EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 December 2010
EMA/CHMP/678167/2010
Human Medicines Development and Evaluation

Assessment Report
For
TASIGNA
(nilotinib)

Procedure No.: EMEA/H/C/000798/II/0029

Variation Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted

7 Westferry Circus • Canary Wharf • London E14 4HB • United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

1. Introduction

Chronic Myelogenous Leukaemia (CML) is a myeloproliferative disorder which accounts for 15% of cases of leukemia in adults and is characterized by a clonal expansion of hematopoietic stem cells which harbor a chromosomal rearrangement of the long arms of chromosome 9 and 22, forming the Philadelphia chromosome (Ph) which is detected in approximately 95% of CML patients (Nowell 1960, Rowley 1973). This leads to the formation of a novel fusion gene BCR-ABL, which encodes a constitutively active protein tyrosine kinase. The presence of the BCR-ABL fusion gene product has been shown to contribute to growth factor independence, increased proliferation, genomic instability, suppression of apoptosis and alteration of the adhesive properties of CML cells (Daley 1990, Kelliher 1990, Hazarika, 2008, Jarkowski, 2008).

CML consists of three distinct phases: chronic phase (CP), accelerated phase (AP) and blast crisis (BC) phase. The majority of patients are diagnosed in CP, and may then progress to AP and ultimately to the BC (Enright and McGlave 2000, Hazarika et al 2008). If left untreated, patients diagnosed with CML have a life expectancy of 3-5 years.

The management and prognosis of patients with CML-CP changed dramatically in 1998, with the introduction into clinical trials of imatinib, a tyrosine kinase inhibitor (TKI) developed specifically to inhibit the kinase activity of the BCR-ABL fusion protein. Survival of patients treated with imatinib is substantially prolonged relative to historical controls and median overall survival has not yet been established (Roy et al, 2006, O'Brien et al 2008) and imatinib is considered the current standard of care in the first line setting. Resistance and intolerance have however been reported following treatment with imatinib.

Nilotinib is an adenosine triphosphate-competitive inhibitor of BCR-ABL, a fusion protein created by chromosomal rearrangement of the long arms of chromosomes 9 and 22, forming the Philadelphia (Ph) chromosome. BCR-ABL is a constitutively active tyrosine kinase and drives the pathology of chronic myelogenous leukemia (CML), a myeloproliferative disorder characterized by a clonal expansion of hematopoietic stem cells expressing the BCR-ABL gene. Nilotinib is a second-generation inhibitor of BCR-ABL, with a similar mechanism of action to imatinib, but with greater binding affinity for wild-type BCR-ABL kinase and improved target selectivity.

Tasigna was designated as an orphan medicinal product (EU/3/06/375) on 22 May 2006.

Tasigna (nilotinib) 200 mg hard capsules was granted a marketing authorization in the European Union on 19 November 2007. It is currently indicated, at a recommended dose of 400 mg twice daily for the *treatment of adults with chronic phase and accelerated phase Philadelphia chromosome positive chronic myelogenous leukaemia (CML) with resistance or intolerance to prior therapy including imatinib. Efficacy data in patients with CML in blast crisis are not available.*

The purpose of this type II variation application (C.I.6.a) is to seek approval for Tasigna (nilotinib) in the treatment of adult patients with **newly** diagnosed Philadelphia chromosome positive (Ph+) chronic myelogenous leukemia in chronic phase (CML-CP) at a recommended dose of 300 mg twice daily.

Consequently, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 5.3 of the Summary of Product Characteristics (SmPC) and the package leaflet have been updated. Annex II has been updated to include the updated version of the risk management plan (version 8.1). The Marketing Authorisation Holder also took the opportunity to update the product information with the latest QRD template.

The Marketing Authorisation Holder (MAH) of Tasigna has also submitted in parallel an extension application for Tasigna 150 mg hard capsules, pursuant to Article 2(a) of Commission Regulation (EC) No 1085/2003 and Annex II (point 2 iii) (EMEA/H/C/798/X/0028).

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/60/2009 for the following condition(s):

- Gastro-intestinal stromal tumour

on the granting of a product-specific waiver.

- Chronic myeloid leukaemia

on the agreement of a paediatric investigation plan (PIP) with a deferral.

The PIP is not yet completed.

2. Non-clinical aspects

2.1 Introduction

In this application, the MAH provided results of a juvenile developmental study initiated as part of the paediatric investigation plan and an updated environmental risk assessment.

2.2 Toxicology

Reproduction Toxicity

The MAH submitted two additional studies: an oral juvenile development dose range-finding study in rats and an oral juvenile development study in rats.

Study no. 0870247: An oral (gavage) juvenile development dose range-study in rats

The study was conducted in juvenile Wistar Hannover rats for dose range-finding for the juvenile development study. This study was not conducted under Good Laboratory Practices (GLP).

The test article AMN107 (nilotinib) was administered by gavage at doses of 6, 20, 60 and 180 mg/kg/day. Test article-related mortality and moribund state occurred at doses ≥ 60 mg/kg/day. At 180 mg/kg/day, 4 females and 8 males were found dead and 2 females were sacrificed moribund by postpartum day 13 and the remaining animals in this group were terminated on postpartum day 13. At 60 mg/kg/day, 3 females and 7 males were found dead and 2 females and 1 male were sacrificed moribund by postpartum day 14 and the remaining animals in these groups were terminated on that day. There was no mortality at doses ≤ 20 mg/kg/day. Decreased activity was the only test article-related clinical sign and was noted at doses ≥ 60 mg/kg/day. Body weight parameters were decreased at doses ≥ 20 mg/kg/day, with mean body weights at 20 mg/kg/day reduced by approximately 7% in both sexes compared to control values at the end of the study.

Study no. 0870248: An oral (gavage) juvenile development study in rats

The scope of this GLP study was to determine the potential adverse effects of AMN017 on the postnatal development of the rat. Juvenile Wistar Hannover rats were administered AMN107 (nilotinib) at doses of 2, 6 and 20/mg/kg/day from the first week post partum through young adult.

Standard development parameters were determined and, during recovery, selected animals were observed for behavioural parameters and/or fertility assessments.

No test article-related mortality and no effect on clinical signs were noted in the study. At 20 mg/kg/day a reduction in body weight parameters and food consumption was noted, which was gender unspecific. Dose-related increases in absolute and relative (to body and brain) weights were present in both sexes at a dose of 20 mg/kg/day in the heart, kidney and spleen. In male pituitary and thyroid weight increases were present at doses ≥ 6 mg/kg/day. There were no test article-related effects noted on the developmental landmarks of eye opening or vaginal opening.

Preputial separation appeared to be slightly delayed in males at ≥ 6 mg/kg/day and that may be related to the decreased body weight noted at that dose level. At the end of the evaluation period 95 % (38 out of 40) and 92.5% (37 out of 40) males had achieved criteria at 6 mg/kg/day and 20 mg/kg/day respectively compared to 100% (40 out of 40) of control male pups.

Auditory startle response and pupillary response were not affected by the test article and there were no test article-related effects noted for mating and fertility, motor activity, M-water maze or passive avoidance testing.

There were no test article-related changes in clinical pathology.

Slight to severe skin scabs/ulceration and a constellation of associated skin microscopic findings were present in all Pathology animal groups (males only). Although the incidence of skin lesions was increased in the dosed groups, this was not considered test article-related since the underlying microscopic lesion in the control animal was of similar type, grade and location (ear or shoulder) as the lesions in dosed animals.

Exposure to AMN107 increased proportionally with increasing dose for both male and female, juvenile and adult rats over the dose range tested. Exposure to AMN107 was approximately 2- to 13- fold higher in juvenile rats (Day 7 post partum) compared to the exposure observed in adult rats (Day 70 post partum). No gender difference was observed for juvenile rats after a single dose of AMN107. However, after multiple dosing of AMN107 for 64 days, exposure to AMN107 in female adult rats was 1.5- to 4-fold higher than the exposure observed in male adult rats at the dose levels tested. The day 70 values obtained in this study were similar to the adult rat values seen after repeated dosing in the 26-week study in rats.

In conclusion, exposure to AMN107 was approximately 2- to 13- fold higher in juvenile rats (Day 7 post partum) compared to the exposure observed in adult rats (Day 70 post partum).

Ecotoxicity/environmental risk assessment

The MAH submitted an environmental risk assessment of Tasigna according to the principles of the guideline EMEA/CHMP/SWP/4447/00.

Based on data on Daphnia magna, effects on microorganism, sub-chronic effects on fish early life stage, at the predicted environmental concentration (PEC) and calculation of PEC/PNEC ratios, it can be concluded that nilotinib HCl would not represent a relevant risk to surface water and groundwater microorganisms (sewage treatment plant). Therefore, no specific risk precautionary and safety measures have been required by CHMP.

However algae toxicity and fish chronic toxicity need to be further characterised. In addition, in view of the physico chemical characteristics of nilotinib, the potential for bioconcentration and effect studies on the terrestrial compartment should be provided. At the request of CHMP, the MAH committed to perform such studies as follow-up measures (FUM). An overview of environmental endpoints is presented in the table below:

SUMMARY TABLE on ERA

Substance (INN/Invented Name): Nilotinib hydrochloride					
CAS-number (if available): 923288-90-8					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD117	3.6 (at pH 7.0)			Potential PBT (N)
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surfacewater}$ refined with prevalence of the orphan disease)	0.028	µg/L			> 0.01 threshold
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Water solubility		< 0.013mg/L			
n-Octanol/water coefficient	OECD 117 (HPLC method)	log Pow (30°C, pH 7) = 3.6			Value > 3 triggers a BCF study (OECD 305)
Adsorption-Desorption	OECD 106 and US EPA-OPPTS	Sludge Koc = 5'104 – 16'510 Soil Koc = 105'561 – 558'974			Koc>10000, implies possible contamination of soil
Ready Biodegradability Test (Study NOV258)	OECD 301 B	22.3 % / 28 d k_{STP} = 0			not readily biodegradable
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308				Requested as FUM
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC not determined	72h-EC50 > 100	mg/L	Retesting needed to determine NOEC (FUM)
Daphnia magna Reproduction Test	OECD 211	NOEC-21d PNEC	12.7 0.59	µg/L µg/L	No risk (PEC/PNEC >1)
Toxic Effects on Embryos and Larvae of Zebrafish		7d-NOEC (hatching rate)	2.6	µg/L	Cannot replace OECD 210
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC		µg/L	Requested as FUM
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	≥ 300	mg/L	
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF		L/kg	Requested as FUM
Aerobic and anaerobic transformation in soil	OECD 307	DT50 %CO_2			Requested as FUM
Soil Micro organisms: Nitrogen Transformation Test	OECD 216	%effect		mg/kg	Requested as FUM
Terrestrial Plants, Growth Test/*Species*	OECD 208	NOEC		mg/kg	Requested as FUM
Earthworm, Acute Toxicity Tests	OECD 207	NOEC		mg/kg	Requested as FUM
Collembola, Reproduction Test	ISO 11267	NOEC		mg/kg	Requested as FUM
Sediment dwelling organism (Study A94116)	OECD 219	NOEC	≥ 38 (real)	µg/kg	Chironomus riparius.

2.3 Discussion on non-clinical aspects

A juvenile developmental study was initiated as part of the paediatric investigation plan. The effects of nilotinib upon gestation, parturition and lactation in rats and the development of the pups were shown. All other aspects in the nonclinical program remain unchanged.

The selection of endpoints in the study was appropriate. Toxicokinetic data were presented, that confirmed appropriate exposure levels in different treatment groups.

Standard development parameters were determined and, during recovery, selected animals were observed for behavioural parameters. After clarification of open items the study is now considered appropriate for determination of permanent functional deficits.

In a juvenile rat toxicity study, pups were treated with 2, 6 and 20 mg/kg nilotinib via oral gavage from post-natal day 7 to 70. Based on a reduction in body weight in both genders and a delayed preputial separation in males (which may be associated with the reduction in weight), the NOAEL was stated as 6 mg/kg. An identical NOAEL was established in a 26-week study conducted in adult rats. The plasma exposure level at the NOAEL was higher in the juvenile than in the adult rats, hence the juvenile animals did not exert increased sensitivity to nilotinib relative to adults. In addition, no new target organs were identified in the juvenile animals. Based on CNS development, a post-natal day 7 rat, approximately corresponds to a newborn child. Section 5.3 of the SmPC has been updated further to these results.

No new or unexpected toxicities were noted in the juvenile rat as compared to adults of this species. There was no apparent difference in exposure to AMN107 between male and female juvenile rats after single dose. After multiple oral doses, exposure to AMN107 in female adult rats was higher than that in male adult rats for all dose levels. In general, the exposure to AMN107 increased proportionally with increasing dose over the dose range tested in both juvenile and adult rats.

Based on available data nilotinib would not represent a relevant risk to surface water and groundwater microorganisms (sewage treatment plant) at the predicted environmental concentration. Therefore, no specific risk precautionary and safety measures have been required by CHMP. However, further characterisation of algae toxicity, fish chronic toxicity and effect studies on the terrestrial compartment were requested by CHMP. The MAH has committed to submit as follow-up measures these environmental studies in an updated ERA.

2.4 Conclusion on the non-clinical aspects

In conclusion, no new or unexpected toxicities were noted in the juvenile rat as compared to adults of this species.

3 Clinical aspects

3.1 Introduction

An overview of the clinical studies conducted in support of this application is provided in the table below.

Table 1 – Overview of clinical studies

Clinical study	Study design
Clinical Pharmacology studies	
Study CAMN107A2127	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.
Modeling Report for Study CAMN107A2303	Population PK and PK/PD analysis of nilotinib in adult patients with newly diagnosed Philadelphia chromosome positive (Ph+) chronic myelogenous leukemia in chronic phase
Pivotal Phase III study	
Study CAMN107A2303	A phase III multi-center, open-label, randomized study of imatinib versus nilotinib in adult patients with newly diagnosed Philadelphia chromosome positive (Ph+) chronic myelogenous leukemia in chronic phase (CML-CP)
Phase II Studies providing supportive data	
Study CAMN107A2101E2	Phase II component of study CAMN107A2101 to evaluate the efficacy and safety of nilotinib in patients with imatinib-resistant or intolerant CML-CP.
Study CAMN107A2101E1	Phase II component of study CAMN107A2101 evaluating the efficacy and safety of nilotinib in patients with imatinib-resistant or intolerant CML-AP.
Supportive study for the validity of the primary efficacy variable (MMR at 12 months) as endpoint	
Study CSTI571A0106 PCR Prognostic value of residual disease detection by BCR-ABL polymerase chain reaction	Phase III study of STI571 versus Interferon-α (IFN-α) combined with Cytarabine (Ara-C) in patients with newly diagnosed previously untreated Philadelphia chromosome positive (Ph+) chronic myelogenous leukemia in chronic phase (CML-CP).

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

3.2 Clinical Pharmacology

Pharmacokinetics

Bioavailability

Study No. CAMN107A2127 was a randomized, open-label, three-period crossover study including 48 healthy volunteers comparing the bioavailability of nilotinib when administered as intact capsule or the capsule content mixed with yogurt or applesauce in healthy subjects. This study was initiated as part of the paediatric investigation plan.

After single oral administration of nilotinib dispersed in yogurt a slightly higher rate of absorption was shown as compared to a single oral administration of nilotinb as two intact capsules. Administration of nilotinib with the capsule contents dispersed in yogurt resulted in 31%, 11% and 8% increase in C_{max}, $AUC_{0\text{-}tlast}$ and $AUC_{0\text{-}\infty}$ respectively, showing bioequivalence in terms of AUC, but not of C_{max}.

On the other hand, single oral administration of 400 mg nilotinib, where the capsule contents were dispersed in two teaspoons of applesauce, showed similar nearly identical extent and rate of absorption as compared to the single oral administration of 400 mg nilotinib as two intact capsules; thus bioequivalence between these two treatments could be established for both AUC and C_{max}.

Dose-proportionality

Dose proportionality was assessed as a part of the pivotal study CAMN107A2303 where one of the secondary objectives was to evaluate the pharmacokinetics (PK) of nilotinib at 300 mg BID and 400 mg BID, as well as imatinib 400 mg QD or permitted dose.

Full PK profiles were obtained for subsets of the patient population (global full-PK group) and the Japanese population (Japanese full-PK group). Full pharmacokinetic profiles of nilotinib were obtained from 34 patients, with 19 patients from the global group (9 in the 300 mg BID arm and 10 in the 400 mg BID arm), and 15 patients from the Japanese group (8 in the 300 mg BID arm and 7 in the 400 mg BID arm). Three patients (one patient in the 300 mg BID arm and two patients in the 400 mg BID arm of the global group) were excluded from the statistical summary due to insufficient concentration data obtained over the required 12-hour dosing interval. The pharmacokinetic profiles of nilotinib in the global and Japanese groups were compared in a population pharmacokinetic modeling analysis. In addition, a population PK study was performed using a sparse sampling technique for all treated study patients, where PK sampling was performed at steady state of nilotinib therapy.

Serum concentrations of nilotinib, imatinib and its metabolite CGP74588 were determined using a validated liquid chromatography-tandem mass spectrometry (LC MS/MS) assay with a lower limit of quantification of at least 2.50 ng/mL.

Results of PK parameters are summarised in the table below.

Table 2 – Summary of nilotinib PK parameters by treatment arm (global full-PK group)

Statistics	Cmin (ng/mL)	Cmax (ng/mL)	AUC(0-tlast) (h.ng/mL)	Tmax (h)	CL/F (L/h)	Tlast (h)	Clast (ng/mL)
Nilotinib 300 mg BID							
N	**8**	**8**	**8**	**8**	**8**	**8**	**8**
Mean (SD)	1555 (528.8)	1788 (538.0)	15642 (4250.8)		20.2 (4.58)		1122 (602.1)
CV% mean	34.0	30.1	27.2		22.62		53.7
Geo-mean	1487	1721	15203		19.73		1026
CV% geo-mean	32.1	29.6	25.2		25.16		43.1
Median (Q2)	1430	1555	14446	1.47	20.8	12.00	859
[Q1; Q3]	[1250; 1740]	[1340; 2300]	[12806; 17411]	[0.50; 2.04]	[17.3; 23.5]	[11.95; 12.00]	[822; 1172]
[Min; Max]	[971; 2630]	[1280; 2630]	[11318; 24495]	[0.00; 3.02]	[12.3; 26.5]	[11.90; 12.00]	[760; 2510]
Nilotinib 400 mg BID							
N	**8**	**8**	**8**	**8**	**8**	**8**	**8**
Mean (SD)	1306 (715.1)	1534 (650.5)	13068 (6170.5)		38.2 (19.71)		747 (345.7)
CV% mean	54.8	42.4	47.2		51.63		46.3
Geo-mean	1149	1409	11740		34.07		657
CV% geo-mean	57.4	47.4	54.3		54.32		64.1
Median (Q2)	915	1440	11689	1.50	34.3	11.98	806
[Q1; Q3]	[752; 2080]	[1002; 2125]	[7925; 18678]	[0.00; 2.02]	[21.5; 53.0]	[11.86; 12.01]	[442; 1035]
[Min; Max]	[654; 2300]	[729; 2410]	[5723; 22235]	[0.00; 5.00]	[18.0; 69.9]	[11.38; 12.07]	[228; 1180]

CV% = coefficient of variation (%) = sd/mean×100.

CV% geo-mean = sqrt (exp (variance for log transformed data)-1)×100.

Q1 = 25th percentile , Q3 = 75th percentile, Q2 = 50th percentile which corresponds to median.

For Tmax and Tlast, only median, Q1, Q3, minimum and maximum are provided.

There was considerable overlap in the nilotinib exposure (C_{min}, C_{max} and $AUC_{0\text{-}tlast}$) between 300 mg BID and 400 mg BID arms. Based on the pooled data from the two full-PK groups, the nilotinib exposure was 13.4% higher in the 400 mg BID arm than in the 300 mg BID arm. The average nilotinib trough and peak concentrations over 12 months were 17.8% and 14.7% higher in the 400 mg BID arm than in the 300 mg BID arm.

The trough and peak concentrations of nilotinib were found to remain relatively stable over the 12-month treatment course in both 300 mg BID and 400 mg BID arms. The inter- and intra-patient variability in nilotinib concentrations was similar between the two doses. The overall inter-patient variability was moderate, which is also consistent with previous findings in patients with imatinib resistant or intolerant CML.

Discussion and conclusions on clinical pharmacology

Relative bioavailability was demonstrated between nilotinib administered as intact capsules and capsule content dispersed in applesauce but not between intact capsules and capsule content dispersed in yogurt. Thus some foods influence the bioavailability of nilotinib, which is adequately addressed in the Product Information.

With regard to dose proportionality, no significant difference was noted comparing the two groups of nilotinib (300 mg and 400 mg). $AUC_{0\text{-}tlast}$ represented an approximately 13.4% higher exposure in the 400 mg BID arm than 300 mg BID arm, compared to a 33% higher exposure expected for dose proportionality. These results indicate a less than proportional increase in nilotinib exposure between these two doses, which is consistent with previous observations of a plateau in the relationship between nilotinib exposure and dose at ≥400 mg nilotinib dose.

3.3 Clinical efficacy

3.3.1 Introduction

An overview of studies contributing to the efficacy and safety data in this submission is provided in Table 3.

The efficacy and safety of nilotinib in newly diagnosed patients with CML-CP have been evaluated in a phase III, randomized, open-label study comparing two different doses of nilotinib (300 mg b.i.d. and 400 mg b.i.d.) with imatinib 400 mg q.d. (Study CAMN107A2303). The MAH did not seek scientific advice at the CHMP for the pivotal study of this application.

The efficacy and safety of nilotinib are further supported by the 24 month follow-up data of the phase II component of a phase IA/II study including patients with imatinib-resistant or intolerant CML-CP (Study CAMN107A2101E2) or CML-AP (Study CAMN107A2101E1). These 24-month follow-up data were also submitted as post-authorisation commitments (FUM 032 and FUM 033) and the product information has been updated accordingly in variation EMEA/H/C/798/II/0031 (Commission Decision on 26 August 2010).

The Study CSTI571A0106 PCR Report (conducted with imatinib) was included in this submission to support the validity of Major Molecular Response (MMR) at 12 months as a predictive endpoint of long term outcome and as the primary efficacy variable in study CAMN107A2303.

Table 3 – Summary of efficacy and safety studies

Source of data	Details
Pivotal Phase III study	
Study CAMN107A2303 Imatinib versus nilotinib in adult patients with newly diagnosed Ph+ CML-CP	Randomized, open label, phase III study, N=846 patients (First patient randomized: 06-Sep-07, last patient randomized: 30-Sep-08) Data cut-off for interim: 02-Sep-09 Patients randomized 1:1:1 to nilotinib 300 mg b.i.d. (282 patients), nilotinib 400 mg b.i.d. (281 patients) or imatinib 400 mg q.d. (283 patients) Primary efficacy endpoint: rate of MMR at 12 months Key secondary endpoint: rate of durable MMR at 24 months (will be analyzed at the 24 month analysis) The secondary endpoint of rate of best complete cytogenetic response (CCyR) by Month 12 was considered the main secondary endpoint for the 12 month analysis. Other secondary endpoints: rates of BCR-ABL/ABL ratio ≤0.01% and ≤0.0032%, time to and duration of MMR, time in MMR, rate of confirmed MMR by 12 months time to and duration of CCyR, rate of confirmed CHR by 3 and 12 months, event-free survival (EFS), progression-free survival (PFS), time to progression to accelerated phase or blast crisis (AP/BC), overall survival (OS) All safety data included
Phase II Studies providing supportive data	
Study CAMN107A2101E2 Nilotinib in patients with imatinib resistant/ intolerant Ph+ CML-CP without other prior tyrosine kinase inhibitor (TKI) treatment	Open label, non-randomized phase II study, N=321 patients (First patient enrolled: 21-Apr-05, last patient enrolled: 26-Apr-06) Data cut-off for 120 DSUR: 04-Sep-06; Data cut-off for 24 month CSR: 20-Apr-08 Patients received nilotinib 400 mg b.i.d. Primary efficacy endpoint: rate of major cytogenetic response (MCyR). Secondary endpoints include: duration of MCyR, time to AP/BC, OS. All safety data included
Study CAMN107A2101E1 Nilotinib in patients with imatinib resistant/intolerant Ph+ CML-AP without other prior TKI treatment	Open label, non-randomized phase II study, N=137 patients (First patient enrolled: 09-May-05, last patient enrolled: 30-Jan-07) Data cut-off for 120 DSUR: 23-Sep-06; Data cut-off for 24 month CSR: 29-Aug-08 Patients received nilotinib 400 mg b.i.d. Primary efficacy endpoint: rate of confirmed hematologic response (HR) Secondary endpoints include: duration of HR, time to progression, OS. All safety data included
Supportive study for the validity of the primary efficacy variable (MMR at 12 months) as endpoint	
Study CSTI571A0106 PCR Prognostic value of residual disease detection by BCR-ABL polymerase chain reaction	Randomized, open label, Phase III N=476 patients in the imatinib arm who had at least 1 PCR sample available (PCR population) PCR report establishing the predictive value MMR at 12 months for favorable long term clinical outcome.

3.3.2 Dose response study

No specific dose-responses studies were submitted. The choice of dose for the products administered in the pivotal trial was based on the following considerations. Imatinib 400 mg QD was selected as the comparator as this was considered by the MAH to be the current standard of care. Dose escalation from 400 mg QD to 400 mg BID of imatinib was allowed for patients with suboptimal response and treatment failure.

The recommended dosage of nilotinib in the treatment of adult patients with imatinib-resistant/intolerant Ph+ CML-CP or CML-AP is 400 mg BID. Therefore, nilotinib 400 mg BID was selected as one of the two nilotinib treatment arms.

The 300 mg BID dosing regimen was selected for the second nilotinib treatment arm based on results of study CAMN107A2101 which showed a positive correlation between nilotinib PK exposure and several response parameters, where 400 mg QD (similar drug exposure to 200 mg BID) had lower response than 400 mg BID, pointing to an intermediate dose level such as 300 mg BID as more likely to produce a better response than 200 mg BID and possibly to result in an improved safety profile compared to the 400 mg BID dose.

A 600 mg QD dose was not considered, as study CAMN107A2101 had shown a plateau in the dose-exposure relationship of nilotinib at doses ≥ 400 mg when administered QD under the currently prescribed food condition, 2 h after or 1 h before food. This finding also prompted the use of a divided dose regimen (BID) to increase systemic exposure of nilotinib.

3.3.3 Main study: Study CAMN107A2303

Methods

The pivotal study CAMN107A2303 was a phase III multi-center, open label, randomized study to assess the efficacy and safety of nilotinib versus imatinib in adult patients with newly diagnosed Ph+ CML-CP. Two doses of nilotinib, 300 mg b.i.d. and 400 mg b.i.d. were compared to imatinib 400 mg q.d. Each nilotinib arm was compared independently to the imatinib arm.

Study Participants

The target population was adult patients with cytogenetically confirmed newly diagnosed Ph+ CML-CP. Patients had to have been within 6 months of diagnosis of their disease and previously untreated for CML, except for hydroxyurea and/or anagrelide. In emergent cases where the patient required disease management while awaiting study start, commercial imatinib at any dose could be prescribed to the patient for up to 2 weeks prior to entering the study if clinically indicated.

Patients had to meet all inclusion criteria within 2 weeks of randomization (bone marrow examinations had to be within 42 days) to enter the study.

Treatments

Patients received imatinib (400 mg daily) or nilotinib (300 mg or 400 mg BID) on an outpatient basis.

Objectives

The primary objective was to compare the rate of major molecular response (MMR) at 12 months of nilotinib 400 mg BID and 300 mg BID with that of imatinib 400 mg QD in patients with newly diagnosed, previously untreated Ph+ CML-CP. For this 12 month analysis, the rate of complete cytogenetic response (CCyR) by month 12, which is the best CCyR rate up to month 12, was considered as the main secondary endpoint.

Other secondary objectives included the rates of patients with %BCR-ABL/ABL ratio of ≤ 0.01% and ≤ 0.0032% (referred to as BCR-ABL ratio hereafter), time to and duration of MMR and CCyR, event-free survival (EFS), progression-free survival (PFS), time to progression to AP/BC and overall survival (OS).

Outcomes/endpoints

Primary endpoint: Rate of MMR at 12 months defined as the proportion of patients with BCR-ABL/ABL ratio ≤ 0.1% by International Scale, measured by RQ-PCR. Patients without assessment at 12 months were considered as non-responders, unless both 9 and 15 months assessments indicated MMR.

Key secondary endpoint (for 24 month analysis): Rate of Durable MMR at 24 months defined as the proportion of patients who have MMR at both 12 and 24 months and no loss of MMR in between those two time points.

Main secondary endpoint for 12 months analysis: Rate of Best CCyR by 12 months defined as the proportion of patients with CCyR (0% Ph+) at or before 12 months.

Other secondary efficacy endpoints for the 12 month analysis:. rates of BCR-ABL/ABL ratio ≤0.01% and ≤0.0032%, time to and duration of MMR, time in MMR, rate of confirmed MMR by 12 months time to and duration of CCyR, rate of confirmed CHR by 3 and 12 months, event-free survival (EFS), progression-free survival (PFS), time to progression to accelerated phase or blast crisis (AP/BC), overall survival (OS), all safety data included.

Sample size

The two primary comparisons were: nilotinib 400 mg BID vs. imatinib 400 mg QD and nilotinib 300 mg BID vs. imatinib 400 mg QD (superiority test). To test the null hypothesis that odds ratio was equal to 1 vs. not equal to 1 (with odds ratio 1.83 corresponding to a 15% increase from 40% to 55% in MMR rate) based on the stratified (according to the Sokal risk score into three strata, high risk, intermediate and low risk groups) CMH test at a 5% level of significance and with a 90% power, approximately 699 patients in total (233 patients in each treatment arm) were needed. After adjusting for a 10% drop-out rate, 257 patients per arm and 771 patients in total needed to be enrolled to have 90% power to detect a 15% difference between nilotinib 400 mg BID and imatinib 400 mg QD, assuming that the MMR rate of imatinib is 40% and the MMR rate of nilotinib is 55%. With this samples size, the study also had a 90% power to detect a 15% difference between the nilotinib 300 mg BID and imatinib 400 mg QD arm, if the comparison between nilotinib 400 mg BID and imatinib 400 mg QD arm was significant.

This sample size was only powered to detect the differences specified above between the nilotinib 400 mg BID arm and the imatinib arm, and between the nilotinib 300 mg BID arm and the imatinib arm, sequentially, and was not powered to detect the difference between the two nilotinib arms, hence lack of statistical significance does not imply that the nilotinib arms are the same.

Randomisation

Randomization was stratified by Sokal risk group (low, intermediate, high) at time of diagnosis.

Blinding (masking)

This was an open-label study.

Statistical methods

The primary objective was to compare: (1) MMR rate at 12 months with nilotinib 400 mg BID vs. imatinib 400 mg QD; (2) MMR rate at 12 months with nilotinib 300 mg BID vs. imatinib 400 mg QD. The null hypothesis for both the comparisons was that there is no difference in MMR rate at 12 months between nilotinib and imatinib. The corresponding alternative hypothesis was that the MMR rate at 12 months is different between nilotinib and imatinib. A two-sided stratified Cochran-Mantel-Haenzel (CMH) test based on the randomization stratum was used to test the null hypothesis at the significant level of 0.05. To protect the overall type-one error, a step-down testing procedure was applied for the comparisons (1) and (2), i.e. the MMR rate with nilotinib 400 mg BID vs. imatinib 400 mg QD was compared first; if it is significant at 5% level, the MMR rate with nilotinib 300 mg BID vs. imatinib 400 mg QD was compared. Otherwise, none of the comparisons was significant at 5% level. The MMR rate at 12 months was presented along with the 95% confidence interval by randomization stratum and treatment group. In addition, 95% confidence intervals were provided for the differences in the MMR rates at 12 months for each pairwise comparison.

Confidence intervals for all response rates were provided by using the Pearson-Clopper method. Confidence intervals for the differences in any response rates between treatment groups were provided using the Wald method.

The full analysis set (FAS) consisted of all patients who were randomized into the study. The per-protocol set (PPS) consisted of all FAS patients who received at least one dose of study medication and did not have any major protocol violations. Patients were analyzed according to the treatment to which they were randomized.

Efficacy was analyzed using the full analysis set (FAS) and included all randomized patients according to the treatment they were randomized to (intent-to-treat principle). Safety was analyzed for all patients who received at least one dose of study medication according to the medication actually received as start of study.

Per protocol, the MMR rate at 12 months was first compared between nilotinib 400 mg BID and imatinib using a Cochran-Manzel Haenszel test (CMH test) stratified by Sokal risk group at 5% level of significance. Following the step-down procedure to protect against overall type-one error, the MMR rate at 12 months was then compared between nilotinib 300 mg BID and imatinib 400 mg QD at 5% level of significance.

There were two planned interim analyses to assess the futility of continuing nilotinib 300 mg BID arm. The first interim analysis was performed after about 20% of the randomized patients (150 patients in total, 50 patients in each arm) have been treated for 6 months. The second interim

analysis was performed after about 40% of the randomized patients (294 patients in total, 98 patients in each arm) had been treated for 6 months.

An independent Data Monitoring Committee (IDMC) was responsible for reviewing the planned interim analyses results.

Results

Participant flow

A total of 771 patients were originally planned to be randomized 1:1:1 among the nilotinib 300 mg BID, nilotinib 400 mg BID, and imatinib 400 mg QD. However, due to the large number of patients that entered screening during the last 15 days of enrolment, a total of 846 patients were randomized (283 patients in the imatinib 400 mg QD, 282 patients in the nilotinib 300 mg BID arm and 281 patients in the nilotinib 400 mg BID arm) in 35 countries using 217 sites. Three patients randomized to each of the nilotinib treatment arms and 4 patients randomized to the imatinib arm did not receive any study drug.

The number of patients in the full analysis set (FAS) was distributed equally. The per-protocol set (PPS) consisted of all FAS patients who received at least one dose of study medication and did not have any major protocol violations. Patients were analyzed according to the treatment to which they were randomized. 110 patients had at least one major protocol violation but were balanced between treatment arms.

As of the data cut-off date of 2 September 2009, a total of 690 patients were still receiving study treatment: 224 patients (79.2%) in the imatinib arm, 236 patients (83.7%) in the nilotinib 300 mg BID arm and 230 patients (81.9%) in the nilotinib 400 mg BID arm. A total of 156 patients had discontinued study treatment: the highest discontinuation rate was 59 patients (20.8%) in the imatinib arm, followed by 51 patients (18.1%) in the nilotinib 400 mg BID arm and 46 patients (16.3%) in the nilotinib 300 mg BID arm.

Patients discontinued most frequently due to safety-related reasons. The highest incidence of combined AEs/abnormal laboratory values leading to study discontinuation was observed in the nilotinib 400 mg BID arm (31 patients, 11.1%), followed by the imatinib arm (24 patients, 8.5%) and the nilotinib 300 mg BID arm (19 patients, 6.7%). Two deaths were reported as the primary reason for discontinuation, both in the nilotinib 300 mg BID arm (one patient died due to small intestinal obstruction, the other committed suicide). These deaths were not considered causally related to study medication by the investigator.

Table 4 – Study CAMN107A2303 Participant flow

ENROLLMENT Randomized n = 846 (1:1:1, Stratified by Sokal score)				
	Arm	**Imatinib 400 mg QD** Increased to 800 mg if required)	**Nilotinib 300 mg BID.**	**Nilotinib 400 mg BID.**
ALLOCATION	**Allocated to Intervention** N = 846 (FAS)	283	282	281
	Received allocated intervention N = 836	279	279	278
	Did not receive allocated intervention (=randomized but not treated) **n = 10**	4	3	4
FOLLOW UP	**Lost to follow up** n =5	1	2	2
	Discontinued intervention n =156	59 (20.8%)	46 (16.3%)	51 (18.1%)
ANALYSIS	**Analyzed** n = 846 **FAS**	283	282	281
	Excluded from analyses n = 110 a)	39	39	32
	Analyzed n = 736, **PPS** b)	244	243	249
Cut of 2. sep 2009	**Still on study drug** N = 690	224 (79.2%)	236 (83.7%)	230 (81.9%)

a) Reasons (= major protocol violations):
Ph+ chromosome not confirmed
Concomitant administration of strong CYP3A4 inhibitors and inducers during study
Chronic phase CML not confirmed
Atypical transcripts at baseline
Patient with another primary malignancy except if the other primary malignancy is neither currently clinically significant or requiring active intervention
Patients did not receive at least one dose of study drug (n = 10; Excluded from Per- Potocol Set as well as safety)
b) Per protocol (all FAS who received at least one dose of study medication and did not have major protocol violations).

Recruitment

The First patient first visit occurred on 31 July 2007. The data cut-off date for the 12-month primary analysis was on 2 September 2009 (all patients completed 12-month evaluation or discontinued from the study early). The study is ongoing.

Conduct of the study

There were no amendments with major impact to the study protocol.

Baseline data

Demographic summary and baseline characteristics in Study CAMN107A2303 are presented in the table below.

Table 5 –Demographic summary and baseline characteristics – Study CAMN107A2303 (FAS)

Demographic variable	Imatinib 400 mg QD N = 283	Nilotinib 300 mg BID N = 282	Nilotinib 400 mg BID N = 281
Age (years)			
Mean ± SD	47.1 ± 14.34	47.2 ± 14.53	46.7 ± 13.90
Median	46.0	47.0	47.0
25^{th} – 75^{th} percentile	36.0-58.0	35.0-58.0	36.0-57.0
Range	18-80	18-85	18-81
Age category n (%)			
<35 years	63 (22.3)	67 (23.8)	65 (23.1)
≥35 - <45 years	67 (23.7)	50 (17.7)	59 (21.0)
≥45 - <55 years	63 (22.3)	72 (25.5)	65 (23.1)
≥55 - <65 years	55 (19.4)	57 (20.2)	64 (22.8)
≥65 years	35 (12.4)	36 (12.8)	28 (10.0)
Sex – n (%)			
Male	158 (55.8)	158 (56.0)	175 (62.3)
Female	125 (44.2)	124 (44.0)	106 (37.7)
Race – n (%)			
Caucasian	187 (66.1)	170 (60.3)	185 (65.8)
Black	7 (2.5)	12 (4.3)	11 (3.9)
Asian	71 (25.1)	76 (27.0)	66 (23.5)
Native American	1 (0.4)	0	2 (0.7)
Other	17 (6.0)	24 (8.5)	17 (6.0)
Sokal risk group			
Low	104 (36.7)	103 (36.5)	103 (36.7)
Intermediate	101 (35.7)	101 (35.8)	100 (35.6)
High	78 (27.6)	78 (27.7)	78 (27.8)

The time since initial diagnosis of CML was similar across treatment arms, with a median time since diagnosis of 28.0 days in the imatinib arm, 31.0 days in the nilotinib 300 mg BID arm and 31.0 days in the nilotinib 400 mg BID arm. The extent of extramedullary involvement was comparable across treatment arms, with less than half of all patients having extramedullary involvement.

Numbers analysed

Table 6 – Analysis populations – Study CAMN107A2303

Patient population	Imatinib 400 mg QD N = 283 n (%)	Nilotinib 300 mg BID N = 282 n (%)	Nilotinib 400 mg BID N = 281 n (%)
Full analysis set (FAS)	283 (100)	282 (100)	281 (100)
Per protocol set (PPS)	244 (86.2)	243 (86.2)	249 (88.6)

Outcomes and estimation

Primary endpoint: Major molecular response (MMR)

The results for the primary efficacy endpoint, MMR rate at 12 months, are summarized in Table 7.

Table 7 –Major molecular response (MMR) rate at 12 months – with imputation[1] – Study CAMN107A2303 (FAS)

	Imatinib 400 mg QD N = 283	Nilotinib 300 mg BID N = 282	Nilotinib 400 mg BID N = 281
Response – n (%)	63 (22.3)	125 (44.3)	120 (42.7)
95% CI for response (%)	[17.6, 27.6]	[38.4, 50.3]	[36.8, 48.7]
No response – n (%)	220 (77.7)	157 (55.7)	161 (57.3)
CMH test p-value for response rate (vs. imatinib)		<0.0001	<0.0001
Difference in response rate (vs. imatinib)		22.1	20.4
95% CI for difference in response rate (%)		[14.5, 29.6]	[12.9, 28.0]

[1] One patient in the nilotinib 300 mg BID arm with missing PCR assessment at 12 months was imputed as having MMR at 12 months as the patient had MMR both at 9 months and at 15 months.
Patients without assessment at 12 months are considered as non-responders, unless both 9 and 15 months assessments indicated response.
CMH test is stratified by Sokal risk group.

In the PPS, the MMR rate at 12 months was 24.2% in the imatinib arm, 44.4% in the nilotinib 300 mg BID arm and 42.2% in the nilotinib 400 mg BID arm. The differences between the MMR rates in each of the nilotinib arms compared with the imatinib arm were both statistically significant at p<0.0001. The result for the PPS was consistent with the results in the FAS. In conclusion the primary endpoint, MMR, was met for both doses of nilotinib.

Secondary endpoints

- Durable MMR at 24 months

The results for the key secondary endpoint "durable MMR" at 24 months are not available yet. The MAH has committed to submit the results as soon as they are available.

- Best CCyR by 12 months

Best CCyR rates by 12 months (main secondary endpoint), includes patients who achieved CCyR at or before the 12 month time point as responders, were higher in the nilotinib treatment arms than in the imatinib arm (Table 8).

Table 8 – Best CCyR rate by 12 months – Study CAMN107A2303 (FAS)

	Imatinib 400 mg QD N = 283	Nilotinib 300 mg BID N = 282	Nilotinib 400 mg BID N = 281
Response – n (%)	184 (65.0)	226 (80.1)	219 (77.9)
95% CI for response - %	[59.2, 70.6]	[75.0, 84.6]	[72.6, 82.6]
No response – n (%)	99 (35.0)	56 (19.9)	62 (22.1)
CMH test p-value for response rate (vs. imatinib)		<0.0001	0.0005
Difference in response rate (vs. imatinib)		15.1	12.9
95% CI for difference in response rate - %		[7.9, 22.4]	[5.5, 20.3]

CMH test is stratified by Sokal risk group

For the PPS, the best CCyR rates were higher in the nilotinib 300 mg BID and nilotinib 400 mg BID arms (81.1% and 79.5%, respectively) than in the imatinib arm (65.6%).

By 6 months, the best CCyR rates in the nilotinib 400 mg BID and nilotinib 300 mg BID arms (63.0% and 66.7%, respectively) were higher than in the imatinib arm (44.5%) The cumulative incidence of CCyR over time is graphically displayed in Figure 1. By the cut-off date, CCyR was

achieved by 70.7% of patients in the imatinib arm, 81.6% of patients in the nilotinib 300 mg BID arm and 80.1% of patients in the nilotinib 400 mg BID arm.

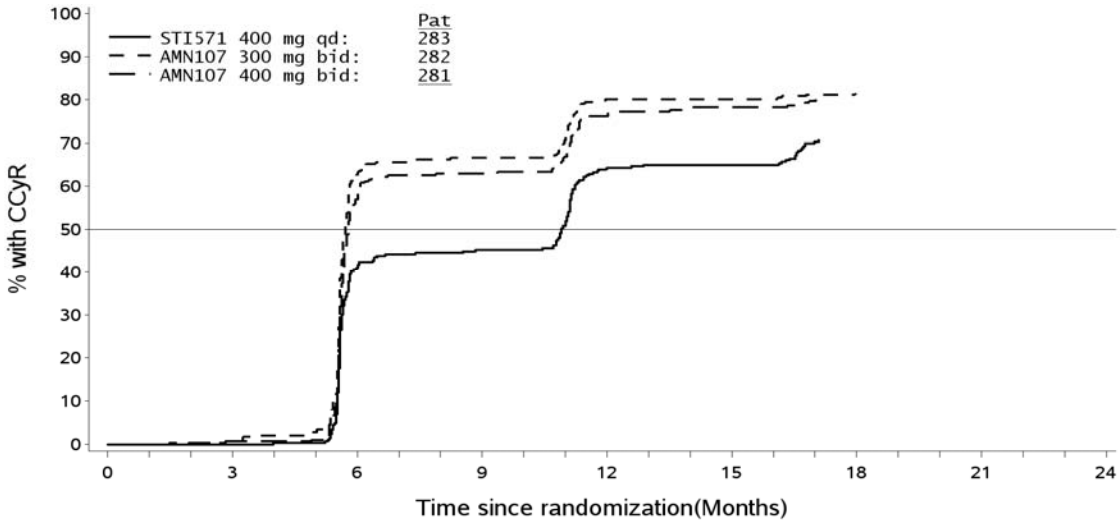

Figure 1 - Cumulative incidence of CCyR – Study CAMN107A2303 (FAS)

The result for the PPS of best CCyR at 12 months was consistent with the results in the FAS.

- Rate of best confirmed MMR by 12 months

Best confirmed MMR rates by 12 months were 19.8%, 44.3% and 39.5% for the imatinib, nilotinib 300 mg BID and nilotinib 400 mg BID arms, respectively (p-value < 0.0001 for the comparison of each nilotinib arm vs. imatinib).

- Rate of BCR-ABL/ABL ratio ≤ 0.01% and ≤ 0.0032% at 12 months

The rate of BCR-ABL/ABL ratios of ≤ 0.01% at 12 months was 3.9% in the imatinib arm, 11.7% in the nilotinib 300 mg BID arm (p-value=0.0005) and 8.5% in the nilotinib 400 mg BID arm (p-value=0.0221).

The rate of BCR-ABL/ABL ratios of ≤ 0.0032% at 12 months was 0.4% in the imatinib arm, 4.3% in the nilotinib 300 mg BID arm (p-value=0.0020) and 4.6% in the nilotinib 400 mg BID arm (p-value=0.001).

Information as to the frequency, type and time of occurrence of resistant BCR/ABL mutations against nilotinib respectively imatinib, in particular of the TKI-multi resistant mutation T315I, was very limited due to the low number of events. However, there was no case of T315I mutation observed up to date.

- Time to response (MMR, CCyR)

Median time to first MMR for patients who achieved MMR was 8.31 months (range 2.8-17.3 months) in the imatinib arm, compared to either nilotinib arm 5.72 months (range 1.9-19.9 months) in the 300 mg BID arm and 5.78 months (range 2.6-19.7 months) in the 400 mg BID arm. MMR was achieved by 30.4% of patients in the imatinib arm, 57.1% of patients in the nilotinib 300 mg BID arm and 54.4% of patients in the nilotinib 400 mg BID arm. Furthermore, Kaplan Meier estimates of time to first MMR show the probability of achieving MMR at different time

points were higher in both nilotinib arms compared to the imatinib arm (HR=1.5774 and stratified log-rank p<0.0001 between nilotinib 400 mg BID and imatinib, HR=2.5665 and stratified log-rank p<0.0001 between nilotinib 300 mg BID and imatinib).

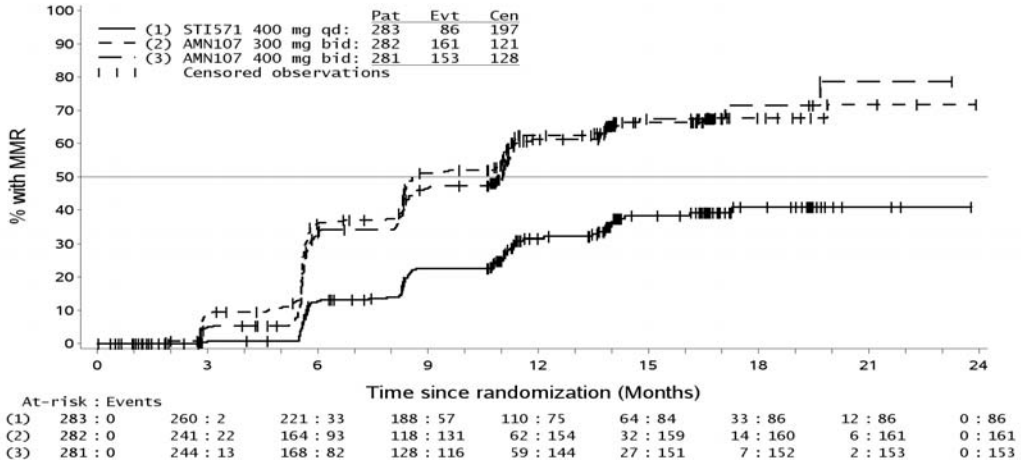

Figure 2 - Kaplan-Meier estimates of time to first MMR – Study CAMN107A2303 (FAS)

There were no differences in the median time to first CCyR in the three treatment groups. For patients who achieved CCyR, the median time to first CCyR was 5.8 months (range 4.0 to 17.1 months), 5.6 months (range 1.5 to 18.0 months) and 5.7 months (range 1.9 to 17.0) in the imatinib arm, the nilotinib 300 mg BID arm and the nilotinib 400 mg BID arm respectively. CCyR was achieved by 70.7%, 81.6% and 80.1% of patients by the cut-off day in the imatinib arm, the nilotinib 300 mg BID arm and the nilotinib 400 mg BID arm respectively.

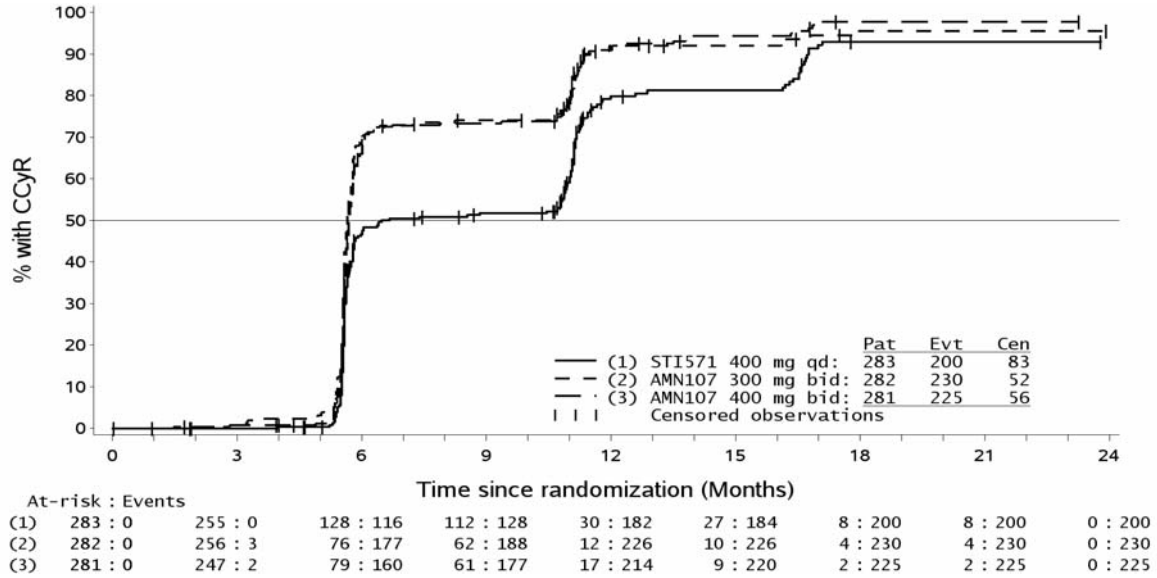

Figure 3 - Kaplan-Meier estimates of time to first CCyR – Study CAMN107A2303 (FAS)

The results of the Kaplan-Meier analyses of time to first CCyR for all patients showed the probability of achieving CCyR at different time points was significantly higher in each nilotinib arm compared to the imatinib arm (HR=1.2381 and stratified log-rank p<0.0001 between nilotinib 400 mg BID and imatinib, HR=1.5952 and stratified log-rank p<0.0001 between nilotinib 300 mg BID and imatinib).

- Duration of responses (MMR, CCyR):

Duration of MMR: No difference between treatments arms has been observed with the current duration of follow-up. There were only a total of 11/400 events. Updated results on duration of MMR every 12 months will be provided as a post authorisation commitment. Mutational analysis will be also regularly updated.

Duration of CCyR: The estimated proportions of patients maintaining CCyR for at least 6 months were 97.9%, 99.3% and 100% for the imatinib, nilotinib 300 mg BID and nilotinib 400 mg BID arms, respectively. There were only very few events observed(5/655). Updated results on duration of CCyR every 12 months will be provided as a post authorisation commitment.

- Time in MMR

Time in MMR for both responders and non-responders, where for patients who never achieved MMR "time in MMR" was set to 0 days (loss of MMR at day 0), showed estimated rates of maintaining MMR for 12 months: 29.6%, 53.3% and 51.9% in imatinib 400 mg QD, nilotinib 300 mg BID and nilotinib 400 mg BID arms, respectively. The Kaplan-Meier estimates of time in MMR among all patients showed it is too early to conclude about time in MMR, because > 80 % of the patients were censored (as they were still in MMR).

- Rate of confirmed complete hematologic response (CHR) by 3 and 12 months

The rate of confirmed CHR by 12 months was slightly higher in the imatinib arm but the Cochran-Manzel-Haenszel test p-value for response rate in each nilotinib arm vs. the imatinib was non significant. The response for best CHR status by months 12 were n = 264, 93.3 % [95% CI: 89.7, 95.9], n = 253, 89.7 % [95% CI: 85.6, 93.0] and n = 249, 88.6 % [95% CI: 84.3, 92.1] in imatinib 400 mg QD, nilotinib 300 mg BID and nilotinib 400 mg BID arms, respectively.

Differences in response rate in each nilotinib arm vs. the imatinib arm for the rate of confirmed CHR by 3 months was even smaller and also non significant.

- Long-term outcomes

Event-free survival (EFS)

Table 9 – Kaplan-Meier estimates of EFS on treatment – Study CAMN107A2303 (FAS)

Efficacy parameter	Imatinib 400 mg QD N = 283	Nilotinib 300 mg BID N = 282	Nilotinib 400 mg BID N = 281
Event-free survival (months)			
Number of events / censored	13/270	6/276	1/280
Median [95% CI]	NA [NA]	NA [NA]	NA [NA]
25^{th} -75^{th} percentiles	NA	NA	NA
Range (events)	1.5-18.9	1.0-11.2	8.1-8.1
Range (all patients)	0.0-22.3	0.0-22.5	0.0-22.1
Hazard ratio (HR) vs. imatinib		0.4428	0.2756
95% CI for hazard ratio		(0.1682, 1.1656)	(0.0997, 0.7623)
Log-rank test p-value (vs. imatinib)		0.0898	0.0012
Estimated rate (%) [95% CI] at			
3 months	99.3 [98.2, 100]	99.6 [98.9, 100]	100 [100, 100]
6 months	97.0 [95.0,99.0]	98.5 [97.0, 100]	100 [100, 100]
9 months	96.6 [94.4,98.8]	98.1 [96.4,99.7]	99.6 [98.8, 100]
12 months	95.7 [93.1,98.2]	97.6 [95. 7,99.5]	99.6 [98.8, 100]

Log-rank test is stratified by Sokal risk group

Progression-free survival (PFS) on treatment

Table 10 – Kaplan-Meier estimates of PFS on treatment – Study CAMN107A2303 (FAS)

Efficacy parameter	Imatinib 400 mg QD N = 283	Nilotinib 300 mg BID N = 282	Nilotinib 400 mg BID N = 281
Progression-free survival (months)			
Number of events / censored	11/272	4/278	1/280
Median [95% CI]	NA [NA]	NA [NA]	NA [NA]
25th-75th percentiles	NA	NA	NA
Range (events)	1.5-18.9	1.0-7.7	8.1-8.1
Range (all patients)	0.0-22.3	0.0-22.5	0.0-22.1
Hazard ratio (HR) vs. imatinib		0.3460	0.2997
95% CI for hazard ratio		(0.1101, 1.0873)	(0.1076, 0.8343)
Log-rank test vs. imatinib		0.0570	0.0037
Estimated rate (%) [95% CI] at			
3 months	99.6 [98.9, 100]	99.6 [98.9, 100]	100 [100, 100]
6 months	97.4 [95.4,99.3]	98.9 [97.6, 100]	100 [100, 100]
9 months	97.0 [94.9,99.0]	98.5 [97.0, 100]	99.6 [98.8, 100]
12 months	96.5 [94.3,98.8]	98.5 [97.0, 100]	99.6 [98.8, 100]

Log-rank test is stratified by Sokal risk group

Progression to AP/BC on treatment

The patients who progressed to AP or BC on treatment were 11 in the imatinib arm, 2 in the nilotinib 300 mg BID arm and 1 in the nilotinib 400 mg BID arm. None of these 14 patients achieved MMR during the study. Three of the 11 patients in the imatinib arm who progressed to AP/BC achieved CCyR during the study. The log-rank test vs. imatinib was statistically significant, p= 0.0095, for nilotinib 300 mg BID and also statistically significant, p= 0.0037, for nilotinib 400 mg BID. The estimated rates of patients free from progression to AP/BC at 12 months were 96.5%, 99.3% and 99.6%, respectively. When considering also patients with clonal evolution as having progressed to AP/BC, 5 additional patients in the imatinib treatment arm and 2 additional patients in the nilotinib 400 mg BID arm were considered as having progressed to AP/BC by the cut off date.

Overall survival (OS)

Table 11 – Kaplan-Meier estimates of OS – Study CAMN107A2303 (FAS)

Efficacy parameter	Imatinib 400 mg QD N = 283	Nilotinib 300 mg BID N = 282	Nilotinib 400 mg BID N = 281
Overall survival (months)			
Number of events / censored	4/279	3/279	2/279
Median [95% CI]	NA [NA]	NA [NA]	NA [NA]
25th-75th percentiles	NA	NA	NA
Range (events)	6.9-13.3	5.9-14.5	8.8-11.0
Range (all patients)	0.2-22.4	0.1-23.0	0.1-22.5
Hazard ratio (HR) vs. imatinib		0.7796	0.7108
95% CI for hazard ratio		(0.1743, 3.4866)	(0.3042, 1.6608)
Log-rank test vs. imatinib		0.7439	0.4215
Estimated rate (%) [95% CI] at			
3 months	100 [100, 100]	100 [100, 100]	100 [100, 100]
6 months	100 [100, 100]	99.6 [98.9, 100]	100 [100, 100]
9 months	99.3 [98.3, 100]	99.3 [98.3, 100]	99.6 [98.9, 100]
12 months	99.3 [98.3, 100]	99.3 [98.3, 100]	99.2 [98.2, 100]

Log-rank test is stratified by Sokal risk group

The estimated OS rate (%) at 12 months was 99.3, 99.3 and 99.2 in the treatment groups respectively. The log-rank test vs. imatinib was non significant for both nilotinib doses. The MAH committed to provide yearly updates on overall survival.

3.3.4 Clinical studies in special populations

No studies in special populations were submitted. It is reflected in the SmPC that the safety and efficacy of Tasigna in paediatric patients from birth to less then 18 years have not yet been established. Therefore its use in paediatric patients is not recommended due to a lack of data on safety and efficacy. Hepatic impairment is known from earlier studies to have a modest effect on the pharmacokinetics and is reflected in the SmPC. Since nilotinib is metabolized and not renally excreted total body clearance is not anticipated to decrease in patients with renal impairment which is also reflected in the SmPC.

3.3.5 Supportive studies

Study CAMN107A2101E2 was a Phase II open-label, non-randomized study conducted to evaluate the efficacy and safety of nilotinib in patients with imatinib resistant or intolerant CML-CP.

Study CAMN107A2101E1 was a Phase II open-label, non-randomized study conducted to evaluate the efficacy and safety of nilotinib in patients with imatinib resistant or intolerant CML-AP.

These were the pivotal studies of the initial marketing authorisation of Tasigna.

The 24-month follow-up data from these studies were considered as supportive of this application and the long term efficacy data are summarised in the table below.

Table 12 – Summary of Results from 24 months follow-up for Study CAMN107A2101E1 and Study CAMN107A2101E2

	Study CAMN107A2101E1	**Study CAMN107A2101E2**
Type of study	Open-label randomized phase II study	Open-label randomized phase II study
Type of patients	imatinib-resistant or intolerant CML-AP	imatinib-resistant or intolerant CML-CP
Number of patients	137	321
Still in treatment at cut-off, n (%)	20 (14.6%)	124 (38.6%)
Reasons for discontinuations	Disease progression: 43.8% AE´s: 17.5%	Disease progression: 27.4% AE´s: 19.0%
Median treatment duration (months)	8.7	18.4
Primary endpoint	Best overall confirmed HR which includes CHR, marrow response or no evidence of leukemia and return to chronic phase	Best overall rate of MCyR
Results from the ITT population	69/137 (50.4%) achieved confirmed HR (95% CI: 41.7%-59.0%) 41/137 (29.9%) patients achieved CHR.	165/321 (51.4%) achieved MCyR 118/321 (36.8%) achieved CCyR.
Duration of MCyR (study CAMN107A2101E2)	------	76.8% (95% CI: 69.6%-84.0%) who achieved MCyR were maintaining response at 24 months. The median duration had not been reached at the time of data cut-off.
Duration of HR (study CAMN107A2101E1)	53.0% (95% CI: 39.2% - 66.7%) Median duration of confirmed HR was 24.2 months	-------
Time to progression **[to AP/BC in Study CAMN107A2101E2]** **[to BC in Study CAMN107A2101E1]**	15,9 months	Median time to progression to AP/BC has not been reached at the time of data cut-off.
Overall Survival (estimated rate)	70% (95% CI: 62.0% – 77.9%)	87% (95% CI: 83.3–90.9)

The patients in the supportive studies are different from the patients in the proposed indication. The primary endpoints are different from another and from the primary endpoint in the pivotal study. A direct comparability is therefore not possible. However, the supportive studies show that a majority of patients maintained their responses at 24 months. These data sets have also been submitted as post-authorisation commitments (FUM 032 and FUM 033) and the product information has been updated accordingly in variation EMEA/H/C/798/II/0031 (Commission Decision on 26 August 2010).

The Study CSTI571A0106 PCR Report (conducted with imatinib) was included in this submission to support the validity of Major Molecular Response (MMR) at 12 months as a predictive endpoint of long term outcome and as the primary efficacy variable in study CAMN107A2303. The use of MMR as a relevant surrogate primary endpoint is based on long-term (84 months) results from the pivotal study of Imatinib (Glivec), study CSTI571A0106. A scientific advice was provided in 2005 for that study CSTI571A0106, where the CHMP accepted MMR at 12 month as an appropriate primary endpoint supported by secondary endpoints.

3.3.6 Discussion on clinical efficacy

The purpose of this submission is to extend the therapeutic indication and seek approval for Tasigna in the treatment of adult patients with newly diagnosed Philadelphia chromosome positive (Ph+) chronic myelogenous leukemia in chronic phase (CML-CP).

The efficacy and safety of nilotinib in newly diagnosed patients with CML-CP have been evaluated in a phase III, multi-center randomized, open-label study comparing two different doses of nilotinib (300 mg bid and 400 mg bid) with imatinib 400 mg qd (Study CAMN107A2303). Patients were randomized 1:1:1 to nilotinib 300 mg bid (282 patients), nilotinib 400 mg bid (281 patients) or imatinib 400 mg qd (283 patients).

The open-label design of the pivotal study is of minor concern because the majority of the molecular, cytogenetic and haematological endpoints are objectively determined.

The inclusion/exclusion criteria were adequate and reflected the proposed indication and the anticipated risks involved in the treatment with nilotinib and imatinib.

MMR at 12 months defined as </= 0.1% BCR/ABL ratio measured by RQ-PCR was chosen as primary endpoint. The use of MMR as a relevant surrogate primary endpoint is based on long-term (84 months) results from the pivotal study of Imatinib (Glivec), study CSTI571A0106. A scientific advice was provided in 2005 for that study CSTI571A0106, where the CHMP accepted MMR at 12 month as an appropriate primary endpoint supported by secondary endpoints.

It is well known that molecular monitoring of CML patients by real time quantitative PCR (RQ-PCR) is of clinical value. However, there have been some difficulties in standardizing the RQ-PCR analysis. Progress has been made following proposals for new International Scale for the BCR-ABL measurement. All analysis of BCR/ABL transcripts was made at one single independent central reference laboratory. The MAH made efforts in order to minimize the difficulties there are to overcome problems of standardizing the RQ-PCR analysis.

The secondary endpoints were considered relevant to support the primary endpoint and as part of CML response criteria.

Baseline characteristics were well balanced across the treatment arms and the study population reflected the target population of the intended indication.

For the primary endpoint, the MMR at 12 months rates were as follows: 63/283 patients (22.3%) treated with imatinib achieved MMR, compared to 125/282 patients (44.3%) in the nilotinib 300 mg BID arm ($p<0.0001$ vs. imatinib) and 120/281 patients (42.7%) in the nilotinib 400 mg BID arm ($p<0.0001$ vs. imatinib). These are very promising results indicating substantial higher efficacy for the second generation TKI nilotinib as compared to imatinib. However, longer follow-up is needed for conclusive results on risk of progression to AP/BC and on overall survival which will be submitted as a post-authorisation commitment.

The MMR rate reported with imatinib in this pivotal study appeared to be lower than would have been expected based on literature data (Glivec Summary of product Characteristics and Hughes TP, NEJM 2003), where MMRs ≥ 39% have been reported. The molecular monitoring in CAMN107A2303 followed the relatively new standardization of molecular monitoring for chronic myeloid leukemia. Furthermore one central PCR laboratory performed all the analysis. This ensures comparable and precise results. If MMR status is only determined for those subjects who achieved CCyR (as in study CSTI571A0106 comparing imatinib to IFN + Ara-C), the rate of MMR is expected to be higher compared to measuring in all patients. Therefore, the MAH provided satisfactory responses as to the robustness of the submitted results and to the reasons for any discrepancies seen to previous published data.

The results for the key secondary endpoint "durable MMR" at 24 months are not available yet. The MAH has committed to submit the results as soon as they are available.

The main secondary efficacy endpoint best CCyR rates by 12 months were higher in the nilotinib treatment arms compared to the imatinib treatment arm. The differences in the nilotinib best CCyR rates were significant when compared to imatinib best CCyR.

Secondary endpoints for which only statistical significance for nilotinib 400 mg B.I.D treatment arm (and non significant for nilotinib 300 mg B.I.D treatment arm) was seen were the long-term outcomes EFS and PFS. The results are immature (too few events) and therefore it is difficult to conclude.

The results for secondary endpoints requiring longer follow-up "Duration of responses (MMR, CCyR)" and "Time in MMR" are currently not available.

The study was not powered to detect a difference in efficacy between the two doses of nilotinib. The dose of nilotinib 300 mg BID was selected as the optimal dose referring to the SmPC. The nilotinib 300 mg BID treatment arm met the primary endpoint and the same secondary endpoint as the nilotinib 400 mg B.I.D treatment arm except for the long-term outcomes EFS and PFS which was only met for nilotinib 400 mg B.I.D treatment arm. These two long-term endpoints are considered important. Thus far, there is no indication that efficacy as measured by MMR or CCyR is impaired by the lower dose of nilotinib. However, the MAH has committed to submit further analyses comparing the nilotinib 300 mg and 400 mg arms when 24 months data become available and to further comment on the proposed dose recommendation at that time.

Nilotinib as well as dasatinib are known to be effective in patients with Ph+ CML that have relapsed after prior use of imatinib. However, the efficacy of treatment when used after refractoriness to or relapse after nilotinib is yet unknown. The MAH committed to make proposals to prospectively collect response data (type, magnitude and duration) in patients receiving second line therapy after relapse or disease progression with nilotinib.

3.3.7 Conclusions on the clinical efficacy

MMR at 12 months for both doses of nilotinib was substantially higher than for imatinib and the differences are statistically significant and are considered to be of clinical importance. Support was given from the majority of secondary endpoints. Analyses of OS and some other long term secondary endpoints [Duration of responses (MMR, CCyR), time in MMR] were immature as very few events had happen and therefore no conclusion can be drawn yet. On the other hand no detrimental effect on any secondary endpoint was seen when compared to the only approved other effective standard medication for the new proposed indication.

3.4 Clinical safety

Patient exposure

In this application, the safety data was primarily generated from the pivotal Phase III study CAMN107A2303 with newly diagnosed patients with CML-CP. Eight hundred and thirty-six (836) patients who had at least one dose of study drug were included in the safety population.

Supportive safety data was also provided with 24 month follow-up data from two Phase II treatment arms of a Phase IA/II study consisting of a total of 458 patients with imatinib-resistant or intolerant CML-CP (Study CAMN107A2101E2, n=321) and CML-AP (Study CAMN107A2101E1, n= 137) who were treated with nilotinib 400 mg b.i.d. for at least 24 months (unless discontinued).

Table 13 –Summary of safety studies

Study	Study type	Population	Patients treated	Treatment/dose (mg)	Median exposure (Range) in months
Pivotal Phase III study					
CAMN107A 2303	Phase III, open-label, randomized	Patients with newly diagnosed Ph+ CML-CP	280 279 277	imatinib/400 mg QD nilotinib/300 mg BID nilotinib/400 mg BID	13.8 (0.0-22.4) 13.8 (0.1-22.5) 13.8 (0.2-22.4)
Supportive Phase II studies					
CAMN107A 2101E2	Phase II, open-label	Patients with imatinib-resistant/ intolerant Ph+ CML-CP without other prior TKI treatment other than imatinib	321	nilotinib/400 mg BID	18.4 (0.0-36.0)
CAMN107A 2101E1	Phase II, open-label	Patients with imatinib-resistant/ intolerant Ph+ CML-AP without other prior TKI treatment other than imatinib	137	nilotinib/400 mg BID	8.7 (0.1-38.1)

Exposure (months)= (last dose − start date of study drug + 1) / 30.4375
CAMN107A2303: First patient randomized 06-Sep-07; Last patient randomized 30-Sep-08; Data cut-off 02-Sep-09
CAMN107A2101E2: First patient enrolled 21-Apr-05; Last patient enrolled 26-Apr-06;
Data cut-off for 120-DSUR 04-Sep-06; Data cut-off for 24 month CSR: 20-Apr-08
CAMN107A2101E1: First patient enrolled 09-May-05; Last patient enrolled 30-Jan-07;
Data cut-off for 120-DSUR 23-Sep-06; Data cut-off for 24 month CSR 29-Aug-08

Approximately 5300 patients (inclusive healthy volunteers, patients in expanded access and compassionate-use programs) have been exposed to nilotinib in Novartis-sponsored clinical studies as of 31 July 2009 (data lock point of the 4th PSUR). No unexpected or new safety concern was identified.

Adverse events

A summary of most frequent study drug-related adverse events (AEs) by preferred term is presented in Table 14. Overall, the pattern of study drug-related AEs were similar to what was observed for all AEs regardless of study drug relationship. Most of the AEs were grade 1-2.

The most frequently reported study drug-related AEs with higher rates in the nilotinib groups than in the imatinib group were rash, ALT increase, headache, alopecia, pruritus, and hyperbilirubinemia. The most frequently reported study drug-related AEs with higher rates in the imatinib group were nausea, muscle spasms, diarrhoea, neutropenia, leukopenia, vomiting, anaemia, and events related to oedema (peripheral, face, eyelid and periorbital oedema).

Table 14 – Adverse events suspected to be study-drug related by preferred term (at least 5% in any group) – Study CAMN107A2303 (Safety set)

	All grades			Grades 3-4		
	Imatinib 400 mg QD N = 280	Nilotinib 300 mg BID N = 279	Nilotinib 400 mg BID N = 277	Imatinib 400 mg QD N = 280	Nilotinib 300 mg BID N = 279	Nilotinib 400 mg BID N = 277
Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Patients with ≥ 1 suspected drug-related AE	256 (91.4)	249 (89.2)	262 (94.6)	94 (33.6)	103 (36.9)	120 (43.3)
Rash	32 (11.4)	86 (30.8)	100 (36.1)	4 (1.4)	1 (0.4)	7 (2.5)
Alanine aminotransferase increased	13 (4.6)	55 (19.7)	68 (24.5)	6 (2.1)	13 (4.7)	15 (5.4)
Headache	23 (8.2)	39 (14.0)	58 (20.9)	0	3 (1.1)	3 (1.1)
Nausea	86 (30.7)	32 (11.5)	54 (19.5)	0	1 (0.4)	3 (1.1)
Thrombocytopenia	48 (17.1)	48 (17.2)	52 (18.8)	22 (7.9)	28 (10.0)	31 (11.2)
Alopecia	11 (3.9)	22 (7.9)	36 (13.0)	0	0	0
Hyperbilirubinaemia	5 (1.8)	40 (14.3)	36 (13.0)	0	7 (2.5)	9 (3.2)
Pruritus	15 (5.4)	41 (14.7)	36 (13.0)	0	1 (0.4)	1 (0.4)
Aspartate aminotransferase increased	10 (3.6)	26 (9.3)	31 (11.2)	2 (0.7)	5 (1.8)	4 (1.4)
Neutropenia	56 (20.0)	40 (14.3)	29 (10.5)	37 (13.2)	33 (11.8)	23 (8.3)
Myalgia	28 (10.0)	27 (9.7)	28 (10.1)	0	1 (0.4)	0
Blood bilirubin increased	2 (0.7)	22 (7.9)	26 (9.4)	1 (0.4)	3 (1.1)	5 (1.8)
Fatigue	22 (7.9)	30 (10.8)	25 (9.0)	1 (0.4)	0	2 (0.7)
Vomiting	40 (14.3)	13 (4.7)	24 (8.7)	0	0	3 (1.1)
Anaemia	38 (13.6)	17 (6.1)	23 (8.3)	11 (3.9)	5 (1.8)	7 (2.5)
Dry skin	7 (2.5)	20 (7.2)	22 (7.9)	0	0	0
Arthralgia	19 (6.8)	16 (5.7)	21 (7.6)	0	0	0
Hypophosphataemia	17 (6.1)	22 (7.9)	21 (7.6)	4 (1.4)	3 (1.1)	5 (1.8)
Leukopenia	42 (15.0)	22 (7.9)	21 (7.6)	12 (4.3)	6 (2.2)	5 (1.8)
Lipase increased	10 (3.6)	22 (7.9)	19 (6.9)	7 (2.5)	18 (6.5)	10 (3.6)
Diarrhoea	60 (21.4)	22 (7.9)	18 (6.5)	3 (1.1)	2 (0.7)	0
Muscle spasms	67 (23.9)	20 (7.2)	17 (6.1)	2 (0.7)	0	2 (0.7)
Abdominal pain upper	14 (5.0)	25 (9.0)	16 (5.8)	2 (0.7)	1 (0.4)	0
Constipation	2 (0.7)	23 (8.2)	15 (5.4)	0	0	1 (0.4)
Oedema peripheral	38 (13.6)	14 (5.0)	15 (5.4)	0	0	0
Asthenia	19 (6.8)	20 (7.2)	14 (5.1)	0	1 (0.4)	1 (0.4)
Dyspepsia	8 (2.9)	10 (3.6)	14 (5.1)	0	0	0
Abdominal pain	8 (2.9)	15 (5.4)	12 (4.3)	0	0	1 (0.4)
Face oedema	23 (8.2)	1 (0.4)	6 (2.2)	1 (0.4)	0	0
Pain in extremity	19 (6.8)	11 (3.9)	6 (2.2)	1 (0.4)	0	1 (0.4)
Eyelid oedema	37 (13.2)	2 (0.7)	5 (1.8)	1 (0.4)	0	1 (0.4)
Periorbital oedema	34 (12.1)	1 (0.4)	2 (0.7)	2 (0.7)	0	0

AEs are presented in descending order of frequency according to the nilotinib 400 mg BID all grades group.

All of these adverse events related to identified or potential safety issues; significant bleeding, GI haemorrhages, pancreatitis, rash, hepatotoxicity, effusions and ischemic heart disease are known from earlier indications (Ph+CML-CP/AP with resistance or intolerance to prior therapy) and are reflected in the SmPC for the new proposed indication. The MAH has committed to submit safety updates of significant bleeding, hepatotoxicity, fluid retention, rash and ischemic heart disease as a follow-up measure.

Prolongation of QTc > 500 ms was not observed in the pivotal study. In the analysis of possible symptomatic QT prolongation, it was equal in the three treatment arms and no cases of torsade de pointes, sudden death, ventricular tachycardia, ventricular fibrillation and flutter, and seizures were found. The only adverse event that could potentially be related to QT interval prolongation was syncope. Three cases of syncope in each of the nilotinib treatment groups were found. There was no evidence that syncope in any of the patients was of cardiac origin.

The "abnormal QTcF interval values" and "change from baseline in QTcF interval" are higher in the nilotinib treatment arms compared to the imatinib arm (QTcF increase from baseline exceeding 60 ms was seen in 3 subjects, one in the nilotinib 300 mg BID group and 2 subjects in the nilotinib 400 mg BID group). Furthermore nilotinib 400 mg BID arm had higher values compared to the nilotinib 300 mg BID arm.

It is important to be particular observant concerning safety issues in the first line treatment of CML. Hence the precaution measures in the SmPC of QT prolongation, interaction with other medicinal products and the undesirable effects are endorsed as well as the comprehensive RMP described on QT prolongation.

The MAH has committed to submit safety updates of "symptomatic QT prolongation" (Torsade de pointes, sudden death, ventricular tachycardia, ventricular fibrillation, ventricular flutter, syncope, convulsion) and QT interval values in the PSURs.

Serious adverse event/deaths/other significant events

Table 15 – Deaths, other serious or clinically significant adverse events or related discontinuations – Study CAMN107A2303 (Safety set)

Deaths, serious or significant events	Imatinib 400 mg QD N = 280 n (%)	Nilotinib 300 mg BID N = 279 n (%)	Nilotinib 400 mg BID N = 277 n (%)
AE(s)	275 (98.2)	274 (98.2)	273 (98.6)
Deaths within 28 days of discontinuation	0	2 (0.7)	1 (0.4)
Serious AEs (including death)	38 (13.6)	34 (12.2)	48 (17.3)
Drug-related serious AEs	13 (4.6)	11 (3.9)	24 (8.7)
AEs leading to discontinuation	25 (8.9) [1]	19 (6.8)	30 (10.8) [2]
Drug-related AEs leading to discontinuation	24 (8.6)	18 (6.5)	28 (10.1)
AEs leading to dose adjustment or interruption	123 (43.9)	141 (50.5)	166 (59.9)

[1] 24 patients from the imatinib 400 mg QD randomized arm and 1 patient from nilotinib 400 mg QD randomized arm who was actually treated with imatinib.
[2] 31 patients discontinued from the nilotinib 400 mg BID. randomized arm (1 patient not counted in nilotinib 400 mg QD arm as the patient was actually treated with imatinib).

The three *deaths* which occurred on treatment or within 28 days of discontinuation were all from the nilotinib 300/400 mg groups (n =2 / n = 1). None of these 3 deaths were considered related to study drug by the investigator.

Table 16 –Serious adverse events regardless of relationship to treatment by preferred term (at least 2 patients in any group) – Study CAMN107A2303 (Safety set)

	All grades			Grades 3-4		
Preferred term	Imatinib 400 mg QD N = 280 n (%)	Nilotinib 300 mg BID N = 279 n (%)	Nilotinib 400 mg BID N = 277 n (%)	Imatinib 400 mg QD N = 280 n (%)	Nilotinib 300 mg BID N = 279 n (%)	Nilotinib 400 mg BID N = 277 n (%)
Patients with ≥ 1 SAE	38 (13.6)	34 (12.2)	48 (17.3)	24 (8.6)	25 (9.0)	33 (11.9)
Abdominal pain	2 (0.7)	2 (0.7)	4 (1.4)	0	2 (0.7)	2 (0.7)
Neutropenia	1 (0.4)	3 (1.1)	4 (1.4)	1 (0.4)	3 (1.1)	4 (1.4)
Thrombocytopenia	2 (0.7)	5 (1.8)	4 (1.4)	2 (0.7)	5 (1.8)	4 (1.4)
Back pain	1 (0.4)	1 (0.4)	3 (1.1)	1 (0.4)	1 (0.4)	1 (0.4)
Vomiting	3 (1.1)	1 (0.4)	3 (1.1)	1 (0.4)	0	2 (0.7)
Angina pectoris	1 (0.4)	1 (0.4)	2 (0.7)	1 (0.4)	1 (0.4)	1 (0.4)
Dyspnoea	0	1 (0.4)	2 (0.7)	0	1 (0.4)	1 (0.4)
Febrile neutropenia	0	1 (0.4)	2 (0.7)	0	1 (0.4)	2 (0.7)
Gastrointestinal haemorrhage	0	1 (0.4)	2 (0.7)	0	1 (0.4)	2 (0.7)
Hepatic function abnormal	0	0	2 (0.7)	0	0	2 (0.7)
Nausea	2 (0.7)	0	2 (0.7)	1 (0.4)	0	1 (0.4)
Headache	0	2 (0.7)	1 (0.4)	0	1 (0.4)	0
Pyrexia	2 (0.7)	1 (0.4)	1 (0.4)	0	0	0
Leukopenia	2 (0.7)	1 (0.4)	0	2 (0.7)	0	0
Rectal haemorrhage	0	2 (0.7)	0	0	1 (0.4)	0

SAEs are presented in descending order of frequency according to the nilotinib 400 mg BID all grades group.

The number of patients who experienced any study drug-related *serious adverse events* (SAE) by preferred term was low and the frequencies were comparable across treatment groups.

Laboratory findings

Haematology: Patients with newly occurring or worsening haematology abnormalities in the pivotal study were very frequently reported. The percentage of patients experiencing newly occurring or worsening haematology abnormalities was bigger in the Imatinib treatment arm compared to both nilotinib arms, both in all grades and in grade 3-4 with the exception of grade 3-4 decrease in platelet count. The proportion of newly occurring or worsening haematology abnormalities when comparing the two nilotinib arms are either more frequent in the nilotinib 300 mg BID or in the two treatment arms, except for the platelet counts. The haematology abnormalities are described in the currently approved indication as well.

Clinical chemistry: The most frequent newly occurring or worsening biochemistry abnormalities (all grades) in the nilotinib treatment arms were: ALT increase (65.9% / 73.3%), bilirubin increased (53.4 / 61.7 %), AST increased (40.1 / 48.4%), hyperglycaemia (35.8 / 40.8%), phosphate decreased (31.5 /33.9%), lipase increased (24.0 / 28.9%), alkaline phosphatase increased (21.1 / 27.4 %) and amylase increased (15.1 /18.4%) in the nilotinib 300 mg BID and nilotinib 400 mg BID respectively.

Most frequent occurring or worsening biochemistry abnormalities in the nilotinib arms compared to the imatinib arm were bilirubin increased, hyperglycaemia, lipase increased and cholesterol increased.

The biochemistry abnormality phosphate decreased, alkaline phosphatase increased, hypocalcemia, creatinine increased and hypokalaemia were more frequent in the Imatinib arm.

Discontinuation due to adverse events

AEs (all grades) leading to discontinuation had the lowest frequency in the nilotinib 300 mg BID group (6.8%), followed by the imatinib group (8.9%) and the nilotinib 400 mg BID group (10.8%). The AEs most frequently leading to discontinuation were thrombocytopenia (0.7, 1.1, 2.5%), neutropenia (1.4, 1.1, 0.7%), hyperbilirubinemia, (0.4, 1.4, 0.7%), ALT increased (1.1, 0.4, 0.4%) and platelet count decreased (0.4, 0.4, 0.7%) in the imatinib/nilotinib300 mg BID/ nilotinib 400mg BID respectively. Thrombocytopenia, neutropenia, and platelet count decreased were mainly grade 3-4. Hyperbilirubinemia and ALT increased were mainly grade 1-2. Discontinuations due to hyperbilirubinemia and thrombocytopenia were more frequent with nilotinib than imatinib, whereas discontinuations due to ALT increase were more frequent with imatinib.

The frequency of AEs (all grades) leading to dose interruption or dose reduction was lowest in the imatinib group (43.9%), followed by the nilotinib 300 mg BID group (50.5%) and the nilotinib 400 mg BID group (59.9%). The most frequent AEs leading to dose interruption or reduction with the highest incidence in one of the nilotinib treatment arms were ALAT increased (11.5/15.2%), thrombocytopenia (9.0/11.6%) and rash (3.2/6.9%) in the nilotinib300 mg BID/ nilotinib 400mg BID respectively. The corresponding frequency for imatinib were ALAT increased (3.2%), thrombocytopenia (8.9%) and rash (0.7%). The most frequent AE leading to dose interruption or reduction with the highest incidence in one of the nilotinib treatment arms was neutropenia (12.5%) with corresponding frequency for nilotinib 300 / 400 mg BID of 11.8 / 7.6% respectively. The majority of thrombocytopenia and neutropenia reports were grade 3-4 in all three treatment groups.

Supportive safety data

An overview of safety data generated since the last update (data cut-off of 23 September 2006) in studies CAMN107A2101E1 and CAMN107A2101E2 has been presented. The safety data generated in both studies is considered supportive for the present submission. It includes safety data from a total of 458 patients with imatinib resistant or intolerant CML-CP or CML-AP who completed 24 months of treatment or discontinued early (data cut-off of 29 August 2008).

The two study groups CML-CP and CML-AP are not quite comparable with those patients in the pivotal study, submitted for the first line indication because they have been ill for longer time (half of them > 5 years), they have received prior imatinib and approximately 90% received other neoplastic treatment as well. However, the types of the most frequent AEs are consistent with that of the pivotal study.

Concerning the QTc prolongation absolute QTcF > 480 has increased from 1.6 % to 2.2%in the CML-CP group and from 0% to 2.9% in the CML-AP group. The absolute QTcF > 500 ms has increased from 0.9% to 1.2% in the CML-CP group with no cases in the CML-AP group. A total of 6.2% and 10.2% withdrew their consent in the CML-CP and CML-AP current analysis respectively. It has doubled compared to the last update with data cut-off of 23 September 2006.

Post marketing experience

Tasigna is currently approved in more than 80 countries worldwide and is indicated for the treatment of chronic phase and accelerated phase Ph+ CML in adult patients resistant or intolerant to at least one prior therapy including imatinib. The post-marketing experience with nilotinib has been reviewed on an ongoing basis in the Periodic Safety Update Reports.

All potential risks (sudden death, ischemic heart disease, cardiac failure, drug-induced liver injury, photosensitivity, diabetes mellitus, severe cutaneous adverse reactions, hyperthyroidism) and identified risks (QT prolongation, myelosuppression, severe hemorrhage, severe infections, pancreatitis, fluid retention, hypophosphatemia) in the nilotinib Risk Management Plan (RMP) have been reviewed cumulatively, and no significant differences in the overall frequency or pattern of these risks have been identified.

The safety profile of nilotinib remains consistent with the information provided in the core datasheet of the product. There are no new events reported from post-marketing experience which have not previously been observed during clinical trials.

3.4.1 Discussion on clinical safety

The safety database supporting this new indication in adult patients with newly diagnosed Philadelphia chromosome positive (Ph+) chronic myelogenous leukemia in chronic phase (CML-CP) consisted of patients from the pivotal phase III study CAMN107A2303 and included 836 patients, 556 of whom received nilotinib treatment.

Overall the risk profile of imatinib and nilotinib seems to be well known. However, as imatinib is the first line standard treatment in CML-CP and was approved some years earlier, the long-term safety database for imatinib is more substantiated. Long-term safety data on nilotinib from the pivotal trials in the second line treatment are available, which failed to identify signals for previously unknown late onset toxicity at the 24 month analysis.

In pivotal study CAMN107A2303, most AEs were grade 1-2. The most frequently reported AE with higher incidence in the nilotinib 300/400 mg B.I.D compared to the imatinib group were rash, headache and ALAT increase in the nilotinib 300 mg BID and 400 mg BID group respectively. The most frequently reported AE with higher incidence in the imatinib group compared to nilotinib 300/400 mg BID were nausea, diarrhea, muscle spasms and vomiting. Furthermore, oedema was seen more frequently in the imatinib arm.

The incidence of SAEs was lowest in the nilotinib 300 mg BID group (12.2%), followed by the imatinib group (13.6%) and the nilotinib 400 mg BID group (17.3%). By preferred term, the frequencies of SAEs were comparable across treatment groups. No SAE was experienced by more than 5 patients in any treatment group. The number of patients who experienced any study drug-related SAE by preferred term was small and the frequencies were comparable across treatment groups. The most frequent SAEs that were experienced by at least 3 patients in any treatment group were (in a decreasing order of frequency) thrombocytopenia, neutropenia, abdominal pain, vomiting and back pain.

Overall, no concerns are raised when comparing imatinib with nilotinib concerning discontinuations. Adverse events leading to dose interruptions or dose reductions were lowest in the imatinib group compared to the nilotinib groups.

The incidences of AEs related to cardiac disorders were low overall, mostly grade 1-2, and slightly more frequent in the nilotinib groups than in the imatinib group. The incidence of AEs related to ischemic heart disease was higher in the nilotinib 400 mg BID group (2.5%) than in the two other study groups (0.7% each). Approximately half of these AEs in each group were grade 3-4. These AEs were considered study drug-related by the investigator in 1.1% of patients in the nilotinib 400 mg BID group, and one of these AEs led to discontinuation due to angina pectoris. The frequencies of SAEs were in line with those of AEs.

Although it is noticed the "symptomatic QT prolongation" was equal in the three treatment-arms and no episode of torsade de pointes or sudden death was observed, the "abnormal QTcF interval values" and "change from baseline in QTcF interval" are higher in the nilotinib treatment arms compared to the Imatinib arm. Furthermore nilotinib 400 mg BID arm had higher values compared to the nilotinib 300 mg B.I.D arm. In the supporting studies, QTcF increased with time. The clinical significance of the "abnormal QTcF interval values" and "change from baseline in QTcF interval" has been adequately discussed by the MAH.

Pancreatitis was reported as an AE for 2 patients in the imatinib group, 3 patients in the nilotinib 300 mg BID group and 5 patients in the nilotinib 400 mg BID group. All were grade 1-2, and all except one were considered study drug-related by the investigator. One patient in the imatinib group and one patient in the nilotinib 400 mg BID group discontinued the study due to AEs of acute pancreatitis suspected to be study drug-related by the investigator.

Hepatotoxicity AEs were reported more frequently in the nilotinib 400 mg BID group compared to other treatment groups. No grade 3-4 hepatotoxicity events were observed in the nilotinib 300 mg BID group. The incidence of hepatotoxicity AEs related to study drug was higher in the nilotinib groups compared to imatinib. The majority of those AEs were of grades 1-2, seldom led to study drug discontinuation, and occasionally led to dose interruption or dose reduction.

Patients with newly occurring or worsening haematology abnormalities in the pivotal study are very frequently reported. The percentage of patients experience newly occurring or worsening haematology abnormalities is bigger in the imatinib treatment arm compared to both nilotinib arms.

Most frequent occurring or worsening biochemistry abnormalities in the nilotinib arms compared to the imatinib arm were bilirubin increased, hyperglycaemia, lipase increased and cholesterol increased. The biochemistry abnormality phosphate decreased, alkaline phosphatase increased,

hypocalcaemia, creatinine increased and hypokalaemia were more frequent in the imatinib arm. Except for increased cholesterol all the biochemistry abnormality are known from currently approved indication (Ph+CML-CP/AP with resistance or intolerance to prior therapy), they are mainly of grade 1-2 and do not raise new concerns.

Overall a total of 9 (1.1 %) patients died during the pivotal study. No more deaths occurred in each nilotinib treatment arm compared to the imatinib arm. But the three deaths which occurred on treatment or within 28 days of discontinuation were all from the nilotinib 300/400 groups (n =2 / n = 1). None of these 3 deaths were considered related to study drug by the investigator. No special concerns are raised.

3.4.2 Conclusions on the clinical safety

Nilotinib is proposed for first line treatment in adult patients with newly diagnosed Ph+ CML-CP. Safety issues and the risks linked are always of concern especially in first line treatment of a disease where other treatment options are available. The most frequently reported AE in the nilotinib groups were rash, headache and ALAT increase. In the imatinib group it was nausea, diarrhoea, muscle spasms and vomiting. Abnormal QTcF interval values and QTcF changes from baseline were found to be higher in the nilotinib groups although no difference in the symptomatic QT prolongation was seen. The clinical significance has been satisfactorily discussed. Furthermore long term safety data is important. The MAH has committed to provide long term safety data. In conclusion, the safety profile of nilotinib did not indicate any new or unexpected major safety concerns.

3.4 Risk management plan

In this application, the MAH submitted an update to the risk management plan (version 8.1). No new safety concerns have been identified in the clinical trial program supporting the new proposed indication, and therefore the pharmacovigilance plan has not been changed. This is endorsed. Regarding risk minimisation the MAH has chosen to manage most of the risks associated with nilotinib treatment by labelling and routine pharmacovigilance. Additionally, the MAH is carrying out risk minimisation activities in the form of educational material for selected safety concerns. The proposed additional risk minimisation activities have not been changed from the last RMP and are still adequate. The MAH has also adequately considered how medication errors can be reduced for the new proposed indication.

Table 17 –Summary of the risk management plan

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Important identified risks		
QT prolongation	Routine pharmacovigilance activities including cumulative analysis in PSUR. Follow-up of serious cases of prolonged QT interval, ventricular arrhythmia, sudden death, and syncope received from spontaneous and post marketing surveillance and in global clinical trials, using a targeted questionnaire/checklist. Collect additional categorical QT safety data in two open-label, randomized studies with ongoing monitoring of ECGs and echocardiograms (CAMN107A2303) and monitoring of overall safety data through patient disposition, death listings and Investigator Notifications (CAMN107A2201) by DMC. Monitoring of ECG data in global clinical trials. Expedited safety reporting to the FDA.	**Routine Risk Minimisation Activities** This item is communicated through current labelling: SPC Sections 4.4 and 5.3. Relevant preferred terms reported as ADRs in SPC Section 4.8. **Enhanced Risk Minimisation Activities** Educational material: Patient/Caregivers Material – all countries where allowed by local regulation Physicians/Pharmacists/Nurses Material
Myelo-suppression	Routine pharmacovigilance activities including cumulative analysis in PSUR. Follow-up of serious cases received from spontaneous and post marketing surveillance and in global clinical trials, using a targeted questionnaire/checklist. Monitoring of laboratory data in global clinical trials.	This item is communicated through current labelling: SPC Sections 4.2 and 4.4. Relevant preferred terms reported as ADRs in SPC Section 4.8.
Significant bleeding	Routine pharmacovigilance activities including cumulative analysis in PSUR. Follow-up of serious cases received from spontaneous and post marketing surveillance and in global clinical trials, using a targeted questionnaire/checklist.	Relevant preferred terms reported as ADRs in SPC Section 4.8.
Severe infections	Routine pharmacovigilance activities including cumulative analysis in PSUR. Follow-up of serious cases received from spontaneous and post marketing surveillance and in global clinical trials, using a targeted questionnaire/checklist.	Relevant preferred terms reported as ADRs in SPC Section 4.8.
Hepatic transaminase and bilirubin elevations	Routine pharmacovigilance activities including cumulative analysis in PSUR. Monitoring of laboratory data in global clinical trials. Targeted follow up as defined for Drug induced liver injury.	This item is communicated through current labelling: SPC Sections 4.2 and 5.3. Relevant preferred terms reported as ADRs in SPC Section 4.8.
Pancreatitis, lipase and amylase elevations	Routine pharmacovigilance activities including cumulative analysis in PSUR. Follow-up of serious cases received from spontaneous and post marketing surveillance and in global clinical trials, using a targeted questionnaire/checklist. Monitoring of laboratory data in global clinical trials.	This item is communicated through current labelling: SPC Sections 4.2, 4.4 and relevant preferred terms reported as ADRs SPC Section 4.8.

Rash	Routine pharmacovigilance activities including cumulative analysis in PSUR.	Relevant preferred terms reported as ADRs in SPC Section 4.8.
Fluid retention	Routine pharmacovigilance activities including cumulative analysis in PSUR. Follow-up of serious cases received from spontaneous and post marketing surveillance and in global clinical trials, using a targeted questionnaire/checklist.	Relevant preferred terms reported as ADRs in SPC Section 4.8. Educational material (EU only).
Blood glucose increase	Routine pharmacovigilance activities including cumulative analysis in PSUR Collect additional targeted laboratory data including fasting glucose, HbA1c, insulin levels and C-peptide in a Phase III open-label, randomized study of imatinib versus nilotinib (CAMN107A2303) with review of safety issues by DMC. Monitoring of laboratory data in global clinical trials. Targeted follow up as defined for Diabetes mellitus.	Relevant preferred terms reported as ADRs in SPC Section 4.8..
Hypo-phosphataemia	Routine pharmacovigilance activities including cumulative analysis in PSUR Monitoring of laboratory data in global clinical trials.	Relevant preferred terms reported as ADRs in SPC Section 4.8.
Important potential risks		
Sudden death	Routine pharmacovigilance activities including cumulative analysis in PSUR. Follow-up of serious cases received from spontaneous and post marketing surveillance and in global clinical trials, using a targeted questionnaire/checklist. Expedited safety reporting to the FDA. Collection of additional categorical QT safety data and moninotring of ECG data as defined for QT prolongation.	This item is communicated through current labelling: SPC Section 4.4 and 4.8; as pertains to QT prolongation, this is addressed in the additional risk minimization activities in Table 4-1
Ischaemic heart disease	Routine pharmacovigilance activities including cumulative analysis in PSUR. Follow-up of serious cases received from spontaneous and post marketing surveillance and in global clinical trials, using a targeted questionnaire/checklist. Collect additional cardiac safety data including ECGs and echocardiograms in two open-label, randomized studies with ongoing SAE monitoring (CAMN107A2303) and monitoring of overall safety data through patient disposition, death listings and Investigator Notifications (CAMN107A2201) by DMC. Expedited safety reporting to the FDA.	Relevant preferred terms reported as ADRs in SPC Section 4.8.

Cardiac failure	Routine pharmacovigilance activities including cumulative analysis in PSUR. Follow-up of serious cases received from spontaneous and post marketing surveillance and in global clinical trial reports, using a targeted questionnaire/checklist. Collect additional cardiac safety data including ECGs and echocardiograms in two open-label, randomized studies with ongoing SAE monitoring (CAMN107A2303) and monitoring of overall safety data through patient disposition, death listings and Investigator Notifications (CAMN107A2201) by DMC.	This item is communicated through current labelling: SPC Sections 4.2. Relevant preferred terms reported as ADRs in SPC Section 4.8. Educational materials (EU only).
Drug induced liver injury	Routine pharmacovigilance activities including cumulative analysis in PSUR. Follow-up of serious case received from spontaneous and post marketing surveillance and in global clinical trials, using a targeted questionnaire/checklist.	Relevant preferred terms reported as ADRs in SPC Section 4.8.
Photosensitivity	Routine pharmacovigilance activities including cumulative analysis in PSUR.	This item is communicated through current labelling SPC Section 5.3.; Relevant preferred terms reported as ADRs in SPC Section 4.8.
Diabetes Mellitus	Routine pharmacovigilance activities including cumulative analysis in PSUR. Follow-up of serious cases received from spontaneous and post marketing surveillance and in global clinical trials, using a targeted questionnaire/checklist. Collect additional targeted laboratory data including fasting glucose, HbA1c, insulin levels and C-peptide in a Phase III open-label, randomized study of imatinib versus nilotinib (CAMN107A2303) with review of safety issues by DMC.	Relevant preferred terms reported as ADRs in SPC Section 4.8.
Severe Cutaneous Adverse Reactions	Routine pharmacovigilance activities including cumulative analysis in PSUR. Follow-up of serious cases received from spontaneous and post marketing surveillance and in global clinical trials, using a targeted questionnaire/checklist.	Relevant preferred terms reported as ADRs in SPC Section 4.8.
Hyperthyroidism	Routine pharmacovigilance activities including cumulative analysis in PSUR.	Relevant preferred terms reported as ADRs in SPC Section 4.8.
Important identified interactions		
Strong CYP3A4 inhibitors	Routine pharmacovigilance activities including cumulative analysis in PSUR. Expedited safety reporting to the FDA.	**Routine Risk Minimisation Activities** This item is communicated through current labelling SPC Sections 4.4 and 4.5. **Enhanced Risk Minimisation Activities** Educational material: Patient/Caregivers Material – all countries where allowed by local regulation Physicians/Pharmacists/Nurses Material
Strong CYP3A4 Inducers	Routine pharmacovigilance activities including cumulative analysis in PSUR. Expedited safety reporting to the FDA.	This item is communicated through current labelling: SPC Sections 4.4 and 4.5. **Enhanced Risk Minimisation Activities** Educational material (EU only)

Food	Routine pharmacovigilance activities including cumulative analysis in PSUR. Expedited safety reporting to the FDA.	**Routine Risk Minimisation Activities** This item is communicated through current labeling SPC Sections 4.2, 4.4, 4.5 and 5.2. **Enhanced Risk Minimisation Activities** Educational material Patient/Caregivers Material – all countries where allowed by local regulation Physicians/Pharmacists/Nurses Material
Important potential interactions		
P-gp inhibitors	Routine pharmacovigilance activities including cumulative analysis in PSUR. Expedited safety reporting to the FDA.	This item is communicated through current labelling: SPC Section 4.5.
Drugs Eliminated by CYP3A4, CYP2C8, CYP2C9, CYP2D6 or UGT1A1 and P-gp Substrates	Routine pharmacovigilance activities including cumulative analysis in PSUR. Expedited safety reporting to the FDA. A drug-drug interaction clinical study is planned to evaluate the inductive effect of nilotinib on CYP enzymes (CAMN107A2128).	This risk is communicated through current labelling: SPC Section 4.5.
Drugs that may prolong the QT interval	Routine pharmacovigilance activities including cumulative analysis in PSUR. Expedited safety reporting to the FDA.	**Routine Risk Minimisation Activities** This item is communicated through current labelling SPC Sections 4.4 and 4.5. **Enhanced Risk Minimisation Activities** Educational materials Patient/Caregivers Material – all countries where allowed by local regulation Physicians/Pharmacists/Nurses Material
Hormonal contraceptives	Routine pharmacovigilance activities including cumulative analysis in PSUR. Expedited safety reporting to the FDA. A drug-drug interaction clinical study is planned to evaluate the inductive effect of nilotinib on CYP enzymes (CAMN107A2128).	This risk is communicated through current labelling as they pertain to CYP3A4 substrates: SPC Section 4.5.
Important missing information		
Pregnancy	Routine pharmacovigilance activities including review in PSUR. Pregnancy registry for imatinib and nilotinib (CSTI571A2403).	This item is communicated through current labelling: SPC Sections 4.6 and 5.3.
Paediatric patients	Routine pharmacovigilance activities including review in PSUR. A paediatric investigation plan has been agreed upon with the PDCO and FDA.	This item is communicated through current labelling: SPC Section 4.2.
Renal impairment	Routine pharmacovigilance activities including review in PSUR.	This item is communicated through current labelling: SPC Section 4.2.
Hepatic impairment	Routine pharmacovigilance activities including review in PSUR.	**Routine Risk Minimisation Activities** This item is communicated through current labelling SPC Sections 4.2 and 4.4. Relevant preferred terms reported as ADRs in SPC Section 4.8. **Enhanced Risk Minimisation Activities** Educational material Patient/Caregivers Material – all countries where allowed by local regulation Physicians/Pharmacists/Nurses Material

Patients with uncontrolled or significant cardiac disease	Routine pharmacovigilance activities including review in PSUR.	**Routine Risk Minimisation Activities** This item is communicated through current labelling SPC Sections 4.2 and 4.4. **Enhanced Risk Minimisation Activities** Educational material Patient/Caregivers Material – all countries where allowed by local regulation Physicians/Pharmacists/Nurses Material

The CHMP, having considered the data submitted in the application, is of the opinion that the current risk minimisation activities as described in the conditions or restrictions with regard to the safe and effective use of the medicinal product are adequate for the proposed new indication.

3.5 Benefit-risk balance

Benefits

- Beneficial effects

The efficacy and safety of nilotinib in newly diagnosed patients with CML-CP have been evaluated in a phase III, multi-center randomized, open-label study comparing two different doses of nilotinib (300 mg bid and 400 mg bid) with imatinib 400 mg q.d. (Study CAMN107A2303). Patients were randomized 1:1:1 to nilotinib 300 mg bid. (282 patients), nilotinib 400 mg bid (281 patients) or imatinib 400 mg q.d. (283 patients).

MMR rate at 12 months was doubled in both nilotinib arms in comparison to imatinib. There was no difference in MMR rate for the two doses of nilotinib. Consistent superiority was also demonstrated for secondary endpoints regarding cytogenetic response (CCyR, MCyR). Furthermore, significantly more patients progressed to AP/BC in the imatinib arm (n=11) than in both nilotinib arms (n=3) in the 12 month analysis.

These results indicate higher efficacy for nilotinib compared to imatinib. The response observed in terms of MMR rate and secondary endpoints is expected to result in a clinically relevant effect in terms of relevant long-term clinical endpoints.

- Uncertainty in the knowledge about the beneficial effects.

Overall 7-year survival for patients with newly diagnosed CML treated with imatinib is now 86%, therefore MMR is the only realistic primary endpoint. For patients achieving MMR the 7-year survival is close to 92% and the freedom from progression to AP/BC rate at 7-years is above 95%. Therefore, the long-term efficacy of nilotinib as compared to imatinib cannot be reliably assessed for many years. However, OS needs to be provided post approval on a yearly basis.

Another uncertainty is whether the selected first-line dose of nilotinib 300 mg BID may be inferior in terms of long-term efficacy as compared to the currently approved second-line dose of 400 mg BID. Thus far, there is no indication that efficacy as measured by MMR or CCyR is impaired by the lower dose of nilotinib. However, the dose issue needs to be revisited when 24 months data become available.

Risks

- Unfavourable effects

The observed safety profile for imatinib and nilotinib in the pivotal study was consistent with the known safety profile for both compounds. There were no new or unexpected major findings. The risk profiles of nilotinib and imatinib differ but are overall well known and, with exception of a significant trend for hyperlipidemia in particular hypercholesterinemia, no new safety signals were observed in the pivotal trial. Overall, nilotinib's hepatotoxicity and QT prolongation are the most important risk but seemed to be manageable provided the contraindications and warnings are followed. In conclusion, the safety profile of nilotinib 300 mg b.i.d. is different to but not worse than that of imatinib and is acceptable in the intended indication. It appears more favourable than for nilotinib 400 mg b.i.d.

The MAH is however asked to provide further discussion on the dose recommendation and also to commit to provide long term safety data on key safety issues.

- Uncertainty in the knowledge about the unfavourable effects

Currently only 12 months safety data are available. However, data for the key secondary endpoint will be available after 24 months. This will be submitted in the first quarter of 2011 as committed by the MAH.

Data on the frequency, types and time course of development of nilotinib resistant BCR/ABL mutations, in particular of the TKI- multiresistant mutation T315I may be helpful, however are very limited. At least it could be concluded that at the time being no single case of T315I mutation was identified.

Nilotinib as well as dasatinib are known to be effective in patients with BCR-ABL+ CML that have relapsed after prior use of imatinib. However, the efficacy of treatment when used after refractoriness to or relapse after nilotinib is yet unknown. The MAH committed to make proposals to prospectively collect response data (type, magnitude and duration) in patients receiving second line therapy after relapse or disease progression with nilotinib.

Benefit-risk balance

The higher MMR and CCyR at 12 months achieved with nilotinib as compared to imatinib for first-line use establishes the efficacy of nilotinib in this indication but longer follow-up is needed for conclusive results on the rate of progression to AC/BC and on overall survival.

The observed safety profile for nilotinib in the pivotal study was consistent with the known safety profile. There are so far no indications that nilotinib has any detrimental effects on OS as compared to imatinib. The safety was better for nilotinib 300 mg BID as compared to the currently approved dose of 400 mg BID. A small difference in QT prolonging effect in favour of imatinib needs careful monitoring including regular OS updates.

In conclusion, in view of the convincing efficacy data and no major concerns in terms of clinical safety, the benefit-risk balance is considered to be positive.

3.5.1 Discussion on the benefit-risk balance

Exhaustive clinical trial data were submitted to establish the efficacy of nilotinib based on 12 month data on MMR and other secondary endpoints. Although long-term data are lacking, the level of evidence presented is sufficient to expect that the effects observed at 12 months should result in a clinically relevant effect in terms of relevant long-term clinical endpoints.

The data submitted provide adequate reassurance for the efficacious and safe use of nilotinib in the first line treatment of chronic CML. It is considered acceptable that long-term data is submitted as a post-authorisation commitment.

In conclusion, in view of the convincing efficacy data and no major concerns in terms of clinical safety, the benefit-risk balance is considered to be positive.

3.6 Orphan medicinal products

3.6.1 imilarity with authorised orphan medicinal products

The CHMP is of the opinion that Tasigna is not similar to Sprycel but similar to Glivec within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000 (See appendix 1).

3.6.2 Market exclusivity

The holder of the marketing authorisation for Glivec has given his consent to the MAH.

3.7 Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Tasigna in the treatment of of adult patients with newly diagnosed Philadelphia chromosome positive chronic myelogenous leukaemia (CML) in the chronic phase was favourable and therefore recommended the granting of this extension of indication.

In addition, the CHMP, with reference to Article 8 of Regulation EC No 141/2000, considers Tasigna to be similar (as defined in Article 3 of Commission Regulation EC No. 847/2000) to Glivec for the same therapeutic indication.

However, the holder of the marketing authorisation for Glivec has given his consent to the MAH.

Furthermore, the CHMP takes note that the agreed Paediatric Investigation Plan is not fully completed. Only some of the measures have been completed as some of the studies are deferred. The CHMP reviewed the already available data of studies subject to this plan and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet (PL) has been submitted by the MAH and has been found acceptable for the following reasons: no significant changes are made to the PL.