Clinical trial results:
A multi-center, open-label, pharmacokinetic study of oral nilotinib in pediatric patientswith newly diagnosed chronic phase (CP) Ph+ CML, with CP or accelerated phase (AP) Ph+ CMLresistant/intolerant to imatinib and/or dasatinib, or with refractory/relapsed Ph+ ALL

Summary

EudraCT number	2010-018419-14
Trial protocol	FR GB DE NL IT
Global end of trial date	01 July 2015

Results information

Result version number	v1 (current)
This version publication date	31 March 2016
First version publication date	31 March 2016

Trial information

Trial identification

Sponsor protocol code	CAMN107A2120

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01077544
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,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-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	01 July 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	01 July 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to characterize the PK of nilotinib in pediatric patients with newly diagnosed CP-Ph+ CML, or CP or AP-Ph+ CML resistant/intolerant to imatinib and/or dasatinib, or refractory/relapsed Ph+ ALL to standard therapy.

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	14 April 2011
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: 4
Country: Number of subjects enrolled	Italy: 4
Country: Number of subjects enrolled	Netherlands: 4
Country: Number of subjects enrolled	United Kingdom: 3
Worldwide total number of subjects	15
EEA total number of subjects	15

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)	10
Adolescents (12-17 years)	5

Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Patients were enrolled into 2 strata of two age groups: Group 1: at least 7 patients ages 1 year to < 10 years, and Group 2: at least 7 patients ages ≥ 10 years to < 18 years.

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	Group 1

Arm description:

1 year to < 10 years pediatric patients with newly diagnosed CP-Ph+ CML, or CP or AP-Ph+ CML resistant/intolerant to imatinib and/or dasatinib, or relapsed/refractory Ph+ ALL (acute lymphoblastic leukemia) treated at the proposed dose of 230 mg/m2 bid.

Arm type	Experimental
Investigational medicinal product name	Nilotinib
Investigational medicinal product code	AMN107
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Nilotinib capsules were delivered in bottles with dose strengths of 50mg, 150mg and 200mg. Patients were administered nilotinib 230 mg/m2 (per BSA) bid, orally, rounded to the nearest 50 mg (max single dose 400 mg) for 28 days (1 cycle) for up to 12 cycles prior to protocol amendment 3 and up to 24 cycles post amendment 3. Capsules were to be swallowed whole with water. Apple sauce (puréed apple) may have been used as a vehicle for dosing where capsules were not able to be swallowed whole with water.

Arm title	Group 2

Arm description:

>= 10 years to <18 years pediatric patients with newly diagnosed CP-Ph+ CML, or CP or AP-Ph+ CML resistant/intolerant to imatinib and/or dasatinib, or relapsed/refractory Ph+ ALL (acute lymphoblastic leukemia) treated at the proposed dose of 230 mg/m2 bid.

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Dosage and administration details:

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Number of subjects in period 1	Group 1	Group 2
Started	8	7
Completed	5	2
Not completed	3	5
Adverse event, non-fatal	-	1
New Cancer Therapy	3	3
Disease Progression	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Group 1
Reporting group description:	
1 year to < 10 years pediatric patients with newly diagnosed CP-Ph+ CML, or CP or AP-Ph+ CML resistant/intolerant to imatinib and/or dasatinib, or relapsed/refractory Ph+ ALL (acute lymphoblastic leukemia) treated at the proposed dose of 230 mg/m2 bid.	
Reporting group title	Group 2
Reporting group description:	
>= 10 years to <18 years pediatric patients with newly diagnosed CP-Ph+ CML, or CP or AP-Ph+ CML resistant/intolerant to imatinib and/or dasatinib, or relapsed/refractory Ph+ ALL (acute lymphoblastic leukemia) treated at the proposed dose of 230 mg/m2 bid.	

Reporting group values	Group 1	Group 2	Total
Number of subjects	8	7	15
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	8	0	8
Adolescents (12-17 years)	0	7	7
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous | Units: Years			
arithmetic mean	6.8	13.7	
standard deviation	± 1.16	± 2.81	-
Gender, Male/Female Units: Participants			
Female	3	4	7
Male	5	3	8

End points

End points reporting groups

Reporting group title	Group 1

Reporting group description:

1 year to < 10 years pediatric patients with newly diagnosed CP-Ph+ CML, or CP or AP-Ph+ CML resistant/intolerant to imatinib and/or dasatinib, or relapsed/refractory Ph+ ALL (acute lymphoblastic leukemia) treated at the proposed dose of 230 mg/m2 bid.

Reporting group title	Group 2

Reporting group description:

>= 10 years to <18 years pediatric patients with newly diagnosed CP-Ph+ CML, or CP or AP-Ph+ CML resistant/intolerant to imatinib and/or dasatinib, or relapsed/refractory Ph+ ALL (acute lymphoblastic leukemia) treated at the proposed dose of 230 mg/m2 bid.

Primary: Summary of nilotinib non-compartmental PK parameters: Cmax

End point title	Summary of nilotinib non-compartmental PK parameters: Cmax[1]

End point description:

The full PK profiles of nilotinib in pediatric patients were assessed using serial sampling following a single 230 mg/m2 dose on Cycle 1 Day 1.

End point type	Primary

End point timeframe:

Cycle 1 Day 1

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 performed for PK Analysis.

End point values	Group 1	Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	7		
Units: ng/mL				
geometric mean (geometric coefficient of variation)	405.111 (± 42.5)	402.715 (± 35.2)		

Statistical analyses

No statistical analyses for this end point

Primary: Summary of nilotinib non-compartmental PK parameters: Tmax

End point title	Summary of nilotinib non-compartmental PK parameters:

End point description:

The full PK profiles of nilotinib in pediatric patients were assessed using serial sampling following a single 230 mg/m2 dose on Cycle 1 Day 1.

End point type	Primary

End point timeframe:

Cycle 1 Day 1

Notes:

[2] - 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 performed for PK Analysis.

End point values	Group 1	Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	7		
Units: hr				
median (full range (min-max))	2 (1.02 to 7.08)	3 (2 to 7.88)		

Statistical analyses

No statistical analyses for this end point

Primary: Summary of nilotinib non-compartmental PK parameters: AUClast (last = 24h)

End point title	Summary of nilotinib non-compartmental PK parameters: AUClast (last = 24h)[3]

End point description:

The full PK profiles of nilotinib in pediatric patients were assessed using serial sampling following a single 230 mg/m2 dose on Cycle 1 Day 1.

End point type	Primary

End point timeframe:

Cycle 1 Day 1

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 performed for PK Analysis.

End point values	Group 1	Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	7		
Units: ng*h/mL				
geometric mean (geometric coefficient of variation)	4160.969 (± 38.5)	5707.368 (± 51.2)		

Statistical analyses

No statistical analyses for this end point

Primary: Summary of nilotinib non-compartmental PK parameters: AUC0-12h

End point title	Summary of nilotinib non-compartmental PK parameters: AUC0-12h[4]

End point description:

The full PK profiles of nilotinib in pediatric patients were assessed using serial sampling following a single 230 mg/m2 dose on Cycle 1 Day 1.

End point type	Primary

End point timeframe:

Cycle 1 Day 1

Notes:

[4] - 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 performed for PK Analysis.

End point values	Group 1	Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	7		
Units: ng*h/mL				
geometric mean (geometric coefficient of variation)	2795.782 (± 35.7)	3393.296 (± 30.4)		

Statistical analyses

No statistical analyses for this end point

Primary: Summary of nilotinib steady-state PK parameters: AUCss

End point title	Summary of nilotinib steady-state PK parameters: AUCss[5]

End point description:

The steady-state PK profiles of nilotinib in pediatric patients were estimated using trough sampling following multiple 230 mg/m2 bid doses

End point type	Primary

End point timeframe:

Cycle 1 Day 8 - Cycle 1 Day 28

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 performed for PK Analysis.

End point values	Group 1	Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	7		
Units: ng*h/mL				
geometric mean (geometric coefficient of variation)	15129.182 (± 38)	14383.076 (± 33.6)		

Statistical analyses

No statistical analyses for this end point

Primary: Summary of nilotinib steady-state PK parameters: CLF (body surface area (BSA) adjusted)

End point title	Summary of nilotinib steady-state PK parameters: CLF (body surface area (BSA) adjusted)[6]

End point description:

The steady-state PK profiles of nilotinib in pediatric patients were estimated using trough sampling

following multiple 230 mg/m2 bid doses

End point type	Primary

End point timeframe:

Cycle 1 Day 8 - Cycle 1 day 28

Notes:

[6] - 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 performed for PK Analysis.

End point values	Group 1	Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	7		
Units: L/h/m^2)				
geometric mean (geometric coefficient of variation)	15.356 (± 38.7)	15.922 (± 37)		

Statistical analyses

No statistical analyses for this end point

Primary: Summary of nilotinib steady-state PK parameters: Cmin

End point title	Summary of nilotinib steady-state PK parameters: Cmin[7]

End point description:

The full PK profiles of nilotinib in pediatric patients were assessed using serial sampling following a single 230 mg/m2 dose.

End point type	Primary

End point timeframe:

Cycle 1 Day 8 - Cycle 1 Day 28

Notes:

[7] - 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 performed for PK Analysis.

End point values	Group 1	Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	7		
Units: ng/mL				
geometric mean (geometric coefficient of variation)	804.791 (± 33.7)	1072.85 (± 20.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Ph+ CML participants with confirmed complete hematologic response (CHR)

End point title	Number of Ph+ CML participants with confirmed complete hematologic response (CHR)

End point description:

A confirmed complete hematological response (CHR) is defined when all of the following criteria are achieved at two consecutive assessments, at least 4 weeks apart: white blood cell (WBC) count < 10 × 109/L; platelet < 450 × 109/L; basophils < 5%; no blasts and promyelocytes in peripheral blood (PB); myelocytes + metamyelocytes < 5% in PB; and no extramedullary involvement. The information used for hematological assessment was to be obtained from the laboratory and extramedullary data, all merged by patient and date.

End point type	Secondary

End point timeframe:

minimum of 12 cycles (28 days per cycle)

End point values	Group 1	Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	6		
Units: Participants				
Yes	5	5		
No	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Ph+ CML participants with cytogenic response

End point title	Number of Ph+ CML participants with cytogenic response

End point description:

Cytogenetic response was initially assessed as the percentage of Ph+ metaphases in the bone marrow (BM) and performed within 21 days prior to study entry. A major cytogenetic response (0% to 35% Ph+ metaphases test positive for the Philadelphia chromosome) combines both complete cytogenetic (CCyR) and partial cytogenetic response (PCyR). CCyR implies 0% Ph+ metaphases in the BM, PCyR is > 0% to 35%, minor cytogenetic response (mCyR) is > 35% to 65%, minimal response is > 65% to 95% and no response is > 95% Ph+ metaphases in the BM.

End point type	Secondary

End point timeframe:

minimum of 12 cycles (28 days per cycle)

End point values	Group 1	Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	6		
Units: Participants				
Complete cytogenic response (CCyR)	2	2		
Partial cytogenic response (PCyR)	0	1		
Minor cytogenic response (mCyR)	0	1		
Minimal	0	0		
None	0	0		
Absence of Ph+ at baseline	3	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Ph+ CML participants with major molecular response (MMR)

End point title	Number of Ph+ CML participants with major molecular response (MMR)

End point description:

The bcr-abl gene fusion encodes for a BCR-ABL fusion protein. Depending on the precise location of the fusion, the molecular weight of this protein can range from 185 to 210 kDa. Consequently BCR-ABL is referred to as p185 or p210 transcript. For the patients expressing the major BCR-ABL transcript p210, molecular response was defined and reported as the percent ratio of BCR-ABL transcripts/control gene transcripts converted to a reference standard according to the International Scale (IS). A major molecular response (MMR) is defined as a BCR-ABL/control gene ratio ≤ 0.1% (equal to a 3 log reduction in BCR-ABL transcripts) on the IS. In this study, the control gene was abl.

End point type	Secondary

End point timeframe:

minimum of 12 cycles (28 days per cycle)

End point values	Group 1	Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	6		
Units: Participants				
Yes	1	2		
No	4	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Efficacy endpoints for Ph+ ALL patients

End point title	Efficacy endpoints for Ph+ ALL patients

End point description:

Best Response in Ph+ ALL patients was defined as either Complete Remission (CR) with platelet recovery, Complete Remission (CR) with incomplete platelet recovery, Partial Remission (PR) or Stable disease. Stable disease was defined is defined as failure to qualify for either CR, PR, or progressive disease.

End point type	Secondary

End point timeframe:

minimum of 12 cycles (28 days per cycle)

End point values	Group 1	Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	1		
Units: Participants				
Complete Remission with platelet recovery	2	1		
Complete Remission w/incomplete platelet recovery	0	0		
Partial remission	0	0		
Stable disease	1	0		
Progressive disease	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All adverse events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Age 1 to less than 10 years
Reporting group description:	
Age 1 to less than 10 years	
Reporting group title	Age 10 to less than 18 years
Reporting group description:	
Age 10 to less than 18 years	

Serious adverse events	Age 1 to less than 10 years	Age 10 to less than 18 years	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 8 (25.00%)	3 / 7 (42.86%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	0 / 8 (0.00%)	2 / 7 (28.57%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Influenza like illness			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Appendix disorder			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Age 1 to less than 10 years	Age 10 to less than 18 years	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 8 (100.00%)	7 / 7 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	2 / 8 (25.00%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Catheter site pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Fatigue			
subjects affected / exposed	2 / 8 (25.00%)	0 / 7 (0.00%)	
occurrences (all)	4	0	
Malaise			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Mucosal inflammation			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	

Pyrexia			
subjects affected / exposed	1 / 8 (12.50%)	1 / 7 (14.29%)	
occurrences (all)	3	1	
Xerosis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			
Vulvovaginal pruritus			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 8 (25.00%)	2 / 7 (28.57%)	
occurrences (all)	7	2	
Oropharyngeal pain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Pharyngeal erythema			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Productive cough			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	3	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 8 (37.50%)	1 / 7 (14.29%)	
occurrences (all)	4	1	
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 8 (37.50%)	0 / 7 (0.00%)	
occurrences (all)	6	0	
Bilirubin conjugated increased			
subjects affected / exposed	1 / 8 (12.50%)	1 / 7 (14.29%)	
occurrences (all)	1	1	
Blood bilirubin increased			

subjects affected / exposed	2 / 8 (25.00%)	3 / 7 (42.86%)		
occurrences (all)	7	4		
Blood bilirubin unconjugated increased				
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)		
occurrences (all)	0	1		
Blood creatinine increased				
subjects affected / exposed	0 / 8 (0.00%)	2 / 7 (28.57%)		
occurrences (all)	0	3		
Blood phosphorus decreased				
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)		
occurrences (all)	1	0		
Blood sodium decreased				
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)		
occurrences (all)	1	0		
Blood urea increased				
subjects affected / exposed	0 / 8 (0.00%)	2 / 7 (28.57%)		
occurrences (all)	0	3		
Blood uric acid increased				
subjects affected / exposed	0 / 8 (0.00%)	2 / 7 (28.57%)		
occurrences (all)	0	2		
Electrocardiogram QT prolonged				
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)		
occurrences (all)	1	0		
Haematocrit decreased				
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)		
occurrences (all)	0	1		
Haemoglobin decreased				
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)		
occurrences (all)	0	1		
Neutrophil count increased				
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)		
occurrences (all)	0	1		
Platelet count decreased				
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)		
occurrences (all)	0	1		

Red blood cell count decreased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Weight decreased			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
White blood cell count decreased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
White blood cell count increased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 8 (50.00%)	2 / 7 (28.57%)	
occurrences (all)	12	5	
Paraesthesia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Presyncope			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Syncope			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Haemolytic anaemia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Leukopenia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	3	
Lymphopenia			

subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	2	
Neutropenia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	2	
Thrombocytopenia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	2	
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 8 (0.00%)	2 / 7 (28.57%)	
occurrences (all)	0	2	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 8 (12.50%)	2 / 7 (28.57%)	
occurrences (all)	1	2	
Abdominal pain upper			
subjects affected / exposed	1 / 8 (12.50%)	1 / 7 (14.29%)	
occurrences (all)	1	1	
Constipation			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Diarrhoea			
subjects affected / exposed	1 / 8 (12.50%)	3 / 7 (42.86%)	
occurrences (all)	2	7	
Nausea			
subjects affected / exposed	0 / 8 (0.00%)	3 / 7 (42.86%)	
occurrences (all)	0	3	
Odynophagia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
Toothache			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Vomiting			

subjects affected / exposed	3 / 8 (37.50%)	3 / 7 (42.86%)	
occurrences (all)	7	4	
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	2 / 8 (25.00%)	2 / 7 (28.57%)	
occurrences (all)	2	2	
Skin and subcutaneous tissue disorders			
Dermatitis atopic			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
Dry skin			
subjects affected / exposed	0 / 8 (0.00%)	2 / 7 (28.57%)	
occurrences (all)	0	2	
Dyshidrotic eczema			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Eczema			
subjects affected / exposed	2 / 8 (25.00%)	1 / 7 (14.29%)	
occurrences (all)	3	1	
Exfoliative rash			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Psoriasis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Rash			
subjects affected / exposed	3 / 8 (37.50%)	2 / 7 (28.57%)	
occurrences (all)	6	2	
Rash erythematous			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Rash maculo-papular			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Rash papular			

subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Skin lesion			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 8 (0.00%)	3 / 7 (42.86%)	
occurrences (all)	0	5	
Back pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
Bone pain			
subjects affected / exposed	1 / 8 (12.50%)	1 / 7 (14.29%)	
occurrences (all)	1	1	
Muscle spasms			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Neck pain			
subjects affected / exposed	1 / 8 (12.50%)	1 / 7 (14.29%)	
occurrences (all)	2	1	
Pain in extremity			
subjects affected / exposed	3 / 8 (37.50%)	1 / 7 (14.29%)	
occurrences (all)	7	1	
Tendon pain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Device related infection			

subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Ear infection			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Folliculitis			
subjects affected / exposed	0 / 8 (0.00%)	2 / 7 (28.57%)	
occurrences (all)	0	2	
Fungal skin infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Hand-foot-and-mouth disease			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Lip infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	4	
Nasopharyngitis			
subjects affected / exposed	4 / 8 (50.00%)	0 / 7 (0.00%)	
occurrences (all)	10	0	
Oral candidiasis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Otitis media			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Rhinitis			
subjects affected / exposed	3 / 8 (37.50%)	1 / 7 (14.29%)	
occurrences (all)	4	1	
Skin infection			
subjects affected / exposed	0 / 8 (0.00%)	2 / 7 (28.57%)	
occurrences (all)	0	2	
Tinea pedis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Tonsillitis			

subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	2	
Upper respiratory tract infection			
subjects affected / exposed	1 / 8 (12.50%)	1 / 7 (14.29%)	
occurrences (all)	2	2	
Metabolism and nutrition disorders			
Hypoalbuminaemia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 October 2010	Amendment 1: The study was in the startup phase; no patients had been enrolled to date. As this was the first planned study of AMN107 (nilotinib) in the pediatric patient population, the primary purpose of this global amendment was to further enhance safety parameters related to this population. Consistent with this goal, additional ECG monitoring, additional clarification on assessments for disease monitoring and addition of a washout period for CYP3A4 inhibitors and inducers were implemented. Finally, this amendment clarified the disease response criteria for patients with Ph+ ALL.
17 February 2012	Amendment 2: The primary purpose of this global amendment was to align all language relative to pregnancy detection and prevention with the nilotinib program language and the internal Novartis pregnancy guideline requirements. An additional purpose was to extend the duration of the study to 24 cycles to provide continued drug supply access to patients benefiting from treatment, as well as obtain additional safety, tolerability and activity data. The final purpose of this amendment was to implement some clarifications and a correction, namely, the washout period for myelosuppressive chemotherapy in exclusion criteria #10. At the time of this amendment, 7 patients were enrolled.
07 August 2013	Amendment 3: The original title, "A multi-center, open-label, pharmacokinetic study of oral nilotinib in pediatric patients with Gleevec® (imatinib)-resistant/intolerant Ph+ CML chronic phase (CP) or accelerated phase (AP) or with refractory/relapsed Ph+ ALL" was modified to the current title "A multi-center, open-label, pharmacokinetic study of oral nilotinib in pediatric patients with newly diagnosed chronic phase (CP) Ph+ CML, with CP or accelerated phase (AP) Ph+ CML resistant/intolerant to imatinib and/or dasatinib, or with refractory/relapsed Ph+ ALL. The primary purpose of this global amendment was to expand the current patient population in order to assist in completing enrollment for the younger age group by including pediatric patients with (1) Newly diagnosed CP-Ph+ CML and (2) CP or AP-Ph+ CML resistant/intolerant to imatinib and/or dasatinib. At the time of this amendment, 9 patients were enrolled. The inclusion of newly diagnosed CP-Ph+ CML patients reflected the approval of the adult indication in this patient group and was based on the expected positive benefit risk ratio in the pediatric population. The inclusion of dasatinib-resistant or -intolerant Ph+ CML patients was based on the feedback from the pediatric community to reflect the current clinical practice of treating newly diagnosed pediatric CP-Ph+ CML patients with second generation TKIs as well as with imatinib.
07 August 2013	Amendment 3 Continued: The expansion of the patient population was also reflected in the Pediatric Investigational Plan (PIP) and Written Request (WR), which were approved by the EMA and FDA, respectively. In addition, FDA requested the implementation of additional safety monitoring measures in newly diagnosed CP-Ph+ CML patients as a condition to enroll these patients in the study.
14 April 2014	Amendment 4: Amendment 4: The study was in the enrollment phase with a total of 12 enrolled patients as of 14-Feb-2014. Group 1 (younger age cohort; 1 year to < 10 years) had enrolled 5 patients to date as of 14-Feb-2014. Group 2 (older age cohort; ≥ 10 years to < 18 years) completed enrollment with 7 patients and an IA was conducted per protocol. As a result of the IA, the dose of 230 mg/m2 bid was confirmed as the recommended Phase II dose in the ≥ 10 years to < 18 years age group. The primary purpose of amendment 4 was to implement modifications to align with the latest version of Investigator's Brochure of the product AMN107 (nilotinib, Tasigna®), Edition 9 dated 26-Jun-2013 (and upcoming Edition 10) regarding management of ischemic vascular or cardiovascular events.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported