



Clinical trial results:

A multi-center, open label, non-controlled Phase II study to evaluate the efficacy and safety of oral nilotinib in pediatric patients with newly diagnosed Ph+ chronic myelogenous leukemia (CML) in chronic phase (CP) or with Ph+ CML in CP or accelerated phase (AP) resistant or intolerant to either imatinib or dasatinib.

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use <https://www.novctrd.com/CtrdWeb/home.nov> for complete trial results.

Summary

EudraCT number	2013-000200-41
Trial protocol	IT ES HU BE AT GB NL DE FR
Global end of trial date	28 August 2020

Results information

Result version number	v1
This version publication date	13 March 2021
First version publication date	13 March 2021

Trial information

Trial identification

Sponsor protocol code	CAMN107A2203
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01844765
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)	Yes
EMA paediatric investigation plan number(s)	EMA-000290-PIP01-08
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	28 August 2020
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	28 August 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

- To assess efficacy of nilotinib in pediatric patients with Ph+ CMLCPresistant or intolerant to either imatinib or dasatinib

- To assess efficacy of nilotinib in pediatric patients with Ph+ CMLAP resistant or intolerant to either imatinib or dasatinib

- To assess efficacy of nilotinib in pediatric patients with newly diagnosed Ph+ CML-CP

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	20 August 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 5
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	Hungary: 1

Country: Number of subjects enrolled	Italy: 8
Country: Number of subjects enrolled	Japan: 9
Country: Number of subjects enrolled	Korea, Republic of: 5
Country: Number of subjects enrolled	Malaysia: 1
Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	Russian Federation: 4
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	Thailand: 6
Country: Number of subjects enrolled	Turkey: 2
Country: Number of subjects enrolled	United States: 13
Worldwide total number of subjects	59
EEA total number of subjects	17

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)	18
Adolescents (12-17 years)	41
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

3 cohorts were planned based on disease classification. In 1 cohort no patients (pts) were enrolled so results presented are based on 2 cohorts. 34 imatinib/dasatinib resistant/intolerant CML-CP pts & 25 newly diagnosed CML-CP pts were enrolled. 1 imatinib/dasatinib resistant/intolerant pt did not receive study drug & was excluded from analysis.

Pre-assignment

Screening details:

Minimum 50 pediatric patients (pts) to be enrolled in the study. At least 15 were to be Ph+ CML-CP pts resistant/intolerant to either imatinib or dasatinib, & at least 15 newly diagnosed Ph+ CML-CP pts. There was no requirement on the minimum number of pts to be enrolled in the Cohort of CML-AP resistant/intolerant to either imatinib or dasatinib.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Resistant/intolerant Ph+ CML in CP

Arm description:

Patients resistant or intolerant to either imatinib or dasatinib

Arm type	Experimental
Investigational medicinal product name	Nilotinib 230 mg/m2 bid
Investigational medicinal product code	AMN107
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Nilotinib was administered orally at 230 mg/m2 bid for 28 days (one Cycle) and for a total of up to 66 Cycles (or discontinued early)

Arm title	Newly diagnosed and untreated Ph+ CML in first CP
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Arm description:

Patients newly diagnosed in Chronic phase. Diagnosis within 6 months of date of first cytogenetic analysis confirming Philadelphia chromosome with (9;22) translocation by standard conventional cytogenetic analysis

Arm type	Experimental
Investigational medicinal product name	Nilotinib 230 mg/m2 bid
Investigational medicinal product code	AMN107
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Nilotinib was administered orally at 230 mg/m2 bid for 28 days (one Cycle) and for a total of up to 66 Cycles (or discontinued early)

Number of subjects in period 1	Resistant/intolerant Ph+ CML in CP	Newly diagnosed and untreated Ph+ CML in first CP
Started	34	25
Treated	33	25
Untreated	1 ^[1]	0 ^[2]
Completed	19	10
Not completed	15	15
Consent withdrawn by subject	2	3
Disease progression	1	-
Adverse event, non-fatal	6	8
Protocol deviation	2	-
Administrative problems	3	4
Untreated	1	-

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This is because 1 patients who was enrolled was not treated, so the disposition was provided although the patient did not continue and was not treated in this study.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The number of subjects at this milestone for this arm does match what is in the arm.

Baseline characteristics

Reporting groups

Reporting group title	Resistant/intolerant Ph+ CML in CP
Reporting group description: Patients resistant or intolerant to either imatinib or dasatinib	
Reporting group title	Newly diagnosed and untreated Ph+ CML in first CP
Reporting group description: Patients newly diagnosed in Chronic phase. Diagnosis within 6 months of date of first cytogenetic analysis confirming Philadelphia chromosome with (9;22) translocation by standard conventional cytogenetic analysis	

Reporting group values	Resistant/intolerant Ph+ CML in CP	Newly diagnosed and untreated Ph+ CML in first CP	Total
Number of subjects	34	25	59
Age Categorical Units: Participants			
1 to < 12 years	12	6	18
12 to < 18 years	22	19	41
Sex: Female, Male Units:			
Female	13	12	25
Male	21	13	34
Race/Ethnicity, Customized Units: Subjects			
Caucasian	13	18	31
Black	3	0	3
Asian	16	7	23
Native American	1	0	1
Other	1	0	1

End points

End points reporting groups

Reporting group title	Resistant/intolerant Ph+ CML in CP
Reporting group description:	
Patients resistant or intolerant to either imatinib or dasatinib	
Reporting group title	Newly diagnosed and untreated Ph+ CML in first CP
Reporting group description:	
Patients newly diagnosed in Chronic phase. Diagnosis within 6 months of date of first cytogenetic analysis confirming Philadelphia chromosome with (9;22) translocation by standard conventional cytogenetic analysis	
Subject analysis set title	All patients
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All patients enrolled in the study	

Primary: Rate of Major Molecular Response (MMR) at 6 cycles for Ph+ CML CP patients resistant or intolerant to imatinib or dasatinib

End point title	Rate of Major Molecular Response (MMR) at 6 cycles for Ph+ CML CP patients resistant or intolerant to imatinib or dasatinib ^{[1][2]}
End point description:	
MMR is defined as $\leq 0.1\%$ BCR-ABL/control gene (ABL) % by international scale, or equivalent to ≥ 3 log reduction of BCR-ABL transcript from standardized baseline, measured by RQ-PCR (Real time quantitative polymerase chain reaction). BCR-ABL is the fusion gene from breakpoint cluster region and Abelson genes. A patient was counted as having MMR at 6 cycles if the patient met the MMR criteria at the Cycle 6 Visit.	
End point type	Primary
End point timeframe:	
6 cycles	

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 analysis was planned for this endpoint

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was planned for this endpoint

End point values	Resistant/intolerant Ph+ CML in CP			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: Percentage of participants				
number (confidence interval 95%)	39.4 (22.9 to 57.9)			

Statistical analyses

No statistical analyses for this end point

Primary: MMR rate by 12 cycles in newly diagnosed Ph+ CML-CP patients

End point title	MMR rate by 12 cycles in newly diagnosed Ph+ CML-CP patients ^{[3][4]}
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End point description:

MMR is defined as $\leq 0.1\%$ BCR-ABL/control gene (ABL) % by international scale, or equivalent to ≥ 3 log reduction of BCR-ABL transcript from standardized baseline, measured by RQ-PCR (Real time quantitative polymerase chain reaction). BCR-ABL is the fusion gene from breakpoint cluster region and Abelson genes. A patient was counted as having MMR by 12 cycles if the patient met the MMR criteria at least once at any time between first study drug intake and Cycle 12 visit included.

End point type	Primary
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End point timeframe:

12 cycles

Notes:

[3] - 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 analysis was planned for this endpoint

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was planned for this endpoint

End point values	Newly diagnosed and untreated Ph+ CML in first CP			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: Percentage of participants				
number (confidence interval 95%)	64.0 (42.5 to 82.0)			

Statistical analyses

No statistical analyses for this end point

Primary: Rate of complete cytogenetic response (CCyR) at 12 cycles in newly diagnosed Ph+ CML-CP patients

End point title	Rate of complete cytogenetic response (CCyR) at 12 cycles in newly diagnosed Ph+ CML-CP patients ^{[5][6]}
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End point description:

Cytogenetic response is assessed as the percentage of Philadelphia positive (Ph+) metaphases in the bone marrow. Complete Cytogenetic Response (CCyR) is defined as 0% of Ph+ metaphases. A patient was counted as CCyR at 12 cycles if the patient met the CCyR criteria at the Cycle 12 Visit.

End point type	Primary
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End point timeframe:

12 cycles

Notes:

[5] - 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 analysis was planned for this endpoint

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was planned for this endpoint

End point values	Newly diagnosed and untreated Ph+ CML in first CP			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: Percentage of participants				
number (confidence interval 95%)	64.0 (42.5 to 82.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: MMR rate by time points in Ph+ CML-CP patients resistant or intolerant to imatinib or dasatinib

End point title	MMR rate by time points in Ph+ CML-CP patients resistant or intolerant to imatinib or dasatinib ^[7]
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End point description:

Major molecular response (MMR) was defined as BCR-ABL/ABL % \leq 0.1% by IS as measured by RQ-PCR, confirmed by duplicate analysis of the same sample.

End point type	Secondary
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End point timeframe:

By 3, 6, 9 , 12, 24, 36, 48, 66 cycles (1 cycle = 28 days)

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was planned for this endpoint

End point values	Resistant/intolerant Ph+ CML in CP			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: Percentage of participants				
number (confidence interval 95%)				
By cycle 3	36.4 (20.4 to 54.9)			
By cycle 6	45.5 (28.1 to 63.6)			
By cycle 9	51.5 (33.5 to 69.2)			
By cycle 12	57.6 (39.2 to 74.5)			
By cycle 18	57.6 (39.2 to 74.5)			
By cycle 24	57.6 (39.2 to 74.5)			
By cycle 36	57.6 (39.2 to 74.5)			
By cycle 48	60.6 (42.1 to 77.1)			
By cycle 66	60.6 (42.1 to 77.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: MMR rate by time points in newly diagnosed Ph+ CML-CP patients

End point title	MMR rate by time points in newly diagnosed Ph+ CML-CP patients ^[8]
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End point description:

Major molecular response (MMR) was defined as BCR-ABL/ABL % \leq 0.1% by IS as measured by RQ-PCR, confirmed by duplicate analysis of the same sample.

End point type	Secondary
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End point timeframe:

by 3, 6, 9, 12, 24, 36, 48, 66 cycles (1 cycle = 28 days)

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was planned for this endpoint

End point values	Newly diagnosed and untreated Ph+ CML in first CP			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: Percentage of participants				
number (confidence interval 95%)				
By cycle 3	12.0 (2.5 to 31.2)			
By cycle 6	52.0 (31.3 to 72.2)			
By cycle 9	56.0 (34.9 to 75.6)			
By cycle 12	64.0 (42.5 to 82.0)			
By cycle 18	68.0 (46.5 to 85.1)			
By cycle 24	68.0 (46.5 to 85.1)			
By cycle 36	76.0 (54.9 to 90.6)			
By cycle 48	76.0 (54.9 to 90.6)			
By cycle 66	76.0 (54.9 to 90.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Best BCR-ABL ratio categories for resistant/intolerant Ph+ CML - overall

End point title	Best BCR-ABL ratio categories for resistant/intolerant Ph+ CML - overall ^[9]
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End point description:

MMR is defined as $\leq 0.1\%$ BCR-ABL/control gene (ABL) % by international scale, or equivalent to ≥ 3 log reduction of BCR-ABL transcript from standardized baseline, measured by RQ-PCR (Real time quantitative polymerase chain reaction). BCR-ABL is the fusion gene from breakpoint cluster region and Abelson genes. BCR-ABL ratio by percentage: > 0.0032 to $\leq 0.01\%$ is equal to a log reduction category of ≥ 4 to <4.5 -log reduction (MR4); BCR-ABL ratio by percentage: $\leq 0.0032\%$ is equal to a log reduction category of ≥ 4.5 -log reduction (MMR4.5)

End point type	Secondary
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End point timeframe:

up to 66 cycles (1 cycle = 28 days)

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was planned for this endpoint

End point values	Resistant/intolerant Ph+ CML in CP			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: Percentage of participants				
number (not applicable)				
$\leq 0.0032\%$	12.1			
$> 0.0032\% - \leq 0.01\%$	15.2			
$> 0.01\% - \leq 0.1\%$	33.3			
$> 0.1\% - \leq 1\%$	21.2			
$> 1\% - \leq 10\%$	9.1			
$> 10\%$	6.1			
Atypical transcripts at baseline	3.0			

Statistical analyses

No statistical analyses for this end point

Secondary: Best BCR-ABL ratio categories for newly diagnosed Ph+ CML-CP - Overall

End point title	Best BCR-ABL ratio categories for newly diagnosed Ph+ CML-CP - Overall ^[10]
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End point description:

MMR is defined as $\leq 0.1\%$ BCR-ABL/control gene (ABL) % by international scale, or equivalent to ≥ 3 log reduction of BCR-ABL transcript from standardized baseline, measured by RQ-PCR (Real time quantitative polymerase chain reaction). BCR-ABL is the fusion gene from breakpoint cluster region and Abelson genes. BCR-ABL ratio by percentage: > 0.0032 to $\leq 0.01\%$ is equal to a log reduction category of ≥ 4 to <4.5 -log reduction (MR4); BCR-ABL ratio by percentage: $\leq 0.0032\%$ is equal to a log reduction category of ≥ 4.5 -log reduction (MMR4.5)

End point type	Secondary
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End point timeframe:

up to 66 cycles (1 cycle = 28 days)

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was planned for this endpoint

End point values	Newly diagnosed and untreated Ph+ CML in first CP			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: Percentage of participants				
number (not applicable)				
≤ 0.0032%	44.0			
>0.0032% - ≤ 0.01%	12.0			
>0.01% - ≤ 0.1%	20.0			
>0.1% - ≤ 1%	8.0			
>1% - ≤ 10%	8.0			
>10%	8.0			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first MMR among imatinib or dasatinib resistant or intolerant CML-CP patients who achieved MMR

End point title	Time to first MMR among imatinib or dasatinib resistant or intolerant CML-CP patients who achieved MMR ^[11]
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End point description:

Time from first study drug intake to first MMR amongst imatinib or dasatinib resistant or intolerant patients with CML-CP computed only for patients who achieved MMR.

End point type	Secondary
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End point timeframe:

From first dosing to the first MMR within 66 cycles period

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was planned for this endpoint

End point values	Resistant/intolerant Ph+ CML in CP			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: months				
median (confidence interval 95%)	2.79 (0.03 to 5.75)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first MMR among newly diagnosed Ph+ CML-CP patients who achieved MMR

End point title	Time to first MMR among newly diagnosed Ph+ CML-CP patients who achieved MMR ^[12]
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End point description:

Time to MMR is the time from first study drug intake to first major molecular response computed only for participants who achieved MMR.

End point type	Secondary
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End point timeframe:

From first dosing to the first MMR within 66 cycles period

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was planned for this endpoint

End point values	Newly diagnosed and untreated Ph+ CML in first CP			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: Months				
median (confidence interval 95%)	5.59 (5.52 to 10.84)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of first MMR among patients who were resistant or intolerant to either imatinib or dasatinib who achieved MMR

End point title	Duration of first MMR among patients who were resistant or intolerant to either imatinib or dasatinib who achieved MMR ^[13]
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End point description:

Duration of MMR is defined as the time between the date of the first MMR and the date of confirmed loss of MMR (i.e. the earliest of confirmed loss of MMR, CML-related death or progression to AP or BC). Participants without loss of MMR were censored at the last molecular assessment date.

End point type	Secondary
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End point timeframe:

from MMR until confirmed loss of MMR (Assessed up to 66 cycles)

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was planned for this endpoint

End point values	Resistant/intolerant Ph+ CML in CP			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: months				
median (confidence interval 95%)	999 (999 to 999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of first MMR among newly diagnosed patients who achieved MMR

End point title	Duration of first MMR among newly diagnosed patients who achieved MMR ^[14]
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End point description:

Duration of MMR is defined as the time between the date of the first MMR and the date of confirmed loss of MMR (i.e. the earliest of confirmed loss of MMR, CML-related death or progression to AP or BC). Participants without loss of MMR were censored at the last molecular assessment date.

End point type	Secondary
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End point timeframe:

from MMR until confirmed loss of MMR (Assessed up to 66 cycles)es)

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was planned for this endpoint

End point values	Newly diagnosed and untreated Ph+ CML in first CP			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: months				
median (confidence interval 95%)	999 (999 to 999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Best Complete Cytogenetic Response (CCyR) categories in Ph+ CML-CP patients resistant or intolerant to imatinib or dasatinib - overall

End point title	Best Complete Cytogenetic Response (CCyR) categories in Ph+ CML-CP patients resistant or intolerant to imatinib or dasatinib - overall ^[15]
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End point description:

- Complete cytogenetic response (CCyR) - 0% Ph+ metaphases
- Partial cytogenetic response (PCyR) - >0 to 35% Ph+ metaphases

- Minor cytogenetic response (mCyR) - >35 to 65% Ph+ metaphases
- Minimal - >65 to 95% Ph+ metaphases
- None - >95 to 100% Ph+ metaphases
- Major cytogenetic response (MCyR) - 0 to 35% Ph+ metaphases. A major response combines both complete and partial responses.

End point type	Secondary
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End point timeframe:

up to 66 cycles

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was planned for this endpoint

End point values	Resistant/intolerant Ph+ CML in CP			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: Percentage of participants				
number (not applicable)				
Major cytogenetic response: Complete	81.1			
Major cytogenetic response: Partial	3.0			
Minimal	3.0			
None	3.0			
Missing	9.1			

Statistical analyses

No statistical analyses for this end point

Secondary: Best Complete Cytogenetic Response (CCyR) in newly diagnosed Ph+ CML-CP patients - Overall

End point title	Best Complete Cytogenetic Response (CCyR) in newly diagnosed Ph+ CML-CP patients - Overall ^[16]
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End point description:

Complete cytogenetic response (CCyR) - 0% Ph+ metaphases

No response - >95 to 100% Ph+ metaphases

End point type	Secondary
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End point timeframe:

up to 66 cycles

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was planned for this endpoint

End point values	Newly diagnosed and untreated Ph+ CML in first CP			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: Percentage of participants				
number (confidence interval 95%)	84.0 (63.9 to 95.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of time to first complete cytogenetic response (CCyR) in newly diagnosed Ph+ CML-CP patients

End point title	Summary of time to first complete cytogenetic response (CCyR) in newly diagnosed Ph+ CML-CP patients ^[17]
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End point description:

Cytogenetic response is assessed as the percentage of Philadelphia positive (Ph+) metaphases in the bone marrow. Complete Cytogenetic Response (CCyR) is defined as 0% of Ph+ metaphases. A patient was counted as having CCyR by 6 cycles (respectively 12 cycles) if the patient met the CCyR criteria at least once at any time between first study drug intake and cycle 6 (cycle 12 respectively) visit included.

End point type	Secondary
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End point timeframe:

From first dosing to the first CCyR up to 66 cycles

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was planned for this endpoint

End point values	Newly diagnosed and untreated Ph+ CML in first CP			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: months				
median (confidence interval 95%)	5.55 (5.49 to 5.59)			

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan-Meier estimates of time to first complete cytogenetic response (CCyR) in newly diagnosed Ph+ CML-CP patients

End point title	Kaplan-Meier estimates of time to first complete cytogenetic response (CCyR) in newly diagnosed Ph+ CML-CP patients ^[18]
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End point description:

Cytogenetic response is assessed as the percentage of Philadelphia positive (Ph+) metaphases in the bone marrow. Complete Cytogenetic Response (CCyR) is defined as 0% of Ph+ metaphases. A patient was counted as having CCyR by 6 cycles (respectively 12 cycles) if the patient met the CCyR criteria at least once at any time between first study drug intake and cycle 6 (cycle 12 respectively) visit included.

End point type	Secondary
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End point timeframe:

From first dosing to the first CCyR up to 66 cycles

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was planned for this endpoint

End point values	Newly diagnosed and untreated Ph+ CML in first CP			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: months				
median (confidence interval 95%)	5.6 (5.5 to 5.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan-Meier estimates of duration of first complete cytogenetic response (CCyR) among patients who achieved CCyR in newly diagnosed Ph+ CML-CP patients

End point title	Kaplan-Meier estimates of duration of first complete cytogenetic response (CCyR) among patients who achieved CCyR in newly diagnosed Ph+ CML-CP patients ^[19]
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End point description:

Cytogenetic response is assessed as the percentage of Philadelphia positive (Ph+) metaphases in the bone marrow. Complete Cytogenetic Response (CCyR) is defined as 0% of Ph+ metaphases. A patient was counted as having CCyR by 6 cycles (respectively 12 cycles) if the patient met the CCyR criteria at least once at any time between first study drug intake and cycle 6 (cycle 12 respectively) visit included.

End point type	Secondary
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End point timeframe:

From CCyR to loss of CCyR up to 66 cycles

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was planned for this endpoint

End point values	Newly diagnosed and untreated Ph+ CML in first CP			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: months				
median (confidence interval 95%)	999 (999 to			

Statistical analyses

No statistical analyses for this end point

Secondary: Best major cytogenetic response (MCyR) rate by time point in Newly diagnosed Ph+ CML patients

End point title	Best major cytogenetic response (MCyR) rate by time point in Newly diagnosed Ph+ CML patients ^[20]
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End point description:

Major cytogenetic response (MCyR) - 0 to 35% Ph+ metaphases. A major response combines both complete and partial responses.

End point type	Secondary
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End point timeframe:

6, 12, 18, 24, 36, 48, 66 cycles

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was planned for this endpoint

End point values	Newly diagnosed and untreated Ph+ CML in first CP			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: Percentage of participants				
number (confidence interval 95%)				
by cycle 6	88.0 (68.8 to 97.5)			
by cycle 12	88.0 (68.8 to 97.5)			
by cycle 18	88.0 (68.8 to 97.5)			
by cycle 24	88.0 (68.8 to 97.5)			
by cycle 36	88.0 (68.8 to 97.5)			
by cycle 48	88.0 (68.8 to 97.5)			
by cycle 66	88.0 (68.8 to 97.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of time to first major cytogenetic response (MCyR) among patients who achieved MCyR in newly diagnosed CML-CP patients

End point title	Summary of time to first major cytogenetic response (MCyR) among patients who achieved MCyR in newly diagnosed CML-CP patients ^[21]
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End point description:

Major cytogenetic response (MCyR) - 0 to 35% Ph+ metaphases. A major response combines both complete and partial responses.

End point type	Secondary
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End point timeframe:

up to 66 cycles

Notes:

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was planned for this endpoint

End point values	Newly diagnosed and untreated Ph+ CML in first CP			
Subject group type	Reporting group			
Number of subjects analysed	22			
Units: months				
median (confidence interval 95%)	5.55 (5.52 to 5.59)			

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan-Meier estimates of time to first major cytogenetic response (MCyR) in newly diagnosed CML-CP patients

End point title	Kaplan-Meier estimates of time to first major cytogenetic response (MCyR) in newly diagnosed CML-CP patients ^[22]
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End point description:

Major cytogenetic response (MCyR) - 0 to 35% Ph+ metaphases. A major response combines both complete and partial responses.

End point type	Secondary
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End point timeframe:

up to 66 cycles

Notes:

[22] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was planned for this endpoint

End point values	Newly diagnosed and untreated Ph+ CML in first CP			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: months				
median (confidence interval 95%)	5.55 (5.52 to 5.59)			

Statistical analyses

No statistical analyses for this end point

Secondary: Best Complete Hematological Response (CHR) by time point

End point title	Best Complete Hematological Response (CHR) by time point ^[23]
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End point description:

Complete Hematological Response (CHR) was defined as

- WBC count <10×10⁹/L
- platelet count <450×10⁹/L
- basophils <5%
- no blasts and promyelocytes in peripheral blood
- myelocytes+metamyelocytes <5% in peripheral blood
- no evidence of extramedullary disease, including spleen and liver
- Assessment confirmation after at least 4 weeks for newly diagnosed Ph+ CML-CP

End point type	Secondary
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End point timeframe:

cycle 3, 6, 9, 12, 18, 24, 36, 48, 66

Notes:

[23] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was planned for this endpoint

End point values	Newly diagnosed and untreated Ph+ CML in first CP			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: Percentage of participants				
number (confidence interval 95%)				
by cycle 3	76.0 (54.9 to 90.6)			
by cycle 6	84.0 (63.9 to 95.5)			
by cycle 9	88.0 (68.8 to 97.5)			
by cycle 12	92.0 (74.0 to 99.0)			
by cycle 18	92.0 (74.0 to 99.0)			
by cycle 24	92.0 (74.0 to 99.0)			
by cycle 36	92.0 (74.0 to 99.0)			

by cycle 48	92.0 (74.0 to 99.0)			
by cycle 66	92.0 (74.0 to 99.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of time to first Complete Hematological Response (CHR) among patients who achieved confirmed CHR in newly diagnosed CML-CP patients

End point title	Summary of time to first Complete Hematological Response (CHR) among patients who achieved confirmed CHR in newly diagnosed CML-CP patients ^[24]
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End point description:

Complete Hematological Response (CHR) was defined as

- WBC count <10×10⁹/L
- platelet count <450×10⁹/L
- basophils <5%
- no blasts and promyelocytes in peripheral blood
- myelocytes+metamyelocytes <5% in peripheral blood
- no evidence of extramedullary disease, including spleen and liver
- Assessment confirmation after at least 4 weeks for newly diagnosed Ph+ CML-CP

End point type	Secondary
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End point timeframe:

from first dosing to CHR, UP TO 66 CYCLES

Notes:

[24] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was planned for this endpoint

End point values	Newly diagnosed and untreated Ph+ CML in first CP			
Subject group type	Reporting group			
Number of subjects analysed	23			
Units: months				
median (confidence interval 95%)	0.95 (0.72 to 2.76)			

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan-Meier estimates of time to first Complete Hematological Response (CHR) in newly diagnosed CML-CP patients

End point title	Kaplan-Meier estimates of time to first Complete Hematological Response (CHR) in newly diagnosed CML-CP patients ^[25]
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End point description:

Complete Hematological Response (CHR) was defined as

- WBC count <10×10⁹/L

- platelet count <450×10⁹/L
- basophils <5%
- no blasts and promyelocytes in peripheral blood
- myelocytes+metamyelocytes <5% in peripheral blood
- no evidence of extramedullary disease, including spleen and liver
- Assessment confirmation after at least 4 weeks for newly diagnosed Ph+ CML-CP

End point type	Secondary
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End point timeframe:

from first dosing to CHR, UP TO 66 CYCLES

Notes:

[25] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was planned for this endpoint

End point values	Newly diagnosed and untreated Ph+ CML in first CP			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: months				
median (confidence interval 95%)	1.0 (1.0 to 2.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Disease Progression for Imatinib or Dasatinib Resistant or Intolerant CML-CP Patients - Kaplan-Meier estimates

End point title	Time to Disease Progression for Imatinib or Dasatinib Resistant or Intolerant CML-CP Patients - Kaplan-Meier estimates ^[26]
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End point description:

Time to disease progression is the time from the date of first study drug intake to the date of event defined as the first progression to AP or BC (from CP) or to BC (from AP) or the date of CML-related death occurring on treatment, whichever was earlier.

End point type	Secondary
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End point timeframe:

From first dosing to the disease progression within 66 cycles

Notes:

[26] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was planned for this endpoint

End point values	Resistant/intolerant Ph+ CML in CP			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: months				
median (confidence interval 95%)	999 (999 to 999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Event Free Survival in imatinib/dasatinib resistant/intolerant CML-CP patients

End point title	Event Free Survival in imatinib/dasatinib resistant/intolerant CML-CP patients ^[27]
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End point description:

Event Free Survival is defined as the time from the date of first study drug intake to the first occurrence of any of the following loss of CHR, loss of MCyR (PCyR + CCyR), progression to AP/BC (from CP) or to BC (from AP), or death from any cause. (Including events only during treatment)

End point type	Secondary
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End point timeframe:

From first dosing to the disease progression or death up to 66 cycles

Notes:

[27] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was planned for this endpoint

End point values	Resistant/intolerant Ph+ CML in CP			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: months				
median (confidence interval 95%)	999 (999 to 999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Event Free Survival in newly diagnosed CML-CP patients

End point title	Event Free Survival in newly diagnosed CML-CP patients ^[28]
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End point description:

Event Free Survival is defined as the time from the date of first study drug intake to the first occurrence of any of the following loss of CHR, loss of MCyR (PCyR + CCyR), progression to AP/BC (from CP) or to BC (from AP), or death from any cause. (Including events only during treatment)

End point type	Secondary
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End point timeframe:

From first dosing to the disease progression or death up to 66 cycles

Notes:

[28] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was planned for this endpoint

End point values	Newly diagnosed and untreated Ph+ CML in first CP			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: months				
median (confidence interval 95%)	999 (999 to 999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS) in Imatinib/dasatinib resistant/intolerant CML-CP - Kaplan-Meier estimates

End point title	Overall survival (OS) in Imatinib/dasatinib resistant/intolerant CML-CP - Kaplan-Meier estimates ^[29]
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End point description:

Overall survival is defined as the time from the date of first study drug intake to the date of death due to any cause. If a patient is not known to have died, survival will be censored at the date of their last assessment for patients on study and date of last contact for patients in follow-up.

End point type	Secondary
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End point timeframe:

from first dosing to death up to 66 cycles

Notes:

[29] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was planned for this endpoint

End point values	Resistant/intolerant Ph+ CML in CP			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: months				
median (confidence interval 95%)	999 (999 to 999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS) in newly diagnosed CML-CP patients

End point title	Overall survival (OS) in newly diagnosed CML-CP patients ^[30]
End point description:	
Overall survival is defined as the time from the date of first study drug intake to the date of death due to any cause. If a patient is not known to have died, survival will be censored at the date of their last assessment for patients on study and date of last contact for patients in follow-up.	
End point type	Secondary
End point timeframe:	
from first dosing to death up to 66 cycles	

Notes:

[30] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was planned for this endpoint

End point values	Newly diagnosed and untreated Ph+ CML in first CP			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: months				
median (confidence interval 95%)	999 (999 to 999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacodynamics (BCR-ABL transcript levels determined with standard protocols in peripheral blood): best MMR status by cycle

End point title	Pharmacodynamics (BCR-ABL transcript levels determined with standard protocols in peripheral blood): best MMR status by cycle
End point description:	
BCR-ABL is the fusion gene from breakpoint cluster region and Abelson genes. BCR-ABL transcript levels were summarized by cohort and time point.	
End point type	Secondary
End point timeframe:	
By 3, 6, 9, 12, 18, 24, 36, 48, 66 cycles	

End point values	Resistant/intolerant Ph+ CML in CP	Newly diagnosed and untreated Ph+ CML in first CP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	25		
Units: Percentage of participants				
number (confidence interval 95%)				
By Cycle 3	36.4 (20.4 to 54.9)	12.0 (2.5 to 31.2)		

By Cycle 6	45.5 (28.1 to 63.6)	52.0 (31.3 to 72.2)		
By Cycle 9	51.5 (33.5 to 69.2)	56.0 (34.9 to 75.6)		
By Cycle 12	57.6 (39.2 to 74.5)	64.0 (42.5 to 82.0)		
By Cycle 18	57.6 (39.2 to 74.5)	68.0 (46.5 to 85.1)		
By Cycle 24	57.6 (39.2 to 74.5)	68.0 (46.5 to 85.1)		
By Cycle 36	57.6 (39.2 to 74.5)	76.0 (54.9 to 90.6)		
By Cycle 48	60.6 (42.1 to 77.1)	76.0 (54.9 to 90.6)		
By Cycle 66	60.6 (42.1 to 77.1)	76.0 (54.9 to 90.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics (PK): Steady state concentration of nilotinib in Imatinib/dasatinib resistant/intolerant CML-CP patients

End point title	Pharmacokinetics (PK): Steady state concentration of nilotinib in Imatinib/dasatinib resistant/intolerant CML-CP patients ^[31]
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End point description:

PK was analyzed only when all patients has completed 12 cycles on treatment or discontinued the study treatment early.

End point type	Secondary
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End point timeframe:

Cycle 1 Day 8

Notes:

[31] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was planned for this endpoint

End point values	Resistant/intolerant Ph+ CML in CP			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: ng/mL				
geometric mean (geometric coefficient of variation)	1407.89 (± 41.67)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Steady state concentration of nilotinib in newly diagnosed CML-CP patients

End point title	Pharmacokinetics: Steady state concentration of nilotinib in newly diagnosed CML-CP patients ^[32]
End point description: PK was analyzed only when all patients has completed 12 cycles of treatment or discontinued the study treatment early.	
End point type	Secondary
End point timeframe: Cycle 1 Day 8	
Notes: [32] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: No statistical analysis was planned for this endpoint	

End point values	Newly diagnosed and untreated Ph+ CML in first CP			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: ng/mL				
geometric mean (geometric coefficient of variation)	1274.30 (\pm 46.21)			

Statistical analyses

No statistical analyses for this end point

Secondary: Growth Data: Abnormal height Standard deviation scores (SDS) changes by cohort

End point title	Growth Data: Abnormal height Standard deviation scores (SDS) changes by cohort
End point description: To assess long term effect on growth, development and maturation of nilotinib treatment in pediatric patients with Ph+ CML in participants with both a baseline and post-baseline value.	
End point type	Secondary
End point timeframe: from first dosing to 66 cycles	

End point values	Resistant/intolerant Ph+ CML in CP	Newly diagnosed and untreated Ph+ CML in first CP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	24		
Units: Percentage of participants				
number (not applicable)				
Decrease from baseline of 1 SDS category	27.3	32.0		
Decrease from baseline of 2 SDS categories	3.0	16.0		

Decrease from baseline of 3 SDS categories	6.1	4.0		
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Statistical analyses

No statistical analyses for this end point

Secondary: Acceptability (including palatability) of dose forms used after first dose, cycle 1 and cycle 12 study drug formulation

End point title	Acceptability (including palatability) of dose forms used after first dose, cycle 1 and cycle 12 study drug formulation
End point description: Acceptability of the study drug was evaluated from a questionnaire completed by patients, with the help from parents or caregivers at visits. The Questionnaire to capture patient assessment of palatability (very good to very bad) and acceptability of taking the medication (very easy to very hard to administration).	
End point type	Secondary
End point timeframe: up to Cycle 12	

End point values	All patients			
Subject group type	Subject analysis set			
Number of subjects analysed	58			
Units: Percentage of participants				
number (not applicable)				
Cycle(C)1 Day(D)1:Completed questionnaire-Patients	75.9			
C1D1:Completed questionnaire - Parents/Caregivers	22.4			
C1D1: Patients who swallowed capsule whole	91.4			
C1D1: Patients had capsule mixed with apple sauce	6.9			
C1D1:Pts reported no taste/unable to answer quest.	43.1			
C1D1:Patients reported taste as good/very good	12.1			
C1D1:Patients reported taste as not good/not bad	34.5			
C1D1:Reported capsule to be v. easy/easy to admin	79.3			
C1D28: Completed questionnaire - Patients	55.2			
C1D28:Completed questionnaire- Parents/Caregivers	22.4			
C12D28: Completed questionnaire - Patients	55.2			
C12D28:Completed questionnaire- Parents/Caregivers	22.4			

Statistical analyses

No statistical analyses for this end point

Secondary: Mutational assessment of BCR-ABL

End point title	Mutational assessment of BCR-ABL
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End point description:

Emerging signs of resistance to nilotinib

End point type	Secondary
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End point timeframe:

up to 66 cycles

End point values	Resistant/intolerant Ph+ CML in CP	Newly diagnosed and untreated Ph+ CML in first CP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	25		
Units: Percentage of participants				
number (not applicable)				
Pts. with ≥ 1 eval. post-BL mutational analysis	39.4	32.0		
Patients with any emergent mutation on treatment	0.0	0.0		
Pts with multiple emergent mutations on treatment	0.0	0.0		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Long term effect of nilotinib on bone metabolism

End point title	Long term effect of nilotinib on bone metabolism
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End point description:

The summary of bone age and Dual-energy X-ray absorptiometry (DEXA) by cohort. Alteration of bone biochemical markers of hand and wrist X-Ray evaluation was observed in bone age standard deviation scores (SDS) and for bone mineral density for DEXA before and after treatment with nilotinib.

End point type	Other pre-specified
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End point timeframe:

Cycle 66

End point values	Resistant/intolerant Ph+ CML in CP	Newly diagnosed and untreated Ph+ CML in first CP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	25		
Units: Percentage of participants				
arithmetic mean (standard deviation)				
X-ray	-0.61 (± 1.703)	999 (± 999)		
DEXA	-0.35 (± 1.243)	-0.70 (± 1.043)		

Statistical analyses

No statistical analyses for this end point

Post-hoc: All Collected Deaths

End point title	All Collected Deaths
End point description:	
On treatment deaths were collected from FPFT up to 30 days after study drug discontinuation, for a maximum duration of 64.5 months (treatment duration ranged from 0.7 to 63.5 months). Deaths post treatment survival follow up were collected after the on- treatment period, up to approx. 7 years.	
End point type	Post-hoc
End point timeframe:	
approx. 64.5 month, approx. 7 years	

End point values	Resistant/intolerant Ph+ CML in CP	Newly diagnosed and untreated Ph+ CML in first CP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	25		
Units: Participants				
On-treatment deaths	0	0		
Total Deaths	1	3		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

On treatment deaths were collected from FPFT up to 30 days after study drug discontinuation, for a maximum duration of 64.5 months. Deaths post treatment survival follow up were collected after the on- treatment period, up to approx. 7 years.

Adverse event reporting additional description:

Adverse Event: Any sign or symptom that occurs during the study treatment plus the 30 days post treatment.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	23.0
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Reporting groups

Reporting group title	Resistant/intolerant Ph+ CML in CP
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Reporting group description:

Patients resistant or intolerant to either imatinib or dasatinib

Reporting group title	Newly diagnosed and untreated Ph+ CML in first CP
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Reporting group description:

Patients newly diagnosed in Chronic phase. Diagnosis within 6 months of date of first cytogenetic analysis confirming Philadelphia chromosome with (9;22) translocation by standard conventional cytogenetic analysis

Reporting group title	All Patients
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Reporting group description:

All of the patients enrolled in the study.

Serious adverse events	Resistant/intolerant Ph+ CML in CP	Newly diagnosed and untreated Ph+ CML in first CP	All Patients
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 33 (33.33%)	4 / 25 (16.00%)	15 / 58 (25.86%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Vascular disorders			
Hyperaemia			
subjects affected / exposed	1 / 33 (3.03%)	0 / 25 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 33 (6.06%)	0 / 25 (0.00%)	2 / 58 (3.45%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Investigations			
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 33 (0.00%)	1 / 25 (4.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight decreased			
subjects affected / exposed	0 / 33 (0.00%)	1 / 25 (4.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Muscle strain			
subjects affected / exposed	1 / 33 (3.03%)	0 / 25 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Facial paralysis			
subjects affected / exposed	0 / 33 (0.00%)	1 / 25 (4.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 33 (0.00%)	1 / 25 (4.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 33 (0.00%)	1 / 25 (4.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Leukocytosis			
subjects affected / exposed	1 / 33 (3.03%)	0 / 25 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphadenitis			

subjects affected / exposed	1 / 33 (3.03%)	0 / 25 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 33 (0.00%)	1 / 25 (4.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 33 (0.00%)	1 / 25 (4.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoids thrombosed			
subjects affected / exposed	1 / 33 (3.03%)	0 / 25 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toothache			
subjects affected / exposed	1 / 33 (3.03%)	0 / 25 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatomegaly			
subjects affected / exposed	1 / 33 (3.03%)	0 / 25 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperbilirubinaemia			
subjects affected / exposed	0 / 33 (0.00%)	1 / 25 (4.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 33 (0.00%)	1 / 25 (4.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Endocrine disorders			
Growth hormone deficiency			
subjects affected / exposed	1 / 33 (3.03%)	0 / 25 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Bone swelling			
subjects affected / exposed	1 / 33 (3.03%)	0 / 25 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaw cyst			
subjects affected / exposed	1 / 33 (3.03%)	0 / 25 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 33 (3.03%)	0 / 25 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	1 / 33 (3.03%)	0 / 25 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	1 / 33 (3.03%)	0 / 25 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			
subjects affected / exposed	1 / 33 (3.03%)	1 / 25 (4.00%)	2 / 58 (3.45%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malaria			

subjects affected / exposed	1 / 33 (3.03%)	0 / 25 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillitis			
subjects affected / exposed	1 / 33 (3.03%)	0 / 25 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tooth infection			
subjects affected / exposed	1 / 33 (3.03%)	0 / 25 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	1 / 33 (3.03%)	1 / 25 (4.00%)	2 / 58 (3.45%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 33 (3.03%)	0 / 25 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Resistant/intolerant Ph+ CML in CP	Newly diagnosed and untreated Ph+ CML in first CP	All Patients
Total subjects affected by non-serious adverse events			
subjects affected / exposed	33 / 33 (100.00%)	25 / 25 (100.00%)	58 / 58 (100.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 33 (9.09%)	2 / 25 (8.00%)	5 / 58 (8.62%)
occurrences (all)	4	2	6
Hypotension			
subjects affected / exposed	3 / 33 (9.09%)	1 / 25 (4.00%)	4 / 58 (6.90%)
occurrences (all)	5	1	6
General disorders and administration site conditions			

Asthenia			
subjects affected / exposed	1 / 33 (3.03%)	2 / 25 (8.00%)	3 / 58 (5.17%)
occurrences (all)	2	3	5
Fatigue			
subjects affected / exposed	0 / 33 (0.00%)	6 / 25 (24.00%)	6 / 58 (10.34%)
occurrences (all)	0	11	11
Malaise			
subjects affected / exposed	2 / 33 (6.06%)	1 / 25 (4.00%)	3 / 58 (5.17%)
occurrences (all)	2	2	4
Non-cardiac chest pain			
subjects affected / exposed	1 / 33 (3.03%)	3 / 25 (12.00%)	4 / 58 (6.90%)
occurrences (all)	1	4	5
Pyrexia			
subjects affected / exposed	11 / 33 (33.33%)	9 / 25 (36.00%)	20 / 58 (34.48%)
occurrences (all)	18	13	31
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	2 / 33 (6.06%)	1 / 25 (4.00%)	3 / 58 (5.17%)
occurrences (all)	3	1	4
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	1 / 33 (3.03%)	3 / 25 (12.00%)	4 / 58 (6.90%)
occurrences (all)	2	3	5
Gynaecomastia			
subjects affected / exposed	2 / 33 (6.06%)	2 / 25 (8.00%)	4 / 58 (6.90%)
occurrences (all)	2	2	4
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 33 (9.09%)	7 / 25 (28.00%)	10 / 58 (17.24%)
occurrences (all)	5	10	15
Dyspnoea			
subjects affected / exposed	1 / 33 (3.03%)	3 / 25 (12.00%)	4 / 58 (6.90%)
occurrences (all)	1	3	4
Nasal congestion			
subjects affected / exposed	3 / 33 (9.09%)	1 / 25 (4.00%)	4 / 58 (6.90%)
occurrences (all)	7	2	9

Oropharyngeal pain subjects affected / exposed occurrences (all)	7 / 33 (21.21%) 8	2 / 25 (8.00%) 3	9 / 58 (15.52%) 11
Rhinitis allergic subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	2 / 25 (8.00%) 3	2 / 58 (3.45%) 3
Rhinorrhoea subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2	3 / 25 (12.00%) 4	5 / 58 (8.62%) 6
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1	2 / 25 (8.00%) 2	3 / 58 (5.17%) 3
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all)	10 / 33 (30.30%) 18	11 / 25 (44.00%) 22	21 / 58 (36.21%) 40
Amylase increased subjects affected / exposed occurrences (all)	3 / 33 (9.09%) 5	0 / 25 (0.00%) 0	3 / 58 (5.17%) 5
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	8 / 33 (24.24%) 11	9 / 25 (36.00%) 20	17 / 58 (29.31%) 31
Blood bilirubin increased subjects affected / exposed occurrences (all)	12 / 33 (36.36%) 24	10 / 25 (40.00%) 17	22 / 58 (37.93%) 41
Blood cholesterol increased subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2	2 / 25 (8.00%) 3	4 / 58 (6.90%) 5
Blood creatine phosphokinase increased subjects affected / exposed occurrences (all)	3 / 33 (9.09%) 5	0 / 25 (0.00%) 0	3 / 58 (5.17%) 5
Blood creatinine increased subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	2 / 25 (8.00%) 2	2 / 58 (3.45%) 2
Blood glucose increased			

subjects affected / exposed	2 / 33 (6.06%)	1 / 25 (4.00%)	3 / 58 (5.17%)
occurrences (all)	2	2	4
Blood triglycerides increased			
subjects affected / exposed	0 / 33 (0.00%)	2 / 25 (8.00%)	2 / 58 (3.45%)
occurrences (all)	0	2	2
Electrocardiogram QT prolonged			
subjects affected / exposed	5 / 33 (15.15%)	1 / 25 (4.00%)	6 / 58 (10.34%)
occurrences (all)	6	1	7
Gamma-glutamyltransferase increased			
subjects affected / exposed	4 / 33 (12.12%)	1 / 25 (4.00%)	5 / 58 (8.62%)
occurrences (all)	5	2	7
Lipase increased			
subjects affected / exposed	3 / 33 (9.09%)	1 / 25 (4.00%)	4 / 58 (6.90%)
occurrences (all)	6	1	7
Neutrophil count decreased			
subjects affected / exposed	2 / 33 (6.06%)	3 / 25 (12.00%)	5 / 58 (8.62%)
occurrences (all)	2	4	6
Platelet count decreased			
subjects affected / exposed	0 / 33 (0.00%)	5 / 25 (20.00%)	5 / 58 (8.62%)
occurrences (all)	0	10	10
Weight decreased			
subjects affected / exposed	2 / 33 (6.06%)	3 / 25 (12.00%)	5 / 58 (8.62%)
occurrences (all)	2	3	5
Weight increased			
subjects affected / exposed	1 / 33 (3.03%)	3 / 25 (12.00%)	4 / 58 (6.90%)
occurrences (all)	1	3	4
Injury, poisoning and procedural complications			
Arthropod sting			
subjects affected / exposed	2 / 33 (6.06%)	0 / 25 (0.00%)	2 / 58 (3.45%)
occurrences (all)	2	0	2
Fall			
subjects affected / exposed	2 / 33 (6.06%)	0 / 25 (0.00%)	2 / 58 (3.45%)
occurrences (all)	3	0	3
Joint injury			

subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2	0 / 25 (0.00%) 0	2 / 58 (3.45%) 2
Ligament sprain subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	2 / 25 (8.00%) 2	2 / 58 (3.45%) 2
Procedural pain subjects affected / exposed occurrences (all)	3 / 33 (9.09%) 3	1 / 25 (4.00%) 1	4 / 58 (6.90%) 4
Congenital, familial and genetic disorders Gilbert's syndrome subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1	2 / 25 (8.00%) 2	3 / 58 (5.17%) 3
Cardiac disorders Palpitations subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	2 / 25 (8.00%) 2	2 / 58 (3.45%) 2
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1	3 / 25 (12.00%) 4	4 / 58 (6.90%) 5
Headache subjects affected / exposed occurrences (all)	13 / 33 (39.39%) 20	14 / 25 (56.00%) 57	27 / 58 (46.55%) 77
Hypoaesthesia subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2	0 / 25 (0.00%) 0	2 / 58 (3.45%) 2
Paraesthesia subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 4	2 / 25 (8.00%) 3	4 / 58 (6.90%) 7
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	4 / 33 (12.12%) 5	3 / 25 (12.00%) 4	7 / 58 (12.07%) 9
Leukopenia subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	2 / 25 (8.00%) 2	2 / 58 (3.45%) 2

Neutropenia subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1	2 / 25 (8.00%) 9	3 / 58 (5.17%) 10
Thrombocytopenia subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1	3 / 25 (12.00%) 6	4 / 58 (6.90%) 7
Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1	2 / 25 (8.00%) 2	3 / 58 (5.17%) 3
Eye disorders Conjunctival haemorrhage subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	2 / 25 (8.00%) 2	2 / 58 (3.45%) 2
Ocular hyperaemia subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1	3 / 25 (12.00%) 4	4 / 58 (6.90%) 5
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)	3 / 33 (9.09%) 3	6 / 25 (24.00%) 7	9 / 58 (15.52%) 10
Abdominal pain upper subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1	3 / 25 (12.00%) 4	4 / 58 (6.90%) 5
Constipation subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1	2 / 25 (8.00%) 4	3 / 58 (5.17%) 5
Dental caries subjects affected / exposed occurrences (all)	3 / 33 (9.09%) 4	0 / 25 (0.00%) 0	3 / 58 (5.17%) 4
Diarrhoea subjects affected / exposed occurrences (all)	7 / 33 (21.21%) 7	4 / 25 (16.00%) 4	11 / 58 (18.97%) 11
Gastrooesophageal reflux disease subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	2 / 25 (8.00%) 3	2 / 58 (3.45%) 3
Nausea			

subjects affected / exposed occurrences (all)	8 / 33 (24.24%) 8	10 / 25 (40.00%) 13	18 / 58 (31.03%) 21
Odynophagia subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	2 / 25 (8.00%) 2	2 / 58 (3.45%) 2
Vomiting subjects affected / exposed occurrences (all)	7 / 33 (21.21%) 8	8 / 25 (32.00%) 12	15 / 58 (25.86%) 20
Hepatobiliary disorders Hyperbilirubinaemia subjects affected / exposed occurrences (all)	4 / 33 (12.12%) 14	8 / 25 (32.00%) 26	12 / 58 (20.69%) 40
Skin and subcutaneous tissue disorders Acne subjects affected / exposed occurrences (all)	4 / 33 (12.12%) 5	4 / 25 (16.00%) 4	8 / 58 (13.79%) 9
Alopecia subjects affected / exposed occurrences (all)	4 / 33 (12.12%) 4	2 / 25 (8.00%) 3	6 / 58 (10.34%) 7
Dermatitis subjects affected / exposed occurrences (all)	4 / 33 (12.12%) 4	2 / 25 (8.00%) 4	6 / 58 (10.34%) 8
Dry skin subjects affected / exposed occurrences (all)	3 / 33 (9.09%) 3	0 / 25 (0.00%) 0	3 / 58 (5.17%) 3
Erythema subjects affected / exposed occurrences (all)	4 / 33 (12.12%) 4	4 / 25 (16.00%) 5	8 / 58 (13.79%) 9
Keratosis pilaris subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2	0 / 25 (0.00%) 0	2 / 58 (3.45%) 2
Madarosis subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2	0 / 25 (0.00%) 0	2 / 58 (3.45%) 2
Pruritus			

subjects affected / exposed	0 / 33 (0.00%)	3 / 25 (12.00%)	3 / 58 (5.17%)
occurrences (all)	0	10	10
Rash			
subjects affected / exposed	7 / 33 (21.21%)	11 / 25 (44.00%)	18 / 58 (31.03%)
occurrences (all)	12	16	28
Rash maculo-papular			
subjects affected / exposed	5 / 33 (15.15%)	3 / 25 (12.00%)	8 / 58 (13.79%)
occurrences (all)	16	5	21
Rash papular			
subjects affected / exposed	2 / 33 (6.06%)	1 / 25 (4.00%)	3 / 58 (5.17%)
occurrences (all)	8	1	9
Urticaria			
subjects affected / exposed	3 / 33 (9.09%)	1 / 25 (4.00%)	4 / 58 (6.90%)
occurrences (all)	3	2	5
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 33 (15.15%)	4 / 25 (16.00%)	9 / 58 (15.52%)
occurrences (all)	7	5	12
Back pain			
subjects affected / exposed	3 / 33 (9.09%)	2 / 25 (8.00%)	5 / 58 (8.62%)
occurrences (all)	3	2	5
Bone pain			
subjects affected / exposed	1 / 33 (3.03%)	2 / 25 (8.00%)	3 / 58 (5.17%)
occurrences (all)	2	2	4
Muscular weakness			
subjects affected / exposed	1 / 33 (3.03%)	2 / 25 (8.00%)	3 / 58 (5.17%)
occurrences (all)	1	2	3
Musculoskeletal pain			
subjects affected / exposed	2 / 33 (6.06%)	1 / 25 (4.00%)	3 / 58 (5.17%)
occurrences (all)	2	2	4
Myalgia			
subjects affected / exposed	3 / 33 (9.09%)	4 / 25 (16.00%)	7 / 58 (12.07%)
occurrences (all)	4	12	16
Pain in extremity			

subjects affected / exposed occurrences (all)	9 / 33 (27.27%) 9	7 / 25 (28.00%) 9	16 / 58 (27.59%) 18
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	3 / 33 (9.09%)	0 / 25 (0.00%)	3 / 58 (5.17%)
occurrences (all)	3	0	3
Cystitis			
subjects affected / exposed	2 / 33 (6.06%)	0 / 25 (0.00%)	2 / 58 (3.45%)
occurrences (all)	2	0	2
Ear infection			
subjects affected / exposed	0 / 33 (0.00%)	2 / 25 (8.00%)	2 / 58 (3.45%)
occurrences (all)	0	2	2
Gastroenteritis			
subjects affected / exposed	0 / 33 (0.00%)	6 / 25 (24.00%)	6 / 58 (10.34%)
occurrences (all)	0	11	11
Influenza			
subjects affected / exposed	4 / 33 (12.12%)	2 / 25 (8.00%)	6 / 58 (10.34%)
occurrences (all)	7	2	9
Nasopharyngitis			
subjects affected / exposed	5 / 33 (15.15%)	7 / 25 (28.00%)	12 / 58 (20.69%)
occurrences (all)	15	15	30
Otitis media acute			
subjects affected / exposed	0 / 33 (0.00%)	2 / 25 (8.00%)	2 / 58 (3.45%)
occurrences (all)	0	2	2
Parotitis			
subjects affected / exposed	2 / 33 (6.06%)	1 / 25 (4.00%)	3 / 58 (5.17%)
occurrences (all)	2	1	3
Pharyngitis			
subjects affected / exposed	3 / 33 (9.09%)	3 / 25 (12.00%)	6 / 58 (10.34%)
occurrences (all)	4	4	8
Rhinitis			
subjects affected / exposed	4 / 33 (12.12%)	4 / 25 (16.00%)	8 / 58 (13.79%)
occurrences (all)	9	4	13
Upper respiratory tract infection			
subjects affected / exposed	10 / 33 (30.30%)	7 / 25 (28.00%)	17 / 58 (29.31%)
occurrences (all)	18	9	27

Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	5 / 33 (15.15%)	1 / 25 (4.00%)	6 / 58 (10.34%)
occurrences (all)	5	1	6
Hyperuricaemia			
subjects affected / exposed	0 / 33 (0.00%)	2 / 25 (8.00%)	2 / 58 (3.45%)
occurrences (all)	0	2	2
Vitamin D deficiency			
subjects affected / exposed	2 / 33 (6.06%)	1 / 25 (4.00%)	3 / 58 (5.17%)
occurrences (all)	2	1	3

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 September 2014	<p>To fulfill the EMA PDCO agreement for the assessment of potential long-term safety & efficacy issues in relation to pediatric nilotinib use, the study duration was extended from 24 to 66 Cycles.</p> <p>To revise the primary efficacy endpoint as recommended by the FDA. For Cohort 1, "Rate of major cytogenetic response (MCyR) by 12 months" was revised to "Rate of MCyR at 6 Cycles" & for Cohort 3, "Rate of MCyR by 12 months" was revised to "Rate of complete cytogenetic response (CCyR) at 12 cycles".</p> <p>To add event free survival as a new secondary endpoint, 2 sensitivity analyses for disease progression, collection of additional bio specimens from patients participating on the clinical study for future research studies (Children's Oncology Group's sites only), pre- & post-dose ECG measurements throughout the study in order to provide additional safety information in regards to nilotinib's effect on QT prolongation.</p> <p>To describe in more detail the censoring method for K-M analyses of duration of response, time to progression, overall survival & event free survival.</p> <p>To clarify cholesterol testing during the conduct of the study, assessment of blood glucose at baseline & during the conduct of this study, patient inclusion/exclusion criteria, study treatment dosing & pregnancy testing; to incorporate feedback received from Investigators during study start-up; to harmonize dose reductions guidelines of nilotinib across Novartis-sponsored Tassigna study protocols & to update dose reduction guidelines for cardiac QT, ischemic vascular or cardiovascular events.</p> <p>To incorporate precautions on the use for antacid drugs in alignment with the Tassigna Prescribing Information & EU SmPC & to incorporate guidance for the management of increases of serum cholesterol & blood glucose, as well as other cardiac risk factors, ischemic vascular or ischemic cardiovascular events and also to further define ischemic vascular and ischemic cardiovascular events as AESI, including their reporting modalities.</p>
04 May 2015	<p>The main purpose of this amendment was to adjust the minimum total sample size, as well as the minimum sample size of the newly diagnosed Ph+ CML-CP (Cohort 3), to reflect the agreements with the US FDA and the EMA PDCO and the updated feasibility assessment in view of the very low incidence of Ph+ CML in the pediatric population and the actual study accrual rates, and to enable timely availability of information in this population.</p> <p>The original study enrollment target was planned for a minimum of 65 total patients of which at least 50 would be Ph+CML newly diagnosed. Based on enrollment forecasts at the time of amendment and regulatory requirements, a reduction in the sample size to at least 50 patients in total with at least 15 newly diagnosed Ph+ CML-CP patients would support a timely completion of the study and timely access of the available information to the medical community.</p> <p>Additional changes in this amendment included confirmation of the dose in the patients aged 1 to <10 for this study as a result of the second interim analysis of study CAMN107A2120 and administrative changes.</p>
08 February 2016	<p>The primary endpoint for Cohort 1 was revised to enable an assessment of the impact of therapy in patients with Ph+ CML-CP resistant or intolerant to either imatinib or dasatinib. The rationale for this change was that as part of routine study monitoring, it was observed that a significant number of patients enrolling in this Cohort were already in MCyR or CCyR at baseline. This finding was also consistent with findings from a recently published study (Zwaan et al 2013). The protocol was additionally amended, to remove the binary endpoints related to CHR, MCyR and CCyR which were no longer appropriate measures to evaluate the therapeutic effect of nilotinib in this patient population. The determination of BCR-ABL molecular response was also clarified.</p>

18 April 2016	The primary purpose for the amendment was to include hepatitis B virus testing as one of the study procedures and to identify study patients who might be at risk of hepatitis B virus reactivation.
05 May 2017	<p>The primary purposes for this amendment were to define the discontinuation of development and growth assessments (X-ray of hand and wrist) in the study once skeletal maturity of a patient in post-puberty stage was confirmed by last x-ray and to include HbA1c in the clinical chemistry assessment.</p> <p>The guidance on co-administration of drugs with a "known", "possible" or "conditional" risk of Torsades de Pointes was updated, and additional discontinuation criteria were added based on the update in Novartis Safety guidance.</p> <p>The definitions for loss of CHR, loss of MMR and disease progression, as well as description of methods for growth and development analyses were clarified. In addition, description of analysis for exploratory objectives were clarified to be based on standard deviation scores (SDS).</p>

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 999 as data points in this record are not an accurate representation of the clinical trial results. Please use <https://www.novctrd.com/CtrdWeb/home.nov> for complete trial results.

Notes: