Clinical trial results:
A Phase IV single-arm, multicenter, open-label study assessing deep molecular response in adult patients with newly diagnosed Philadelphia chromosome-positive CML in chronic phase after two years of treatment with nilotinib 300 mg BID

Summary

EudraCT number	2015-000968-34
Trial protocol	DE
Global end of trial date	25 March 2021

Results information

Result version number	v1 (current)
This version publication date	06 April 2022
First version publication date	06 April 2022

Trial information

Trial identification

Sponsor protocol code	CAMN107ADE20

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02546674
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	25 March 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	25 March 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this trial was to evaluate the proportion of participants who are in deep molecular response MR4.5 (IS) at 24 months of study treatment, measured in a standardized EUTOS MR4.5 laboratory.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 February 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 171
Worldwide total number of subjects	171
EEA total number of subjects	171

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	128
From 65 to 84 years	42
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The study was conducted across 73 centers in 1 country (Germany).

Pre-assignment

Screening details:

A total of 179 participants were screened in this study of which 8 discontinued screening phase and 171 participants were enrolled in the study

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Nilotinib

Arm description:

Participants with newly diagnosed CML in chronic phase received nilotinib 300 mg BID

Arm type	Experimental
Investigational medicinal product name	Nilotinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

A daily dose of 300 mg was given to all participants as two 150 mg capsules BID. The prescription of study drug was not study dependent and followed medical needs of the participant only. The study treatment was administered for 24 months.

Number of subjects in period 1	Nilotinib
Started	171
Completed	123
Not completed	48
Adverse event, serious fatal	1
Physician decision	13
Adverse event, non-fatal	19
Protocol Deviation	2
Progressive Disease	2
Pregnancy	1
Subject/Guardian Decision	6
Lost to follow-up	1
Withdrawal of Informed Consent	3

Baseline characteristics

Reporting groups	
Reporting group title	Nilotinib
Reporting group description:	
Participants with newly diagnosed CML in chronic phase received nilotinib 300 mg BID	

Reporting group values	Nilotinib	Total	
Number of subjects	171	171	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	128	128	
From 65-84 years	42	42	
85 years and over	1	1	
Age Continuous Units: Years			
arithmetic mean	55.2		
standard deviation	± 13.87	-	
Sex: Female, Male Units: Participants			
Female	63	63	
Male	108	108	
Race/Ethnicity, Customized Units: Subjects			
Caucasian	170	170	
Asian	1	1	

End points

End points reporting groups

Reporting group title	Nilotinib
Reporting group description:	
Participants with newly diagnosed CML in chronic phase received nilotinib 300 mg BID	

Primary: Percentage of participants with deep molecular response MR4.5 at 24 months of study treatment

End point title	Percentage of participants with deep molecular response MR4.5 at 24 months of study treatment[1]

End point description:

Percentage of participants who were in deep molecular response MR4.5 (IS) at 24 months measured in a standardized EUTOS (European Treatment and Outcome Study for CML) MR4.5 laboratory. MR4.5 was defined as either (i) detectable disease ≤ 0.0032% BCR-ABL (fusion gene from breakpoint cluster region and Abelson genes) (IS) or (ii) undetectable disease in cDNA with 32000–99999 ABL1 transcripts or 77000–239999 glucuronidase beta (GUSB) transcripts.
Responders: Participants with a MR4.5 at 24 months, or if the assessment at this time point was missing, with a MR4.5 at 21 months
Non-responders: Participants dropping out early or not providing sufficient data for any other reason. Participants who achieved MR4.5 before 24 months, but was no longer in MR4.5 at 24 months or progressed (or was no longer in MR4.5 at 21 months if evaluation at 24 months was missing).
Confidence intervals were calculated based on the Exact Clopper-Pearson method.

End point type	Primary

End point timeframe:

Month 24 and Month 21 (if assessment at Month 24 was missing)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses were planned for this endpoint

End point values	Nilotinib			
Subject group type	Reporting group			
Number of subjects analysed	156			
Units: Percentage of participants				
number (confidence interval 95%)	35.3 (27.79 to 43.30)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with MR4 at 24 months of study treatment.

End point title	Percentage of participants with MR4 at 24 months of study treatment.

End point description:

Percentage of participants with MR4 at 24 months of study treatment. MR4 (IS) is defined as either (i) detectable disease ≤0.01% BCR-ABL by IS or (ii) undetectable disease in cDNA with 10000 – 31999 ABL1 transcripts or 24000 – 76999 GUSB transcripts.
Confidence intervals were calculated based on the Exact Clopper-Pearson method.

End point type	Secondary

End point timeframe:

Month 24

End point values	Nilotinib			
Subject group type	Reporting group			
Number of subjects analysed	156			
Units: Percentage of participants				
number (confidence interval 95%)	44.9 (36.91 to 53.03)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with major molecular response (MMR) at 12 months of study treatment

End point title	Percentage of participants with major molecular response (MMR) at 12 months of study treatment

End point description:

Percentage of participants with MMR at 12 months of study treatment. MMR is defined as ≤ 0.1% BCR-ABL by IS, or equivalent to ≥ 3 log reduction of BCR-ABL transcript from standardized baseline. Confidence intervals were calculated based on the Exact Clopper-Pearson method.

End point type	Secondary

End point timeframe:

Month 12

End point values	Nilotinib			
Subject group type	Reporting group			
Number of subjects analysed	156			
Units: Percentage of participants				
number (confidence interval 95%)	60.3 (52.12 to 67.99)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with complete cytogenetic response (CCyR) at 6 months of study treatment

End point title	Percentage of participants with complete cytogenetic response (CCyR) at 6 months of study treatment

End point description:

Percentage of participants with CCyR at 6 months of study treatment. Cytogenetic response was assessed as the percentage of Philadelphia positive (Ph+) metaphases in the bone marrow (a review of a minimum of 20 metaphases was required). CCyR was defined as a value of 0% Ph+ metaphases in bone marrow.
Confidence intervals were calculated based on the Exact Clopper-Pearson method.

End point type	Secondary

End point timeframe:

Month 6

End point values	Nilotinib			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: Percentage of participants				
number (confidence interval 95%)	89.5 (66.86 to 98.70)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival

End point title	Progression-free survival

End point description:

Progression-free survival is defined as the time from the date of start of study treatment to the date of the first documented disease progression to accelerated phase (AP)/ blast crisis (BC) or death from any cause, whichever is earlier.
AP is defined as:
≥ 15% blasts in the peripheral blood or one marrow aspirate, but <30% blasts in both the peripheral blood and bone marrow aspirate
≥ 30% blasts plus promyelocytes in peripheral blood or bone marrow aspirate
≥ 20% basophils in the peripheral blood or bone marrow Thrombocytopenia (<100 x 109/Liter) that is unrelated to therapy
Evidence of clonal evolution
BC is defined as:
≥ 30% blasts in peripheral blood or bone marrow aspirate
Appearance of extramedullary involvement other than hepatosplenomegaly proven by biopsy (i.e., chloroma)

End point type	Secondary

End point timeframe:

From date of start of treatment to first documented disease progression to AP/ BC or death, assessed up to 24 months

End point values	Nilotinib			
Subject group type	Reporting group			
Number of subjects analysed	162			
Units: Months				
median (confidence interval 95%)	9999 (9999 to 9999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to progression to AP/BC

End point title	Time to progression to AP/BC

End point description:

Time to progression to AP/BC is defined as the time from the date of start of study treatment to the date of earliest transformation to AP/BC, or CML-related death.
AP is defined as:
≥ 15% blasts in the peripheral blood or one marrow aspirate, but <30% blasts in both the peripheral blood and bone marrow aspirate
≥ 30% blasts plus promyelocytes in peripheral blood or bone marrow aspirate
≥ 20% basophils in the peripheral blood or bone marrow Thrombocytopenia (<100 x 109/L) that is unrelated to therapy
Evidence of clonal evolution (with consensus of SC only)
BC is defined as:
≥ 30% blasts in peripheral blood or bone marrow aspirate
Appearance of extramedullary involvement other than hepatosplenomegaly proven by biopsy (i.e., chloroma)

End point type	Secondary

End point timeframe:

From the date of start of study treatment to the date of earliest transformation to AP/BC or CML-related death, assessed up to 24 months

End point values	Nilotinib			
Subject group type	Reporting group			
Number of subjects analysed	162			
Units: Months				
median (confidence interval 95%)	9999 (9999 to 9999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (EORTC QLQ-C30): global health status (GHS)/quality of life (QoL)

End point title	Change From Baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30

	(EORTC QLQ-C30): global health status (GHS)/quality of life (QoL)

End point description:

The EORTC QLQ-C30 is a patient completed 30 item questionnaire that is composed of both multi-item scales and single-item measures. These include five functional scales, three symptom scales, six single items and a GHS/QoL scale.
The GHS/QoL scale has 7 possible scores of responses (1=very poor to 7=excellent). Scores were averaged and transformed to 0 to 100. Higher scores indicate better quality of life.
A positive change from Baseline indicates improvement.

End point type	Secondary

End point timeframe:

Baseline, month 3, month 6, month 12, month 18 and month 24

End point values	Nilotinib			
Subject group type	Reporting group			
Number of subjects analysed	162			
Units: Score on a scale				
arithmetic mean (standard deviation)				
Month 3 (n=113)	5.1 (± 22.39)			
Month 6 (n=109)	6.3 (± 20.29)			
Month 12 (n=99)	6.0 (± 25.09)			
Month 18 (n=85)	4.0 (± 26.34)			
Month 24 (n=38)	2.4 (± 27.05)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (EORTC QLQ-C30): Physical functioning

End point title	Change From Baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (EORTC QLQ-C30): Physical functioning

End point description:

The EORTC QLQ-C30 is a patient completed 30 item questionnaire that is composed of both multi-item scales and single-item measures. These include five functional scales, three symptom scales, six single items and a global health status/QoL scale.
For the physical functioning scale, participants self-rated levels of difficulty in doing strenuous activities, taking a walk, how much they needed to stay in bed or a chair, or needed help with eating, dressing, bathing, using the toilet. The physical functioning scale had 4 possible scores (1=not at all, 2=a little, 3=quite a bit, 4=very much). Scores were averaged and transformed to 0 to 100. Higher scores indicate better functioning. A positive change from baseline indicates improvement in physical functioning.

End point type	Secondary

End point timeframe:

Baseline, month 3, month 6, month 12, month 18 and month 24

End point values	Nilotinib			
Subject group type	Reporting group			
Number of subjects analysed	162			
Units: Score on a scale				
arithmetic mean (standard deviation)				
Month 3 (n=115)	0.2 (± 15.52)			
Month 6 (n=112)	0.7 (± 16.58)			
Month 12 (n=102)	-1.4 (± 18.70)			
Month 18 (n=88)	-0.7 (± 18.45)			
Month 24 (n=38)	-3.2 (± 22.51)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (EORTC QLQ-C30): Role functioning

End point title	Change From Baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (EORTC QLQ-C30): Role functioning

End point description:

The EORTC QLQ-C30 is a patient completed 30 item questionnaire that is composed of both multi-item scales and single-item measures. These include five functional scales, three symptom scales, six single items and a global health status/QoL scale.
For the role functioning scale, participants self-rated how much they were limited in doing work or daily activities, or in pursuing hobbies or other leisure time activities during the past week. The role functioning scale had 4 possible scores (1=not at all, 2=a little, 3=quite a bit, 4=very much). Scores were averaged and transformed to 0 to 100. Higher scores indicate better functioning. A positive change from baseline indicates improvement in role functioning.

End point type	Secondary

End point timeframe:

Baseline, month 3, month 6, month 12, month 18 and month 24

End point values	Nilotinib			
Subject group type	Reporting group			
Number of subjects analysed	162			
Units: Score on a scale				
arithmetic mean (standard deviation)				
Month 3 (n=115)	-0.1 (± 33.22)			
Month 6 (n=111)	2.0 (± 29.19)			
Month 12 (n=102)	0.5 (± 32.11)			
Month 18 (n=87)	0.4 (± 34.57)			
Month 24 (n=38)	0.4 (± 35.41)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (EORTC QLQ-C30): Emotional functioning

End point title	Change From Baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (EORTC QLQ-C30): Emotional functioning

End point description:

The EORTC QLQ-C30 is a patient completed 30 item questionnaire that is composed of both multi-item scales and single-item measures. These include five functional scales, three symptom scales, six single items and a global health status/QoL scale.
For the emotional functioning scale, participants self-rated how much they felt tense, worried, irritable or depressed during the past week. The emotional functioning scale had 4 possible scores (1=not at all, 2=a little, 3=quite a bit, 4=very much). Scores were averaged and transformed to 0 to 100. Higher scores indicate better functioning. A positive change from baseline indicates improvement in emotional functioning.

End point type	Secondary

End point timeframe:

Baseline, month 3, month 6, month 12, month 18 and month 24

End point values	Nilotinib			
Subject group type	Reporting group			
Number of subjects analysed	162			
Units: Score on a scale				
arithmetic mean (standard deviation)				
Month 3 (n=114)	8.1 (± 20.73)			
Month 6 (n=110)	8.6 (± 22.06)			
Month 12 (n=101)	7.2 (± 25.59)			
Month 18 (n=85)	4.7 (± 24.48)			
Month 24 (n=38)	0.0 (± 21.14)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (EORTC QLQ-C30): Cognitive functioning

End point title	Change From Baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (EORTC QLQ-C30): Cognitive functioning

End point description:

The EORTC QLQ-C30 is a patient completed 30 item questionnaire that is composed of both multi-item scales and single-item measures. These include five functional scales, three symptom scales, six single items and a global health status/QoL scale.
For the cognitive functioning scale, participants self-rated the extent of difficulty in concentrating on things or remembering things during the past week. The cognitive functioning scale had 4 possible scores (1=not at all, 2=a little, 3=quite a bit, 4=very much). Scores were averaged and transformed to 0 to 100. Higher scores indicate better functioning. A positive change from baseline indicates

improvement in cognitive functioning.

End point type	Secondary

End point timeframe:

Baseline, month 3, month 6, month 12, month 18 and month 24

End point values	Nilotinib			
Subject group type	Reporting group			
Number of subjects analysed	162			
Units: Score on a scale				
arithmetic mean (standard deviation)				
Month 3 (n=114)	-2.3 (± 20.67)			
Month 6 (n=110)	-3.8 (± 23.10)			
Month 12 (n=101)	-7.1 (± 24.65)			
Month 18 (n=85)	-8.0 (± 27.77)			
Month 24 (n=38)	-8.3 (± 28.67)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (EORTC QLQ-C30): Social functioning

End point title	Change From Baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (EORTC QLQ-C30): Social functioning

End point description:

The EORTC QLQ-C30 is a patient completed 30 item questionnaire that is composed of both multi-item scales and single-item measures. These include five functional scales, three symptom scales, six single items and a global health status/QoL scale.
For the social functioning scale, participants self-rated how much their physical condition or medical treatment interfered with their family life and social activities during the past week. The social functioning scale had 4 possible scores (1=not at all, 2=a little, 3=quite a bit, 4=very much). Scores were averaged and transformed to 0 to 100. Higher scores indicate better functioning. A positive change from baseline indicates improvement in social functioning.

End point type	Secondary

End point timeframe:

Baseline, month 3, month 6, month 12, month 18 and month 24

End point values	Nilotinib			
Subject group type	Reporting group			
Number of subjects analysed	162			
Units: Score on a scale				
arithmetic mean (standard deviation)				
Month 3 (n=114)	-0.7 (± 26.83)			
Month 6 (n=110)	0.3 (± 26.03)			

Month 12 (n=100)	-1.2 (± 27.95)			
Month 18 (n=85)	-1.2 (± 28.15)			
Month 24 (n=38)	-9.2 (± 28.13)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Chronic Myeloid Leukemia specific 24 (EORTC QLQ-CML 24): Symptom burden

End point title	Change From Baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Chronic Myeloid Leukemia specific 24 (EORTC QLQ-CML 24): Symptom burden

End point description:

The EORTC QLQ-CML 24 is an internationally developed disease specific health-related quality of life questionnaire for CML patients. The questionnaire is composed of four multi-item scales and two single-item scales. The module consists of 24 items assessing symptoms burden (13 items), impact on worry/mood (4 items), impact on daily life (3 items), satisfaction with care and information (2 items) body image problems (1 item) and satisfaction with social life (1 item). The items were measured on four levels: 1=not at all, 2=a little, 3=quite a bit, 4=very much. For each domain, scores were averaged and transformed to 0 to 100. A higher score in symptom burden domain indicates a worse outcome. A negative change from baseline indicates improvement.

End point type	Secondary

End point timeframe:

Baseline, month 3, month 6, month 12, month 18 and month 24

End point values	Nilotinib			
Subject group type	Reporting group			
Number of subjects analysed	162			
Units: Score on a scale				
arithmetic mean (standard deviation)				
Month 3 (n=104)	2.9 (± 13.90)			
Month 6 (n=105)	2.4 (± 13.76)			
Month 12 (n=95)	3.6 (± 14.29)			
Month 18 (n=79)	2.5 (± 12.85)			
Month 24 (n=38)	3.2 (± 14.46)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Chronic Myeloid Leukemia specific 24 (EORTC QLQ-CML 24): Impact on worry/mood

End point title	Change From Baseline in European Organization for Research

	and Treatment of Cancer Quality of Life Questionnaire Chronic Myeloid Leukemia specific 24 (EORTC QLQ-CML 24): Impact on worry/mood

End point description:

The EORTC QLQ-CML 24 is an internationally developed disease specific health-related quality of life questionnaire for CML patients. The questionnaire is composed of four multi-item scales and two single-item scales. The module consists of 24 items assessing symptoms burden (13 items), impact on worry/mood (4 items), impact on daily life (3 items), satisfaction with care and information (2 items) body image problems (1 item) and satisfaction with social life (1 item). The items were measured on four levels: 1=not at all, 2=a little, 3=quite a bit, 4=very much. For each scale, scores were averaged and transformed to 0 to 100. A higher score in impact on worry/mood domain indicates a worse outcome. A negative change from baseline indicates improvement.

End point type	Secondary

End point timeframe:

Baseline, month 3, month 6, month 12, month 18 and month 24

End point values	Nilotinib			
Subject group type	Reporting group			
Number of subjects analysed	162			
Units: Score on a scale				
arithmetic mean (standard deviation)				
Month 3 (n=104)	-3.4 (± 27.01)			
Month 6 (n=105)	-4.7 (± 26.04)			
Month 12 (n=95)	-6.0 (± 25.55)			
Month 18 (n=78)	-3.8 (± 28.40)			
Month 24 (n=38)	-2.0 (± 25.22)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Chronic Myeloid Leukemia specific 24 (EORTC QLQ-CML 24): Impact on daily life

End point title	Change From Baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Chronic Myeloid Leukemia specific 24 (EORTC QLQ-CML 24): Impact on daily life

End point description:

The EORTC QLQ-CML 24 is an internationally developed disease specific health-related quality of life questionnaire for CML patients. The questionnaire is composed of four multi-item scales and two single-item scales. The module consists of 24 items assessing symptoms burden (13 items), impact on worry/mood (4 items), impact on daily life (3 items), satisfaction with care and information (2 items) body image problems (1 item) and satisfaction with social life (1 item). The items were measured on four levels: 1=not at all, 2=a little, 3=quite a bit, 4=very much. For each domain, scores were averaged and transformed to 0 to 100. A higher score in impact on daily life domain indicates a worse outcome. A negative change from baseline indicates improvement.

End point type	Secondary

End point timeframe:

Baseline, month 3, month 6, month 12, month 18 and month 24

End point values	Nilotinib			
Subject group type	Reporting group			
Number of subjects analysed	162			
Units: Score on a scale				
arithmetic mean (standard deviation)				
Month 3 (n=64)	-3.6 (± 25.59)			
Month 6 (n=64)	-6.4 (± 24.07)			
Month 12 (n=62)	-6.2 (± 26.50)			
Month 18 (n=47)	-6.4 (± 27.87)			
Month 24 (n=20)	-10.0 (± 31.61)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Chronic Myeloid Leukemia specific 24 (EORTC QLQ-CML 24): Satisfaction with care and information

End point title	Change From Baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Chronic Myeloid Leukemia specific 24 (EORTC QLQ-CML 24): Satisfaction with care and information

End point description:

The EORTC QLQ-CML 24 is an internationally developed disease specific health-related quality of life questionnaire for CML patients. The questionnaire is composed of four multi-item scales and two single-item scales. The module consists of 24 items assessing symptoms burden (13 items), impact on worry/mood (4 items), impact on daily life (3 items), satisfaction with care and information (2 items) body image problems (1 item) and satisfaction with social life (1 item). The items were measured on four levels: 1=not at all, 2=a little, 3=quite a bit, 4=very much. For each domain, scores were averaged and transformed to 0 to 100. A higher score in satisfaction with care and information domain indicates a higher level of satisfaction. A positive change from baseline indicates increasing satisfaction.

End point type	Secondary

End point timeframe:

Baseline, month 3, month 6, month 12, month 18 and month 24

End point values	Nilotinib			
Subject group type	Reporting group			
Number of subjects analysed	162			
Units: Score on a scale				
arithmetic mean (standard deviation)				
Month 3 (n=62)	4.3 (± 30.47)			
Month 6 (n=60)	5.6 (± 33.71)			
Month 12 (n=60)	-0.6 (± 34.30)			
Month 18 (n=46)	2.2 (± 30.35)			

Month 24 (n=19)	12.3 (± 30.35)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Chronic Myeloid Leukemia specific 24 (EORTC QLQ-CML 24): Body image problems

End point title	Change From Baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Chronic Myeloid Leukemia specific 24 (EORTC QLQ-CML 24): Body image problems

End point description:

The EORTC QLQ-CML 24 is an internationally developed disease specific health-related quality of life questionnaire for CML patients. The questionnaire is composed of four multi-item scales and two single-item scales. The module consists of 24 items assessing symptoms burden (13 items), impact on worry/mood (4 items), impact on daily life (3 items), satisfaction with care and information (2 items) body image problems (1 item) and satisfaction with social life (1 item). The items were measured on four levels: 1=not at all, 2=a little, 3=quite a bit, 4=very much. For each domain, scores were averaged and transformed to 0 to 100. A higher score in body image problems domain indicates a worse outcome. A negative change from baseline indicates improvement.

End point type	Secondary

End point timeframe:

Baseline, month 3, month 6, month 12, month 18 and month 24

End point values	Nilotinib			
Subject group type	Reporting group			
Number of subjects analysed	162			
Units: Score on a scale				
arithmetic mean (standard deviation)				
Month 3 (n=63)	2.1 (± 32.72)			
Month 6 (n=64)	3.1 (± 28.92)			
Month 12 (n=62)	7.0 (± 28.40)			
Month 18 (n=47)	5.7 (± 31.33)			
Month 24 (n=20)	3.3 (± 35.71)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Chronic Myeloid Leukemia specific 24 (EORTC QLQ-CML 24): Satisfaction with social life

End point title	Change From Baseline in European Organization for Research

	and Treatment of Cancer Quality of Life Questionnaire Chronic Myeloid Leukemia specific 24 (EORTC QLQ-CML 24): Satisfaction with social life

End point description:

The EORTC QLQ-CML 24 is an internationally developed disease specific health-related quality of life questionnaire for CML patients. The questionnaire is composed of four multi-item scales and two single-item scales. The module consists of 24 items assessing symptoms burden (13 items), impact on worry/mood (4 items), impact on daily life (3 items), satisfaction with care and information (2 items) body image problems (1 item) and satisfaction with social life (1 item). The items were measured on four levels: 1=not at all, 2=a little, 3=quite a bit, 4=very much. For each domain, scores were averaged and transformed to 0 to 100. A higher score in satisfaction with social life domain indicates a higher level of satisfaction. A positive change from baseline indicates increasing satisfaction.

End point type	Secondary

End point timeframe:

Baseline, month 3, month 6, month 12, month 18 and month 24

End point values	Nilotinib			
Subject group type	Reporting group			
Number of subjects analysed	162			
Units: Score on a scale				
arithmetic mean (standard deviation)				
Month 3 (n=60)	3.9 (± 34.22)			
Month 6 (n=62)	9.7 (± 39.76)			
Month 12 (n=61)	6.6 (± 41.19)			
Month 18 (n=47)	8.5 (± 39.60)			
Month 24 (n=19)	14.0 (± 30.05)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from first dose of study treatment until end of study treatment plus 30 days post treatment, up to maximum duration of 25 months

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	Nilotinib (AMN107)

Reporting group description:

Nilotinib (AMN107)

Serious adverse events	Nilotinib (AMN107)		
Total subjects affected by serious adverse events			
subjects affected / exposed	38 / 171 (22.22%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder cancer			
subjects affected / exposed	1 / 171 (0.58%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Breast cancer			
subjects affected / exposed	1 / 171 (0.58%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oral papilloma			
subjects affected / exposed	1 / 171 (0.58%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin cancer			

subjects affected / exposed	1 / 171 (0.58%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Squamous cell carcinoma of the vulva				
subjects affected / exposed	1 / 171 (0.58%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Transformation to acute myeloid leukaemia				
subjects affected / exposed	1 / 171 (0.58%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Extremity necrosis				
subjects affected / exposed	1 / 171 (0.58%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Hypertension				
subjects affected / exposed	1 / 171 (0.58%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Peripheral vascular disorder				
subjects affected / exposed	1 / 171 (0.58%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Peripheral arterial occlusive disease				
subjects affected / exposed	3 / 171 (1.75%)			
occurrences causally related to treatment / all	2 / 5			
deaths causally related to treatment / all	0 / 0			
Thrombosis				
subjects affected / exposed	1 / 171 (0.58%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration				

site conditions				
Fatigue				
subjects affected / exposed	1 / 171 (0.58%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General physical health deterioration				
subjects affected / exposed	1 / 171 (0.58%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Non-cardiac chest pain				
subjects affected / exposed	1 / 171 (0.58%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pain				
subjects affected / exposed	1 / 171 (0.58%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Emphysema				
subjects affected / exposed	1 / 171 (0.58%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumothorax				
subjects affected / exposed	1 / 171 (0.58%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary oedema				
subjects affected / exposed	1 / 171 (0.58%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Depression				

subjects affected / exposed	2 / 171 (1.17%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Investigations			
Troponin increased			
subjects affected / exposed	1 / 171 (0.58%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Craniocerebral injury			
subjects affected / exposed	1 / 171 (0.58%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fall			
subjects affected / exposed	1 / 171 (0.58%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Fracture displacement			
subjects affected / exposed	1 / 171 (0.58%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Postoperative ileus			
subjects affected / exposed	1 / 171 (0.58%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rib fracture			
subjects affected / exposed	1 / 171 (0.58%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 171 (0.58%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Atrial fibrillation			
subjects affected / exposed	1 / 171 (0.58%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac arrest			
subjects affected / exposed	1 / 171 (0.58%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Cardiac failure congestive			
subjects affected / exposed	1 / 171 (0.58%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Coronary artery disease			
subjects affected / exposed	2 / 171 (1.17%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Coronary artery occlusion			
subjects affected / exposed	1 / 171 (0.58%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myocardial infarction			
subjects affected / exposed	1 / 171 (0.58%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Tachyarrhythmia			
subjects affected / exposed	1 / 171 (0.58%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sinus node dysfunction			
subjects affected / exposed	1 / 171 (0.58%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			

Cerebrovascular accident				
subjects affected / exposed	1 / 171 (0.58%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Facial nerve disorder				
subjects affected / exposed	1 / 171 (0.58%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
IIIrd nerve paralysis				
subjects affected / exposed	1 / 171 (0.58%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Loss of consciousness				
subjects affected / exposed	1 / 171 (0.58%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	1 / 171 (0.58%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Anaemia				
subjects affected / exposed	1 / 171 (0.58%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood loss anaemia				
subjects affected / exposed	1 / 171 (0.58%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lymphadenopathy				
subjects affected / exposed	1 / 171 (0.58%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Thrombocytopenia				

subjects affected / exposed	2 / 171 (1.17%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Neutropenia				
subjects affected / exposed	1 / 171 (0.58%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Eye disorders				
Visual impairment				
subjects affected / exposed	1 / 171 (0.58%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal pain				
subjects affected / exposed	2 / 171 (1.17%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Gastritis				
subjects affected / exposed	2 / 171 (1.17%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Haemorrhoids thrombosed				
subjects affected / exposed	1 / 171 (0.58%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pancreatitis				
subjects affected / exposed	1 / 171 (0.58%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Acute kidney injury				
subjects affected / exposed	1 / 171 (0.58%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Renal colic				
subjects affected / exposed	1 / 171 (0.58%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal failure				
subjects affected / exposed	1 / 171 (0.58%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ureterolithiasis				
subjects affected / exposed	1 / 171 (0.58%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary incontinence				
subjects affected / exposed	1 / 171 (0.58%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Spinal pain				
subjects affected / exposed	1 / 171 (0.58%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
COVID-19				
subjects affected / exposed	1 / 171 (0.58%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infectious pleural effusion				
subjects affected / exposed	1 / 171 (0.58%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infective exacerbation of chronic obstructive airways disease				

subjects affected / exposed	1 / 171 (0.58%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Soft tissue infection			
subjects affected / exposed	1 / 171 (0.58%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 171 (0.58%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	1 / 171 (0.58%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Nilotinib (AMN107)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	148 / 171 (86.55%)		
Investigations			
Gamma-glutamyltransferase increased			
subjects affected / exposed	9 / 171 (5.26%)		
occurrences (all)	9		
Alanine aminotransferase increased			
subjects affected / exposed	12 / 171 (7.02%)		
occurrences (all)	13		
Vascular disorders			
Hypertension			
subjects affected / exposed	10 / 171 (5.85%)		
occurrences (all)	13		
Nervous system disorders			

Dizziness			
subjects affected / exposed	11 / 171 (6.43%)		
occurrences (all)	11		
Headache			
subjects affected / exposed	29 / 171 (16.96%)		
occurrences (all)	43		
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	15 / 171 (8.77%)		
occurrences (all)	27		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	34 / 171 (19.88%)		
occurrences (all)	49		
Oedema peripheral			
subjects affected / exposed	10 / 171 (5.85%)		
occurrences (all)	13		
Pyrexia			
subjects affected / exposed	11 / 171 (6.43%)		
occurrences (all)	13		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	11 / 171 (6.43%)		
occurrences (all)	12		
Abdominal pain upper			
subjects affected / exposed	17 / 171 (9.94%)		
occurrences (all)	18		
Diarrhoea			
subjects affected / exposed	20 / 171 (11.70%)		
occurrences (all)	23		
Constipation			
subjects affected / exposed	14 / 171 (8.19%)		
occurrences (all)	14		
Dyspepsia			
subjects affected / exposed	10 / 171 (5.85%)		
occurrences (all)	15		

Nausea			
subjects affected / exposed	20 / 171 (11.70%)		
occurrences (all)	23		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	10 / 171 (5.85%)		
occurrences (all)	12		
Dyspnoea			
subjects affected / exposed	13 / 171 (7.60%)		
occurrences (all)	13		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	25 / 171 (14.62%)		
occurrences (all)	27		
Dry skin			
subjects affected / exposed	18 / 171 (10.53%)		
occurrences (all)	18		
Rash			
subjects affected / exposed	26 / 171 (15.20%)		
occurrences (all)	27		
Pruritus			
subjects affected / exposed	37 / 171 (21.64%)		
occurrences (all)	48		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	22 / 171 (12.87%)		
occurrences (all)	33		
Back pain			
subjects affected / exposed	18 / 171 (10.53%)		
occurrences (all)	19		
Muscle spasms			
subjects affected / exposed	15 / 171 (8.77%)		
occurrences (all)	19		
Myalgia			
subjects affected / exposed	11 / 171 (6.43%)		
occurrences (all)	11		

Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	 31 / 171 (18.13%) 41		
Metabolism and nutrition disorders Hypercholesterolaemia subjects affected / exposed occurrences (all)	 14 / 171 (8.19%) 14		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 April 2016	The primary purpose of this amendment is to include hepatitis B virus testing as one of the study procedures, to identify study patients who may be at risk of hepatitis B reactivation.
06 November 2017	The main purpose was to add an Interim Analysis of the data to the planned procedures and to prolong the recruitment period.
15 February 2021	The main purpose was to correct minor issues in previous versions and clarify exploratory points prior to data base lock.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to EudraCT system limitations, which EMA is aware of, data using 9999 as data points in this record are not an accurate representation of the clinical trial results.

Notes: