25 February 2016
EMA/207552/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Tasigna

nilotinib

Procedure no: EMEA/H/C/000798/P46/050

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Introduction

On 10 December 2015, the MAH submitted a completed paediatric study for Tasigna (nilotinib), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended. A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH states that study CAMN107A2120, "A multi-center, open-label, pharmacokinetic study of oral nilotinib in paediatric 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" is part of a clinical development program. The extension application consisting of the full relevant data package (i.e. containing several studies) is expected to be submitted by 12/2016. A line listing of all the concerned studies is given below.

Study title	Study number	Date of completion	Date of submission of final study report
An oral (gavage) juvenile development dose range-finding (DFR) study in rats	0870247	21-Nov-2008	02-Sep-2009
An oral (gavage) juvenile development study in rats	0870248	07-Aug-2009	02-Sep-2009

Study title	Study number	Date of completion	Date of submission of final study report
A randomized, open label, three-period crossover study comparing the bioavailability of nilotinib when administered as intact capsule or the capsule content mixed with yogurt or applesauce in healthy subjects.	CAMN107A2127	19-Jul-2009	02-Sep-2009
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.	CAMN107A2120	01-Jul-2015	Dec 2015
A multi-center, open label, non-controlled phase II study to evaluate 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.	CAMN107A2203	ongoing	N/A

No changes to the paediatric information in the current Tasigna SmPC are proposed as a result of this specific study.

2.2. Information on the pharmaceutical formulation used in the study

Patients were administered nilotinib 230 mg/m2 bid, administered hard capsules in dosage strengths of 50 mg, 150 mg and 200 mg.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

CAMN107A2120, "A multi-center, open-label, pharmacokinetic study of oral nilotinib in paediatric 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".

At present Tasigna (nilotinib) is indicated in the European Union (EU) for the treatment of adult patients with:

- newly diagnosed Philadelphia chromosome positive chronic myelogenous leukemia (CML) in the chronic phase,
- chronic phase and accelerated phase Philadelphia chromosome positive CML with resistance or intolerance to prior therapy including imatinib.

Nilotinib is administered orally and is available as hard capsule in dosage strengths of 150 mg and 200 mg.

2.3.2. Clinical study CAMN107A2120

CAMN107A2120, "A multi-center, open-label, pharmacokinetic study of oral nilotinib in paediatric 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".

Description

Methods

Objective

The primary objective of the multi-center, open-label phase I [Study CAMN107A2120] was to characterize the pharmacokinetics (PK) of nilotinib in paediatric 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 twice daily (bid). The dose of 230 mg/m2 bid in this population was based on the adult recommended dose (400 mg bid) scaled to body surface area (BSA).

The secondary objectives included the assessment of safety and activity (hematologic, cytogenetic and molecular responses) of nilotinib in paediatric patients.

Study design

Study CAMN107A2120 was a multi-center, open-label study to characterize the PK of nilotinib in the study population administered as 230 mg/m2 bid to paediatric patients.

Study population /Sample size

The planned study population was 14 paediatric patients (maximum of 24 patients): 7 patients ages 1 year to < 10 years (Group 1) and 7 patients ages≥ 10 years to < 18 years (Group 2) with imatinib/dasatinib resistant/intolerant Ph+ CML in CP or AP, or Ph+ ALL refractory/relapsed to standard therapy. The analyzed study population included 15 paediatric patients: 8 patients (7 were PK-evaluable) ages 1 year to < 10 years (Group 1) and 7 patients ages ≥ 10 years to < 18 years (Group 2).

Treatments

Patients were administered nilotinib 230 mg/m2 bid (except for Cycle 1 Day1 in which a daily dose was administered), orally, rounded to the nearest 50 mg (maximum 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. Upon completion of a minimum of 12 cycles (28 days per cycle) of treatment, patients who were benefiting from the treatment with nilotinib, as determined by the Investigator, were offered the option to receive extended therapy with nilotinib.

The selection of dose was based on the following:

The approved adult dose of nilotinib for the treatment of imatinib resistant / intolerant Ph+ CML in CP or AP is 400 mg bid. The equivalent dose, based on an average BSA of 1.73 m2 in adults, is 230 mg/m2 bid, which was the dose investigated in this study. Additional reasons for the use of 230 mg/m2 bid include:

- The maximum tolerated dose (MTD) of nilotinib was determined to be 600 mg bid (equivalent to approximately 350 mg/m2), and the proposed 230 mg/m2 bid dose for paediatric patients is below this MTD.
- It is desirable to achieve the same exposure in paediatric patients as in adult patients, considering similar pathology of the disease and expression of BCR-ABL oncoprotein in both adult and paediatric patients.
- The use of 400 mg bid in adults and either 300 mg bid or 400 mg bid in a limited number of paediatric patients in the Compassionate Use Program revealed a favorable safety profile.

On Day 1, only a single 230 mg/m2 dose of nilotinib was administered in the morning in order to obtain the full PK profile over 24 hours.

Statistical Methods

Full analysis set (FAS): consists of all patients who passed the screening and are enrolled into the study. Patients may or may not have taken study drug. The FAS is used for all demographic and baseline characteristics, unless otherwise specified.

Pharmacokinetic Analysis Set (PAS): consists of all patients who received the nilotinib dose on Day 1, had an evaluable Day 1 PK profile or provided at least one evaluable steady state trough concentration. The PK set was used for all the concentration summaries and plots, and all the PK parameter summaries and analyses unless otherwise specified.

Safety set: consists of all patients who received at least one dose of nilotinib. The Safety set was used for all core safety summaries and all Section 14 listings, unless otherwise specified.

Table 11-1 Analysis sets by age group (FAS)

Analysis set	Group 1 1 year to < 10 years N = 8 n (%)	Group 2 ≥ 10 years to < 18 years N = 7 n (%)	All pediatric patients N = 15 n (%)
Full analysis set (FAS)	8 (100)	7 (100)	15 (100)
PK analysis set (PAS)	7 (87.5)	7 (100)	14 (93.3)
Safety set	8 (100)	7 (100)	15 (100)

PK = pharmacokinetic
Full analysis set (FAS): consists of all patients enrolled into the study. Patients may or may not have taken study drug.
PK analysis set (PAS): consists of all patients who received the nilotinib dose on Day 1, have an evaluable Day 1 PK profile or provide at least one steady state trough concentration.
Safety set: consists of all patients who received at least one dose of nilotinib.
Source: Table 14.1-2.1

Results

Recruitment / Number analysed

Table 10-1 Patient disposition by age group (FAS)

Disposition	Group 1 1 year to < 10 years N = 8 n (%)	Group 2 ≥ 10 years to < 18 years N = 7 n (%)	All pediatric patients N = 15 n (%)
Patient enrolled	8 (100)	7 (100)	15 (100)
Primary reason for end of treatment			
Treatment duration completed as per protocol	5 (62.5)	2 (28.6)	7 (46.7)
New cancer therapy	3 (37.5)	3 (42.9)	6 (40.0)
Adverse Events	0	1 (14.3)	1 (6.7)
Disease progression	0	1 (14.3)	1 (6.7)
Primary reason for study evaluation completion			
Follow-up phase completed as per protocol	5 (62.5)	3 (42.9)	8 (53.3)
New cancer therapy	3 (37.5)	3 (42.9)	6 (40.0)
Disease progression	0	1 (14.3)	1 (6.7)

FAS=full analysis set
Source: Table 14.1-1.1

Fifteen patients in two age groups were enrolled in the study (Group 1: ages 1 year to < 10 years: 8 patients; Group 2: ages ≥ 10 years to < 18 years: 7 patients).

Overall, 7 (7/15, 46.7%) patients completed treatment as per protocol (Group 1: 5 (62.5%) patients; Group 2: 2 (28.6%) patients). The primary reason for treatment discontinuation was new cancer therapy in 6 (40%) patients (Group 1: 3 (37.5%) patients; Group 2: 3 (42.9%) patients). Of note, among the 6 patients with new cancer therapy, 1 patient with Ph+ ALL had a CRp and then had a stem cell transplant with subsequent treatment with chimeric antigen receptor, and five patients with CML were considered to have an inadequate response, four of whom went onto stem cell transplant, and the fifth patient, was switched to dasatinib. Additionally, 1 (14.3%) patient in Group 2 discontinued treatment due to an AE and disease progression.

Data sets analyzed

The data analysis sets are shown in Table 11-1:

- FAS: all eligible patients enrolled in the study. Patients may or may not have taken study drug.
- PAS: all patients who received the nilotinib dose on Day 1, had an evaluable Day 1 PK profile or provided at least one steady-state trough concentration.
- Safety set: all patients who received at least one dose of study drug.

The FAS was used for all efficacy analyses, demographic and baseline characteristics, and listings. The safety set was used for safety analysis. Of note, in this study, because all enrolled patients actually received study medication, the FAS and safety sets are identical and include all patients. The PAS was used for the PK analysis. One patient in Group 1: ages 1 year to < 10 years had PK samples collected that were deemed not evaluable due to a storage temperature excursion at the investigative site.

Table 11-1 Analysis sets by age group (FAS)

Analysis set	Group 1 1 year to < 10 years N = 8 n (%)	Group 2 ≥ 10 years to < 18 years N = 7 n (%)	All pediatric patients N = 15 n (%)
Full analysis set (FAS)	8 (100)	7 (100)	15 (100)
PK analysis set (PAS)	7 (87.5)	7 (100)	14 (93.3)
Safety set	8 (100)	7 (100)	15 (100)

PK = pharmacokinetic
Full analysis set (FAS): consists of all patients enrolled into the study. Patients may or may not have taken study drug.
PK analysis set (PAS): consists of all patients who received the nilotinib dose on Day 1, have an evaluable Day 1 PK profile or provide at least one steady state trough concentration.
Safety set: consists of all patients who received at least one dose of nilotinib.
Source: Table 14.1-2.1

Baseline data

Table 11-2 Demographics and other baseline characteristics by age group for pediatric and adult patients (FAS)

	Group 1 1 year to < 10 years N = 8 n (%)	Group 2 ≥ 10 years to < 18 years N = 7 n (%)	All pediatric patients N = 15 n (%)	All adult [1] patients N=17 n (%)
Age (years)				
n	8	7	15	17
Median	7.0	15.0	9.0	49.0
Mean (SD)	6.8 (1.16)	13.7 (2.81)	10.0 (4.12)	49.1 (17.44)
[Min; Max]	[5 ; 9]	[10 ; 17]	[5 ; 17]	[21 ; 72]
Sex				
Female	3 (37.5)	4 (57.1)	7 (46.7)	8 (47.1)
Male	5 (62.5)	3 (42.9)	8 (53.3)	9 (52.9)
Race				
Asian	1 (12.5)	1 (14.3)	2 (13.3)	1 (5.9)
Black	0	0	0	1 (5.9)
Caucasian	6 (75.0)	6 (85.7)	12 (80.0)	13 (76.5)
Missing	1 (12.5)	0	1 (6.7)	2 (11.7)
Native American	0	0	0	0
Other	0	0	0	0
Pacific Islander	0	0	0	0

Ethnicity				
Missing	1 (12.5)	1 (14.3)	2 (13.3)	15 (88.2)
Chinese	0	0	0	0
Hispanic/Latino	0	0	0	2 (11.8)
Indian (Indian subcontinent)	1 (12.5)	0	1 (6.7)	0
Japanese	0	0	0	0
Mixed Ethnicity	0	1 (14.3)	1 (6.7)	0
Other	6 (75.0)	5 (71.4)	11 (73.3)	0
Weight (kg)				
n	8	7	15	17
Median	24.75	49.50	29.00	78.10
Mean (SD)	24.60 (4.739)	48.89 (17.533)	35.93 (17.328)	83.85 (25.440)
[Min; Max]	[17.0 ; 29.9]	[27.0 ; 76.8]	[17.0 ; 76.8]	[45.6 ; 132.5]
Height (cm)				
n	8	7	15	17
Median	120.5	164.0	129.0	170.0
Mean (SD)	119.9 (7.49)	158.0 (16.32)	137.7 (23.02)	169.6 (11.14)
[Min; Max]	[105 ; 129]	[132 ; 178]	[105 ; 178]	[152 ; 184]
Body mass index (kg/m^2)				
n	8	7	15	17
Median	16.858	17.612	17.280	25.800
Mean (SD)	16.962 (1.7654)	18.944 (3.4563)	17.887 (2.7795)	29.241 (9.2024)
[Min; Max]	[15.01 ; 20.14]	[15.50 ; 24.24]	[15.01 ; 24.24]	[16.90 ; 50.20]
Body surface area (m^2)				
n	8	7	15	17
Median	0.915	1.500	0.990	1.954
Mean (SD)	0.900 (0.1119)	1.444 (0.3339)	1.154 (0.3647)	1.968 (0.3153)
[Min; Max]	[0.70 ; 1.03]	[0.98 ; 1.95]	[0.70 ; 1.95]	[1.42 ; 2.47]

[1] For all the adult patients from study CAMN107A2101 whose PK data are used as reference.
BMI = body mass index; (kg/m^2) = weight (kg) / (height (m))^2; BSA = body surface area; recommended calculation was the Mosteller formula (BSA (m^2) = ([Height(cm) x Weight(kg)] / 3600)½); FAS=full analysis set; SD = standard deviation
Race: The categories for race for studies A2101 and A2120 have been aligned according to Guidance for Industry on Collection of Race and Ethnicity Data in Clinical Trials (2005).
Source: Table 14.1-3.1; Listing 16.2.4-1.1

Disease history

Overall, 11 Ph+ CML patients had a median time since initial diagnosis of Ph+ CML of 25.30 months with a range from 3.7 to 84.9 months. Four Ph+ ALL patients had a median time since initial diagnosis of Ph+ ALL of 37.90 months with a range from 14.8 to 46 months.

In Group 1, the median time since initial diagnosis of Ph+ CML was 45.2 months with a range from 11.4 to 84.9 months. The median time since initial diagnosis of Ph+ ALL was 42.7 months with a range from 33.1 to 46 months.

In Group 2, time since the initial diagnosis of disease was much more recent than time reported in Group 1. The median time since initial diagnosis of Ph+ CML was 22.9 months.

The time since initial diagnosis of Ph+ ALL was 14.8 months for the 1 patient in Group 2.

Prior antineoplastic therapy

All 15 patients had a prior regimen of at least one antineoplastic medication. Additionally, of the 8 patients in Group 1, 1 (12.5%) patient had prior radiotherapy, and of 7 patients in Group 2, only 3 (42.9%) patients had prior surgery (i.e. stem cell transplantation).

Pharmacokinetic results

The full PK profiles of nilotinib in paediatric patients were assessed using serial sampling following a single 230 mg/m2 dose on Cycle 1 Day 1. The steady-state PK of nilotinib in paediatric patients was evaluated with the trough concentrations obtained on Cycle 1 Day 8, 15, 22, and 28 following the administration of 230 mg/m2 bid.

The PK exposure of nilotinib following the single dose appeared to be comparable between Group 1 (1 year to < 10 years) and Group 2 (≥ 10 years to < 18 years). The geometric means of maximum blood/serum concentration (Cmax), AUC from time zero to the last quantifiable concentration point (AUClast) and AUC0-12h were approximately 405 ng/mL, 4161 and 2796 ng*h/mL in Group 1, and 403 ng/mL, 5707 and 3393 ng*h/mL in Group 2, respectively.

The coefficient of variation (CV; %) for the geometric means was 30% or higher in both groups (Table 2-1).

Table 2-1 Summary of nilotinib non-compartmental PK parameters for Cycle 1 Day 1 by age group (PAS)

Age Group	Statistics	Cmax (ng/mL)	Tmax (h)	AUClast (ng*h/mL)	AUC0-12h (ng*h/mL)
Group 1: Age 1 year to < 10 years	n[1]	7	7	7	7
	Mean (SD)	433.286 (163.1050)	N/A	4397.063 (1500.786)	2932.341 (917.1243)
	CV% mean	37.6	N/A	34.1	31.3
	Geo-mean	405.111	N/A	4160.969	2795.782
	CV% geo-mean	42.5	N/A	38.5	35.7
	Median	407.000	2.000	4374.288	2895.676
	[Min; Max]	[222.00; 669.00]	[1.02; 7.08]	[2116.92; 6820.32]	[1490.13; 4098.21]
Group 2: Age ≥ 10 years to < 18 years	n[1]	7	7	7	7
	Mean (SD)	422.857 (140.8314)	N/A	6313.115 (3193.430)	3531.036 (1141.116)
	CV% mean	33.3	N/A	50.6	32.3
	Geo-mean	402.715	N/A	5707.368	3393.206
	CV% geo-mean	35.2	N/A	51.2	30.4
	Median	397.000	3.000	5704.000	3331.763
	[Min; Max]	[231.00; 636.00]	[2.00; 7.88]	[2759.76; 12625.46]	[2316.18; 5754.96]
All pediatric patients	n[1]	14	14	14	14
	Mean (SD)	428.071 (146.4978)	N/A	5355.089 (2595.136)	3231.689 (1041.969)
	CV% mean	34.2	N/A	48.5	32.2
	Geo-mean	403.911	N/A	4873.211	3080.043
	CV% geo-mean	37.3	N/A	46.8	33.5
	Median	402.000	2.525	4727.179	3087.408
	[Min; Max]	[222.00; 669.00]	[1.02; 7.88]	[2116.92; 12625.46]	[1490.13; 5754.96]

AUC = area under the curve; CSR = clinical study report; CV% = coefficient of variation (%) = SD/mean*100; Geo-mean = geometric mean; CV% Geo-mean = sqrt ((exp (variance for log transformed data)-1))*100; Last = 24 hrs; PAS = PK analysis set; PK = pharmacokinetic; SD = standard deviation; Tmax = time to reach maximum serum concentration

[1] = number of patients with corresponding PK parameter available.

Source: [Study CAMN107A2120-CSR-Table 14.2-1.1]

No marked difference was observed between Group 1 and 2 with regard to the steady-state PK exposure and clearance of nilotinib. The geometric means were approximately 15129 and 14383 ng*h/mL for the steady-state AUC from time zero to the end of the dosing interval (AUCtau; tau = 12 hours), and 15.356 and 15.922 L/h/m2 for the BSA-adjusted CL/F (apparent systemic (or total body)

clearance from plasma (or serum or blood) following extravascular administration), respectively (Table 2-2).

Table 2-2 Summary of nilotinib steady-state PK parameters estimated from noncompartmental analysis (PAS)

Age Group	Statistics	AUCss (ng*h/mL)	CL/F (BSA adjusted) (L/h/m^2)	Cmin (ng/mL)
Group 1: Age 1 year to < 10 years	n[1]	7	7	7
	Mean (SD)	16036.175 (6017.8590)	16.231 (5.4766)	842.262 (270.1217)
	CV% mean	37.5	33.7	32.1
	Geo-mean	15129.182	15.356	804.791
	CV% geo-mean	38.0	38.7	33.7
	Median	14420.130	16.127	877.000
	[Min; Max]	[9032.53; 26984.92]	[7.94; 22.99]	[549.00; 1236.67]
Group 2: Age ≥ 10 years to < 18 years	n[1]	7	7	7
	Mean (SD)	15006.959 (4413.9681)	16.928 (7.1759)	1091.917 (221.7097)
	CV% mean	29.4	42.4	20.3
	Geo-mean	14383.076	15.922	1072.850
	CV% geo-mean	33.6	37.0	20.5
	Median	14046.393	16.533	1055.667
	[Min; Max]	[7943.94; 19807.20]	[11.72; 32.11]	[835.67; 1435.00]
All pediatric patients	n[1]	14	14	14
	Mean (SD)	15521.567 (5098.2195)	16.579 (6.1433)	967.089 (270.4515)
	CV% mean	32.8	37.1	28.0
	Geo-mean	14751.413	15.637	929.204
	CV% geo-mean	34.5	36.3	30.9
	Median	14268.403	16.330	979.792
	[Min; Max]	[7943.94; 26984.92]	[7.94; 32.11]	[549.00; 1435.00]

AUC = area under the curve; AUCss = AUCtau for bid dose at steady state; CL/F = apparent systemic clearance from plasma; Cmin = lowest trough concentration observed as the average value of the evaluable Ctrough from Cycle 1 Day 8, 15, 22, and 28; CSR = clinical study report; CV% = coefficient of variation (%) = SD/mean*100; Geo-mean = geometric mean; CV% Geo-mean = sqrt ((exp (variance for log transformed data)-1))*100; PAS = PK analysis set; PK = pharmacokinetic; SD = standard deviation.

[1] number of patients with corresponding PK parameter available

All pediatric patients:1 year to < 18 years

Source: [Study CAMN107A2120-CSR-Table 14.2-1.2]

Steady-state PK parameters were then compared with reference data obtained in adult patients in [Study CAMN107A2101]. The reference data used from the adult study consisted of all patients who received 400 mg bid, and had valid steady state PK parameters on Cycle 1 Day 15. The steady-state PK exposure and clearance of nilotinib in the paediatric patients administered 230 mg/m2 bid were similar (within 2-fold) to those observed in adult patients administered 400 mg bid. The geometric mean ratio (90% CI) of steady-state AUC (paediatrics divided by adults) was 0.885 (0.683, 1.145),

0.841 (0.650, 1.089), and 0.863 (0.701, 1.061) for Group 1, Group 2 and all paediatric patients, respectively (Table 2-3). The geometric mean ratio (90% confidence interval (CI)) of BSA-adjusted CL/F was 1.276 (0.971, 1.677), 1.323 (1.007, 1.739), and 1.300 (1.044, 1.618) for Group 1, Group 2, and all paediatric patients, respectively.

Table 2-3 Summary of geometric-mean ratio of steady-state PK parameters estimated from non-compartmental analysis in paediatric population compared to adult population with 90% CI by age group (PAS)

					Age Group Comparison		
						90% CI	
PK Parameter (unit)	Age group	N[1]	Adjusted Geo-mean	Comparison	Geo-mean Ratio	Lower	Upper
AUCss (ng*h/mL)	Adult	17	17102.856				
	Group 1: Age 1 year to < 10 years	7	15129.182	Group 1 / Adult	0.885	0.683	1.145
	Group 2: Age ≥ 10 years to < 18 years	7	14383.076	Group 2 / Adult	0.841	0.650	1.089
	All pediatric	14	14751.413	All pediatric / Adult	0.863	0.701	1.061
CL/F (BSA adjusted) (L/h/m^2)	Adult	17	12.033				
	Group 1: Age 1 year to < 10 years	7	15.356	Group 1 / Adult	1.276	0.971	1.677
	Group 2: Age ≥ 10 years to < 18 years	7	15.922	Group 2 / Adult	1.323	1.007	1.739
	All pediatric	14	15.637	All pediatric / Adult	1.300	1.044	1.618

ANOVA = analysis of variance ; AUCss = AUCtau for bid dose at steady state; BSA = body surface area; CI = confidence interval; CL/F = apparent systemic clearance from plasma; CSR = clinical study report; Geo-mean = geometric mean; PK = pharmacokinetic

All pediatric patients: 1 year to <18 years

Adult: patients from study AMN107A2101 whose PK data are used as reference.

ANOVA model of the log-transformed PK parameters. Included in the model was age group as main effect. Results were back transformed to get adjusted geometric mean, geometric mean ratio and 90% CI.

[1] number of subjects with evaluable PK data.

Source: [Study CAMN107A2120-CSR-Table 14.2-1.3]

The PK of nilotinib was similar between 1 year to < 10 years and ≥ 10 years to < 18 years after either single or multiple doses. The PK results in all patients in this study dosed with nilotinib 230 mg/m2 bid demonstrated that the AUCtau and BSA-adjusted CL/F of nilotinib at steady state were within a two-fold range of the reference data for nilotinib 400 mg bid in adult Ph+ CML patients. This dose provided similar PK exposure to that of reference data for nilotinib 400 mg bid in adult Ph+ CML patients.

Efficacy results

Efficacy was measured through hematologic, cytogenetic, and molecular responses. A summary of the efficacy evaluation (best calculated response status during study treatment) is shown in Table 2-4.

Table 2-4 Summary of best calculated response status within response category during study treatment, by indication and age group (FAS)

Variable	Group 1 1 year to < 10 years N = 8 n (%)	Group 2 ≥ 10 years to < 18 years N = 7 n (%)	All pediatric patients N = 15 n (%)
- CML patients	5 (62.5)	6 (85.7)	11 (73.3)
Confirmed complete hematologic response (CHR)*			
Yes	5 (100)	5 (83.3)	10 (90.9)
No	0 (0.0)	1 (16.7)	1 (9.1)
Cytogenetic response			
Complete (CCyR)	2 (40.0)	2 (33.3)	4 (36.4)
Partial (PCyR)	0	1 (16.7)	1 (9.1)
Minor (mCyR)	0	1 (16.7)	1 (9.1)
Minimal	0	0	0
None	0	0	0
Absence of Ph+ at baseline	3 (60.0)	1 (16.7)	4 (36.4)
Major Molecular response (MMR)			
Yes	1 (20.0)	2 (33.3)	3 (27.3)
No	4 (80.0)	4 (66.7)	8 (72.7)
- ALL patients	3 (37.5)	1 (14.3)	4 (26.7)
Complete Response			
Complete remission with platelet recovery (CR)	2 (66.7)	1 (100)	3 (75.0)
Complete remission with incomplete platelet recovery (CRp)	0	0	0
Partial remission	0	0	0
Stable disease	1 (33.3)	0	1 (25.0)
Progressive disease	0	0	0

ALL = acute lymphoblastic leukemia; CML = chronic myeloid leukemia; CSR = clinical study report; FAS = full analysis set; Ph+ = Philadelphia (Ph)-positive

* confirmed complete hematologic response is defined by two complete hematologic responses at least 4 weeks apart and there cannot be any assessment in between which indicates no response.

% is calculated for each response variable within indication and age group.

Response categories are separate, patients may present response for multiple response variables within the indication.

Source: [Study CAMN107A2120–CSR-Table 14.2-3.1]

Of 11 Ph+ CML patients (5 patients in Group 1, 6 patients in Group 2), 10 (90.9%) patients achieved confirmed complete haematological response (CHR), and 1 patient satisfied CHR criteria which was not confirmed at another visit within 4 weeks. Of 11 Ph+ CML patients, 4 (36.4%) patients achieved complete cytogenetic response (CCyR), 2 patients in each age group (Group 1 (2, 40%); Group 2 (2, 33.3%). One patient in Group 2 (1, 16.7%) achieved partial cytogenetic response (PCyR) and another 1 patient (1, 16.7%) achieved minor cytogenetic response (mCyR). Major cytogenetic response (CCyR or PCyR) was achieved in 2 patients in Group 1 (40%) and 3 patients in Group 2 (50.0%).

MMR was achieved in 3 Ph+ CML patients (27.3%), 1 patient in Group 1 (20%) and 2 patients in Group 2 (33.3%).

Of the 4 Ph+ ALL patients, complete remission with platelet recovery (CR) was achieved in 3 patients (75%): 2 patients in Group 1 (66.7%) and 1 patient in Group 2 (100%). Stable disease was observed in the 1 remaining Group 1 patient (33.3%).

Safety results

Exposure

For all 15 patients, the median time on treatment was 10.87 months and similar in both age groups (10.96 vs 10.78 months for Group 1 and Group 2, respectively). The majority (12, 80%) of patients were treated for at least 12 months. The median duration of exposure was 10.64 months and similar in both age groups (10.55 vs 10.78 months for Group 1 and Group 2, respectively).

For all patients, the median actual dose intensity was 453.9 mg/m2/day which is close to the actual planned dose. The median relative dose intensity was 98.68% and comparable between both age groups (101.1% vs 97.86% for Group 1 and Group 2, respectively).

Adverse events

All 15 patients experienced at least one adverse event (AE) during the study.

Table 12-4 Adverse events regardless of study drug relationship by primary system organ class and age group (Safety set)

Primary System Organ Class	Group 1 1 year to < 10 years N = 8 n (%)	Group 2 ≥ 10 years to < 18 years N = 7 n (%)	All pediatric patients N = 15 n (%)
Any primary system organ class			
Total	8 (100)	7 (100)	15 (100)
Skin and subcutaneous tissue disorders	7 (87.5)	5 (71.4)	12 (80.0)
Infections and infestations	8 (100)	4 (57.1)	12 (80.0)
Gastrointestinal disorders	5 (62.5)	6 (85.7)	11 (73.3)
Nervous system disorders	5 (62.5)	4 (57.1)	9 (60.0)
Musculoskeletal and connective tissue disorders	4 (50.0)	3 (42.9)	7 (46.7)
Investigations	4 (50.0)	3 (42.9)	7 (46.7)
General disorders and administration site conditions	3 (37.5)	4 (57.1)	7 (46.7)
Respiratory, thoracic and mediastinal disorders	3 (37.5)	3 (42.9)	6 (40.0)
Hepatobiliary disorders	2 (25.0)	2 (28.6)	4 (26.7)
Blood and lymphatic system disorders	0	3 (42.9)	3 (20.0)
Ear and labyrinth disorders	0	2 (28.6)	2 (13.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (25.0)	0	2 (13.3)

Primary system organ classes are presented in descending order.
Source: Table 14.3.1-1.2

The majority (80%) of patients experienced AEs suspected to be study-drug related. For all patients, the most frequently reported AEs suspected to be related to study drug were alanine aminotransferase (ALT) increased and rash (4 patients each, 26.7%), followed by aspartate aminotransferase (AST) increased, blood bilirubin increased, and hyperbilirubinemia (3 patients each, 20%).

Table 12-6 Adverse events suspected to be study drug related by preferred term, maximum grade, and age group (Safety set)

	Group 1 1 year to < 10 years N = 8 n (%)		Group 2 ≥ 10 years to < 18 years N = 7 n (%)		All pediatric patients N = 15 n (%)	
	All grades n (%)	Grades 3/4 n (%)	All grades n (%)	Grades 3/4 n (%)	All grades n (%)	Grades 3/4 n (%)
Patients with at least one suspected to be study-drug related AE	6 (75.0)	2 (25.0)	6 (85.7)	2 (28.6)	12 (80.0)	4 (26.7)
Alanine aminotransferase increased	3 (37.5)	0	1 (14.3)	0	4 (26.7)	0
Rash	2 (25.0)	0	2 (28.6)	0	4 (26.7)	0
Aspartate aminotransferase increased	3 (37.5)	0	0	0	3 (20.0)	0
Blood bilirubin increased	2 (25.0)	1 (12.5)	1 (14.3)	0	3 (20.0)	1 (6.7)
Hyperbilirubinaemia	2 (25.0)	1 (12.5)	1 (14.3)	0	3 (20.0)	1 (6.7)
Arthralgia	0	0	2 (28.6)	0	2 (13.3)	0
Dry skin	0	0	2 (28.6)	0	2 (13.3)	0
Fatigue	2 (25.0)	0	0	0	2 (13.3)	0
Folliculitis	0	0	2 (28.6)	0	2 (13.3)	0
Headache	1 (12.5)	0	1 (14.3)	0	2 (13.3)	0
Neutropenia	0	0	2 (28.6)	2 (28.6)	2 (13.3)	2 (13.3)

AE = adverse event
Preferred terms are sorted in descending frequency, as reported in the all pediatric patients column.
A patient with multiple occurrences of an AE under one age group is counted only once in the AE category for that age group.
A patient with multiple severity ratings for an AE is only counted under the maximum rating.
Source: Table 14.3.1-1.6

Serious adverse events

Five patients (33.3%) experienced serious adverse events (SAEs) all of which resolved, 7 patients (46.7%) experienced AEs requiring dose interruption and/or modification, and 1 patient (6.7%) withdrew due to multiple AEs. No deaths occurred during the study. Of the 8 patients in Group 1, 2 (25%) patients experienced SAEs: 1 (12.5%) patient reported appendix disorder and 1 (12.5%) patient reported influenza-like illness and pyrexia. All SAEs were considered not suspected to be study-drug related. Of the 7 patients in Group 2, 3 (42.9%) patients experienced SAEs: 2 (28.6%) patients reported neutropenia (2 SAEs in 1 patient) and 1 (14.3%) patient experienced renal failure. The SAEs of neutropenia were considered suspected to be study-drug related.

No deaths occurred during the study.

Table 12-7 Serious adverse events regardless of study drug relationship by preferred term and age group (Safety set)

Preferred term	Group 1 1 year to < 10 years N = 8 n (%)	Group 2 ≥ 10 years to < 18 years N = 7 n (%)	All pediatric patients N = 15 n (%)
Any preferred term			
Total	2 (25.0)	3 (42.9)	5 (33.3)
Neutropenia	0	2 (28.6)	2 (13.3)
Appendix disorder	1 (12.5)	0	1 (6.7)
Influenza like illness	1 (12.5)	0	1 (6.7)
Pyrexia	1 (12.5)	0	1 (6.7)
Renal failure	0	1 (14.3)	1 (6.7)

AE = adverse event; SAE = serious adverse event
Preferred terms are sorted in descending frequency, as reported in the all pediatric patients column.
A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment. One patient experienced 2 SAEs of neutropenia.
Source: Table 14.3.1-1.9

Adverse Events of special interest (AESI):

No cases of Hy's Law or potential Hy's Law were observed. AESI requiring dose interruption occurred in 3 patients of 8 in Group 1 (37.5%): ALT increased, blood bilirubin increased, hyperbilirubinemia and hypoalbuminemia. Of 7 patients in Group 2, 1 patient experienced a dose interruption for thrombocytopenia (1/7, 14.3%).

One patient of 8 in Group 1 (12.5%) had a grade 0 to grade 2 shift from baseline in lipase increased. No associated AEs were reported and the lipase elevation improved to normal without any intervention.

No episodes of torsades de pointes were reported during the study. Three patients overall (20%) had a QTcF post-baseline increase > 30 ms (1 patient of 8 in Group 1 (12.5%) and 2 patients of 7 in Group 2 (28.6%)). No patients reported a QTcF post-baseline increase > 60 ms. One patient in Group 2 (1, 14.3%) had a new QTcF interval > 450 ms and no patients had a new QTcF interval > 480 ms.

MAH' s Discussion on clinical aspects

The PK of nilotinib was similar between 1 year to < 10 years and ≥ 10 years to < 18 years after either single or multiple doses. The PK results in all patients in this study dosed with nilotinib 230 mg/m2 bid demonstrated that the AUCtau and BSA-adjusted CL/F of nilotinib at steady state were within a two-fold range of the reference data for nilotinib 400 mg bid in adult Ph+ CML patients. This dose provided similar PK exposure to that of reference data for nilotinib 400 mg bid in adult Ph+ CML patients.

Of 11 Ph+ CML patients (5 patients in Group 1, 6 patients in Group 2), 10 (90.9%) patients achieved confirmed CHR, and 1 patient had CHR which was not confirmed at another visit within 4 weeks. Of 11 Ph+ CML patients, 4 patients (36.4%) achieved CCyR, 2 patients in each age group (Group 1 (2, 0%); Group 2 (2, 33.3%)). One patient in Group 2 (1, 16.7%) achieved PCyR and another 1 patient (1, 16.7%) achieved mCyR. Three patients in Group 1 and 1 patient in Group 2 had no Ph+ marrow at baseline. Major cytogenetic response in this study includes CCyR or PCyR. Major cytogenetic response was achieved in 2 patients in Group 1 (40%) and 3 patients in Group 2 (50.0%). MMR was achieved in 3 Ph+ CML patients (27.3%) 1 patient in Group 1 (20%) and 2 patients in Group 2 (33.3%). In the 4

Ph+ ALL patients, CR was achieved in 3 patients (75%): 2 patients in Group 1(66.7%) and 1 patient in Group 2 (100%). Stable disease was observed in the 1 remaining patient in Group 1 (33.3%).

The safety profile of paediatric patients dosed with nilotinib 230 mg/m2 bid is consistent with the already well-known safety profile of adult patients treated with nilotinib. There were some low grade shifts in hepatic transaminases as isolated laboratory findings. There was no evidence of vascular morbidities. No deaths were reported.

In conclusion, the study results confirm 230 mg/m2 bid as the recommended dose in paediatric patients (1 year to < 18 years) with newly diagnosed CP-Ph+ CML, or CP or AP-Ph+ CML resistant/intolerant to imatinib and/or dasatinib, or relapsed/refractory Ph+ ALL.

3. Rapporteur's overall conclusion and recommendation

The MAH has provided a completed paediatric study for Tasigna (nilotinib), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

The provided study; CAMN107A2120, a multi-center, open-label, pharmacokinetic study of oral nilotinib in paediatric 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, with the primary objective to characterize the pharmacokinetics (PK) of nilotinib in paediatric 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) along with secondary objectives of safety and activity (hematologic, cytogenetic and molecular responses) of nilotinib in paediatric patients, will be a part an upcoming extension application consisting of the full relevant data package (i.e. containing several studies) and is expected to be submitted by 12/2016. The preliminary discussion and conclusion, as provided by the MAH, is endorsed. As such, the full evaluation of whether the benefit/risk of nilotinib in the paediatric population in the treatment of 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, awaits the submission of the complete data package.

The benefit/risk of the use of nilotinib in the currently approved adult population remains positive.

X Fulfilled:

No further action required, however further data are expected in the context of an extension prior any conclusion on product information amendments is made. The MAH has informed that the application is expected for December 2016.

☐ Not fulfilled:

4. Additional clarification requested

MAH responses to Request for supplementary information

Annex. Line listing of all the studies included in the development program

The studies should be listed by chronological date of completion:

Non clinical studies

Study title	Study number	Date of completion	Date of submission of final study report
An oral (gavage) juvenile development dose range-finding (DFR) study in rats	0870247	21-Nov-2008	02-Sep-2009
An oral (gavage) juvenile development study in rats	0870248	07-Aug-2009	02-Sep-2009

Clinical studies

Study title	Study number	Date of completion	Date of submission of final study report
A randomized, open label, three-period crossover study comparing the bioavailability of nilotinib when administered as intact capsule or the capsule content mixed with yogurt or applesauce in healthy subjects.	CAMN107A2127	19-Jul-2009	02-Sep-2009
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.	CAMN107A2120	01-Jul-2015	Dec 2015
A multi-center, open label, non-controlled phase II study to evaluate 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.	CAMN107A2203	ongoing	N/A