	30 (88.24%)	22 (64.71%)
M24	31	0	3 (9.68%)	5 (16.13%)	7 (22.58%)	10 (32.26%)	6 (19.35%)	28 (90.32%)	23 (74.19%)
FU1	6	0	1 (16.67%)	0 (0.00%)	0 (0.00%)	5 (83.33%)	0 (0.00%)	5 (83.33%)	5 (83.33%)
FU2	2	0	1 (50.00%)	0 (0.00%)	0 (0.00%)	1 (50.00%)	0 (0.00%)	1 (50.00%)	1 (50.00%)
FU3	3	0	1 (33.33%)	1 (33.33%)	0 (0.00%)	0 (0.00%)	1 (33.33%)	2 (66.67%)	1 (33.33%)
FU4	2	0	1 (50.00%)	0 (0.00%)	0 (0.00%)	1 (50.00%)	0 (0.00%)	1 (50.00%)	1 (50.00%)
FU5	1	0	1 (100.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

[1] The total sums were calculated manually.
[2] Follow-up Visit 5 not available for patients with first-line nilotinib therapy.
Note: FU visits only for patients who terminated nilotinib therapy.
FAS: Full analysis set, FU1-FU5: Follow-up visit 1 to 5, M: Visit at Month, MMR: Major molecular response, MR4.0, MR4.5, MR5.0: Deep molecular response according to international standard, N: Number of patients in analysis set, n: Number of patients with observation.

2. Time to achievement of an MMR, MR4.0 and MR4.5

Table 10-27 Time to first MMR. Subgroup of patients who achieved MMR, by treatment line – FAS

Parameter n (%)	Overall N=192	First-line N=144	Subsequent-line N=48
Time to first MMR [days]			
N	103	86	17
n	103	86	17
Mean (SD)	229.6 (152.19)	221.9 (133.12)	268.6 (227.12)
Median	184.0	185.0	184.0
Min, Max	74, 718	57, 689	56, 718
Missing	0	0	0

Note: Time to first MMR = date of molecular examination with first occurrence of MMR - date of first nilotinib intake.
FAS: Full analysis set, Max: maximum, Min: minimum, MMR: Major molecular response, N: Number of patients in analysis set, n: Number of patients with observation, SD: Standard deviation.

Table 10-29 Time to first MR4.0. Subgroup of patients who achieved MR4.0, by treatment line – FAS

Parameter n (%)	Overall N=192	First-line N=144	Subsequent-line N=48
Time to first MR4.0 [days]			
N	84	62	22
n	84	62	22
Mean (SD)	332.8 (212.18)	364.9 (212.50)	242.3 (187.45)
Median	293.5	331.5	173.0
Min, Max	49, 770	82, 762	49, 770
Missing	0	0	0

Note: Time to first MR4.0 = date of molecular examination with first occurrence of MR4.0 - date of first nilotinib intake.
FAS: Full analysis set, Max: maximum, Min: minimum, MR: Deep molecular response, N: Number of patients in analysis set, n: Number of patients with observation, SD: Standard deviation.

Table 10-31 Time to first MR4.5/MR5.0. Subgroup of patients who achieved MR4.5/MR5.0, by treatment line – FAS

Parameter n (%)	Overall N=192	First-line N=144	Subsequent-line N=48
Time to first MR4.5/MR5.0 [days]			
N	98	64	34
n	98	64	34
Mean (SD)	284.0 (190.09)	323.5 (181.62)	209.7 (185.84)
Median	260.5	276.5	141.0
Min, Max	22, 775	86, 756	22, 775
Missing	0	0	0

Note: Time to first MR4.5/MR5.0 = date of molecular examination with first occurrence of MR4.5/MR5.0 - date of first nilotinib intake.
FAS: Full analysis set, Max: maximum, Min: minimum, MR: Deep molecular response, N: Number of patients in analysis set, n: Number of patients with observation, SD: Standard deviation.

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3. Duration of an MMR, MR4.0 and MR4.5

Table 10-28 Duration of first MMR. Subgroup of patients who achieved MMR, by treatment line – FAS

Parameter n (%)	Overall N=192	First-line N=144	Subsequent-line N=48
Duration of first MMR [days]			
N	103	86	17
n	103	86	17
Mean (SD)	254.9 (179.19)	257.0 (177.21)	244.5 (194.21)
Median	194.0	192.5	240.0
Min, Max	0, 671	0, 671	0, 584
Missing	0	0	0

Note: Duration of first MMR = date of molecular response other than MMR (after first occurrence of MMR) - date of first occurrence of MMR. In case no other molecular response than MMR is documented after the first occurrence, date of end of observation period will be taken.
FAS: Full analysis set, Max: maximum, Min: minimum, MMR: Major molecular response, N: Number of patients in analysis set, n: Number of patients with observation, SD: Standard deviation.

Table 10-30 Duration of first MR4.0. Subgroup of patients who achieved MR4.0, by treatment line – FAS

Parameter n (%)	Overall N=192	First-line N=144	Subsequent-line N=48
Duration of first MMR [days]			
N	84	62	22
n	84	62	22
Mean (SD)	168.2 (116.38)	169.5 (128.02)	164.5 (76.84)
Median	168.0	163.0	182.0
Min, Max	0, 569	0, 569	0, 317
Missing	0	0	0

Note: Duration of first MR4.0 = date of molecular response other than MR4.0 (after first occurrence of MR4.0) - date of first occurrence of MR4.0. In case no other molecular response than MR4.0 is documented after the first occurrence, date of end of observation period will be taken.
FAS: Full analysis set, Max: maximum, Min: minimum, MR: Deep molecular response, N: Number of patients in analysis set, n: Number of patients with observation, SD: Standard deviation.

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Table 10-32 Duration of first MR4.5/MR5.0. Subgroup of patients who achieved MR4.5/MR5.0, by treatment line – FAS

Parameter n (%)	Overall N=192	First-line N=144	Subsequent-line N=48
Duration of first MMR [days]			
N	98	64	34
n	98	64	34
Mean (SD)	327.8 (207.99)	308.7 (188.02)	363.9 (240.02)
Median	305.5	320.0	283.5
Min, Max	0, 889	0, 651	0, 889
Missing	0	0	0

Note: Duration of first MR4.5/MR5.0 = date of molecular response other than MR4.5/MR5.0 (after first occurrence of MR4.5/MR5.0) - date of first occurrence of MR4.5/MR5.0. In case no other molecular response than MR4.5/MR5.0 is documented after the first occurrence, date of end of observation period will be taken.
FAS: Full analysis set, Max: maximum, Min: minimum, MR: Deep molecular response, N: Number of patients in analysis set, n: Number of patients with observation, SD: Standard deviation.

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4. Proportion of patients whose molecular response is routinely analyzed by a MR4.5-certified laboratory

Certification of the laboratory
Full Analysis Set - Subgroup of patients with performance of molecular examination

Overall

	Certification of the laboratory											
	Full Analysis Set		Missing		EUTOS-Cert. MMR		EUTOS-Cert. MR4		EUTOS-Cert. MR4.5		None of the known certifications		Unknown	
Visit	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
M3	154	(100.00%)	0	(0.00%)	0	(0.00%)	3	(1.95%)	86	(55.84%)	11	(7.14%)	54	(35.06%)
M6	153	(100.00%)	0	(0.00%)	0	(0.00%)	7	(4.58%)	92	(60.13%)	9	(5.88%)	45	(29.41%)
M9	148	(100.00%)	0	(0.00%)	2	(1.35%)	4	(2.70%)	81	(54.73%)	8	(5.41%)	53	(35.81%)
M12	140	(100.00%)	1	(0.71%)	1	(0.71%)	6	(4.29%)	84	(60.00%)	5	(3.57%)	43	(30.71%)
M18	137	(100.00%)	0	(0.00%)	1	(0.73%)	5	(3.65%)	82	(59.85%)	7	(5.11%)	42	(30.66%)
M24	128	(100.00%)	0	(0.00%)	2	(1.56%)	2	(1.56%)	77	(60.16%)	5	(3.91%)	42	(32.81%)
FU1	19	(100.00%)	0	(0.00%)	0	(0.00%)	0	(0.00%)	12	(63.16%)	2	(10.53%)	5	(26.32%)
FU2	3	(100.00%)	0	(0.00%)	0	(0.00%)	0	(0.00%)	2	(66.67%)	0	(0.00%)	1	(33.33%)
FU3	4	(100.00%)	0	(0.00%)	0	(0.00%)	0	(0.00%)	3	(75.00%)	0	(0.00%)	1	(25.00%)
FU4	3	(100.00%)	0	(0.00%)	0	(0.00%)	0	(0.00%)	1	(33.33%)	0	(0.00%)	2	(66.67%)
FU5	1	(100.00%)	0	(0.00%)	0	(0.00%)	0	(0.00%)	1	(100.00%)	0	(0.00%)	0	(0.00%)

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5. Proportion of European Treatment and Outcome Study for CML (EUTOS)-qualified laboratories that perform qRT-PCR.

Certification of the laboratory at initial visit
Full Analysis Set

Overall

		N	(%)
Full Analysis Set		192	(100.00%)
Certification of the laboratory at initial visit	Missing	2	(1.04%)
	EUTOS-Certification MMR	1	(0.52%)
	EUTOS-Certification MR4	8	(4.17%)
	EUTOS-Certification MR4.5	101	(52.60%)
	None of the known certifications	9	(4.69%)
	Unknown	71	(36.98%)

6. Patient-reported QoL - EORTC QLQ-C30 and EORTC QLQ-CML24

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Table 10-38 EORTC QLQ-C30, global health status / QoL score. Subgroup of patients with filled questionnaire, by treatment line – FAS

Parameter	Visit					
n (%)	Initial Visit	M3	M6	M12	M18	M24
Overall						
EORTC QLQ-C30, global health status / QoL score						
N	112	102	112	106	97	81
n	112	100	110	105	96	79
Mean (SD)	61.0 (25.07)	64.7 (20.93)	67.0 (19.29)	70.1 (20.63)	68.1 (20.29)	69.2 (19.35)
Median	66.7	66.7	66.7	75.0	66.7	66.7
Min, Max	0, 100	17, 100	17, 100	0, 100	17, 100	0, 100
Missing	0	2	2	1	1	2
First-line						
EORTC QLQ-C30, global health status / QoL score						
N	90	84	86	84	72	63
n	90	82	85	83	71	63
Mean (SD)	59.8 (24.21)	63.9 (20.03)	67.5 (18.62)	69.1 (21.48)	68.3 (20.05)	68.0 (20.31)
Median	66.7	66.7	66.7	75.0	66.7	66.7
Min, Max	0, 100	17, 100	17, 100	0, 100	17, 100	0, 100
Missing	0	2	1	1	1	0
Subsequent-line						
EORTC QLQ-C30, global health status / QoL score						
N	22	18	26	22	25	18
n	22	18	25	22	25	16
Mean (SD)	65.9 (28.40)	68.1 (24.96)	65.3 (21.74)	73.9 (16.92)	67.3 (21.37)	74.0 (14.55)
Median	70.8	66.7	58.3	83.3	66.7	70.8
Min, Max	17, 100	17, 100	25, 100	42, 100	25, 100	42, 100
Missing	0	0	1	0	0	2

Note: A high scale score represents a higher response level. Thus, a high score for the global health status / QoL represents a high quality of life.
EORTC QLQ-C30: Patient questionnaire on quality of life, FAS: Full analysis set, M3 – M24: Visit at Month 3 to Month 24, Max: maximum, Min: minimum, N: Number of patients in analysis set, n: Number of patients with observation, QoL: Quality of Life, SD: Standard deviation.

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Table 10-39 Overall item scores of the EORTC QLQ-C30 questionnaire. Subgroup of patients with filled questionnaire in initial visit and M24 visit, overall population – FAS

Parameter	N	n	Mean (SD)	Median	Min, Max
Physical functioning score					
Initial visit	112	112	76.5 (25.41)	86.7	20, 100
M24	81	81	79.3 (21.62)	86.7	7, 100
Role functioning score					
Initial visit	112	112	69.0 (33.92)	83.3	0, 100
M24	81	81	73.3 (26.83)	66.7	0, 100
Emotional functioning score					
Initial visit	112	112	66.6 (27.48)	70.8	0, 100
M24	81	79	68.7 (28.25)	75.0	0, 100
Cognitive functioning score					
Initial visit	112	112	83.8 (22.20)	91.7	0, 100
M24	81	79	78.1 (26.09)	83.3	0, 100
Social functioning score					
Initial visit	112	112	74.4 (27.03)	83.3	0, 100
M24	81	79	75.1 (28.60)	83.3	0, 100

Note: A high scale score represents a higher response level.

EORTC QLQ-C30: Patient questionnaire on quality of life, FAS: Full analysis set, M24: Visit Month 24, Max: Maximum, Min: Minimum, N: Number of patients in analysis set, n: Number of patients with observation, SD: Standard deviation.

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Table 10-40 Overall symptom scores of the EORTC QLQ-C30 questionnaire. Subgroup of patients with filled questionnaire in initial visit and M24 visit, overall population – FAS

Parameter	N	n	Mean (SD)	Median	Min, Max
Symptom score, fatigue					
Initial visit	112	112	37.9 (29.79)	33.3	0, 100
M24	81	81	37.7 (28.36)	33.3	0, 100
Symptom score, nausea and vomiting					
Initial visit	112	112	6.8 (14.93)	0.0	0, 67
M24	81	81	4.5 (10.54)	0.0	0, 50
Symptom score, pain					
Initial visit	112	112	24.0 (29.75)	16.7	0, 100
M24	81	81	26.7 (30.24)	16.7	0, 100
Symptom score, dyspnoea					
Initial visit	112	112	28.9 (35.37)	0.0	0, 100
M24	81	81	27.2 (30.78)	33.3	0, 100
Symptom score, insomnia					
Initial visit	112	112	30.1 (32.87)	33.3	0, 100
M24	81	81	28.0 (30.03)	33.3	0, 100
Symptom score, appetite loss					
Initial visit	112	112	14.3 (25.20)	0.0	0, 100
M24	81	81	9.5 (19.17)	0.0	0, 100
Symptom score, constipation					
Initial visit	112	111	7.2 (19.80)	0.0	0, 100
M24	81	81	12.3 (26.59)	0.0	0, 100
Symptom score, diarrhoea					
Initial visit	112	112	9.5 (20.22)	0.0	0, 67
M24	81	81	7.6 (18.45)	0.0	0, 100

Parameter	N	n	Mean (SD)	Median	Min, Max
Symptom score, financial difficulties					
Initial visit	112	112	10.4 (21.47)	0.0	0, 100
M24	81	79	9.7 (23.96)	0.0	0, 100

Note: A high scale score represents a higher response level.
EORTC QLQ-C30: Patient questionnaire on quality of life, FAS: Full analysis set, M24: Visit Month 24, Max: Maximum, Min: Minimum, N: Number of patients in analysis set, n: number of patients with observation, SD: Standard deviation.

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Table 10-41 Overall item scores of the EORTC QLQ-CML24 questionnaire. Subgroup of patients with filled questionnaire in first and last visit, overall population – FAS

Parameter	N	n	Mean (SD)	Median	Min, Max
Symptom burden score [1]					
Initial visit	114	114	23.4 (15.77)	20.5	0, 74
M24	80	80	26.7 (17.83)	24.4	0, 74
Impact on worry/mood score [1]					
Initial visit	114	114	35.7 (24.55)	33.3	0, 67
M24	80	78	34.0 (26.48)	33.3	0, 50
Impact on daily life score [1]					
Initial visit	114	113	31.1 (26.56)	22.2	0, 100
M24	80	78	24.6 (22.41)	22.2	0, 89
Satisfaction with care and information score [2]					
Initial visit	114	114	85.4 (28.92)	100.0	0, 100
M24	80	78	80.1 (33.01)	100.0	0, 100
Body image problems score [1]					
Initial visit	114	114	31.0 (34.56)	33.3	0, 100
M24	80	78	28.2 (28.97)	33.3	0, 100
Satisfaction with social life score [2]					
Initial visit	114	113	79.4 (31.28)	100.0	0, 100
M24	80	76	75.0 (35.33)	100.0	0, 100

[1] Note: A high score is equivalent to worse or more symptoms/problems.

[2] Note: A high score indicates positive experience or less problems.

EORTC QLQ-CML24: CML add-on module to the patient questionnaire EORTC QLQ-C30, FAS: Full analysis set, M24: Visit Month 24, Max: Maximum, Min: Minimum, N: Number of patients in analysis set, n: Number of patients with observation, SD: Standard deviation.

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7. Patient adherence - Morisky Medication Adherence Scale (MMAS.8)

Table 10-42 Overall MMAS-8 adherence score. Subgroup of patients with filled questionnaire, overall population – FAS

Parameter	FAS N=192		MMAS-8 adherence score		
n (%)	N	Missing	Low adherence	Medium adherence	High adherence
Visit					
Initial visit	95	5 (5.26%)	10 (10.53%)	38 (40.00%)	42 (44.21%)
M3	96	1 (1.04%)	8 (8.33%)	46 (47.92%)	41 (42.71%)
M6	108	0 (0.00%)	8 (7.41%)	50 (46.30%)	50 (46.30%)
M12	103	1 (0.97%)	17 (16.50%)	43 (41.75%)	42 (40.78%)
M18	96	1 (1.04%)	14 (14.58%)	34 (35.42%)	47 (48.96%)
M24	80	0 (0.00%)	12 (15.00%)	33 (41.25%)	35 (43.75%)

FAS: Full analysis set, M3 – M24: Visit at Month 3 to Month 24, MMAS-8: Patient compliance questionnaire (8-item Morisky Medication Adherence Scale), N: Number of patients in analysis set, n: Number of patients with observation.

8. Proportion of patients who discontinue Tyrosine kinase inhibitor (TKI) therapy

Table 10-34 Premature discontinuation from the NIS, by treatment line – FAS

Parameter	Overall	First-line	Subsequent-line
n (%)	N=192	N=144	N=48
Premature discontinuation from the NIS			
Yes	57 (29.69%)	39 (27.08%)	18 (37.50%)
No	134 (69.79%)	104 (72.22%)	30 (62.50%)
Missing	1 (0.52%)	1 (0.69%)	0 (0.00%)

FAS: Full analysis set, N: Number of patients in analysis set, n: Number of patients with observation, NIS: Non-interventional study.

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Table 10-35 Reason for premature discontinuation. Subgroup of patients with premature discontinuation, by treatment line – FAS

Parameter n (%)	Overall N=57	First-line N=39	Subsequent-line N=18
Reason for premature discontinuation (multiple response)			
Adverse Event	17 (29.82%)	10 (25.64%)	7 (38.89%)
Insufficient response	11 (19.30%)	10 (25.64%)	1 (5.56%)
Non-haematological toxicity	7 (12.28%)	6 (15.38%)	1 (5.56%)
Death	5 (8.77%)	4 (10.26%)	1 (5.56%)
Other	5 (8.77%)	4 (10.26%)	1 (5.56%)
Deep molecular response	4 (7.02%)	0 (0.00%)	4 (22.22%)
Progression of disease	4 (7.02%)	4 (10.26%)	0 (0.00%)
New BCR-ABL mutations	3 (5.26%)	3 (7.69%)	0 (0.00%)
Loss of a previously achieved molecular response	2 (3.51%)	2 (5.13%)	0 (0.00%)
Loss of a previously achieved hematologic response	1 (1.75%)	1 (2.56%)	0 (0.00%)
Lost to follow up	3 (5.26%)	1 (2.56%)	2 (11.11%)
General physical deterioration	2 (3.51%)	0 (0.00%)	2 (11.11%)
Lack of compliance	1 (1.75%)	0 (0.00%)	1 (5.56%)
Haematological toxicity	1 (1.75%)	1 (2.56%)	0 (0.00%)
Missing	0 (0.00%)	0 (0.00%)	0 (0.00%)

ABL: Abelson tyrosine kinase, BCR: Breakpoint cluster region, FAS: Full analysis set, N: Number of patients in analysis set, n: Number of patients with observation.

Secondary Outcome Result(s)

Not Applicable.

Other Pre-Specified Outcome Result(s)

No data identified.

Post-Hoc Outcome Result(s)

No data identified.

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Safety Results

Table 10-47 Most common patient based AEs (>5%), by MedDRA SOC and PT, overall population – SAF

MedDRA SOC/PT n (%)	Total N=222	nsAE N=111	SAE N=38	nsADR N=165	SADR N=74
Skin and subcutaneous tissue disorders	93 (41.89%)	17 (15.32%)	1 (2.63%)	80 (48.48%)	0 (0.00%)
Rash	30 (13.51%)	5 (4.50%)	0 (0.00%)	27 (16.36%)	0 (0.00%)
Pruritus	24 (10.81%)	5 (4.50%)	0 (0.00%)	20 (12.12%)	0 (0.00%)
Alopecia	18 (8.11%)	1 (0.90%)	0 (0.00%)	17 (10.30%)	0 (0.00%)
Dry skin	17 (7.66%)	1 (0.90%)	0 (0.00%)	16 (9.70%)	0 (0.00%)
General disorders and administration site conditions	85 (38.29%)	24 (21.62%)	3 (7.89%)	59 (35.76%)	8 (0.81%)
Fatigue	42 (18.92%)	6 (5.41%)	1 (2.63%)	35 (21.21%)	0 (0.00%)
Gastrointestinal disorders	75 (33.78%)	18 (16.22%)	4 (10.53%)	54 (32.73%)	10 (13.51%)
Nausea	19 (8.56%)	4 (3.60%)	1 (2.63%)	15 (9.09%)	1 (1.35%)
Constipation	13 (5.86%)	1 (0.90%)	0 (0.00%)	11 (6.67%)	1 (1.35%)
Diarrhoea	12 (5.41%)	2 (1.80%)	0 (0.00%)	9 (5.45%)	1 (1.35%)
Musculoskeletal and connective tissue disorders	65 (29.28%)	24 (21.62%)	4 (10.53%)	44 (26.67%)	0 (0.00%)
Arthralgia	18 (8.11%)	4 (3.60%)	0 (0.00%)	14 (8.48%)	0 (0.00%)
Myalgia	15 (6.76%)	3 (2.70%)	0 (0.00%)	12 (7.27%)	0 (0.00%)
Pain in extremity	12 (5.41%)	4 (3.60%)	0 (0.00%)	8 (4.85%)	0 (0.00%)
Bone pain	11 (4.95%)	2 (1.80%)	0 (0.00%)	9 (5.45%)	0 (0.00%)
Infections and infestations	55 (24.77%)	30 (27.03%)	8 (21.05%)	17 (10.30%)	4 (5.41%)
Nasopharyngitis	16 (7.21%)	13 (11.71%)	0 (0.00%)	4 (2.42%)	0 (0.00%)
COVID-19	5 (2.25%)	2 (1.80%)	3 (7.89%)	0 (0.00%)	0 (0.00%)

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Nervous system disorders	50 (22.52%)	14 (12.61%)	1 (2.63%)	31 (18.79%)	9 (12.16%)
Headache	17 (7.66%)	3 (2.70%)	0 (0.00%)	14 (8.48%)	0 (0.00%)
Dizziness	11 (4.95%)	6 (5.41%)	0 (0.00%)	6 (3.64%)	0 (0.00%)
Metabolism and nutrition disorders	37 (16.67%)	15 (13.51%)	4 (10.53%)	17 (10.30%)	8 (10.81%)
Diabetes mellitus	5 (2.25%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	5 (6.76%)
Hyperkalaemia	4 (1.80%)	0 (0.00%)	3 (7.89%)	0 (0.00%)	1 (1.35%)
Cardiac disorders	36 (16.22%)	2 (1.80%)	3 (7.89%)	13 (7.88%)	19 (25.68%)
Atrial fibrillation	5 (2.25%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	4 (5.41%)
Cardiac failure	5 (2.25%)	0 (0.00%)	2 (5.26%)	0 (0.00%)	3 (4.05%)
Coronary artery disease	4 (1.80%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	4 (5.41%)
Investigations	36 (16.22%)	5 (4.50%)	1 (2.63%)	26 (15.76%)	7 (9.46%)
Respiratory, thoracic and mediastinal disorders	36 (16.22%)	11 (9.91%)	4 (10.53%)	24 (14.55%)	3 (4.05%)
Dyspnoea	13 (5.86%)	3 (2.70%)	1 (2.63%)	9 (5.45%)	1 (1.35%)
Vascular disorders	26 (11.71%)	3 (2.70%)	2 (5.26%)	12 (7.27%)	10 (13.51%)
Hypertension	12 (5.41%)	3 (2.70%)	1 (2.63%)	5 (3.03%)	4 (5.41%)
Blood and lymphatic system disorders	25 (11.26%)	7 (6.31%)	1 (2.63%)	8 (4.85%)	13 (17.57%)
Thrombocytopenia	9 (4.05%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	9 (12.16%)
Leukopenia	5 (2.25%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	5 (6.76%)
Psychiatric disorders	24 (10.81%)	4 (3.60%)	1 (2.63%)	20 (12.12%)	1 (1.35%)
Injury, poisoning and procedural complications	16 (7.21%)	8 (7.21%)	3 (7.89%)	5 (3.03%)	0 (0.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	16 (7.21%)	2 (1.80%)	8 (21.05%)	4 (2.42%)	5 (6.76%)
Endocrine disorders	12 (5.41%)	4 (3.60%)	1 (2.63%)	3 (1.82%)	4 (5.41%)

Note: Coding was performed using MedDRA Version 25.1.

AE: Adverse event, MedDRA: Medical dictionary for regulatory activities, N: Number of patients in analysis set, n: Number of patients with observation, nsADR: AE classified as non-serious and causality in regard to Nilotinib documented as yes, not assessable or missing, nsAE: AE classified as non-serious and with no causality in regard to Nilotinib, SADR: AE classified as serious and causality in regard to Nilotinib documented as yes, not assessable or missing, SAE: AE classified as serious and with no causality in regard to Nilotinib, SAF: Safety analysis set, SOC: System organ class.

All-Cause Mortality

There was no death in this study

Other Relevant Findings

Not applicable

Conclusion:

This study provided valuable insights into the utilization, effectiveness, safety and tolerability, as well as patient-reported quality of life (QoL) in daily medical practice of treating chronic myeloid leukemia,. A large proportion of patients reached major molecular response (MMR) or deep molecular response (DMR) by the end of the observational period. The scores of the global health status of QoL assessed in the EORTC QLQ-C30 questionnaire improved by the end of the observational period. The observed ADRs were in line with the known safety profile.

Date of Clinical Trial Report

05 June 2023