Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Nilotinib

Proprietary Product Name: Tasigna

Sponsor: Novartis Pharmaceuticals Australia Pty Ltd

October 2011

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to Product Submission

Submission Details

Type of Submission:	Extension of Indications and New Strength
Decision:	Approved
Date of Decision:	26 August 2011
Active ingredient(s):	Nilotinib
Product Name(s):	Tasigna
Sponsor's Name and Address:	Novartis Pharmaceuticals Australia Pty Ltd 54 Waterloo Road North Ryde NSW 2113
Dose form(s):	Capsule
Strength(s):	150 mg and 200 mg
Container(s):	Blister pack
Pack size(s):	28 (weekly) 40, 42 and 112 and 120 (monthly) The weekly pack contains 2 calendar cards (daytime and night time) of 14 capsules or a carton of 28 capsules. The monthly pack consists of 4 packs of 28 capsules or 3 packs of 40 capsules.
Approved Therapeutic use:	Treatment of adult patients with newly diagnosed Philadelphia chromosome positive chronic myeloid leukaemia (CML) in chronic phase. Treatment of adults with chronic phase and accelerated phase Philadelphia chromosome positive chronic myeloid leukaemia (CML) resistant to or intolerant of prior therapy including imatinib.
Route(s) of administration:	Oral
Dosage:	Newly diagnosed Ph+ CML-CP: 300 mg twice daily Ph+CML –CP and CML-AP resistant to or intolerant to at least one prior therapy including imatinib: 400 mg twice daily
ARTG Number:	133086, 171498

Product Background

Nilotinib is an inhibitor of BCR-ABL tyrosine kinase, a protein produced as a result of the Philadelphia chromosome translocation t(9, 22) associated with chronic myeloid leukaemia (CML). Nilotinib (Tasigna) was first approved by the Therapeutic Goods Administration (TGA) on 14 January 2008 for:

the treatment of adults with chronic phase and accelerated phase Philadelphia chromosome positive myeloid leukaemia (CML) resistant to or intolerant of prior therapy including imatinib.

The recommended dose for these conditions is 400 mg twice daily.

This AusPAR describes the evaluation of a submission from Novartis Pharmaceuticals Australia Pty Ltd (the sponsor) to extend the indications of Tasigna (nilotinib) capsules to include:

the treatment of adult patients with newly diagnosed Philadelphia chromosome positive chronic myeloid leukaemia in chronic phase (Ph+ CML-CP).

The submission also seeks to register a new 150 mg strength of nilotinib to support the recommended dose of 300 mg twice daily for the new indication.

Following oral administration, nilotinib reaches peak serum concentration in 3 hours. Its bioavailability is low and variable but increases markedly with food. The drug is extensively metabolised in the liver primarily by cytochrome P450 (CYP) 3A4 and CYP3A5. The mean serum elimination half-life is 16 hours. Serious adverse effects include myelosuppression and cardiac, gastrointestinal and hepatobiliary disorders. Headache, fatigue and gastrointestinal and skin reactions are very common. There are significant potential drug interactions.

Similar registered products are imatinib (Glivec, Novartis) and dasatinib (Sprycel, Bristol-Myers Squibb). Both are registered for the first line Ph+ CML-CP indication. Dasatinib is limited to adults.

Regulatory Status

The product received initial ARTG Registration in January 2008. It was originally designated by the TGA as an Orphan Drug for "the treatment of patients with chronic myeloid leukaemia" on 9 June 2006.

The new indication has been approved in 56 countries to date, including the US, Europe countries, Canada and New Zealand. It was approved by the USA on 17 June 2010, Switzerland on 24 August 2010, the European Union (EU) on 20 December 2010, New Zealand on 14 April 2011 and Canada on 20 June 2011. The sponsor indicated that the clinical data submitted to the TGA was identical to that submitted to the EU and the USA.

Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality Findings

Quality Summary and Conclusions

A quality evaluation was conducted and the data were satisfactory. The 150 mg capsule is a direct scale of the 200 mg capsule.

III. Nonclinical Findings

Nonclinical Summary and Conclusions

There was no requirement for a nonclinical evaluation in a submission of this type.

IV. Clinical Findings

Introduction

The submission included four clinical studies. The pivotal study was a Phase III, multinational, multicentred, randomized, open label efficacy and safety study in 846 patients with newly diagnosed Philadelphia positive (Ph+) chronic myeloid leukaemia in the chronic phase (CML-CP) treated with nilotinib 400 mg twice daily (bd), nilotinib 300 mg bd or imatinib 400 mg once daily (qd). The primary efficacy endpoint of the pivotal study was the major molecular response (MMR) rate at 12 months. The submission included an exploratory polymerase chain reaction (PCR) study provided to support the validity of MMR at 12 months as a predictive endpoint of long term clinical outcome [CSTI571A0106 PCR]. This PCR study investigated the relationship between MMR at 12 months and disease progression at 84 months in 487 patients with CML-CP treated with imatinib in the International Randomized Study of Interferon and STI5171 trial (IRIS). The IRIS trial has been previously evaluated by the TGA and the current Glivec (imatinib) Product Information (PI) includes clinical data from this study.

The submission included two supportive studies which included 24 month follow up efficacy and safety data in 137 patients with Ph+ accelerated phase CML (CML-AP) and 321 patients with Ph+ CML-CP treated with nilotinib [CAMN107A2101E1 and CAMN107A2101E2]. These data were from the Phase II, CML-AP and CML-CP components of a Phase IA/II, multinational, multicentred, open label, dose escalation study to evaluate the safety, tolerability, biologic activity and pharmacokinetic profile of nilotinib in adult patients with imatinib resistant or intolerant CML (chronic phase [CP], accelerated phase [AP] or blast crisis [BC]), relapsed/refractory Ph+ acute lymphoblastic leukaemia (ALL) or other haematologic malignancies [CAMN107A2101]. This study has been previously evaluated by the TGA and the currently approved Tasigna PI includes short term clinical data from this study in CML-AP and CML-CP patients.

Pharmacokinetics

Introduction

The pivotal clinical efficacy and safety study included pharmacokinetic (PK) analyses in a full PK dataset in 34 patients and a population PK (POP-PK) dataset of 550 patients with 4936 PK samples. There were also exploratory PK/Efficacy and PK/Safety analyses. The results of the PK analyses were presented in the sponsor's pivotal *Clinical Study Report* (CSR) and in a separate Modelling Report for the POP-PK study which also included additional analyses of the POP-PK dataset. The POP-PK study was comprehensively documented and met all the requirements outlined in the TGA-adopted EU guideline document on reporting the results of POP-PK analyses.[1] The four populations for the PK analyses were: full PK set consisting of all patients with available full PK profile at any visit (global and Japanese groups); POP-PK set; PK/efficacy set (exploratory analysis) and PK/safety set (exploratory analysis).

Full PK Analysis

The full PK analysis was based on the individual concentration time profiles in the full PK population. The usual range of PK parameters was calculated using standard non-compartmental methods aided by WinNonlin Pro software. The results were summarised

[1] EMEA. Committee for Medicinal Products for Human Use (CHMP), 21 June 2007. Guideline on Reporting the Results of Population Pharmacokinetics Analysis, CPMP/EWP/185990/06.

for each treatment arm using standard statistical methods and dose proportionality analysis was conducted between nilotinib 300 mg bd and 400 mg bd. The focus in this AusPAR is on the results from the two nilotinib treatment arms. The full PK population included 34 patients treated with nilotinib, consisting of 19 patients from the "global" group (9 patients in the 300 mg bd arm and 10 patients in the 400 mg bd arm) and 15 from the "Japanese" group (8 patients in the 300 mg bd arm and 7 patients in the 400 mg bd arm). There were 3 patients excluded from the PK statistical analysis due to insufficient PK concentration data (1 in the 300 mg bd arm and 2 in the 400 mg bd arm of the global group).

The PK parameters in the pooled full PK group (global plus Japanese) are summarised in Table 1. The results for the pooled full PK group showed that steady state nilotinib serum concentrations following 300 mg bd or 400 mg bd were less than dose proportional. The pooled full PK data showed that the mean area under the serum concentration time curve from time zero to the last measurable concentration ($AUC_{0\text{-}tlast}$) was 13.4% higher in the 400 mg bd arm than in the 300 mg bd arm. The mean minimum serum concentration (C_{min}) was 5.9% higher and the maximum serum concentration (C_{max}) was 13.3% higher in the 400 mg bd arm than in the 300 mg bd arm. The results also showed marker inter-subject variability in all PK parameters. In a separate population PK modelling analysis, no significant differences were found in nilotinib PKs between Japanese and global patients.

Table 1: Pivotal Study - Summary of nilotinib PK parameters by treatment arm in the pooled full-PK group (global plus Japanese groups).

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 bd (n=16)							
Mean (SD)	1306 (723.6)	1540 (735.1)	13337 (6173.5)		29.2 (17.79)		844 (561.9)
CV% mean	55.4	47.7	46.3		61.00		66.6
Gmean	1123	1360	11865		25.28		700
CV% Gmean	64.1	58.6	56.8		56.84		71.7
Median	1250	1510	12957	2.00	23.2	12.00	780
[Min; Max]	[369; 2900]	[543; 2990]	[4520; 25764]	[0.00; 7.95]	[11.6; 66.4]	[11.90; 12.17]	[235; 2510]
Nilotinib 400 mg bd (n=15)							
Mean (SD)	1383 (664.4)	1746 (754.7)	15130 (6791.0)		32.8 (16.80)		924 (653.4)
CV% mean	48.1	43.2	44.9		51.27		70.7
Gmean	1239	1595	13656		29.29		777
CV% Gmean	51.9	47.0	51.3		51.28		65.7
Median	1160	1740	12535	2.00	31.9	12.00	837
[Min; Max]	[637; 2650]	[729; 3190]	[5723; 28950]	[0.00; 8.00]	[13.8; 69.9]	[11.38; 12.07]	[228; 3050]

POP-PK Set

Sparse nilotinib samples were collected in the majority of patients in either treatment arm for inclusion in the POP-PK study.[2] In the nilotinib treated patients POP-PK data set (n=550), 59.3% (n=326) were male and 40.7% (n=224) were female, the median age was 47 (range: 18 – 85) years in 550 patients, the median weight was 71.0 (range 34.5 - 162.0) kg in 542 patients, the median height was 168 (range 136 – 194) cm in 540 patients, the median body mass index (BMI) was 24.6 (range 14.9 – 56.9) kg/m^2 in 539 patients, 63.3% were Caucasian and 9.3% were Japanese with the majority of the rest of the population being Asian (non-Japanese) in a total of 550 patients. In the POP-PK set, 275 patients received nilotinib 300 mg bd and 267 received nilotinib 400 mg bd.

The trough (C_{min}) and peak (C_{max}) serum nilotinib concentrations remained relatively stable over 12 months of treatment with both nilotinib 300 mg bd and 400 mg bd. The summary statistics of the average peak and trough concentrations over 12 months are presented in Table 2. The mean nilotinib peak and trough concentrations over 12 months were approximately 14.8% and 15.7% higher, respectively, in the 400 mg bd arm than in the 300 mg bd arm, indicating less than dose proportionality. The inter-patient and intra-patient variability in nilotinib concentrations were similar in the 300 mg bd and 400 mg bd arms. The inter-patient variability (CV%) in the total population (n=542) for nilotinib (combined doses) was estimated to be 47.0% for mean trough concentration and 42.5% for mean peak concentration, while the intra-patient CV% was estimated to be 40.2% for the mean trough concentration and 33.7% for the mean peak concentration.

Table 2: POP-PK Set –Mean trough and peak nilotinib PK steady state exposure over 12 months

	Peak PK Exposure [1] ("Cmax")		Trough PK Exposure [2] ("Cmin")	
	300 mg bd (n=257)	400 mg bd (n=236)	300 mg bd (n=240)	400 mg bd (n=215)
Mean (SD)	1172 (509.6)	1346 (607.8)	1158 (567.9)	1340 (620.8)
CV% mean	43.5	45.2	49.0	46.3
Gmean	1070	1215	1025	1175
CV% Gmean	45.5	48.9	55.0	67.8
Median	1087	1268	1097	1217
[Min; Max]	[269; 34988]	[302; 3403]	[194; 4214]	[5; 3134]

[1] Average peak exposure (C_{max}) is the average 3 hour post-dose concentration over 12 months.

[2] Average trough exposure (C_{min}) is the average pre-dose concentration at steady state over 12 months.

Population Pharmacokinetic Analysis (POP-PK)

The purpose of the POP-PK analysis was to characterize the population PKs of nilotinib in adult patients with newly diagnosed CML-CP and to explore the potential relationship between nilotinib exposure and efficacy and safety endpoints in this target patient population. The POP-PK data were analysed using Nonlinear Mixed Effects Modelling (NONMEM) Software.

The POP-PK dataset included subjects who received the correct nilotinib dose and had no missing post-baseline PK measurements. Of the original 551 patients with a total of 5,520

[2] "Sparse" refers to a technique employed in population pharmacokinetic studies where a small number of samples are obtained from a large number of subjects.

samples of nilotinib in the PK dataset, 550 patients with a total of 4936 PK samples were included in the final dataset. Original samples were excluded from the final dataset if they had been invalidated due to vomiting, if patients received the wrong treatment, if a post-dose sample was taken at exactly the same time as the dose, if date and/or time was missing for a sample, if the concentration was zero, if the sample date was more than 1 day after the last dose, or if a second sample was taken at exactly the same date and time as another sample for the same subject and/or the previous dose time was not clinically feasible. The most common reason for excluding original samples from the final data set was nilotinib concentration being zero, which occurred predominantly in pre-dose samples taken before the first dose.

The structural PK model was a two compartment model, with a zero order process for the absorption of nilotinib and first order process for the elimination of nilotinib. The model parameters were estimated using the first order conditional estimation (FOCE) with INTERACTION, this is an accepted method of analysis and is described in the relevant TGA-adopted POP-PK guidelines. In the final model, clearance (CL) was estimated to be 20.7 L/h, the central volume of distribution (V_1) was estimated to be 75.6 L and the peripheral volume of distribution (V_2) was estimated to be 202 L. The inter-patient variability of nilotinib CL, V_1 and F1 (relative bioavailability) were estimated to be 0.084, 0.52 and 0.2, respectively.

The model identified only dose and gender as significant covariates affecting the relative bioavailability (F1) of nilotinib. Assuming F1=1 for the 300 mg bd dose, the population estimate of F1 was 0.842 for the 400 mg bd dose, indicating a 15.8% decrease in nilotinib bioavailability for the higher dose. The F1 value in males was 0.84 times that in females, indicating a 16% decrease in nilotinib bioavailability. The median steady state trough concentrations in female patients in the 300 mg bd and 400 mg bd arms were approximately 10% and 23% higher, respectively, than in males.

The model tested a number of factors for their effect on nilotinib CL and found that only normalised total bilirubin and aspartate aminotransferase (AST) significantly affected this parameter. Based on the final model, an increase in total bilirubin level from the upper limit of normal (ULN) to 1.5 X ULN, 2 X ULN and 2.5 X ULN was predicted to result in a 14%, 26% and 37% decrease in CL, respectively. These results suggest that significant elevation in total bilirubin may be associated with a moderate increase in nilotinib exposure. The underlying mechanism for the observed effect of total bilirubin on nilotinib CL is unknown. An increase in normalised AST from ULN to 1.5 X ULN and 2 X ULN was predicted to result in 2% and 4% decreases in CL, respectively.

The number of patients in the POP-PK analysis who received concurrent treatment with agents with the potential to alter nilotinib exposure was low (that is, CYP3A4 inhibitors and inducers, proton pump inhibitors [PPIs], H2 blockers). None of the relevant concurrent medications was found to have a significant impact on the PKs of nilotinib but results should be interpreted cautiously due to low patient numbers. The numbers of patients who received concurrent medications of interest were: 4 (0.7%) strong CYP3A4 inhibitors; 48 (8.7%) regular CYP3A4 inhibitors; 51 (9.3%) any CYP3A4 inhibitors; 2 (0.4%) CYP3A4 inducers; 75 (13.6%) PPIs; and 36 (6.6%) H2 Blockers.

Exploratory PK/Efficacy Analysis

The exploratory PK/Efficacy dataset consisted of 487 patients: complete cytogenetic response (CCyR) at 6 months included 362 patients; MMR at 6 months included 454 patients; CCyR at 12 months included 358 patients; MMR or BCR-ABL/BCR ratio at 12 months included 427 patients; and time to first MMR included 487 patients. In the pivotal study, the primary efficacy endpoint was MMR at 12 months and the main secondary

efficacy endpoint was best CCyR by 12 months. Consequently, only the MMR and CCyR exploratory PK/Efficacy results are summarised below.

The MMR and CCyR rates at 12 months plotted against average nilotinib exposure grouped by quartile in the PK/efficacy data set showed no obvious relationship between average trough nilotinib exposure and MMR or CCyR rates at 12 months.

Exploratory PK/Safety Analysis

There was an exploratory analysis of the relationship between nilotinib trough and peak concentrations and changes from baseline in the QT interval corrected using Fridericia's method (QTcF) interval on study Days 8 and 84. It was estimated that a 1000 ng/mL increase in nilotinib serum concentrations was associated with an increase in QTcF in the range 4.2 milliseconds (ms) (based on C_{max} obtained on Day 8 of treatment) to 6.9 ms (based on C_{min} obtained on Day 84 of treatment). For a difference of 200 ng/mL in nilotinib serum concentration (the difference in average C_{max} between 300 mg bd and 400 mg bd) the corresponding increase in QTcF would be 0.8 ms to 1.2 ms based on Day 8 data and 1.1 ms to 1.4 ms based on Day 84 data.

The relationship between haematology and biochemistry abnormalities and nilotinib trough and peak concentrations were also explored (haemoglobin, absolute neutrophils, platelet counts, total bilirubin, alanine aminotransferase [ALT], AST, phosphate, lipase and amylase). The analysis dataset included 550 patients, however, one patient was missing all post-baseline total bilirubin, ALT and AST levels. Therefore, the analysis dataset for total bilirubin, ALT and AST consisted of 549 patients.

The incidences of CTC Grade 3 or 4 worsening from baseline for haematology and blood chemistry abnormalities were low (< 12% and ≤ 7%, respectively).[3] There was no positive correlation between nilotinib exposure and CTC Grade 3 and 4 haematology or blood chemistry abnormalities. Logistic regression analyses were performed on haemoglobin abnormalities and blood chemistry abnormalities all grades. Haemoglobin reduction (all grades), bilirubin levels (all grades), and lipase levels (all grades) were positively correlated with average nilotinib exposure (AUC). ALT levels (all grades) were positively correlated with the highest nilotinib exposure level (AUC upper quartile).

Logistic regression analyses were performed on haemoglobin abnormalities (all grades) and blood chemistry abnormalities (all grades). These analyses found a significant positive correlation between average exposure (AUC) and the incidence of worsening from baseline of haemoglobin, total bilirubin, and lipase (Table 3).

[3] Common Terminology Criteria (CTC) is a standardised classification of side effects used in assessing drugs for cancer therapy, in particular. Specific conditions and symptoms may have values or descriptive comment for each level, but the general guideline is 1 – Mild, 2 – Moderate, 3 – Severe, 4 - Life threatening, 5 - Death.

Table 3: Predicted incidence of all grades haemoglobin, total bilirubin and lipase abnormalities across average exposure ranges at respective median baseline values.

	AUC 16000 ng/mL.hr *	AUC 24000 ng/mL.hr *	AUC 32000 ng/mL.hr
Haemoglobin (baseline haemoglobin = 120 g/L)	31.7%	36.4%	39.9%
Total bilirubin (baseline total bilirubin = 6.84 µmol/L)	29.4%	46.5%	59.5%
Lipase (baseline lipase = 30 U/L)	17.4%	23.8%	29.3%

* AUC of 16000 ng/mL.hr and 24000 ng/mL.hr corresponds to the approximate mean AUC of nilotinib at 200 mg bd and 300 mg bd respectively, in male patients.

Clinical Evaluator's Comments

The PK data showed that there was no dose proportionality between nilotinib 300 mg bd and 400 mg bd, with the exposure parameters for the higher dose being less than dose proportional. Pharmacokinetic non-linearity at doses above 400 mg once daily is a known characteristic of nilotinib and is described in the currently approved Tasigna PI. Exposure to nilotinib over 12 months was stable with both the 300 mg bd and 400 mg bd doses as assessed by the average trough and peak concentrations at 1, 3, 6, 9 and 12 months.

The POP-PK study estimated that nilotinib CL was 20.7 L/h and found that increases in normalised total bilirubin and normalised AST were the only two examined covariates to reduce CL. The reduction in CL with increased total bilirubin might be clinically significant and the reduction in CL with increased AST is unlikely to be clinically significant. There were no age related changes in the central or peripheral volumes of distribution.

The POP-PK study showed that dose and gender were the only two examined covariates to significantly affect nilotinib F1 (relative bioavailability). The F1 was 0.842 for the 400 mg bd dose assuming an F1 of 1 for the 300 mg bd dose. The exposure to nilotinib was greater in females than in males and this is a known characteristic of the PKs of the drug and is described in the currently approved Tasigna PI. The POP-PK model estimated that the following covariates did not significantly influence F1: morning vs evening dose; concomitant use of PPIs or H2 blockers; or race (Asian vs non-Asian, Japanese vs non-Japanese).

The exploratory PK/Efficacy analysis showed that there was no correlation between average nilotinib trough exposure and the MMR rate at 12 months (primary efficacy endpoint) or the CCyR rate at 12 months (secondary efficacy endpoint). The exploratory PK/Safety analysis showed that there was a positive correlation between nilotinib exposure (C_{max} and C_{min}) and increases in the QTcF interval which are unlikely to be clinically significant. The exploratory PK/Safety analysis also showed positive correlations between nilotinib exposure (AUC) and haemoglobin abnormalities (all grades), total bilirubin abnormalities (all grades) and lipase abnormalities (all grades). The observed correlations might be of clinical significance for total bilirubin and of doubtful clinical significance for haemoglobin and lipase.

Pharmacodynamics

There were no new pharmacodynamic data submitted.

Efficacy

Introduction

The submission included four clinical studies. CAMN107A2303 was the pivotal study provided to support the application to extend the indications of Tasigna to include the treatment of adult patients with newly diagnosed Ph+ CML-CP at the recommended dose of 300 mg bd. The primary efficacy endpoint in this open label study was the MMR rate at 12 months in the nilotinib 400 mg bd, nilotinib 300 mg bd and imatinib 400 mg qd treatment arms. The MMR rate at 12 months is considered to be a surrogate endpoint for long term clinical benefit. The submission included an exploratory PCR study provided to support the validity of the MMR rate at 12 months as a predictive surrogate of long term clinical benefit [CSTI571A0106 PCR]. This PCR study investigated the relationship between MMR at 12 months and disease progression at 84 months in patients with CML-CP treated with imatinib in the IRIS trial.

The submission also included 24 month, follow up supportive efficacy data in 137 patients with Ph+ CML-AP and 321 patients with Ph+ CML-CP treated with nilotinib [CAMN107A2101E1 and CAMN107A2101E2]. The supportive data were from the Phase II, CML-AP and CML-CP components of a Phase IA/II, multinational, multicentred, open label, dose escalation study to evaluate the safety, tolerability, biologic activity and pharmacokinetic profile of nilotinib in adult patients with imatinib resistant or intolerant CML (chronic phase, accelerated phase, or blast crisis), relapsed/refractory Ph+ ALL, or other haematological malignancies [CAMN107A2101].

Main (Pivotal) Study – CAMN107A2303

Overview

The submitted pivotal efficacy data was the 12 month analysis of the pre-specified efficacy outcomes from the pivotal study. The pivotal study was sponsored by Novartis, Switzerland and is ongoing. The study has been referred to in the published literature as ENESTnd (Evaluating Nilotinib Efficacy and Safety in Clinical Trials – Newly Diagnosed Patients) and the results of the 12 month analysis have been recently published in the New England Journal of Medicine [Saglio et al, 2010].[4]

The *primary objectives of the 12 month analysis* were to compare the efficacy (major molecular response [MMR] rate at 12 months) of nilotinib 400 mg bd with imatinib 400 mg qd and nilotinib 300 mg bd with imatinib 400 mg qd in adult patients with newly diagnosed, previously untreated Ph+ CML-CP. The study also included a *number of secondary objectives for the 12 month analysis*. The *key secondary objectives for the 24 month analysis* (not reported in the current study) were to compare the rate of durable MMR at 24 months of nilotinib 400 mg bd with imatinib 400 mg qd, and nilotinib 300 mg bd with imatinib 400 mg qd. The study also included exploratory objectives.

The pivotal study was undertaken in 35 countries at 217 centres, including the USA (32 sites), Japan (29 sites), Sweden (9 sites), the UK (5 sites), Canada (5 sites) and Singapore (2 sites). The first patient visit was 31 July 2007 and the data cut-off was 2 September 2009 at which time all patients had completed the 12 month evaluation or had discontinued. The provided CSR was dated 26 November 2009 and included the 12 month primary analysis. The study and amendments were reviewed by the Independent Ethics Committee (IEC) or Institutional Review Board (IRB) for each participating centre. The

[4] Saglio G, Kim D-W, Issaragrisil S et al. Nilotinib versus Imatinib for Newly Diagnosed Chronic Myeloid Leukemia. N Engl J Med 2010; 362: 2251-59.

study was conducted according to the ethical principles of the Declaration of Helsinki and in compliance with Good Clinical Practices. All patients gave written informed consent.

Design and Patient Population

The pivotal study is an open label, multinational, multicentred, randomized, five year, ongoing study comparing nilotinib with imatinib for the treatment of newly diagnosed, previously untreated Ph+ CML-CP patients. The study planned to randomize 771 patients 1:1:1 to imatinib 400 mg qd, nilotinib 400 mg bd or nilotinib 300 mg bd. Randomization was by an Interactive Voice Response System (IVRS) and was stratified according to the Sokal risk score determined at the time of diagnosis. Using the Sokal risk score, patients were classified as low risk (relative risk [RR] < 0.8), intermediate risk (RR ≥ 0.8 ≤ 1.2) or high risk (RR > 2). The Sokal formulation is based on four continuous variables consisting of age, spleen size, peripheral blood platelet count, and percentage of peripheral blood myeloblasts.

The target population was adult patients of either sex aged ≥ 18 years with cytogenetically confirmed newly diagnosed Ph+ CML-CP. Patients had to meet all inclusion criteria within 2 weeks of randomization (apart from bone marrow examination which had to be within 42 days) and meet none of the exclusion criteria. Standard conventional cytogenetic analysis on bone marrow was needed for confirmation of diagnosis of CML-CP with cytogenetic confirmation of Philadelphia chromosome (review of a minimum of 20 metaphases was required). Patients had to have been within 6 months of diagnosis of disease and to have been previously untreated for CML, except for hydroxyurea and/or anagrelide. In emergent cases, imatinib at any dose could be prescribed to the patient for up to 2 weeks prior to entering the study if clinically indicated. Patients were required to be Eastern European Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2.[5] Consequently, patients were at least ambulatory and capable of all self care, but unable to carry out work activities, and to be up and about more than 50% of waking hours (that is, ECOG Grade 2). The exclusion criteria were extensive including patients with impaired cardiac function, or acute or chronic liver, pancreatic or severe renal disease considered unrelated to disease.

The study included usual criteria for premature withdrawal in studies of this type including abnormal laboratory values, abnormal test procedure results, disease progression, condition no longer requires study treatment (may be utilized for subjects who undergo bone marrow transplant), protocol violation, withdrawn consent, loss to follow up, administrative problems, death and other (for example, treatment failure or protocol defined suboptimal response). Patients who discontinued due to a study drug related adverse event (AE) were followed weekly for 4 weeks or until resolution or stabilization of the event, whichever occurred first. Patients with disease progression could discontinue from the study and be offered the option to enter into the extension

[5] ECOG Performance Status. The Eastern Cooperative Oncology Group (ECOG) has developed criteria used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. The following are used:

0 - Fully active, able to carry on all pre-disease performance without restriction

1- Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work

2 - Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours

3 - Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours

4 - Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair

5 – Dead

phase. However, entrance into the extension phase due to intolerance of study drug was not allowed. The planned duration of the extension phase is 5 years. It is also planned that patients who discontinue prematurely will be followed up for survival for up to 5 years from the time of starting the study.

The study plan included safety interim analyses to be undertaken every 6 months from randomization of the first patient. The submitted study included two planned interim analyses for assessing the futility of the nilotinib 300 bd arm. The first interim analysis was performed after about 20% of the randomized patients (150 patients in total, 50 patients in each arm) had been treated for 6 months. In this analysis, the futility boundary for triggering consideration to stop the nilotinib 300 mg bd arm was an MMR rate at 6 months in this arm 8% less than in the imatinib 400 mg qd arm. 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. In this analysis, the futility boundary for triggering consideration to stop the nilotinib 300 mg bd arm was an MMR rate in this arm 1% less than that in the imatinib 400 mg qd arm. In both interim analyses, the futility boundary served only as trigger to consider stopping the nilotinib 300 mg bd treatment arm. The decision to continue the study was made using all the available data at the interim analyses, including the CCyR rate. The study was not stopped for futility. The primary analysis was performed when all patients had completed 12 cycles of treatment or discontinued earlier (all cycles lasted 28 days and were continuous).

Evaluator Comment

This was an open label study and as such is subject to the well known biases associated with this design. However, the risk of bias was mitigated by treatment allocation, dose information and PK data not being uploaded into the study database until it was locked for the primary analysis. Furthermore, the primary efficacy endpoint was objectively determined MMR based on real time quantitative reverse transcriptase PCR (RQ-PCR) which had the potential to further mitigate bias. The study included an active imatinib control rather than a placebo control. This is considered acceptable as imatinib is now considered to be standard treatment for CML-CP. Overall, the study design was considered to be acceptable.

Treatments

Treatment with imatinib or nilotinib was given on an outpatient basis. Nilotinib (300 mg bd or 400 mg bd) doses were given each morning and evening approximately 12 hours apart and were taken without food. Imatinib was initially administered at a dose of 400 mg qd with food and water, with the dose being increased to 400 mg bd for suboptimal response or treatment failure. Therapy with nilotinib or imatinib is to continue for up to 5 years while on study, until progression or treatment failure or the development of intolerance of treatment, or as long as patients have not discontinued from the study or entered the extension protocol.

The protocol specified that dose escalation from imatinib 400 mg daily to 800 mg daily was permitted for suboptimal dose response defined as: at 3 months < CHR; at 6 months < PCyR (Ph+ > 35% by cytogenetic analysis of at least 20 metaphases); at 12 months < CCyR (Ph+ > 0% by cytogenetic analysis of at least 20 metaphases); at 18 months < MMR; and loss of MMR confirmed on two occasions unless associated with CHR or loss of CCyR. No dose escalations were allowed for suboptimal response in patients in the 400 mg bd arm. If response to nilotinib 300 mg bd was suboptimal then patients were allowed to enter an extension phase.

The imatinib or nilotinib dose could be interrupted or reduced according to protocol specified guidelines for study drug related haematological or non-haematological

toxicities. The CTCAE (NCI Common Terminology Criteria for Adverse Events) version 3.0 was used for toxicity and adverse event reporting.[3] Dose reductions below 300 mg daily for imatinib or 400 mg daily for nilotinib were not allowed and patients were discontinued from the study if these minimum doses could not be tolerated. Non-haematological toxicity must have resolved within 28 days in order to resume the study drug at the reduced dose and if toxicity had not resolved after 28 days the patient was discontinued. No dose adjustments were allowed for Grade 1 or 2 haematological toxicity in the imatinib or nilotinib treatment arms. Haematological toxicities must have resolved within 28 days in order to resume the study drug at the reduced dose.

In general, concomitant medications and therapies considered necessary for the supportive care and safety of patients were allowed, provided their use was not protocol prohibited (that is, other investigational drugs, other anticancer agents within the first month of treatment apart from hydroxyurea and/or anagrelide, coumarin derivatives due to CYP2C9 and CYP3A4 metabolism, strong CYP3A4 inhibitors and QT prolonging agents). Selected adverse events could be treated using standard therapies (for example, nausea, vomiting, diarrhoea, recurrent Grade 3 neutropenia, skin rashes and pruritus, peripheral oedema).

Evaluator Comment

Imatinib (Glivec) is a standard treatment for adult patients with newly diagnosed Ph+ CML in the chronic phase. The Glivec PI indicates that imatinib 400 mg qd is the currently recommended dose for the treatment of chronic phase CML with escalations to 600 mg qd being recommended (in the absence of severe adverse drug reactions and severe non-leukaemic related neutropenia or thrombocytopenia) in the following circumstances: disease progression at any time; failure to achieve a satisfactory haematological response after at least 3 months of treatment; failure to achieve a cytogenetic response after 12 months of treatment; or loss of a previously achieved haematological and/or cytogenetic response. In addition, the Glivec PI indicates that further escalation from 600 mg daily (600 mg qd) to 800 mg daily (400 mg bd) in patients with chronic phase CML can be considered if the 600 mg daily dose was associated with no greater than mild toxicity during the initial 4 weeks of treatment. The currently recommended doses of imatinib in patients with CML in the chronic phase are consistent with those in the pivotal study which allowed imatinib to be escalated from 400 mg daily to 800 mg daily for suboptimal response and treatment failure.

The first nilotinib treatment arm selected for comparison with imatinib was 400 mg bd. This nilotinib dose is approved in Australia for the treatment of adults with chronic phase and accelerated phase Ph+ CML resistant to or intolerant of prior therapy including imatinib and the Tasigna PI includes no dose escalation recommendations. Consequently, the use of nilotinib 400 mg bd is considered to be a reasonable first choice treatment arm comparator for imatinib 400 mg qd in adult patients with newly diagnosed CML-CP. Nilotinib 300 mg bd was chosen as the second choice treatment arm for comparison with imatinib 400 mg qd on the basis of the Phase I dose escalation study [CAMN107A2101] in patients with imatinib resistant Ph+ CML and ALL which suggested that a 300 mg bd dose was likely to achieve a better response than 200 mg bd and to have an improved safety profile compared with 400 mg bd.

Primary Efficacy Variable

The primary efficacy variable was the rate of major molecular response (MMR) at 12 months (time window for analysis of the MMR at 12 months [Day 336] was Day 295 to Day 378). The MMR was defined as ≤ 0.1% fusion gene from breakpoint cluster region gene/ BCR gene product (BCR) and Abelson proto-oncogene (ABL)/protein product from BCR-

ABL (BCR-ABL)/ABL % by international scale (IS), which corresponds to a ≥ 3-log reduction of BCR-ABL transcript from standardized baseline. The MMR was measured in the peripheral blood at a centralized laboratory by real time RQ-PCR. The MMR was considered as a binary variable for the purposes of statistical analysis with "responders" being patients achieving MMR and "nonresponders" being patients not achieving MMR, patients with missing PCR evaluations or patients with atypical transcripts at baseline. The association between BCR-ABL transcript levels and molecular response is summarised in Table 4.

Table 4: Association between BCR-ABL transcript levels and molecular response

BCR-ABL/ABL ratio (%) by IS	Log-reduction from standardized baseline	Molecular response
> 0.1 %	< 3-log reduction	No major molecular response
> 0.01 to ≤ 0.1%	≥ 3 to < 4-log reduction	MMR
> 0.0032 to ≤ 0.01%	≥ 4 to < 4.5-log reduction	MMR, ≥ 4 log reduction in BCR-ABL transcript levels
≤ 0.0032%	≥ 4.5-log reduction	MMR, ≥ 4.5 log reduction in BCR-ABL transcript levels

The MolecularMD assay used ABL as the control gene and reported data as a % ratio of BCR-ABL/ABL by international scale (IS), which corresponds to the log reduction scale used in the landmark imatinib study [IRIS] referenced to a standardized baseline. An IS conversion factor of 0.81 was established for the assay through sample exchange. The conversion factor was appropriately validated before the study and verified during the study. The relevant values to determine valid samples and apply the appropriate conversion for the assay are summarised in Table 5.

Table 5: Conversion factor and control gene cut-off for MolecularMD assay

PCR Lab	Control gene	Minimum number of control genes for a sample to be valid.	Minimum number of control genes required for 4-log reduction	Minimum number of control genes required for 4.5-log reduction	Laboratory conversion factor to IS.
MolecularMD	ABL	3,000	8,100	25,614	0.81

The BCR-ABL/ABL ratio (%) equalled (BCR-ABL / ABL) × conversion factor × 100. If the BCR-ABL value was reported as a value of 0, then the value was replaced by 1 and the BCR-ABL ratio was calculated as described. If the number of BCR-ABL transcripts was numerically larger than the number of control gene transcripts, the ratio was set to 100 % and no conversion factor was applied. The PCR laboratory reported "not evaluable" for any samples that failed to reach the minimum number of control gene transcripts required to accept a sample for analysis. In case of undetectable or negative BCR-ABL, if the minimum number of control gene transcripts required to accept a 4 log and 4.5 log reduction was not reached, the PCR lab performed a repeat analysis using a larger sample volume and/or requested a sample redraw. If the BCR-ABL remained below the detection

level but the required minimal control gene copy number was achieved, the PCR laboratory reported the largest number of control gene transcripts.

Evaluator Comment

The study used MMR at 12 months as surrogate measure of long term clinical benefit. In support of this endpoint the submission included an exploratory PCR analysis of data from patients in the IRIS trial which analysed the relationship between MMR at 12 months and event free survival (EFS), time to accelerated phase (AP)/ blast crisis (BC) and overall survival (OS) at 84 months in patients treated with imatinib. This study found that MMR at 12 months (vs no MMR at 12 months) predicts at 84 months improved EFS (91.0% vs 79.4%, p=0.001) and survival free progression to AP/BC (99.0% vs 89.9%, p=0.0004) but not OS (92.5% vs 89.2%, p=0.0197). The exploratory PCR study [CST1571A0106 PCR] is evaluated later in this AusPAR.

The TGA-adopted EU guidelines for the evaluation of anticancer medicines indicate that confirmatory Phase III trials should demonstrate that the investigational product provides clinical benefit.[6] The guidelines state that acceptable primary endpoints include OS and progression free survival (PFS)/disease free survival (DFS) and that if PFS/DFS is the selected primary endpoint then OS should be reported as the secondary endpoint and vice versa. The guidelines also state that tumour markers "convincingly demonstrated to reflect tumour burden can be used, in combination with other measures of tumour burden, to define tumour response and progression". The guidelines further state that a "justification is expected in the study protocol why endpoints such as survival benefit or symptom control cannot be used as a primary measure of patient benefit".

The protocol for the pivotal study included a justification for the use of MMR at 12 month as the primary efficacy endpoint based on published results from the IRIS study which showed that MMR at 12 months was correlated with a reduced risk of disease progression and increased event free survival during the subsequent 60 months [Druker et al, 2006; O'Brien et al 2008].[7,8] In Druker et al 2006, no patient who had CCyR and MMR at 12 months had progressed to the accelerated phase (AP) or blast crisis (BC) at 60 months. Only 2% of patients who had CCyR and MMR at 18 months had progressed to accelerated phase or blast crisis at 60 months. In patients with CCyR and no MMR response at 18 months, 98% had were free from progression to the accelerated phase or blast crisis at 60 months (vs 100% in patients with CCyR and MMR at 18 months; p=0.11). In O'Brien et al 2008, long term follow up of patients who continued to respond to imatinib demonstrated an MMR rate of 85-90% at 5-6 years. Overall, it was considered that the MMR rate at 12 months is an acceptable surrogate for long term clinical benefit, given that nilotinib is not a new chemical entity and is approved for second line treatment of Ph+ CML-CP in patients with imatinib resistant or intolerant disease.

Secondary Efficacy Variables

The key secondary efficacy endpoint is the rate of durable MMR at 24 months (not reported as the provided data included only 12 month analyses of the efficacy endpoints).

[6] EMEA, Committee for Medicinal Products for Human Use (CHMP), 14 December 2005. Guideline on the Evaluation of Anticancer Agents in Man, CPMP/EWP/205/95/Rev. 3/Corr.

[7] Druker BJ, Guilhot F, O'Brien SG et al. Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. NEJM 2006; 355:2408-17.

[8] O'Brien SG, Guilhot F, Goldman JM et al. International Randomized Study of Interferon Versus STI571 (IRIS) 7-year follow-up: sustained survival, low rate of transformation and increased rate of major molecular response (MMR) in patients (pts) with newly diagnosed chronic myeloid leukemia in chronic phase (CML-CP) treated with imatinib (IM) [abstract]. Am Soc Hematol, 2008.

The main secondary efficacy endpoint for the 12 month analysis was considered to be the rate of best complete cytogenetic response (CCyR), defined as 0% Ph+ metaphases in bone marrow by 12 months. The other secondary efficacy variables were:

(a) rate of MMR, BCR-ABL/ABL % of ≤ 0.01% and ≤ 0.0032%, CCyR and major cytogenetic response (MCyR) at each scheduled time point;
(b) rate of best MMR, best BCR-ABL/ABL % of ≤ 0.01% and ≤ 0.0032%, best CCyR and best MCyR by each scheduled time point;
(c) rate of best confirmed MMR, MCyR, CCyR and CHR by each scheduled time point;
(d) time to responses (MMR, BCR-ABL/ABL % of ≤ 0.01% and ≤ 0.0032%, CCyR, MCyR, and CHR);
(e) duration of responses (MMR, BCR-ABL/ABL % of ≤ 0.01% and ≤ 0.0032%, CCyR, MCyR, and CHR);
(f) event-free survival (EFS);
(g) progression-free survival (PFS);
(h) time to progression to AP/BC;
(i) overall survival (OS).

Statistical Considerations

The primary objective of the pivotal study was to compare: (1) the MMR rate at 12 months for nilotinib 400 mg bd and imatinib 400 mg qd; and (2) the MMR rate at 12 months for nilotinib 300 mg bd and imatinib 400 mg qd. The null hypothesis for both comparisons was no difference in MMR rates at 12 months between nilotinib and imatinib and the corresponding alternative hypothesis was MMR rates at 12 months were different for 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 significance level of 0.05. To protect the overall type one error, a step down testing procedure was applied for the two comparisons: that is, the MMR rate for nilotinib 400 mg bd vs imatinib 400 mg qd was compared first; if this was significant at the 5% level, then the MMR rate for nilotinib 300 mg bd vs imatinib 400 mg qd was compared. However, if the initial comparison was considered not significant at the 5% level, then neither of the two comparisons was considered significant at this level. The analyses of the secondary efficacy variables were consistent with that for the primary efficacy variable, apart from no adjustment for multiple comparisons. The MMR rate at 12 months and 95% confidence interval (CI) were provided for randomization stratum and treatment group. Differences with 95% CIs in MMR rates at 12 months were also provided for each pairwise comparison. The Pearson-Clopper method was used to calculate the CI for all response rates. The Wald method was used to calculate the CIs for the differences in response rates between treatment groups.

Patients dropping out or not providing sufficient data were included in the "full analysis set" (FAS) analysis and counted as nonresponders. Only patients with a MMR at 12 months were considered responders. However, if the 12 month PCR evaluation was missing but both the previous (9 month) and next (15 month) PCR evaluations indicated MMR, the 12 month assessment was imputed as MMR. Other analyses included sensitivity analysis for CCyR, analysis of time to response variables by cumulative incidence and Kaplan-Meier (K-M) method, analysis of duration of response variables by the K-M method, analysis of time to response variables by the K-M method, and analysis of event-free survival, progression-free survival, time to progression to AP/BC and overall survival.

The data sets were:

(a) The "full analysis set" (FAS) consisting of all randomized patients. Patients were analysed according to randomized treatment regardless of actual treatment received (that

is, "intention to treat" [ITT] analysis). The FAS was used for all efficacy analyses and demographic and baseline characteristics were presented for this population.

(b) The "per protocol set" (PPS) consisting of all FAS patients who received at least one dose of study medication and did not have any major protocol violations.

(c) The safety set consisting of all patients who received at least one dose of study medication.

(d) The type II diabetes population consisting of all patients in the safety set with type II diabetes at screening.

(e) The full-PK set consisting of all patients with available full PK profile at any visit.

(f) The POP-PK set.

Sample size calculations were based on a power of 90% to detect a 15% increase in the MMR rate at 12 months in the nilotinib arm compared with the imatinib arm, assuming a rate of 40% in the imatinib arm and 55% in the nilotinib arm. The estimated 40% MMR rate in the imatinib arm was based on the IRIS study in which 40% of patients with newly diagnosed CML-CP treated with imatinib 400 mg qd achieved MMR at 12 months. In the current study, the two primary comparisons were: nilotinib 400 mg bd vs imatinib 400 mg qd and nilotinib 300 mg bd vs imatinib 400 mg qd (superiority test). To test the null hypothesis that the 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) CMH test at a 5% level of significance and with a 90% power, approximately 699 patients were needed (233 in each treatment arm). After adjusting for a 10% drop out rate, 257 patients per treatment arm and 771 in total needed to be enrolled to have 90% power to detect a 15% difference between nilotinib 400 mg bd and imatinib 400 mg qd, assuming that the MMR rate of imatinib is 40% and the MMR rate of nilotinib was 55%. With this sample size, the study also had a 90% power to detect a 15% difference between the nilotinib 300 mg bd and imatinib 400 mg qd arm, if the comparison between nilotinib 400 mg bd and imatinib 400 mg qd arm was significant. The actual number of patients randomized to the treatment arms indicates that the study was adequately powered.

Study Population

Disposition

A total of 846 patients were randomized between 6 September 2007 and 30 September 2008 (283 to imatinib 400 qd mg [I400], 281 to nilotinib 400 mg bd [N400] and 282 to nilotinib 300 mg bd [N300]). Three patients randomized to each of the nilotinib treatment arms and 4 patients randomized to the imatinib arm did not receive any study drug.

At 12 months (that is, Day 295 to 378 for assessment of the MMR), 725 (85.7%) of the 846 randomized patients were still on treatment (that is, still on treatment by Day 294 of the study) with the respective numbers for the three treatment arms being 237 (83.7%), 247 (87.6%), and 241 (85.8%) for I400, N300 and N400. By study Day 294, 46 patients (16.3%) in the I400 arm, 35 (12.4%) in the N300 arm and 40 (14.2%) in the N400 arm had discontinued study treatment. Of the patients who had discontinued, the main reason in the three treatment arms were adverse events, which occurred more frequently in the N400 arm (7.8%) than in the N300 arm (3.9%) and the I400 arm (6.7%).

At the data cut-off data of 2 September 2009, a total of 690 patients (81.6%) were still receiving study treatment: 224 (79.2%) in the I400 arm, 236 (83.7%) in the N300 arm and 230 (81.9%) in the N400 arm. Of the 156 patients (18.4%) who had discontinued, the highest discontinuation rate was 20.8% (n=59) in the I400 arm, followed by 18.1% (n=51)

in the N400 arm and 16.3% (n=46) in the N300 arm. The reasons for discontinuation were similar to those at 12 months as were the distributions among the three treatment groups.

Major Protocol Deviations

There were 110 patients with at least one major protocol violation and patients with major protocol violations were well balanced among the treatment arms: 39 (13.8%) I400; 39 (13.8%) N300; and 32 (11.4%) N400. The most frequently reported major protocol violation was no confirmed CML-CP diagnosis at baseline which was reported in 61 patients: 22 (7.8%) I400; 20 (7.1%) N300; and 19 (6.8%) N400. There was a total of 9 patients with no confirmed Ph+ at baseline: 5 (1.8%) I400; 3 (1.1%) N300; and 1 (0.4%) N400.

Demographic and Other Baseline Characteristics

There were no notable differences among the patients in the three treatments arms with respect to age, gender, race, weight or height. The median age [range] was 46 [18-80] years in the I400 arm, 47 [18-85] years in the N300 arm and 47 [18-81] years in the N400 arm. The percentage of patients aged ≥ 65 years was 12.4% (n=35), 12.8% (n=36) and 10.0% (n=28) in the I400, N300 and N400 arms, respectively. There were more male than female patients in each of the three treatment arms: 55.8% (n=158), 56.0% (n=158) and 62.3% (n=175) in the I400, N300 and N400 arms, respectively. More than 60% of all patients were Caucasian, and approximately 25% were Asian. The distribution of the Sokal risk categories among the three treatment arms was similar with low, intermediate and high risk patients making up approximately 36%, 36% and 28% of patients, respectively, in each of the three treatment arms.

More than 98.5% of patients in each of the three treatment arms had been diagnosed with CML within the six months prior to the study. The median time [range] since diagnosis of CML was 28.0 [1-183] days, 31.0 [0-182] days and 31.0 [3-189] days in the I400, N300 and N400 arms, respectively. More than 98.5% of patients in each treatment arm had not been previously treated for CML, apart from protocol allowed treatment with hydroxyurea and/or anagrelide and/or imatinib for emergent cases. More than 70% of patients in each treatment arm had been previously treated with hydroxyurea, while the percentage of patients previously treated with anagrelide ranged from 0 to 2.1% across the three treatment arms. The percentage of patients previously treated with imatinib for ≤ 2 weeks ranged from 9.3% to 11.3% across the three treatment arms.

Extramedullary disease at baseline was similar in the treatment arms: 38.2% (n=108), 41.1% (n=116) and 40.2% (n=113) in the I400, N300 and N400 arms, respectively. The percentage of patients with splenomegaly was similar in the three treatment arms: 37.1% (n=105), 41.1% (m=116) and 39.1% (n=110), for I400, N300 and N400, respectively. Hepatomegaly was less common than splenomegaly but occurred with similar frequency in the treatment arms: 9.5% (n=27), 8.5% (n=24) and 8.9% (n=25), for I400, N300 and N400, respectively. No patients had lymph node or other extramedullary involvement.

In order to comply with the inclusion criteria for CML-CP, all of the following were required prior to treatment: < 15% blasts in peripheral blood and bone marrow aspirate; < 30% blasts plus promyelocytes in peripheral blood and bone marrow aspirate; < 20% basophils in the peripheral blood; ≥ 100 x 10^9/L (≥ 100,000/mm^3) platelets; and no evidence of extramedullary leukaemic involvement, with the exception of hepatomegaly and/or splenomegaly. If the platelet count was < 100 x 10^9/L but all other criteria for CML-CP were fulfilled, then prior medications were reviewed to evaluate the cause of thrombocytopenia. Baseline haematology and bone marrow results were similar for the three treatment groups.

Primary Efficacy Results (MMR)

The MMR rate at 12 months was first compared between nilotinib 400 mg bd and imatinib 400 mg qd using a CMH test stratified by Sokal risk group at the 5% significance level (as per protocol). The MMR rate was statistically significantly greater in the N400 arm than in the I400 arm (42.7% vs 22.3%, respectively, $p < 0.0001$). Following the step down procedure to protect against overall type one error, the MMR rate was then compared between nilotinib 300 mg bd and imatinib 400 mg qd at the 5% significance level. The MMR rate was statistically significantly greater in the N300 arm than in the I400 arm (44.3% vs 22.3%, respectively, $p < 0.0001$). The primary efficacy endpoint of the study was met as both nilotinib arms had statistically significantly higher MMR rates at 12 months compared with the imatinib arm (Table 6).

Table 6: Study [CAMN107A2303] - Major molecular response (MMR) rate at 12 months – with imputation; FAS

	Imatinib 400 mg qd (n=283)	Nilotinib 300 mg bd (n=282)	Nilotinib 400 mg bd (n=281)
MMR rate n (%) 95% CI for response	63 (22.3%) 17.6%, 27.6%	125 (44.3%) 38.4%, 50.3%	120 (42.7%) 36.8%, 48.7%
No MMR n (%)	220 (77.7%)	157 (55.7%)	161 (57.3%)
CMH[1] (p value) for MMR (N vs I)	-	< 0.0001	< 0.0001
MMR difference [95%CI] (N vs I)	-	22.1% [95%CI: 14.5%, 29.5%]	20.4% [95%: 12.9%, 28.0%]

[1] CMH test is stratified by Sokal risk group.

In the PPS, the MMR rate at 12 months was 24.2% (59/244) in the I400 arm, 44.4% (108/243) in the N300 arm and 42.2% (105/249) in the N400 arm. The differences between the MMR rates in each of the nilotinib arms compared with the imatinib arm were both statistically significant ($p < 0.0001$). The MMR rates at 12 months for all Sokal risk groups were statistically significantly higher for both nilotinib treatment arms compared with the imatinib. Higher MMR rates were observed in the N300 arm than in the N400 arm for the Sokal intermediate and high risks groups. However, for the Sokal low risks group, lower response rates were observed in the N300 arm than in the N400 arm.

Evaluator Comment

The MMR rates at 12 months were statistically significantly greater in both the nilotinib treatment arms (300 mg bd and 400 mg bd) compared with the imatinib treatment arm (400 mg qd). The difference in MMR rates between both nilotinib treatment arms and imatinib was greater than 15% which was the protocol specified difference used to calculate power. The study was not powered to detect a statistically significant difference between the two nilotinib treatment arms but the observed rates indicate that there is no dose response between these two arms. The PPS analysis of the MMR at 12 months was consistent with the FAS analysis.

Secondary Efficacy Results

Molecular Responses

The best MMR rates by 12 months (that is, MMR at or before 12 months) were statistically significantly higher ($p < 0.0001$) in both the nilotinib 300 mg bd (54.6% [154/282]) and nilotinib 400 mg bd (51.2% [144/281]) arms compared with the imatinib 400 mg qd arm (26.9% [76/283]). Similarly, the best confirmed MMR rates by 12 months (that is, MMR at

or before 12 months confirmed ≥ 4 weeks later) were statistically significantly higher ($p < 0.0001$) in both the N300 (44.3% [125/282]) and N400 (39.5% [111/281]) arms compared with the I400 arm (19.8% [56/283]). The MMR rates at 3, 6 and 9 months were statistically significantly greater in both the nilotinib arms than in the imatinib arm. The cumulative incidence of the MMR over time shows that the proportion of patients with MMR was consistently higher in the N300 arm than in the I400 and N400 arms. The BCR-ABL/ABL ratio (%) categories at 12 months show that the proportion of patients achieving ratios of ≤ 0.01% to > 0.0032%, and ≤ 0.0032% was greater in both nilotinib arms than in the imatinib arm.

By the data cut-off date, MMR was achieved by 30.4% (86/283) of patients in the I400 arm, 57.1% (161/282) of patients in the N300 arm and 54.4% (153/281) of patients in the N400 arm. The median time to MMR was longer in the I400 arm (8.31 [range: 2.8–17.3] months) than in both the N300 (6.94 [range: 1.9-19.9] months) and N400 (7.44 [range: 2.6-19.7] months) arms. The hazard ratios were 2.6 [95%CI: 2.0, 3.3] for the N300 vs I400 comparison and 1.6 [95%CI: 1.4, 1.8] for the N400 vs I400 comparison. The log rank test stratified by Sokal risk group for both the nilotinib vs imatinib comparisons was $p < 0.0001$. Of the 400 patients with a MMR, 11 lost response (confirmed): 1/86 in the I400, 6/161 in the N300 arm and 4/153 in the N400 arm. Loss of MMR was defined as a BCR-ABL ratio > 0.1%, in association with a ≥ 5-fold rise in BCR-ABL/ABL ratio from the lowest value achieved up to that time point, confirmed by a duplicate analysis of the same sample. Loss of MMR was confirmed by two PCR samples ≥ 4 weeks apart.

Cytogenetic Response

The best complete cytogenetic response (CCyR) by 12 months was the main secondary efficacy endpoint in the 12 month analysis; a CCyR was defined as 0% Ph+ metaphases in bone marrow. Best CCyR rates by 12 months included patients who achieved CCyR at or before the 12 month time point. The best CCyR rates by 12 months were statistically significantly greater in both nilotinib arms than in the imatinib arm and there was no dose response between the two nilotinib arms (Table 7).

Table 7: Study [CAMN107A2303] – Best complete cytogenetic response (CCyR) rate by 12 months; FAS

	Imatinib 400 mg qd (n=283)	Nilotinib 300 mg bd (n=282)	Nilotinib 400 mg bd (n=281)
MMR rate 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 MMR n (%)	99 (35.0%)	56 (19.9%)	62 (22.1%)
CMH[1] (p value) for MMR (N vs I)		p < 0.0001	p < 0.0005
MMR difference [95%CI] (N vs I)		15.1% [95%CI: 7.9%, 22.4%]	12.9% [95%CI: 5.5%, 20.3%]

[1] CMH test is stratified by Sokal risk group.

In the PPS, best CCyR rates were statistically significantly higher in the N300 and N400 arms (81.1% [197/243] and 79.5% [198/249], respectively) than in the I400 arm (65.6% [160/244]). The results were consistent with those in the FAS. The best CCyR rates at 12 months for all Sokal risk groups were higher in both nilotinib arms than in the imatinib arm. In the low risk group, the risk difference between N400 and I400 was statistically significant. In the intermediate group, the risk differences between both nilotinib arms and the imatinib arm were statistically significant. In the high risk group, the risk difference between N300 and N400 was statistically significant.

The best CCyR (confirmed) rates by 12 months were 43.1% (122/283), 61.0% (172/282), and 58.4% (164/281) in the I400, N300 and N400 arms, respectively. The differences between both nilotinib arms and the imatinib arm were statistically significant for the best CCyR (confirmed) rates by 12 months. The best CCyR by 6 months was 44.5% [126/283], 66.7% [188/282] and 63.0% [177/281] in the I400, N300 and N400 arms, respectively. The differences between both nilotinib arms and the imatinib arm were statistically significant for the best CCyR (confirmed) rates by 6 months.

Major cytogenetic response (MCyR) was defined as CCyR or PCyR. Partial cytogenetic response (PCyR) was defined as 1% to 35% Ph+ metaphases of at least 20 metaphases. Minor cytogenetic response was Ph+ 36% to 65% metaphases of at least 20 metaphases. Minimal cytogenetic response was defined as Ph+ 66% to 95% metaphases of at least 30 metaphases. No cytogenetic response was Ph+ > 95% Ph+ metaphases of at least 20 metaphases.

The best MCyR response rates by 6 months were 62.2% (176/283), 71.3% (201/282) and 68.3% (182/282) in the I400, N300 and N400 treatment arms, respectively. By 12 months, these respective percentages had increased to 77.4% (219/283), 84.4% (238/282) and 80.8% (227/281). By 6 months, no cytogenetic response was reported for 3.9% (11/283) of patients in the I400 arm, 0% (0/282) of patients in the N300 arm and 1.1% (3/281) of patients in the N400 arm. By the data cut-off date, the cumulative rate of CCyR was 70.7% [200/283] in the I400 arm, 81.6% [230/282] in the N300 arm and 80.1% [225/281] in the N400 arm. The median time to CCyR was similar in the three treatment arms: 5.8 [range: 4.0 to 17.1] months, 5.6 [range: 1.5 to 18.0] months and 5.7 [range: 1.9 to 17.0] months in the I400, N300 and N400 arms, respectively. The hazard ratios were 1.6 [95%: 1.3, 1.9] for the N300 vs I400 comparison and 1.2 [95%CI: 1.1, 1.4] for the N400 vs I400 comparison. The log rank test stratified by Sokal risk group for both the nilotinib vs imatinib comparisons was $p < 0.0001$. In patients with CCyR, response was lost in 4/200, 1/230 and 0/225 patients in the I400, N300 and N400 treatment arms, respectively.

Complete Haematologic Response (CHR)

The CHR rates at 12 months were similar for the three treatment arms and there were no statistically significant differences between both the nilotinib arms and the imatinib arm. The CHR rates at 12 months were 93.3 % (264/283), 89.7% (253/282) and 88.6% (249/281) in the I400, N300 and N400 arms, respectively. High CHR rates were achieved in all three treatment arms at 3 months and remained consistently high at 6, 9 and 12 months, with no statistically significant differences between both the nilotinib arms and the imatinib arm at the four time points.

Event Free Survival (EFS) on Treatment

The number of patients with an EFS event by the data cut-off date was 13 in the I400 arm (11 progressed to AP/BC, 1 had a confirmed loss of CCyR and 1 had a confirmed loss of CHR), 6 in the N300 arm (2 died due to non CML related causes, 2 progressed to AP/BC, 1 had a confirmed loss of CCyR and 1 had a confirmed loss of CHR) and 1 in the N400 arm (progressed to AP/BC). The Kaplan-Meier estimated rates of EFS at 12 months were 95.7%, 97.6% and 99.6% in the I400, N300 and N400 treatment arms, respectively. The difference in EFS was statistically significant for the N400 vs I400 comparison ($p=0.0012$; log rank test) but not for the N300 vs I400 comparison ($p=0.0898$; log rank test).

Progression to Accelerated Phase (AP) or Blast Crisis (BC) on Treatment

Overall, there were 14 patients who had progressed to AP or BC by the cut-off data: 11 in the I400 arm; 2 in the N300 arm; and 1 in the N400 arm. The Kaplan-Meier estimated rates of patients free from progression to AP/BC at 12 months were 96.5%, 99.3% and

99.6% in the I400, N300 and N400 treatments arms, respectively. There was a statistically significant difference in progression to AP/BC for the N400 vs I400 comparison (p=0.0037; log rank test) and the N300 vs I400 comparison (p=0.0095; log rank test). None of the 14 patients who progressed to AP/BC achieved MMR during the study. However, 3 of the 11 patients in the I400 arm who progressed to AP/BC achieved CCyR during the study.

The study also included a sensitivity analysis of time to progression to AP/BC (including clonal evolution) on treatment defined as the time between date of randomization and death due to CML or progression to AP/BC including clonal evolution under treatment in the core phase of the study. The time was censored at the date of last assessment (haematology, extramedullary disease or cytogenetic evaluation) in the core phase of the study for patients without event. In this analysis, 5 additional patients in the I400 arm and 2 additional patients in the N400 arm were considered to have progressed to AP/BC by the cut-off date. The estimated rates of patients free from progression to AP/BC at 12 months were 95.2%, 99.3%, and 96.8% in the I400, N300, and N400 treatments arms, respectively. There was a statistically significant difference in progression to AP/BC for the N400 vs I400 comparison (p=0.0025; log rank test), and the N300 vs I400 comparison (p=0.0006; log rank test).

Overall Survival

The numbers of patients who had died by the data cut-off date were 4, 3 and 2 in the I400, N300 and N400 treatments arms, respectively. The respective Kaplan-Meier estimated OS rates at 12 months were 99.3%, 99.3% and 99.2%. Two sensitivity analyses were performed on OS rates censored at bone marrow transplant (BMT) (all deaths and CML related deaths only) and the results for both analyses were similar to the main analysis. In the censored at BMT, the Kaplan-Meier estimated OS rates at 12 months for all deaths were 99.3%, 99.3% and 99.2%, and the OS rates for only CML related deaths were 99.3%, 100% and 99.6% in the I400, N300 and N400 treatments arms, respectively.

Clinical Studies in Special Populations – Pivotal Study

Gender

The pivotal study included an analysis of the MMR at 12 months (the primary efficacy endpoint) by gender. In both the male and female subgroups the MMR response rates at 12 months were statistically significantly greater for the N300 vs I400 and the N400 vs I400 comparisons. The MMR rates at 12 months were higher in female patients than in male patients in each of the three treatment arms.

Racial Group

The pivotal study included an analysis of the MMR at 12 months (the primary efficacy endpoint) by racial group. The majority of patients in the study were Caucasian (64.1% [542/846]) followed by Asian (25.2% [213/846]). There were only small percentages of Black (3.6% [30/846]) or Other (7.2% [61/846]) patients and, consequently, no conclusions can be drawn about efficacy in these subgroups. In the Caucasian and Asian subgroups, MMR rates at 12 months were statistically significantly greater for the N300 vs I400 and the N400 vs I400 comparisons.

Age

The pivotal study included an analysis of the MMR at 12 months (the primary efficacy endpoint) by age. The clinical summary of efficacy included a comparison of patients aged < 65 years versus ≥ 65 years. In the < 65 years age group, MMR rates at 12 months were statistically significantly greater with nilotinib for both the N300 vs I400 and the N400 vs

I400 comparisons. However, in the ≥ 65 years age group, while MMR rates at 12 months were higher in both nilotinib treatment arms than in the imatinib treatment arm both the nilotinib vs imatinib comparisons were not statistically significant. The results for patients aged ≥ 65 years age should be interpreted cautiously as the pairwise comparisons between nilotinib and imatinib in this age group were underpowered to detect a statistically significant difference between the treatment arms.

Supportive Studies

Study CAMN107A2101E2 (CML-CP)

Background

The submitted supportive data included Phase II, 24 month, follow up data for 321 patients with imatinib resistant or intolerant chronic myeloid leukaemia in the chronic phase (CML-CP) treated with nilotinib. These patients had received no prior treatment with a tyrosine kinase inhibitor (TKI) other than with imatinib. The data were from the Phase II, CML-AP component of a Phase IA/II, multinational, multicentred, open label, dose escalation study to evaluate the safety, tolerability, biologic activity and pharmacokinetic profile of nilotinib in adult patients with imatinib resistant or intolerant CML (chronic phase, accelerated phase or blast crisis), relapsed/refractory Ph+ ALL or other haematologic malignancies [CAMN107A2101]. Data from this study has been previously evaluated by the TGA and the current Tasigna PI includes information on 320 patients exposed to nilotinib for a median duration of 11.2 months. The new data included information on 321 patients who had either completed 24 months of treatment or discontinued and had been exposed to nilotinib for a median duration of 18.4 months.

The efficacy evaluation focuses primarily on the relevant updated primary and secondary efficacy endpoints. The first patient with CML-CP was dosed on 21 April 2005, the 24 month data cut-off date was 20 April 2008 and the report was dated 16 October 2009. The study protocol and amendments were reviewed by the IEC or IRB for each centre. The study was conducted according to the principles of the Declaration of Helsinki. Informed consent was obtained in writing from each patient. The study was sponsored by Novartis.

Patient Disposition

A total of 321 patients with CML-CP were treated in 15 participating countries at 63 centres. Patient disposition is summarised in Table 8. Of the 321 patients, 61.4% discontinued with the most frequent reasons for premature discontinuation being disease progression (27.4%) and adverse events (19.0%). Discontinuation due to drug related adverse events was observed in 50 (19.0%) patients. Major protocol deviations occurred in 19.0% of all ITT patients and resulted in exclusion from the per protocol efficacy analyses.

Table 8: Supportive Study [CAMN107A2101E1] - Patient disposition (n, %)

Disposition	Total n=321
Treatment ongoing	124 (38.6%)
Discontinued	197 (61.4%)
Reason for Discontinuation	
Disease progression	88 (27.4%)
Adverse Event(s)	61 (19.0%)
Subject withdrew consent	20 (6.2%)
Abnormal laboratory value(s)	2 (0.6%)
Abnormal test procedures	4 (1.2%)
Administrative problems	12 (3.7%)
Death	3 (0.9%)
Protocol violation	4 (1.2%)
Not stated	1 (0.3%)
Lost to follow-up	2 (0.6%)

Patient Demographics

The mean age of the 321 patients was 56.6 years [SD: 13.2], ranging from 21 to 85 years. The majority of patients were aged ≥ 55 years (n=195, 60.7%), male (n=162, 50.5%) and Caucasian (n=297, 92.5%). Nearly all patients were WHO performance status Grade 0 or 1 (n=314, 97.8%).[9] The median time from first diagnosis was 4.8 [range: 0.4 to 22.9] years. About half of all patients (n=158, 49.2%) had been diagnosed with CML ≥ 5 years prior to study entry. Of the 321 patients, the majority had achieved prior cytogenetic response (n=185, 57.6%) and 91.6% (n=294) had achieved prior CHR. Of the 321 patients, 70.4% (n=226) were imatinib resistant and 29.6% (n=95) were imatinib intolerant.

Treatment

The starting dose of nilotinib was 400 mg bd and dose escalation to 600 mg bd was permitted in patients with CML-CP until prohibited by protocol Amendment 11 (11 April 2008). The actual nilotinib median dose intensity was 788.5 [range: 151.0 to 1109.8] mg/day. The estimated median time treatment duration was 18.4 months at the data cut-off date. Exposure duration of ≥ 24 months was observed in 42.1% (135/321) of the patients in the safety population. Dose reductions or interruptions were permitted

[9] WHO performance scale: The World Health Organization (WHO) designed the scale which has categories from 0 to 4 as follows:
0 : fully active and more or less as you were before your illness
1 - cannot carry out heavy physical work, but can do anything else
2 - up and about more than half the day; you can look after yourself, but are not well enough to work
3 - in bed or sitting in a chair for more than half the day; you need some help in looking after yourself
4 - in bed or a chair all the time and need a lot of looking after

according to standard pre-specified criteria. Of the 321 patients, 125 (38.9%) had dose reductions from either 400 mg bd or 600 mg bd, with the most common reason being adverse events (82 patients, 25.5%). Of the 321 patients, 185 (57.6%) had dose interruptions with the most common reason being adverse events (176 patients, 54.8%). Treatment was resumed with a reduced dose after treatment interruption in 27.4% (n=88) of patients. The median cumulative duration of dose interruption was 20 days, and the median percentage of days with dose interruption was 3.9%.

All enrolled patients with CML-CP had received prior treatment with imatinib, and the median highest dose had been 600 [range: 400 to 800] mg and the overall median duration of prior treatment had been 975.5 [range: 9 to 2851] days. The majority of patients (n=285, 88.8%) had been previously treated with anti-neoplastic medication, with the most commonly used agents being hydroxycarbamide (n=266, 82.9%), interferon (n=134, 41.7%) and cytarabine (n=78, 24.3%).

Efficacy Results

Overview

The 24 month follow up data were presented descriptively. Nilotinib was administered open label and there was no control group. No formal hypothesis testing was performed for the 24 month updated efficacy analysis. The number and percentage of patients with MCyR, confirmed MCyR, CCyR and CHR were presented with 95% CIs. Loss of MCyR and loss of CHR were calculated as percentages relative to the patients with MCyR and CHR, respectively. Number and percentage of patients with MMR were reported for all patients and also for patients with CCyR and CHR. Time to event variables were calculated and summarised using the Kaplan-Meier (K-M) method.

The efficacy analysis in patients with CML-CP was based on the ITT population and included all 321 patients who had received at least one dose of study medication. The safety population also included 321 patients consisting of all patients who received at least one dose of study medication and had at least one post baseline safety assessment. In this study the ITT and safety populations were identical. The “per protocol” (PP) population (haematologic response) included 276 patients and the PP population (cytogenetic response) included 263 patients.

The efficacy data were presented using two analysis methods based on the ITT population (conventional ITT and primary ITT analyses). In the conventional ITT analysis, patients were assessed for response regardless of any major protocol violation and actual observed responses for all patients at all visits were considered. In the primary ITT analysis, patients with major protocol violations were considered nonresponders regardless of whether or not they experienced a documented response. In the primary ITT analysis, data were excluded due to patients either not satisfying certain criteria at baseline or having post-baseline assessments performed following a procedure (chemotherapy, platelet pheresis) or use of certain drugs (anagrelide, hydroxyurea) that could potentially impact the interpretability of the assessment. The primary ITT analysis was a more conservative analysis than the conventional ITT analysis. In addition, per protocol analysis of efficacy was presented in which all patients with major protocol violations were excluded from the analysis. The results for all three analyses are provided below for the primary efficacy endpoint, while only the results for the primary ITT analyses are provided below for the secondary efficacy endpoints.

Primary Efficacy Endpoint (Result)

The primary efficacy variable for patients with CML-CP was the overall major cytogenetic response rate (MCyR = complete plus partial cytogenetic response). The results for the

analyses of the primary efficacy variable in the conventional ITT, primary ITT, and PP populations are summarised in Table 9.

Table 9: Supportive Study [CML-CP] – Cytogenetic response rates [n, (%)]

	Conventional ITT (n=321)	Primary ITT (n=321)	Per-protocol (n=263)
MCyR (complete + partial)	190 (59.2%)	165 (51.4%)	165 (62.7%)
[95% CI of the MCyR rate]	[53.6%, 64.6%]	[45.8%, 57.0%]	[56.6%, 68.6%]
Complete	141 (43.9%)	118 (36.8%)	118 (44.9%)
Partial	49 (15.3%)	47 (14.6%)	47 (17.9%)
Minor	19 (5.9%)	19 (5.9%)	19 (7.2%)
Minimal	41 (13.1%)	36 (11.2%)	36 (13.7%)
None	36 (11.2%)	33 (10.3%)	33 (12.5%)
Absence of Response			
Progression	12 (3.7%)	9 (2.8%)	9 (3.4%)
Death without response	1 (0.3%)	1 (0.3%)	1 (0.4%)
Not assessable	21 (6.5%)	58 (18.1%)	0

Secondary Efficacy Endpoints (Results)

Major Cytogenetic Response

The median time to MCyR in the primary ITT analysis was 2.8 months [25th-75th percentiles: 1.0, 4.7] and range 0.9 to 28.2 months and the median duration of MCyR at the date of data cut-off was not reached in the primary ITT population. In those patients who had achieved MCyR, it was estimated that at 24 months MCyR was still present in 76.82% [95%CI: 69.4%, 83.99%] of patients in the primary ITT population. The MCyR duration was defined as the time from first occurrence of response to the date of discontinuation due to progressive disease or death.

Complete Cytogenetic Response (CCyR)

The median time to CCyR was 3.4 months [25th-75th percentiles: 2.8, 7.0] and range 0.9 to 26.7 months. The median duration of CCyR at the date of data cut-off was not reached in the primary ITT population. At 24 months, it was estimated that CCyR was still present in 85.3% [95%: 78.12%, 92.59%] of patients in the primary ITT population.

Complete Haematologic Response (CHR)

The CHR rate for patients without CHR at baseline was 70.0% (145/207) [95%CI: 63.3%, 76.2%] in the primary ITT population. The median time to CHR for patients without a CHR at baseline was 1.0 month [25th-75th percentile: 0.9, 1.2] and range 0.9 to 11.8 months in the primary ITT population. The median duration of the CHR was 32.79 months [range: 0.03, 35.15] in the primary ITT population, and 62.41% [95%CI: 53.54, 71.28] of patients were estimated to still be in CHR at 24 months.

Molecular Response

Major molecular response (MMR) was defined as ≤ 0.1% BCR-ABL/control gene % by international scale, with the control gene being either BCR or ABL. Analysis of MMR was performed on 294 patients with relevant baseline data. Of these patients, 82 (27.9%) achieved MMR, with the median time to MMR being 5.6 months [25th-75th percentile: 2.9, 8.3] and range 0.9 to 28.1 months. The MMR rate was higher in patients who had CHR at baseline (38.1%, 40/105), with the median time to MMR being 5.5 months [25th-75th percentile: 2.8, 6.3] and range 0.9 to 25.8 months.

Time to Accelerated Phase (AP) or Blast Crisis (BC)

The median time to AP or BC had not been reached by the date of data cut-off. At 24 months, an estimated 63.72% [95%CI: 57.59%, 69.84%] of patients had not reached AP or BC. Of the 94 patients who progressed to AC or BC, only 9 (3%) had progressed based on actual laboratory values. The remaining 85 patients were considered to have progressed based on the fact that they had either discontinued due to progression or had died.

Time to Progression (TTP)

The median TTP was 33.6 months in the primary ITT population: 116 patients progressed, 205 censored, range 0.1 to 36.0 months.

Overall Survival

The analysis of overall survival reflects all deaths occurring during treatment or after discontinuation of treatment with nilotinib. At the date of data cut-off, the estimated 24 month overall survival rate in the ITT population was 87.05% [95%CI: 83.25%, 90.86%]. The number of deaths in the 321 patients in the ITT population was 44 and the number of censored patients was 277.

Evaluator Comment

Interpretation of the 24 month, follow up data is limited due to the absence of a control group. The efficacy analysis was based on the CML-CP ITT population which included all 321 patients. The efficacy analysis was in the primary ITT and conventional ITT populations. The primary ITT analysis was more conservative than the conventional ITT analysis.

In order to assess the durability of response in the CML-CP patients, the efficacy outcomes in the 6 month follow up data (previously evaluated) have been compared with the efficacy outcomes in the 24 month follow up data (newly submitted). The efficacy outcomes for the 6 month follow up data have been obtained from the currently approved Tasigna PI. The efficacy endpoints of interest are major cytogenetic response, complete haematologic response and overall survival. The primary efficacy endpoint for patients with CML-CP in both the 6 and 24 month data was major cytogenetic response defined as complete plus partial cytogenetic response. The secondary efficacy endpoints for patients with CML-CP included complete haematologic response and overall survival. Data previously evaluated by the TGA indicate that the relevant results in the Tasigna PI for the major cytogenetic response and the complete haematologic response in the patients with CML-CP are from the conventional ITT analysis.

In the conventional ITT population, the major cytogenetic response was 56% [95%CI: 51%, 62%] in the 6 month follow up data (n=320) compared with 59.2% [95%CI: 54%, 65%] in the 24 month follow up data (n=321). The major cytogenetic response was defined as the complete response plus the partial cytogenetic response. The respective response rates for the components of the major cytogenetic response rate in the

conventional ITT population were (6 months vs 24 month): complete cytogenetic response 40% vs 43.9%; and partial cytogenetic response 16% vs 15.3%.

In the conventional ITT population, the complete haematologic response rate was 76% [95%CI: 70%, 82%] in the 6 month follow up data (n=206) compared with 76.3% [95%CI: 70%, 82%] in the 24 month follow up data (n=207). The respective K-M estimates for overall survival at 12 months and 24 months were 96% and 87%.

Study CAMN107A2101E1 [CML-AP]

Background

The submitted data included Phase II, 24 month, follow up data for 137 patients with imatinib resistant or intolerant chronic myeloid leukaemia in the accelerated phase (CML-AP) treated with nilotinib. These patients had received no prior treatment with a tyrosine kinase inhibitor other than with imatinib. The data for the CML-AP patients were from the same previously submitted study as the data for the CML-CP patients. The current Tasigna PI includes information on 119 CML-AP patients exposed to nilotinib for a median duration of 6.6 months from the previously submitted study. The new data included information on 137 patients who had either completed 24 months of treatment or discontinued and had been exposed to nilotinib for a median duration of 8.7 months.

The efficacy evaluation focuses primarily on the relevant updated primary and secondary efficacy endpoint 24 month follow up data. The first patient with CML-AP was dosed on 9 May 2005 and the 24 month data cut-off date was 29 August 2009 and the report was dated 4 November 2009. The study protocol and amendments were reviewed by the IEC or IRB for each centre. The study was conducted according to the principles of the Declaration of Helsinki. Informed consent was obtained in writing from each patient. The study was sponsored by Novartis.

Patient Disposition

A total of 137 patients with CML-AP were treated in 17 participating countries at 55 centres. Patient disposition is summarised in Table 10. Of the 137 patients, 85.4% discontinued prematurely and the most frequent reasons for premature discontinuation were disease progression (43.8%) and adverse events (17.5%). Discontinuation due to drug related adverse events was observed in 14 (10.2%) patients. Major protocol deviations occurred in 27.0% (37/137) of patients and resulted in exclusion from the per protocol efficacy analyses.

Table 10: Supportive Study [CML-AP] - Patient disposition (n, %)]

Disposition	Total n=137
Treatment ongoing*	20 (14.6%)
Continuing in core study	13 (9.5%)
Entered extension study	7 (5.1%)
Discontinued	117 (85.4%)
Reason for Discontinuation	
Disease progression	60 (43.8%)
Adverse Event(s)	24 (17.5%)
Subject withdrew consent	14 (10.2%)
Abnormal laboratory value(s)	7 (5.1%)
Administrative problems	5 (3.6%)
Death**	3 (2.2%)
Protocol violation	2 (1.5%)
Not stated	1 (0.7%)
Lost to follow-up	1 (0.7%)

Patient Demographics

The mean age of the 137 patients was 56.4 years [SD: 13.2], ranging from 22 to 82 years. The majority of patients were aged ≥ 55 years (n=80, 58.4%), male (n=76, 55.5%) and Caucasian (n=109, 79.6%). Nearly all patients were WHO performance status Grade 0 or 1 (n=129, 94.2%). The median time from first diagnosis was 5.9 [range: 0.2 to 24.9] years. More than half of all patients (n=78, 56.9%) had been diagnosed with CML ≥ 5 years prior to study entry. Of the 137 patients, 14.6% (n=20) had achieved prior cytogenetic response, and 7.3% (n=10) had achieved a best response of CHR. Of the 137 patients, 79.6% (n=109) were imatinib resistant and 19.7% (n=27) were imatinib intolerant and no information on status was available on 1 patient.

Treatment

The starting dose of nilotinib was 400 mg bd and dose escalation to 600 mg bd was permitted in patients with CML-AP until prohibited by protocol Amendment 11 (11 April 2008). The actual nilotinib median dose intensity was 780 [range: 150 to 1149] mg/day and the median duration of exposure to nilotinib was 8.7 months (264 [range: 2 to 1160] days). Exposure duration of ≥ 24 months was observed in 25 (18.2%) of the 137 patients in the safety population.

Dose reductions or interruptions were permitted according to standard pre-specified criteria. Of the 137 patients, 55 (40.1%) experienced a dose reduction from either 400 mg bd or 600 mg bd, with the most common reason being adverse events (31 patients, 22.6%). Of the 137 patients, 76 (55.5%) experienced a dose interruption with the most common reason being adverse events (49.6%, 68 patients). There were 37/137 (27.0%) patients who resumed treatment with a reduced dose after treatment interruption. The

median cumulative duration of dose interruption was 23 days, and the median percentage of days with dose interruption was 6.9%.

The median highest dose of prior imatinib in enrolled patients with CML-AP was 600 [range: 200 to 1200] mg and the overall median duration of prior imatinib treatment was 856.5 days. The majority of patients (n=130, 94.9%) had been previously treated with antineoplastic medication, with the most commonly used agents being hydroxycarbamide (n=125, 91.2%), interferon (n=49, 35.8%) and cytarabine (n=35, 25.5%).

Efficacy Results

Overview

The 24month follow up data were presented descriptively. Nilotinib was administered open label and there was no control group. No formal hypothesis testing was performed for the 24 month update efficacy analysis. The descriptive analysis of the CML-AP data was similar to that for the CML-CP. The efficacy analysis in patients with CML-AP was based on the ITT population and included all 137 patients. All patients who received at least one dose of study medication were included in the ITT analysis. The safety population also included 137 patients consisting of all patients who received at least one dose of study medication and had at least one post baseline safety assessment. The ITT and safety populations in this study were identical. The PP population (haematologic response) included 104 patients and the PP population (cytogenetic response) included 120 patients. The efficacy data in the CML-AP patients were presented using the same two analysis methods based on the ITT population as used in the CML-CP patients (that is, conventional ITT and primary ITT analyses). In addition, per protocol analysis of efficacy was presented which excluded all patients with major protocol violations. The results for all three analyses are provided below for the primary efficacy endpoint, while only the results for the primary ITT analyses (apart from CCyR) are provided for the secondary efficacy endpoints.

Primary Efficacy Variable

The primary efficacy variable for patients with CML-AP was the haematologic response (HR) (confirmed after 4 weeks), defined as any of the following: complete HR (CHR); marrow response (MR) / no evidence of leukaemia (NEL); or return to chronic phase (RTC). The results for the analyses of the primary efficacy variable in the conventional ITT, primary ITT, and PP populations are summarised in Table 11.

Table 11: Supportive Study [CAMN107A2101E1] - Confirmed hematologic response rates

	Conventional ITT (n=137)	Primary ITT (n=137)	Per-protocol (n=104)
Hematologic Response Overall	76 (55.5%)	69 (50.4%)	69 (66.3%)
[95% CI of HR Response (%)]	[46.7%, 64%]	[41.7%, 59%]	[56.4%, 75.3%]
Complete hematologic response	43 (31.4%)	41 (29.9%)	41 (39.4%)
Marrow response/no evidence of leukaemia	17 (12.4%)	13 (9.5%)	13 (12.5%)
Return to chronic phase	16 (11.7%)	15 (10.9%)	15 (14.4%)
Absence of Response			
No response (including stable disease)	9 (6.6%)	8 (5.8%)	8 (7.7%)
Progression without response	17 (12.4%)	20 (14.6%)	20 (19.2%)
Death without response	2 (1.5%)	2 (1.5%)	2 (1.9%)
Not assessable	33 (24.1%)	38 (27.7%)	5 (4.8%)

Hematologic response (HR) = complete hematologic response (CHR) + marrow response (MR)/no evidence of leukaemia (NEL) + return to chronic phase (RTC).

Secondary Efficacy Variables

Time to Haematologic Response and Duration of Haematologic Response

The median time to first confirmed HR was 1.0 month [25th-75th percentile: 1.0, 1.9], range 0.8 to 11.1 months in the primary ITT population. The overall duration of confirmed HR, defined as time from first occurrence of response to the date of discontinuation due to PD or death for patients with confirmed HR, was 24.21 [range: 2.17, 37.16] months in the primary ITT population. In those patients who had achieved HR, it was estimated that at 24 months HR was maintained in 53% [95%CI: 39%, 67%] of patients in the primary ITT population.

Cytogenetic Response

The overall major cytogenetic response (MCyR) rates for the three efficacy analyses are provided in Table 12. The MCyR was defined a complete plus partial cytogenetic responses.

Table 12: Supportive Study [CML-AP] – Cytogenetic response rates

	Conventional ITT (n=137)	Primary ITT (n=137)	Per-protocol (n=120)
Major (complete + partial) 95% CI of MCyR (%)	44 (32.1%) 24.4%, 40.6%	41 (29.9%) 22.4%, 38.3%	41 (34.2%) 25.8%, 43.4%
Complete	29 (21.2%)	27 (19.7%)	27 (22.5%)
Partial	15 (10.9%)	14 (10.2%)	14 (11.7%)
Minor	17 (12.4%)	17 (12.4%)	17 (14.2%)
Minimal	33 (24.1%)	31 (22.6%)	31 (25.8%)
None	21 (15.3%)	19 (13.9%)	19 (15.8%)

The median time to achieve MCyR was 2.8 [range: 0.9, 27.6] months in both the conventional ITT and primary ITT populations. MCyR was maintained in 66.15% [95%CI: 49.98%, 82.31%] of patients in the conventional ITT population and 62.71% [95%CI: 45.17%, 80.25%] in the primary ITT population maintaining response at 24 months. The median duration of MCyR was not reached up to the data cut-off for the conventional ITT population but was 32.7 months for the primary ITT population.

Major Molecular Response

Major molecular response (MMR) was defined as ≤ 0.1% BCR-ABL/control gene % by international scale, with the control gene being either BCR or ABL. Analysis of MMR was performed on 109 patients with relevant baseline data. Of these patients, 14 (12.8%) achieved MMR, with the median time to MMR being 10.2 [25th-75th percentile: 2.9, 13.8] months and range 1.9 to 17.1 months.

Time to Progression

In the primary ITT population, 72 of the 137 patients progressed (65 censored) with the median time to progression (TTP) being 15.9 months [95%CI: 10.1-20.1], [25th-75th percentile: 5.6 to not reached] and range 0.1 to 38.1 months. For patients with a confirmed HR, TTP was defined as the time from the start of nilotinib to the earliest date of the following: loss of response or discontinuation due to PD or death. For patients without a confirmed HR, TTP was defined as the time from the start of nilotinib to the earliest date of the following: progression (date of assessment with PD which is not followed by assessment better than PD); or discontinuation due to PD or death. For patients for whom none of these events were reported, TTP was censored at the cut-off date or at the discontinuation date (for patients who discontinued due to other reasons).

Overall Survival

At the date of data cut-off, the Kaplan-Meier estimate of overall survival at 24 months was 70% [95%CI: 62%, 78%]. There had been 45 deaths in the 137 patients in the ITT population (92 censored).

Evaluator Comment

Interpretation of the provided 24 month follow up data is limited due to the absence of a control group. In addition, the patients in this study were not representative of those being proposed for treatment as the disease was CML-AP rather than CML-CP. The efficacy analysis was based on the ITT population which included all 137 patients. Efficacy was analysed in the primary ITT and conventional ITT populations. The primary ITT analysis is considered to be the more conservative of the two ITT analyses.

In order to assess the durability of response in the CML-AP patients, the efficacy outcomes in the 6 month follow up data (previously evaluated) were compared with the efficacy outcomes in the 24 month follow up data (newly submitted). The efficacy outcomes for the 6 month follow up data have been obtained from the currently approved Tasigna PI. The efficacy endpoints of interest in the CML-AP patients are overall confirmed haematologic response, major cytogenetic response and overall survival. The primary efficacy endpoint was overall confirmed haematologic response for patients with CML-AP in both the 6 month and 24 month follow up data. The secondary efficacy endpoints for patients with CML-AP included major cytogenetic response and overall survival. Data previously evaluated by the TGA indicate that the relevant results in the Tasigna PI for the confirmed haematological response and major cytogenetic response in patients with CML-AP are from the conventional ITT analysis.

In the ITT population, the confirmed overall haematological response rate was 47% [95%CI: 38%, 56%] in the 6 month follow up data compared with 55.5% [95%CI: 47%, 64%] in the 24 month follow up data (n=137). The confirmed overall haematological response rate was defined as complete haematological response, no evidence of leukaemia or return to chronic phase. The respective response rates for the components of the confirmed overall haematological response rates in the conventional ITT populations were (6 months vs 24 months): complete haematologic response 26% vs 31.4%; no evidence of leukaemia 9% vs 12.4%; and return to chronic phase 12% vs 11.7%.

In the conventional ITT population, the major cytogenetic response was 29% [95%CI: 21%, 39%] in the 6 month follow up data (n=119) compared with 32.1% [95%CI: 24%, 41%] in the 24 month follow up data (n=127). The major cytogenetic response was defined as the complete plus the partial cytogenetic response. The respective response rates for the components of the major cytogenetic response rates in the conventional ITT population were (6 months vs 24 months): complete cytogenetic response 16% vs 21.2%; and partial cytogenetic response 13% vs 10.9%. In the ITT populations, the respective K-M estimates for overall survival at 12 months and 24 months were 79% and 70%.

Study CSTI571A0106 PCR

Background

Study ST15171A0106 [IRIS] was a Phase III trial comparing imatinib with interferon-α combined with cytarabine in 1106 patients with newly diagnosed previously untreated Ph+ CML-CP. The study has been previously evaluated by the TGA and clinical data at 84 months of follow up are included in the currently approved imatinib (Glivec) PI. Initially the primary efficacy end point was progression free survival (PFS) but this was later changed to event free survival (EFS) as this endpoint included more events than progression to AP/BC. EFS events were defined as: (1) loss of CHR; (2) loss of MCyR; (3) progression to AP/BC; (4) death during study; (5) increasing WBC despite appropriate therapeutic management when not achieving a CHR.

There have been a number of publications over the last 10 years based on the IRIS data and focussing on MMR as a potential surrogate measure of beneficial outcome in patients with CMP-CP. Overall, the published IRIS molecular response data indicate that there is a positive correlation between MMR and CCyR [Branford et al, 2003; Ross et al, 2006], and between CCyR, MMR, and PFS [Hughes et al, 2006; Druker et al, 2006; O'Brien et al, 2008].[7,8,10,11,12] The published data also suggest that CCyR combined with MMR is associated with greater improvement in EFS/PFS compared with CCyR without MMR.

The submitted data included an analysis of the prognostic value of the molecular response to first line imatinib treatment in patients with CML-CP using RQ-PCR to determine BCR-ABL transcript levels which were then used to calculate BCR-ABL/BCR control gene ratios [CSTI571A0106 PCR]. The PCR study was dated 18 November 2009, the clinical cut-off date was 31 January 2008 and the PCR cut-off date was 18 March 2008. The objective of the PCR study was to demonstrate that MMR at 12 months continues to predict improved outcome at 84 months in terms of maintaining complete cytogenetic response (CCyR), EFS

[10] Branford S, Rudzki Z, Harper A et al. Imatinib produces significantly superior molecular responses compared to interferon alpha plus cytarabine in patients with newly diagnosed chronic myeloid leukemia in chronic phase. Leukemia 2003; 17: 2401-9.

[11] Ross DM, Branford S, Moore S et al. Limited clinical value of regular bone marrow cytogenetic analysis in imatinib-treated chronic phase CML patients monitored by RQ-PCR for BCR-ABL. Leukemia 2006; 20: 664-70.

[12] Hughes T, Branford S. Molecular monitoring of BCR-ABL as a guide to clinical management in chronic myeloid leukaemia. Blood Rev 2006; 20: 29-41.

and time to AP/BC, thereby further validating MMR at 12 months as a surrogate for long term outcome. All analyses in the PCR report were considered to be descriptive and explorative and, consequently, statistically significant findings have to be interpreted having regard to these methodological limitations.

When IRIS was designed, molecular assessment of residual disease by RQ-PCR was considered experimental and therefore molecular response was not included as an endpoint. Molecular assessment was incorporated into the protocol in Amendment 1 as an exploratory endpoint but was required only for patients who achieved CCyR. However, the submitted updated PCR report included additional data from patients who had samples for RQ-PCR taken prior to the achievement of CCyR. These additional data were derived from a substudy in Germany and Australia/New Zealand, as well as from patients treated at other sites interested in molecular assessment with samples obtained prior to the achievement of CCyR.

Method

The control gene (BCR or ABL) was quantified by RQ-PCR and BCR-ABL transcript levels were expressed as a percentage of control gene transcript levels. In order to compare the results between the four laboratories, the primary BCR-ABL/control gene values were converted to an international scale (IS) using different conversion factors for each of the RQ-PCR laboratories.

Patient Population

The PCR population included 476 patients who had received first line treatment with imatinib with at least one blood sample for RQ-PCR evaluations. The PCR population (n=476) in the 84 month PCR analysis was compared with the ITT population (n=533) in the 60 month clinical update. Baseline demographic and disease characteristics of the two populations were similar, as was patient disposition. Of the patients in the PCR population, 68.1% were still receiving imatinib on protocol at the date of data cut-off. Treatment discontinuation had occurred in 27.3% of patients in the PCR population and 34.7% of patients in the ITT population, with the main reason in both populations being "unsatisfactory therapeutic effect" The median duration of treatment in was similar in the PCR and ITT populations (about 82 months) as was median imatinib dose intensity (400 mg/day).

Results – Major Molecular Response (MMR) at 84 Months

The published IRIS data indicate that achievement of MMR at 12 months predicted improved PFS (EFS) and lack of progression to AP/BC at 24 and 60 months. The submitted PCR report showed that achievement of MMR at 12 months continues to predict for a significant improvement in EFS and time to AP/BC at 84 months but not OS (Table 13). MMR was defined as a BCR-ABL/control gene % by IS of ≤ 0.1%.

Table 13: Estimated EFS, time to AP/BC, and overall survival at 84 months by MMR status at 12 months

Outcome 84 months	MMR at 12 months	No MMR at 12 months	MMR vs No MMR
Event-Free Survival	n=153 91.0% [95%CI: 85.4, 96.6]	n=148 79.4% (72.5;86.1)	p=0.0010, log-rank test
Time to AP/BC	n=153 99.0%* [95%CI: 97.1, 100]	n=151 89.9% [95%CI: 84.9, 94.9]	p=0.0004, log-rank test
Overall Survival	n=153 92.5% [95%CI: 87.7, 97.2]	n=152 89.2% [95%CI: 84.1, 94.2]	p=0.1797, log-rank test

*This reflects an event that was recorded as progression between months 72 and 84. The records of this patient were subsequently reviewed and the event was a death not due to CML. Therefore, the time to AP/BC curve for patients who had achieved MMR at 12 months should be 100% at 84 months

The MMR increased over time in patients continuously treated with imatinib with rates being 13% (22/154) at 3 months, 50% (153/305) at 12 months, 70% (73/104) at 24 months, 78% (56/72) at 36 months, 75% (178/238) at 48 months, 85% (232/273) at 60 months, 86% (181/210) at 72 months and 88% (102/116) at 84 months. MMR at 12 months was associated with 90.8% of patients remaining in CCyR at 84 months versus 81.4% of patients not achieving MMR by 12 months (p=0.0097, log rank test).

Evaluator Comment

This was a good quality exploratory study. The PCR population and the ITT population were similar as regards baseline demographics and disease characteristics. Consequently, it is reasonable to assume that the results from the PCR population can be extrapolated to the entire ITT population (including those for whom no PCR data are available). The PCR data showed that MMR at 12 months is a statistically significant predictor of EFS and time to AP/BC at 84 months, but not OS.

Evaluator's Overall Conclusions on Clinical Efficacy

The pivotal study satisfactorily demonstrated that the MMR rate at 12 months (primary efficacy endpoint) was statistically significantly greater ($p < 0.0001$) in both nilotinib treatment arms (300 mg bd and 400 mg bd) compared with the imatinib treatment arm (400 mg qd). The MMR rates at 12 months were 22.3% (63/283), 44.3% (125/282) and 42.4% (120/281) in the I400, N300 and N400 treatment arms respectively. The difference in the MMR rates at 12 months were 22.1% [95%CI: 14.5%, 29.5%] for the N300 vs I400 comparison, and 20.4% [95%CI: 12.9%, 28.0%] for the N400 vs I400 comparison. The median time to MMR was longer in the I400 arm (8.3 months) than in both the N300 (6.9 months) and the N400 (7.4 months) arms.

In the pivotal study, the best CCyR rate by 12 months (the main secondary efficacy endpoint) was also statistically significantly higher in both the nilotinib treatment arms compared with the imatinib treatment arm. The best CCyR rates at 12 months were 65.0% (184/283), 80.1% (226/282) and 77.9% (219/281) in the I400, N300 and N400 treatment arms, respectively: $p<0.0001$ for I400 vs N300 and $p<0.0005$ for imatinib 400 mg vs N400. The difference in the CCyR rates at 12 months were 15.1% [95%CI: 7.9%, 22.4%] for the N300 vs I400 comparison and 12.9% [95%CI: 5.5%, 20.3%] for the N400 vs I400 comparison. The median time to CCyR was similar in the three treatment arms (5.6 to 5.8 months).

In the pivotal study, other secondary efficacy endpoints relating to molecular response and cytogenetic response were generally statistically significantly superior in both nilotinib treatment arms compared with the imatinib treatment arm. However, the CHR rates at 12 months were high in the three treatment arms and there were no statistically significant differences between both the nilotinib arms and the imatinib arm. The K-M estimated EFS rate at 12 months was statistically significantly greater in the N400 arm than in the I400 arm (99.6% vs 95.7%, respectively, p=0.0012, log rank test) but the difference between N300 and I400 arms was not statistically significant (97.6% vs 95.7%, respectively, p=0.0898, log rank test). Progression to AP/BC at 12 months was statistically significantly higher in the I400 arm than in both nilotinib arms. The K-M estimated OS rate at 12 months was high (> 99%) in each of the three treatment arms and there were no statistically significant differences between the nilotinib arms and the imatinib arm.

The supportive studies included 24 month, open label, uncontrolled follow up data in patients with imatinib resistant of intolerant CML-AP or CML-CP treated with nilotinib. Overall, the results showed durability of response from 6 months to 24 months of follow up in patients with CML-CP as assessed by the MCyR and complete HR and patients with CML-AP as assessed by overall confirmed HR and MCyR. However, the OS rate fell in both patients with CML-CP and CML-AP from the 6 month follow up to the 24 month follow up.

Safety

Introduction

The Phase III pivotal study included 836 patients in the safety set with newly diagnosed Ph+ CML-CP with at least 12 months of follow up data who received at least one dose of study drug. The safety set included patients in the imatinib 400 mg qd (I400, n=280), nilotinib 300 mg bd (N300, n=279) and nilotinib 400 mg bd (N400, n=277) treatment arms. The two Phase II supportive studies included 458 patients with imatinib resistant or intolerant Ph+ CML-CP (n=321) or Ph+ CML-AP (n=137) with at least 24 months of follow up data who received at least one dose of nilotinib. The safety data from the pivotal study and the two supportive studies were open label and included all patients who received at least one dose of study drug. The data from the three studies were not pooled due to differences in patient population and study design. The pivotal study included the key safety data which consisted of open label comparisons between the two nilotinib treatment arms and the imatinib treatment arm.

In the pivotal study, adverse events (AEs) were coded using the MedDRA dictionary that provides the system organ class (SOC) and preferred term information. CTCAE version 3.0 was used for reporting AE severity.[13] Treatment emergent AEs starting on or after the date of first study medication (including AEs that started after the discontinuation of the study medication regardless of the number of days after discontinuation but excluding AEs that started in the extension study) were reported. In the two supportive studies, all reported AEs, serious adverse events (SAEs), deaths and other clinically significant events included patients who had these events during nilotinib administration or within the 28 days following the last dose of nilotinib.

Patient Exposure

In the pivotal study, the median time on treatment was 13.8 months in each of the three treatment arms, ranging from 0 months to about 22.5 months. The proportion of patients with time on treatment of ≥ 12 months was 61.1% (n=171), 64.2% (n=179) and 65.0% (n=180), in the I400 (n=280), N300 (n=279) and N400 (n=277) arms, respectively. The respective *median duration of dose interruption* (any reason) was 14.0 days, 18.0 days and

[13] MedDRA: Medical Dictionary for Regulatory Affairs

21.5 days. The most common reason for dose interruption in each of three treatment arms was adverse events followed by dosing error. The *median duration of exposure* in each of the treatment arms was 13.6 months ranging from 0 to about 22.4 months. The *actual mean dose intensity* was 401.5 mg/day [range: 206, 800], 550.4 mg/day [range: 186, 638] and 683.0 mg/day [range: 232, 800] in the I400, N300 and N400 arms, respectively. The actual dose intensity equalled the total time on dose during treatment. The *mean relative dose intensities* were 1.00, 0.92 and 0.85 for the I400, N300 and N400 arms, respectively. The relative dose intensity equalled the actual dose intensity divided by the assigned total daily dose.

In the supportive study involving CML-CP patients (n=321), the median time on treatment was 18.4 [range: 0.0, 36.0] months and in the supportive study involving CML-AP patients (n=137) the median time on treatment was 8.7 [range: 0.1, 38.1] months. In the CML-CP supportive study, 42.1% of patients (n=135) remained on treatment for ≥ 24 months and the mean actual average nilotinib dose intensity was 694.2 [range: 151.0, 1109.8] mg/day. In the CML-AP supportive study, 18.2% (n=25) of patients remained on treatment for ≥ 24 months and the mean actual average nilotinib dose intensity was 690.5 [range: 150.2, 1149.0] mg/day.

Adverse Events

Pivotal Study

In the pivotal study, most patients in each of the three treatments arms experienced at least one AE (all grades): 98.2% (n=275) in the I400 arm, 98.2% (n=274) in the N300 arm and 98.6% (n=273) in the N400 arm. The respective proportions of patients who experienced CTC Grade 3 or 4 AEs were 42.9% (n=120), 45.5% (n=127) and 51.6% (n=143).

SOCs in which AEs occurred more frequently in either nilotinib arm than in the imatinib arm were: *Skin and Subcutaneous Tissue Disorders*; *Investigations*; *Infections and Infestations*; *Nervous System Disorders*; *Respiratory, Thoracic and Mediastinal Disorders*; *Metabolism and Nutrition Disorders*; *Hepatobiliary Disorders*; *Psychiatric Disorders*; *Reproductive System and Breast Disorders*; *Injury Poisoning and Procedural Complications*; *Vascular Disorders*; *Cardiac Disorders*; *Ear and Labyrinth Disorders*; *Renal and Urinary Disorders*; *Neoplasms Benign, Malignant, Unspecified*; *Endocrine Disorders*; and *Pregnancy, Puerperium and Perinatal Conditions*.

SOCs in which AEs occurred more frequently in the imatinib arm than in either of the nilotinib arms were: *Gastrointestinal Disorders*; *Musculoskeletal and Connective Tissue Disorders*; *General Disorders and Administration Site Conditions*; *Blood and Lymphatic System Disorders*; *Eye Disorders*; *Immune System Disorders*; and *Congenital, Familial and Genetic Disorders*.

AEs (any grade) occurring ≥ 5% more frequently in either nilotinib arm compared with the imatinib arm were (N300 vs N400 vs I400): rash (34.4% vs 40.8% vs 15.4%); headache (27.2% vs 40.8% vs 15.4%); ALT increased (21.5% vs 26.0% vs 6.1%); alopecia (10.0% vs 16.6% vs 4.6%); pruritis (17.9% vs 15.2% vs 6.8%); hyperbilirubinaemia (15.1% vs 14.8% vs 2.1%); upper abdominal pain (15.1% vs 11.9% vs 9.3%); AST increased (10.4% vs 11.6% vs 4.3%); constipation (13.6% vs 10.5% vs 4.3%); dry skin (8.2% vs 10.1% vs 3.6%); and blood bilirubin increased (8.2% vs 9.4% vs 0.7%).

AEs (all grades) occurring ≥ 5% more frequently in the imatinib arm than in either nilotinib arm were (N300 vs N400 vs I400): nausea (17.9% vs 24.9% vs 35.4%); diarrhoea (13.3% vs 14.4% vs 33.9%); vomiting (9.0% vs 14.5% vs 20.7%); neutropenia (14.7% vs 10.5% vs 20.4%); muscle spasms (9.7% vs 9.0% vs 26.8%); peripheral oedema (7.5% vs

8.3% vs 16.1%); leucopenia (8.2% vs 7.6% vs 15.4%); facial oedema (1.1% vs 1.8% vs 13.2%); and periorbital oedema (0.4% vs 1.1% vs 12.9%).

The incidence of AEs CTC Grade 3 or 4 was 42.9% (120/277), 45.5% (127/279) and 51.6% (143/277) in the I400, N300 and N400arms, respectively. The most frequently occurring (≥ 2%) AEs CTC Grade 3 or 4 occurring in either nilotinib arm and observed more frequently than in the imatinib arm were (N300 vs N400 vs I400): rash (0.4% vs 2.5% vs 1.4%); headache (2.2% vs 1.4% vs 0%); ALT increased (4.7% vs 5.8% vs 2.1%); thrombocytopenia (10.0% vs 11.2% vs 8.6%); hyperbilirubinaemia (2.5% vs 4.0% vs 0.4%); and lipase increased (6.8% vs 4.7% vs 2.5%). The most frequently occurring (≥ 2%) AEs CTC Grade 3 or 4 occurring in the imatinib arm and observed more frequently than in either nilotinib arm were (N300 vs N400 vs I400): anaemia (3.6% vs 4.0% vs 4.6%); neutropenia (11.8% vs 8.3% vs 13.6%); hypophosphataemia (1.8% vs 2.5% vs 2.9%); and leucopenia (2.5% vs 1.8% vs 4.3%).

The pattern of drug related AEs was consistent with the pattern of AEs regardless of any relationship to treatment. The incidence of drug related AEs was 91.4% (256/280), 89.2% (249/279), and 94.6% (262/277) in the I400, N300 and N400arms respectively. The most frequently occurring (≥ 10%) drug related AEs in either of the nilotinib arms and observed more frequently than in the imatinib arm were (N300 vs N400 vs I400): rash (30.8% vs 36.1% vs 11.4%); headache (14.0% vs 20.9% vs 8.2%); ALT increased (19.7% vs 24.5% vs 4.6%); thrombocytopenia (17.2% vs 18.8% vs 17.1%); alopecia (7.9% vs 13.0% vs 3.9%); fatigue (10.8% vs 9.0% vs 7.9%); pruritus (14.7% vs 13.0% vs 5.4%); hyperbilirubinaemia (14.3% vs 13.0% vs 1.8%); myalgia (9.7% vs 10.1% vs 10.0%); and AST increased (9.3% vs 11.2% vs 3.6%).The most frequently occurring (≥ 10%) drug related AEs in the imatinib arm and observed more frequently than in either nilotinib arm were (N300 vs N400 vs I400): nausea (11.5% vs 19.5% vs 30.7%); diarrhoea (7.9% vs 6.5% vs 21.4%); vomiting (4.7% vs 8.7% vs 14.3%); anaemia (6.1% vs 8.3% vs 13.6%); neutropenia (14.3% vs 10.5% vs 20.0%); muscle spasms (7.2% vs 6.1% vs 23.9%); peripheral oedema (5.0% vs 5.4% vs 13.6%); leucopenia (7.9% vs 7.6% vs 15.0%); eyelid oedema (0.7% vs 1.8% vs 13.2%); and periorbital oedema (0.4% vs 0.7% vs 12.1%).

Evaluator Comment

The incidence of AEs (all grade) regardless of the relationship to the study drug was similar in each of the three treatment arms (> 98%). However, the pattern of AEs differed between the nilotinib and imatinib arms. In the nilotinib arms, the following AEs occurred notably more frequently than in the imatinib arm: rash, pruritus, dry skin, alopecia, headache, ALT increased, AST increased, hyperbilirubinaemia, blood bilirubin increased, upper abdominal pain, and constipation. Grouping these AEs indicates that skin disorders (rash, pruritus, dry skin, alopecia) and hepatobiliary disorders (increased ALT, AST and bilirubin) occurred notably more frequently in the nilotinib arms than in the imatinib arm. In the imatinib arm, the following AEs occurred notably more frequently than in either of the nilotinib arms: nausea; diarrhoea; vomiting; neutropenia; leucopenia; muscle spasms; peripheral oedema; facial oedema; and periorbital oedema. Grouping these AEs indicates that gastrointestinal disorders (nausea, vomiting, diarrhoea), haematological abnormalities (neutropenia, leucopenia) and oedema (peripheral, facial, periorbital) occurred notably more frequently in the imatinib arm than in either of the nilotinib arms. This pattern of differences in events between the nilotinib and imatinib arms was also observed with CTC Grade 3 or 4 AEs.

Supportive Studies

In the CML-CP supportive study, 99.4% (n=319) of patients experienced an AE (all grades) regardless of relationship to study drug and the majority of these were CTC Grade 3 or 4

AEs (78.5%, n=252). There were numerous AEs (all grades) occurring with an incidence of ≥ 10%. The most frequently reported AEs (all grades) occurring with an incidence of ≥ 30% were nausea (36.8%), rash (36.1%), headache (35.2%), thrombocytopenia (33.0%), pruritus (32.1%) and fatigue (31.8%). The most commonly occurring CTC Grade 3 or 4 AEs occurring with an incidence of ≥ 5% were thrombocytopenia (24.0%), neutropenia (17.4%), lipase increased (9.7%) and anaemia (8.1%).

In the CML-AP supportive study, 99.3% (n=136) of patients experienced an AE (all grades). There were numerous AEs (all grades) occurring with an incidence of ≥ 10%. The most common AE (all grades) was thrombocytopenia (46.0%) and the other AEs (all grades) reported by ≥ 20% of patients were anaemia, rash, pyrexia, neutropenia, diarrhoea, fatigue, nausea and pruritis. The most common CTC Grade 3 or 4 AE was thrombocytopenia (39.4%) followed by neutropenia (23.4%), anaemia (16.8%), lipase increased (8.0%) and leucopenia (7.3%).

Evaluator Comment

The CSRs for the CML-CP and CML-AP supportive studies included a comparison of the incidence of important hepatic and pancreatic safety findings per 100 patient years of exposure in the 120 Day Safety Update Report (DSUR) previously evaluated by the TGA and the 24 month follow up data. Overall, the comparisons showed no cumulative risk of hepatic or pancreatic disorders in the two CML populations with longer follow up. The CSRs also included a comparison of the incidence of important selected cardiac adverse events per 100 patient years of patient exposure in the 120 DSUR and the 24 month follow up data. Overall, the comparisons showed no cumulative risk of selected cardiac adverse events in the two CML populations with longer follow up.

Deaths and Other Serious Adverse Events (SAEs)

Pivotal Study

Deaths, other SAEs and other significant AEs are summarised in Table 14.

Table 14: Pivotal Study - Deaths, other serious or clinically significant adverse events or related discontinuations; safety set

Events	Imatinib 400 mg qd (n=280)	Nilotinib 300 mg bd (n=279)	Nilotinib 400 mg bd (n=277)
AE(s)	275 (98.2%)	274 (98.2%)	273 (98.6%)
Deaths within 28 days after discontinuation of study drug	0	2 (0.7)	1 (0.4)
SAEs (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%) [2]	30 (10.8%) [3]
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 discontinued due to AE/abnormal lab values from the imatinib 400 mg qd randomized arm and 1 patient due to AE from nilotinib 400 mg qd randomized arm who actually was treated with imatinib.
[2] 19 patients discontinued due to AE/abnormal lab values from the nilotinib 300 mg bd randomized arm.
[3] 31 patients discontinued due to AE/abnormal lab values from the nilotinib 400 mg bd randomized arm (1 patient with discontinuation due to AE was less counted on nilotinib 400 mg qd randomized arm as the patient was actually treated with imatinib).

There were three deaths occurring within 28 days of discontinuing the study drug: one death occurred in a 57 year old male randomized to N300 who died 2 days after stopping the drug due to a small intestinal obstruction (Day 174 of treatment); one death occurred in a 71 year old male randomized to N300 who committed suicide 2 days after stopping the study drug (Day 232 of treatment); and one death occurred in a 58 year old female randomized to N400 who discontinued treatment due to disease progression and died at home of unknown causes 23 days after stopping the study drug (Day 268 of treatment). The three deaths which occurred within 28 days of discontinuing the study drug were considered by the investigators not to be related to the study drug. No deaths occurred within 28 days of discontinuing the study drug in patients randomized to I400.

There were a total of 6 deaths of which 5 were due to progressive CML and 1 due to gastric cancer considered by the investigator to be causally related to the study drug in a patient in the N400 arm

The SOC (all grades) with the most frequently reported SAEs was *Gastrointestinal Disorders* (3.2%, 4.3% and 4.3% for the N300, N400 and I400 arms, respectively). Other SOCs with at least 5 patients in at least one treatment arm were (N300 vs N400 vs I400): *Blood and Lymphatic System Disorders* (2.5% vs 4.0% vs 1.4%); *Respiratory, Thoracic and Mediastinal Disorders* (1.4% vs 2.2% vs 1.1%); *Musculoskeletal and Connective Tissue Disorders* (0.7% vs 2.2% vs 1.1%); *Infections and Infestations* (2.5% vs 1.8% vs 2.9%); *Cardiac Disorders* (2.2% vs 1.8% vs 0.7%); and *Investigations* (0% vs 1.8% vs 0.4%). SOCs (CTC Grade 3 and 4) occurred less frequently in the I400 arm (8.6%) than in either the N300arm (9.0%) or the N400arm (11.9%).

SAEs occurred less frequently in the N300arm (12.2%) than in the N400 (17.3%) or I400 (13.6%) arms. The majority of SAEs in the three treatment arms were CTC Grade 3 or 4 events. The most frequent (≥ 1.0%) SAEs CTC Grade 3 or 4 events occurring in either of the nilotinib treatment arms and observed more commonly than in the imatinib arm were (N300 vs N400 vs I400): neutropenia (1.1% vs 1.4% vs 0.4%) and thrombocytopenia (1.8% vs 1.4% vs 0.7%). No SAEs (CTC Grade 3 or 4) occurred with a frequency of ≥ 1.0% in the I400 arm.

Evaluator Comment

There were no SAEs occurring with an incidence of ≥ 2.0% in any of the three treatment arms. SAEs (all grades) occurred less frequently in the N300 arm than in the N400or I400 arms. SAEs (all grades) occurring with an incidence of ≥ 1.0% in either nilotinib arm and more frequently than in the imatinib arm were abdominal pain, neutropenia, thrombocytopenia and back pain. There were no SAEs (all grades) occurring with an incidence of ≥ 1.0% in the imatinib treatment arm and more frequently than in either nilotinib arm. The only SAE (all grades) occurring with an incidence of ≥ 1.0% in the I400 arm was vomiting (1.1%) and this SAE occurred with an incidence of 0.4% in the N300 arm and 1.1% in the N400 arm. SAEs (CTC Grade 3 or 4) occurred less frequently in the I400 arm than in the N300 or N400 arms. SAEs (CTC Grade 3 or 4) occurring with an incidence of ≥ 1.0% in either of the nilotinib arms and more frequently than in the imatinib arm were neutropenia and thrombocytopenia. There were no SAEs (CTC Grade 3 or 4) occurring with an incidence of ≥ 1.0% in the I400 arm. Overall, SAEs occurred less frequently in the N300 arm than in the N400 arm.

Other AEs of special interest included cardiac disorders, pancreatitis, and diabetes mellitus parameters. The SOC of *Cardiac Disorders* (all grades) occurred most frequently in the N300 arm (11.5%) followed by the N400 arm (7.9%) and the I400 arm (5.7%). Most of the SOC *Cardiac Disorders* in the three treatment arms were CTC Grade 1 or 2 events and individual preferred term cardiac AEs occurred in < 4% of patients in any treatment arm.

The most frequent cardiac AE in each of the three treatment arms was palpitations (all grades) which occurred in 1.8%, 3.9% and 2.5% of patients in the I400, N300 and N400 arms, respectively. Other cardiac AEs (all grades) occurring at an incidence of ≥ 1% in at least one of the treatment arms were (N300 vs N400 vs I300): angina pectoris 0.4% vs 1.8% vs 0.7%; tachycardia 1.1% vs 1.8% vs 0.4%; bradycardia 1.4% vs 1.1% vs 0.4%; atrial fibrillation 1.4% vs 0.7% vs 0.7%; and A-V block first degree 0% vs 0% vs 1.4%.

There were 7 cases of pancreatitis, none of which were CTC Grade 3 or 4 events. The incidence of pancreatitis was 0.7%, 1.4% and 0.4% in the N300, N400 and I400 arms. All cases of pancreatitis were considered to be drug related by the investigators apart from one of the cases reported in the N300 arm. In the 57 patients with diabetes mellitus (type II), no notable changes occurred in haemoglobin A1c (glycosylated haemoglobin) (HbA1c) or weight in the three treatment arms over 12 months. However, increases in mean fasting blood glucose at 12 months were reported with N300 (n=17, 0.86 mmol/L) and N400 (n=13, 1.5 mmol/L) but not with I400 (n=10, -0.22 mmol/L).

Supportive Studies

In the CML-CP supportive study, there were 8 deaths (2.5%) reported within 28 days of the last dose of nilotinib and 2 of these deaths were suspected as being drug related. Overall, 2 of the 8 patients died suddenly (1 on study Day 20 apparently due to coronary artery disease suspected to be drug related and 1 on Day 265 apparently due to an acute myocardial infarction). The 6 other deaths included: 1x renal failure and sepsis; 1x gastrointestinal ulcer perforation, peritonitis, and multiorgan failure suspected to be drug related; 1x myocardial infarction; 1x pulmonary embolism; 1x disease progression; 1x subdural haemorrhage.

In the CML-CP supportive study, SAEs (all grades) were reported in 37.4% (n=120) of patients and the majority or these were CTC Grade 3 or 4 events (30.5%, n=98). The most frequent SAEs were related to *Cardiac Disorders* (9.3%), followed by *Gastrointestinal Disorders* (6.9%), *General Disorders and Administration Site Conditions* (6.2%), *Blood and Lymphatic System Disorders* (5.6%) and *Musculoskeletal and Connective Tissue Disorders* (5.6%). The most common CTC Grade 3 or 4 SAEs were *Cardiac Disorders* (7.5%) and *Blood and Lymphatic System Disorders* (5.6%). No preferred term SAEs (all grades) occurred with an incidence of ≥ 5%. The most frequently reported (≥ 1%) SAEs (all grades) were thrombocytopenia (3.4%), angina pectoris (2.8%), pyrexia (2.5%), neutropenia (2.2%), coronary artery disease (1.6%), pancreatitis (1.6%), abdominal pain (1.2%), anaemia (1.2%), febrile neutropenia (1.2%), pain in extremity (1.2%), acute myocardial infarction (1.2%) and myocardial infarction (1.2%).

In the CML-CP supportive study, the most frequent SAEs suspected to be related to nilotinib treatment were *Blood and Lymphatic System Disorders* (5.0%), *Gastrointestinal Disorders* (4.0%) and *Musculoskeletal and Connective Tissue Disorders* (2.8%). The most common drug related CTC Grade 3 or 4 SAEs were *Blood and Lymphatic System Disorders* (5.0%), *Musculoskeletal and Connective Tissue Disorders* (2.2%) and *Cardiac Disorders* (2.2%).

In the CML-AP supportive study, there were 13 deaths (9.5%) occurring within 28 days of the last dose of study drug. The most common cause of death was reported as study indication (x5) followed by disease progression (x2) with the remaining causes of death being spinal cord haemorrhage, cardiac failure, cerebral haemorrhage, sepsis, lung infection and metastatic malignant melanoma. Of the causes of death, 2 were "suspected" to be related to the study drug (spinal cord haemorrhage and cerebral haemorrhage).

In the CML-AP supportive study, SAEs (all grades) were experienced by 37.2% (n=51) of patients and these were predominantly CTC Grade 3 or 4 events (30.7%; n=42). The most

frequent SAEs were related to *Blood and Lymphatic System Disorders* (16.8%), followed by *Infections and Infestations* (12.4%), *General Disorders and Administration Site Conditions* (7.3%), and *Musculoskeletal and Connective Tissue Disorders* (6.6%). Most common CTC Grade 3 or 4 SAEs were *Blood and Lymphatic System Disorders* (14.6%), *Infections and Infestations* (9.5%), and *General Disorders and Administration Site Conditions* (5.8%). The most commonly occurring CTC Grade 3 or 4 SAEs were thrombocytopenia (8.0%) and neutropenia (5.8%).

Discontinuation due to Adverse Events

Pivotal Study

In the pivotal study, the incidence of AEs resulting in discontinuation was lowest in the N300 arm (6.8%, 19/279) followed by the I400 arm (8.9%, 25/280) and the N400 arm (10.8%, 30/277). The most common AEs (all grades) leading to discontinuation (≥ 1% in any of the three treatment arms) were (N300 vs N400 vs I400): thrombocytopenia (1.1% vs 2.5% vs 0.7%); hyperbilirubinaemia (1.4% vs 0.7% vs 0.4%); neutropenia (1.1% vs 0.7% vs 1.4%); and ALT increased (0.4% vs 0.4% vs 1.1%). The most common CTC Grade 3 or 4 AEs leading to discontinuation (≥ 1% in any of the three treatment arms) were (N300 vs N400 vs I400): thrombocytopenia (3.2% vs 6.5% vs 6.1%); and neutropenia (0.7% vs 0.7% vs 1.4%).

All other AEs (all grades) resulting in discontinuation occurred at an incidence of ≤ 0.7% (that is, 1 or 2 patients) in the three treatment arms. The incidence of CTC Grade 3 or 4 AEs resulting in discontinuation was lowest in the N300 arm (3.2%, 9/729), followed by the I400 arm (6.1%, 17/280) and the N400 arm (6.5%, 18/277). The only CTC Grade 3 or 4 AE resulting in discontinuation with an incidence of ≥ 1% in at least one of the three treatment arms was thrombocytopenia (1.1%, 2.2% and 0.7% in the N300, N400 and I400 arms, respectively).

The incidence of AEs resulting in dose interruption or reduction was lowest in the I400 arm (43.9%, 123/280) followed by the N300 arm (50.5%) and the N400 arm (59.9%, 166/277). The most frequently reported AE (all grades) in the nilotinib arms resulting in dose interruption or reduction was ALT increased (11.5%, 15.2% and 3.2% in the N300, N400 and I400 arms, respectively). The most frequently reported AE (all grades) resulting in interruption or reduction in dose in the imatinib treatment arm was neutropenia (12.5%, 11.8%, and 7.6% in the I400, N300 and N400 arms, respectively).

Evaluator Comment

The incidence of all individual AEs (all grades) resulting in premature discontinuation was < 2.5% in the three treatment arms. AEs leading to discontinuation were most frequently laboratory related and included thrombocytopenia, neutropenia, hyperbilirubinaemia and increased ALT. Most of the thrombocytopenia and neutropenia AEs were CTC Grade 3 or 4, while most of the hyperbilirubinaemia and increased ALT AEs were CTC Grade 1 or 2.

The most frequently occurring AEs, such as rash, headache and nausea, rarely led to discontinuation. Two patients in the I400 arm discontinued due to diarrhoea (both CTC Grade 3 or 4). Three patients in the I400 arm and 1 patient in the N300 arm discontinued due to rash. Three patients in the nilotinib arms discontinued due to AEs related to cardiac disorders. Two patients (1 in each nilotinib arm) discontinued due to acute grade 1 or 2 pancreatitis and both cases were suspected to be study drug related

Overall, about half of all patients had AEs leading to dose interruption or reduction, with the lowest incidence observed in the I400 arm, followed by the N300 arm and the N400 arm. The most frequent AEs leading to dose interruption or reduction were laboratory related. AEs leading to dose interruption or reduction with a higher incidence in both of

the nilotinib arms than in the imatinib arm were increased ALT, thrombocytopenia, hyperbilirubinaemia and increased lipase. Leucopenia occurred more frequently in the imatinib arm than in both nilotinib arm, as did neutropenia (all grades) but not neutropenia (CTC Grade 3 or 4).

Supportive Studies

In the CML-CP supportive study, AEs (all grades) resulting in permanent nilotinib treatment discontinuation were reported in 21.2% (n=68) of patients and the majority were CTC Grade 3 or 4 AEs (16.8%, n=54). No AEs resulting in discontinuation were reported in ≥ 3.5% of patients. The most frequent AEs (all grades) associated with discontinuation were neutropenia (3.1%), thrombocytopenia (3.1%) and thrombocythaemia (1.6%), and nearly all of these were CTC Grade 3 or 4 AEs. All other AEs associated with discontinuation occurred at an incidence of < 1%.

In the CML-AP supportive study, AEs (all grades) resulting in permanent nilotinib treatment discontinuation were reported in 22.6% (n=31) of patients and the majority were CTC Grade 3 or 4 AEs (16.9%; n=23). The most common AE (all grades and CTC Grade 3 or 4) resulting in discontinuation was thrombocytopenia (11.7% and 9.5%, respectively). No other AEs resulting in discontinuation were reported in > 1.5% of patients.

Laboratory Findings

Pivotal Study

Newly occurring or worsening haematological abnormalities (decreased absolute lymphocyte count, decreased absolute neutrophil count, decreased haemoglobin, decreased total white cell count and decreased platelet count) were reported more frequently in the imatinib arm than in either nilotinib arms (Table 15). Newly occurring or worsening Grade 3 or 4 abnormalities in absolute lymphocytes, absolute neutrophils, haemoglobin and total white blood cell count were all reported more frequently in the imatinib arm than in either nilotinib arm. Only Grade 3 or 4 platelet count decrease was reported less frequently in the imatinib arm than in either of the nilotinib arms. The haematology laboratory findings were consistent with the observed haematological AE profile for the imatinib and nilotinib treatment arms.

Table 15: Pivotal Study – newly occurring or worsening haematological abnormalities; safety set

	All Grades			CTC Grade 3 or 4		
	IT 400 mg qd (n=280)	NT 300 mg bd (n=279)	NT 400 mg bd (n=277)	IT 400 mg qd (n=280)	NT 300 mg bd (n=279)	NT 400 mg bd (n=277)
Absolute lymphocytes	230 (82.1%)	190 (68.1%)	177 (63.9%)	31 (11.1%)	27 (9.7%)	15 (5.4%)
Absolute neutrophils	189 (67.5%)	106 (38.3%)	120 (43.0%)	56 (20.0%)	33 (11.8%)	27 (9.7%)
Haemoglobin	132 (47.1%)	105 (37.6%)	105 (37.9%)	14 (5.0%)	9 (3.2%)	9 (3.2%)
WBC (total)	206 (73.6%)	134 (48.0%)	127 (45.8%)	29 (10.4%)	7 (2.5%)	7 (2.5%)
Platelet count (direct)	156 (55.7%)	133 (47.7%)	136 (49.1%)	24 (8.6%)	28 (10.0%)	33 (11.9%)

There were no relevant differences among the three treatment groups as regards the median time to first newly reported CTC Grade 3 or 4 decreased absolute lymphocytes (28 to 29 days) and decreased absolute neutrophils (56 to 57 days). The median time to decreased platelet count was longer in the I400 arm (54 days) than in the N300 arm (29 days) but similar to that in the N400 arm (55 days). Patient numbers in the nilotinib treatment arms for time to first haemoglobin and WBC CTC Grade 3 or 4 abnormalities were too small (≤ 9 each group) to allow for meaningful comparison with imatinib.

The most frequently reported biochemical abnormalities (all grades) in the nilotinib treatment arms were increased AST and ALT. More than half of all patients in both the N300 (65.9%) and N400 (73.3%) arms had increased ALT levels and the incidence of increased ALT levels in these two arms was about three times that in the imatinib arm (20.4%). The incidence of increased AST was 23.2%, 40.1% and 48.4% in the I400, N300 and N400 arms, respectively. In addition, the incidence of increased total bilirubin (all grades) was about five to six times higher in the N300 (53.4%) and N400 (61.7%) arms than in the I400 arm (9.6%). Other newly occurring or worsening biochemical abnormalities in which the incidence was ≥ 5% in either nilotinib arm compared with the imatinib arm were increased amylase, increased total cholesterol, hyperglycaemia and increased lipase. Newly occurring or worsening biochemical abnormalities in which the incidence was ≥ 5% in the imatinib arm and greater than in either nilotinib arm were increased serum alkaline phosphatase, hypocalcaemia, increased creatinine, hypophosphataemia and hypokalaemia.

The most notable differences between the nilotinib and imatinib treatment arms as regards newly occurring or worsening CTC Grade 3 or 4 biochemical abnormalities (that is, ≥ 5% difference between either nilotinib arm and imatinib) occurred with nilotinib and were increased total bilirubin, hyperglycaemia and increased ALT. There were no newly occurring or worsening CTC Grade 3 or 4 biochemical abnormalities occurring with an incidence of ≥ 5% in the imatinib arm and more frequently than in either of the nilotinib arms. Increased CTC Grade 3 or 4 ALT occurred earlier in the nilotinib arms (21-29 days) than in the imatinib arm (148 days), as did CTC Grade 3 or 4 increased total bilirubin (8-30 days in the nilotinib arms vs 57 days in the imatinib arm) and CTC Grade 3 or 4 increased lipase (8 days in the nilotinib arms vs 56 days in the imatinib arm). Patient numbers in the treatment arms for time to first CTC Grade 3 or 4 abnormalities for the other biochemical parameters were too small to allow for meaningful comparison between nilotinib and imatinib.

Bilirubin levels, both the conjugated and the unconjugated, increased in both of the nilotinib arms during the first week of treatment and then remained at stable elevated levels over the remaining 3 months of observation. ALT levels peaked at 2 weeks after initiation of treatment in both of the nilotinib arms and then fell to stable but higher than normal levels for the remainder of the 3 months of observation. Lipase levels in both nilotinib arms peaked in the first 2 weeks of treatment and then rapidly fell to baseline levels for the remaining 3 months of observation.

Evaluator Comment

The patterns of newly occurring or worsening haematological or biochemical abnormalities in the nilotinib and imatinib treatment arms were notably different. Haematological abnormalities (all grades and CTC Grade 3 or 4) of decreased absolute lymphocytes, decreased absolute neutrophils, haemoglobin and total WBC all occurred more commonly in the imatinib arm than in either of the nilotinib arms. The incidence of decreased platelet count (all grades) was greater in the imatinib arm than in either of the nilotinib arms, while the reverse relationship was seen for the incidence of decreased platelet count (CTC Grade 3 or 4). In the nilotinib arms, liver function abnormalities

(increased ALT, AST and bilirubin levels) occurred notably more frequently in the nilotinib arms than in the imatinib arm and similar findings were observed for lipase, amylase, total cholesterol and glucose levels. Alternatively, increased serum alkaline phosphatase, hypocalcaemia, increased creatinine, hypophosphataemia and hypokalaemia occurred more frequently in the imatinib arm than in the nilotinib arms. There was little difference between the two nilotinib arms in the incidence of haematological abnormalities, while the majority of biochemical abnormalities occurred more frequently in the N400 arm than in the N300 arm.

Supportive Studies

In the CML-CP supportive study, the most frequent newly occurring or worsening CTC Grade 3 or 4 hematologic abnormalities were decreased absolute neutrophil count (31.0%; 98/316), decreased platelet count (29.8%; 95/319), decreased absolute lymphocyte count (26.9%; 85/316), decreased total WBC count (19.2%; 61/318) and decreased haemoglobin level (10.7%; 34/318). The majority of first episodes of Grade 3 and 4 neutropenia and thrombocytopenia occurred within the first 2 months of therapy (median times to first episode of Grade 3 or 4 neutropenia and thrombocytopenia were 60 days and 42 days, respectively) and were relatively brief in duration (median durations of Grade 3 or 4 neutropenia and thrombocytopenia were 15 and 22 days, respectively).

In the CML-CP supportive study, the most frequent newly occurring or worsening CTC Grade 3 or 4 biochemistry abnormalities were increased lipase levels (17.9%; 54/301), decreased phosphate levels (16.9%; 51/301) and hyperglycaemia (12.2%; 38/311). Newly occurring or worsening CTC Grade 3 or 4 increased total bilirubin, ALT and AST levels occurred in 7.3% (23/316), 4.1% (13/318) and 2.5% (8/316) of patients, respectively.

In the CML-AP supportive study, the most frequent newly occurring or worsening CTC Grade 3 or 4 hematologic abnormalities were decreased absolute neutrophil count (42.1%; 56/133), decreased platelet count (41.9%; 52/124), decreased absolute lymphocyte count (38.6%; 51/132), decreased total WBC count (34.1; 46/135) and decreased haemoglobin level (27.4%; 37/135). The majority of first episodes of Grade 3 and 4 neutropenia and thrombocytopenia occurred within the first 2 months of therapy (median times 32 days and 34.5 days, respectively) and were relatively brief in duration (median 17 and 28 days, respectively).

In the CML-AP supportive study, the most frequent newly occurring or worsening CTC Grade 3 or 4 biochemistry abnormalities were increased lipase levels (17.7%; 23/130), hypophosphataemia (15.4%; 20/130), increased total bilirubin levels (9.0%; 12/133), hypokalaemia (8.9%; 12/135), hyperglycaemia (6.1%; 8/131) and hypocalcaemia (5.2%; 7/134). Newly occurring or worsening increased ALT and AST levels occurred in 3.7% (5/135) and 2.3% (3/133) of patients, respectively.

Vital Signs and ECG Changes

Pivotal Study

There were no notable changes in vitals signs (temperature, pulse rate or blood pressure) or weight from baseline over the course of the study (data available to Month 24) in any of the three treatment arms.

ECG assessment was undertaken post-dose on Day 1, and then pre- and post-dose on Day 8 and Months 3, 6, 9 and 12. An absolute QTcF interval of ≥ 450 ms was reported in 7.9% (22/280), 9.7% (27/279) and 11.2% (31/277) of patients in the I400, N300 and N400 treatment arms, respectively. There was only one patient with an absolute QTcF interval of > 480 ms (N400 arm) and no patients with an absolute QTcF interval of > 500 ms.

Increases in QTcF of > 30 ms from baseline were reported in 17.9% (n=50), 25.8% (n=72) and 26.0% (n=72) of patients in the I400, N300 and N400 arms, respectively, while QTcF increases of > 60 ms were reported in only one patient (N400 arm). The highest mean changes from baseline at any post-baseline time point in QTcF were 10.4 ms in the N300 arm and 12.4 ms in the N400 arm. Both of these changes were recorded at the 3 month post-dose measurement. In the I400 arm, the highest mean change from baseline at any post-baseline time point was 7.9 ms recorded at the 6 month pre-dose measurement. There had been no reports of torsades de pointes at the date of data cut-off.

LVEF measurements were undertaken at 3, 6 and 12 months and mean changes from baseline at each of the three time intervals were ≤ 1.4% in each of the three treatment arms. There were no patients in the three treatment arms with a LVEF of < 45% during treatment and no patients with an absolute reduction in LVEF from baseline of more than 15%.

Supportive Studies

In the CML-CP supportive study, the most common ECG finding post-baseline was ventricular premature contractions (VPCs) (18.7%; n=60), followed by atrial premature contractions (APCs) (17.4%; n=56), flat T waves (15.6%; n=50), sinus bradycardia (14.3%; n=46), sinus tachycardia (12.1%; n=39), first degree AV block (11.8%; n=38), inverted T waves (11.8%; n=38) and left anterior hemi-block (10.9%; n=35). However, interpretation of these ECG data is limited by the absence of baseline assessment pre-dose which means that some of the post-baseline ECG findings might have existed prior to treatment.

In the CML-CP supportive study, absolute QTcF > 480 ms and > 500 ms were observed in 2.2% (n=7) and 1.2% (n=4) of patients, respectively. QTcF increase from baseline > 30 ms and > 60 ms were observed in 44.9% (n=144) and 2.5% (n=8) of patients, respectively. No episodes of torsades de pointes were reported. The mean increase from baseline in the LVEF was of 0.2% (SD = 6.9%) in 88 patients with baseline and post-baseline assessments.

In the CML-AP supportive study, the most common post-baseline ECG finding was APC(s) occurring in 20.4% (n=28) of patients. Sinus tachycardia, VPC(s), left anterior hemi-block and flat T waves were reported in 19.7% (n=27), 16.8% (n=23), 16.1% (n=22) and 15.3% (n=21) of patients respectively. However, interpretation of these ECG data is limited by the absence of baseline assessment pre-dose which means that some of the post-baseline ECG findings might have existed prior to treatment.

In the CML-AP supportive study, absolute QTcF > 480 ms and > 500 ms were observed in 2.9% (n=4) and 0% of patients, respectively. QTcF increase from baseline > 30 ms and > 60 ms were observed in 47.4% (n=65) and 8.0% (n=11) of patients, respectively. No episodes of torsades de pointes were reported. The mean increase from baseline in the LVEF was 2.1% (SD=7.12%) in 44 patients with baseline and post-baseline assessments.

Safety in Special Populations

Pivotal Study

Age

The sponsor's *Summary of Clinical Safety* (SCS) included summaries of the pivotal safety data by age category (< 65 years and ≥ 65 years). The incidence of AEs (all grades) in patients aged < 65 years vs ≥ 65 years was 98.4% (240/244) vs 97.2% (35/36), 98.0% (239/244) vs 100% (35/35), and 98.4% (248/252) vs 100% (25/25) in the I400, N300 and N400 arms, respectively. The incidence of CTC Grade 3 or 4 AEs in patients aged < 65 years vs ≥ 65 years was 41.4% vs 52.8%, 44.3% vs 54.3% and 51.2% vs 56.0% in the I400, N300 and N400 arms, respectively. Overall, the incidence of AEs all grades and CTC Grade

3 or 4 was higher in patients aged ≥ 65 years compared with patients aged < 65 years. The nature of the AEs in the two age groups was consistent with those in the overall population. However, the imbalance in patient numbers between those aged < 65 years and ≥ 65 years in each of the three treatment groups limits meaningful interpretation of differences in the AE profile between the two age groups. The percentage of patients aged ≥ 65 years was 12.9%, 12.5% and 9.0% in the I400, N300 and N400 arms, respectively.

Gender

The SCS included summaries of the pivotal safety data by gender. When analysed by gender, the number of patients who experienced AEs (all grades) were similar with 99.4% (155/156), 98.1% (153/156) and 98.3% (170/173) in males, and 96.8% (120/124), 98.4% (121/123) and 99.0% (103/104) in females in the I400, N300 and N400 arms, respectively. In the I400 arm, more females than males experienced AEs of anaemia (21.0% vs 10.9%), eyelid oedema (17.7% vs 9.6%), vomiting (32.3% vs 11.5%), peripheral oedema (25.0% vs 9.0%), face oedema (13.7% vs 5.1%) and pruritus (12.1% vs 2.6%). In the N300 group, more female than male patients experienced AEs of vomiting (14.4% vs 4.5%), ALT increased (27.6% vs 16.7%) and pain (4.9% vs 0.6%). In the N400 group, more females than males experienced AEs of headache (29.3% vs 25.6%) and rash (38.2% vs 31.4%). The incidence of patients with CTC Grade 3 or 4 AEs were similar in the male vs female groups: 42.9% vs 42.7%; 44.2% vs 47.2%; and 52.6% vs 50.0%, in the I400, N300 and N400 arms, respectively.

Newly occurring or worsening abnormal haemoglobin values were observed more frequently in females vs males: 56.5% vs 39.7%; 45.5% vs 31.4%; and 47.1% vs 32.4%, in the I400, N300 and N400 arms respectively. Newly occurring or worsening abnormal platelet count in the I400 and the nilotinib arms were observed at a higher incidence in males (62.2% and 51.9%, respectively) than in females (47.6% and 42.3%, respectively). These rates were similar in males and females in the N400 arm (48.0% and 51.0%, respectively). Other newly occurring or worsening haematology abnormalities were generally observed at incidences that reflect those seen in the overall population, with no clinically relevant differences between genders.

Newly occurring or worsening abnormal total bilirubin values were observed more frequently in males vs females: 13.5% vs 4.8%; 57.7% vs 48.0%; and 64.7% vs 56.7% in the I400, N300 and N400 arms, respectively. Newly occurring or worsening abnormal total cholesterol values were observed more frequently in females vs males: 4.0% vs 1.3%; 28.5% vs 14.7%; and 32.7% vs 13.9% in the I400, N300 and N400 groups, respectively.

Newly occurring or worsening abnormal transaminase levels (AST and ALT) in the N400 arm were higher in females (59.6% for AST and 81.7% for ALT) than in males (41.6% for AST and 68.2% for ALT). In the I400 arm, these rates were, in males, 26.9% for AST and 21.2% for ALT, and in females, 18.5% for AST and 19.4% for ALT. In the N300 arm, these rates were, in males, 38.5% for AST and 62.8% for ALT and in females, 42.3% for AST and 69.9% for ALT.

Newly occurring or worsening abnormal creatinine values in the I400 arm were observed more frequently in males (17.3%) than in females (7.3%). Newly occurring or worsening hypokalaemia was observed more frequently in the I400 arm in females (20.2%) than in males (9.6%). Newly occurring or worsening abnormal phosphate values were observed more frequently in males vs females (51.9% vs 36.3%, 43.6% vs 16.3%, and 41.0% vs 22.1%, in the I400, N300 and N400 arms, respectively).

Race

The SCS included summaries of the pivotal safety data by race (Caucasian, Asian, Black, Other). The number of Black and Other racial groups was too small to meaningfully interpret the data. Similarly, the imbalance in patient numbers between the Caucasian and Asian groups limits meaningful interpretation of the observed differences between the two groups.

Immunological Events

Pivotal Study

Immune system disorders (all grades) were reported uncommonly in the three treatment arms: 2.5% (n=7), 0.7% (n=2) and 1.8% (n=5) in the I400, N300 and N400 arms respectively. Hypersensitivity/drug hypersensitivity AEs occurred in 0.8% (n=2), 0.4% (n=1) and 1.1% (n=3) of patients in the I400, N300 and N400 arms respectively. Allergic oedema was reported in only 1 patient (N400 arm). No immune system disorders (CTC Grade 3 or 4) were reported in any of the three arms.

Postmarketing Experience

The international birth date of nilotinib is 24 July 2007. The cumulative exposure to marketed nilotinib since the international birthdate is estimated to be 3220 patient years. Approximately, 5300 patients have been exposed to nilotinib in Novartis sponsored and investigator initiated studies. The submitted data referred to PSURs collated since the international birth date of the drug but only brief extracts from the first four documents were provided. The sponsor stated that no new safety information has emerged from postmarketing surveillance.

The data included an extensive Risk Management Plan (RMP) dated 11 December 2009. The SCS concluded that "all potential risks (sudden death, ischaemic heart disease, cardiac failure, drug induced liver injury, photosensitivity, diabetes mellitus, severe cutaneous adverse reactions, hyperthyroidism) and identified risks (QT prolongation, myelosuppression, severe haemorrhage, severe infections, pancreatitis, fluid retention, hypophosphataemia) in the nilotinib RMP have been reviewed cumulatively, and no significant differences in the overall frequency or pattern of these risks have been identified". Furthermore it stated that "the safety profile of nilotinib remains consistent with the information provided in the CDS of the product. There are no new events reported from post-marketing experience which have not previously been observed during clinical trails".

Evaluator's Overall Conclusions on Clinical Safety

The pivotal study included 836 patients with newly diagnosed CML-CP with at least 12 months of follow up data who received at least one dose of study drug and were in the imatinib 400 mg qd (n=280), nilotinib 300 mg bd (n=279) or nilotinib 400 mg bd (n=277) treatment arms. The median time on treatment in each of the three arms was 13.8 [range: 0, 22.5] months and the mean [range] actual dose intensity was 400.1 [206-800] mg/day in the I400 arm, 550.4 [186-638] mg/day in the N300 arm and 683.0 [232-800] mg/day in the N400 arm. The percentage of patients in each of the three arms treated for ≥ 12 months was 61.1% (n=171), 64.2% (n=179) and 65.0% (n=180), in the I400 (n=280), N300 (n=279) and N400 (n=277) arms, respectively.

The two supportive studies included 458 patients with imatinib resistant or intolerant CML-CP (n=321) or CML-AP (n=137) with at least 24 months of follow up data who received at least one dose of nilotinib 400 mg. In the CML-CP supportive study, the median time on treatment was 18.4 months [range: 0.0, 36.0] and in the CML-AP supportive study

the median time on treatment was 8.7 months [range: 0.1, 38.1]. In the CML-CP supportive study, 42.1% of patients (n=135) remained on treatment for ≥ 24 months and the mean actual average nilotinib dose intensity was 694.2 mg/day [range: 151.0, 1109.8]. In the CML-AP supportive study, 18.2% (n=25) of patients remained on treatment for ≥ 24 months, and the mean actual average nilotinib dose intensity was 690.5 mg/day [range: 150.2, 1149.0].

In the pivotal study, most patients in each of the three treatments arms experienced at least one AE, and just over half were CTC Grade 1 or 2 AEs in the I400 and N300 arms while just over half were CTC Grade 3 or 4 AEs in the N400 arm. However, while most patients in the imatinib and the nilotinib treatment arms experienced at least one AE the pattern was different between the two drugs. The most frequently reported AEs in either of the nilotinib arms and occurring notably more frequently than in the imatinib arm were hepatobiliary abnormalities (increased ALT, AST, and total bilirubin), skin disorders (rash, pruritis, dry skin, and alopecia) and individual disorders of headache, upper abdominal pain and constipation. The most frequently reported AEs in the imatinib arm and occurring notably more frequently than in either of the nilotinib arms were gastrointestinal disorders (nausea, vomiting and diarrhoea), haematological disorders (neutropenia and leucopenia), oedema (peripheral, facial, and periorbital), and the individual AE of muscle spasm. Similar differences in the AE pattern between imatinib and nilotinib were also observed for CTC Grade 3 or 4 AEs,

In the pivotal study, there were 3 deaths occurring within 28 days of discontinuation of the study drug and all were considered to be unrelated to the study drug (2 with N300; 1 with N400). SAEs were reported most commonly in the N400 arm (17.3%) than in the I400 (13.6%) and N300 (12.2%) arms. The most frequently reported SOC with SAEs in each of the three treatment arms was *Gastrointestinal Disorders* and these disorders occurred less commonly in the N300 arm than in the N400 or I400 arms. There were no SAEs (preferred term) reported with an incidence of ≥ 2% in any of the three treatment arms. SAEs (all grades) occurring with an incidence of ≥ 1.0% in either nilotinib arm and more frequently than in the imatinib arm were abdominal pain, neutropenia, thrombocytopenia and back pain. There were no SAEs (all grades) occurring with an incidence of ≥ 1.0% in the imatinib treatment arm that were reported more frequently than in either of the nilotinib arms.

In the pivotal study, the incidence of AEs resulting in discontinuation was lower in the N300 arm (6.8%) than in the I400 (8.9%) and N400 (10.8%) arms. The most common AEs leading to discontinuation (≥ 1% in any of the three treatment arms) were (N300 vs N400 vs I400): thrombocytopenia (1.1% vs 2.5% vs 0.7%), hyperbilirubinaemia (1.4% vs 0.7% vs 0.4%), neutropenia (1.1% vs 0.7% vs 1.4%) and ALT increased (0.4% vs 0.4% vs 1.1%). The incidence of AEs resulting in dose interruption or reduction was lower in the I400 arm (43.9%) than in the N300 (50.5%) and N400 (59.9%) arms. The most frequently reported AE (all grades) in the nilotinib arms resulting in dose interruption or reduction was ALT increased (11.5%, 15.2% and 3.2% in the N300, N400 and I400 arms, respectively). The most frequently reported AE (all grades) resulting in interruption or reduction in dose in the imatinib treatment arm was neutropenia (11.8%, 7.6% and 12.5% in the N300, N400 and I400 arms, respectively).

In the pivotal study, the patterns of newly occurring or worsening haematological or biochemical abnormalities in the nilotinib and imatinib treatment arms were notably different and consistent with the patterns observed with AEs. All grades and CTC Grade 3 or 4 haematological abnormalities of decreased absolute lymphocytes, decreased absolute neutrophils, decreased haemoglobin and decreased total WBC all occurred more commonly in the imatinib arm than in either of the nilotinib arms. The incidence of

decreased platelet count (all grades) was greater in the imatinib arm than in either of the nilotinib arms, while the reverse relationship was seen for the incidence of decreased platelets count (CTC Grade 3 or 4). In the nilotinib arms, hepatobiliary abnormalities (increased ALT, AST and bilirubin levels) occurred notably more frequently in the nilotinib arms than in the imatinib arm and similar findings were observed for lipase, amylase, total cholesterol and glucose levels. Alternatively, increased serum alkaline phosphatase, hypocalcaemia, increased creatinine, hypophosphataemia and hypokalaemia occurred more frequently in the imatinib arm than in the nilotinib arms.

Overall, the incidence of AEs, SAEs (including death) and laboratory abnormalities (haematological and biochemical) occurred more frequently with nilotinib in the CML-CP and CML-AP supportive studies in imatinib resistant or intolerant patients than with nilotinib in the pivotal study in patients with newly diagnosed CML. This is most likely a function of time as patients in the supportive studies were exposed to nilotinib for at least twice as long (24 months) as patients in the pivotal study (12 months). However, there were no new safety signals seen with nilotinib in the 24 month follow up data from the two supportive studies and the toxicities observed in these two studies were consistent with those in the pivotal study.

Clinical Summary and Conclusions

Clinical Aspects

The pivotal study was a multinational, multicentred, open label study in which patients with newly diagnosed CML-CP were randomised to imatinib 400 mg qd (n=283), nilotinib 300 mg bd (n=282) or nilotinib 400 mg bd (n=281). Randomization was stratified by disease severity based on the Sokal risk score at the time of diagnosis (low, intermediate or high risk). The baseline demographic and disease characteristics were well balanced among the three treatment arms indicating that randomization had been effective. The primary efficacy endpoint at 12 months was the MMR rate and the main secondary efficacy endpoint was the rate of best CCyR by 12 months. There were a number of additional secondary efficacy endpoints assessing molecular response, cytogenetic response, haematologic response, EFS, progression to AP or BC, and overall survival.

The safety population in the pivotal study included 836 patients with at least 12 months of follow up data who had received at least one dose of study drug (280, 279 and 277 in the I400, N300 and N400 arms, respectively). The median time on treatment in each of the three arms was 13.8 [range: 0, 22.5] months and the mean [range] actual dose intensity was 400.1 [206-800] mg/day in the I400 arm, 550.4 [186-638] mg/day in the N300 arm and 683.0 [232-800] mg/day in the N400arm. The percentage of patients in each of the three arms with time on treatment of ≥ 12 months was 61.1% (n=171), 64.2% (n=179) and 65.0% (n=180) in the I400, N300 and N400 arms, respectively. The safety profile of the three treatment arms was satisfactorily characterised with all standard safety parameters being collected and appropriately analysed.

The open label design of the study had the potential to bias the results. However, the risk of bias was mitigated by randomized treatment allocation and the use of objectively determined primary (MMR) and key secondary (best CCyR) 12 month efficacy endpoints. The study included I400 as the active control rather than placebo. This is considered acceptable as imatinib is generally considered to be standard treatment for CML-CP and the use of a placebo control in this disease would be difficult to ethically justify. Overall, the open label and active control methodology was considered to be satisfactory.

The major issue with the study design is considered to be the use of the MMR at 12 months as the primary efficacy endpoint. This endpoint is a surrogate of long term treatment outcome. The submission included RQ-PCR molecular response data from patients with

CML treated with imatinib in the IRIS trial provided to support the use of the MMR at 12 months as the primary efficacy endpoint. These data showed that the MMR at 12 months (versus no MMR at 12 months) predicts at 84 months improved EFS (91.0% vs 79.4%, p=0.001) and survival free progression to AP/BC (99.0% vs 89.9%, p=0.0004) but not OS (92.5% vs 89.2%, p=0.0197). These results were consistent with those from published IRIS data showing that MMR at 12 months was correlated with a reduced risk of disease progression and an increased chance of event free survival during the subsequent 5 years [Druker et al, 2006; O'Brien et al, 2008].[7,8]

However, the TGA approved guidelines for the evaluation of anticancer medicines indicate that confirmatory Phase III trials should demonstrate that the investigational product provides clinical benefit.[6] The guidelines state that acceptable primary endpoints include OS and PFS/DFS and that if PFS/DFS is the selected primary endpoint then OS should be reported as the secondary endpoint and vice versa. The guidelines also state that tumour markers "convincingly demonstrated to reflect tumour burden can be used, in combination with other measures of tumour burden, to define tumour response and progression", but a "justification is expected in the study protocol why endpoints such as survival benefit or symptom control cannot be used as a primary measure of patient benefit".

The pivotal study included a justification for the use of the MMR at 12 months based on published data and the submission included a new RQ-PCR molecular response study provided to support the use of MMR at 12 months as the primary efficacy endpoint. On balance, the sponsor's justification for using the MMR at 12 months as a surrogate for clinical benefit in the pivotal study was considered acceptable. The justification is supported by the fact that nilotinib is not a new chemical entity as it as approved for the treatment of Ph+ CML-CP (and CML-AP) in imatinib resistant or intolerant patients and there are appropriate supportive clinical efficacy data in CML-CP (and CML-AP) suggesting that haematological and cytogenetic responses to nilotinib are durable for up to at least 24 months. However, if the submission was for a new chemical entity for the treatment of Ph+ CML-CP and approval rested on one study in which the MMR at 12 months was the primary efficacy endpoint then the acceptability of this surrogate endpoint would be more problematical.

While the use of the MMR at 12 months in the pivotal study is considered acceptable, it should be a condition of registration that the sponsor submits the results from this study at later time points as soon as they become available. Although the current submission included data suggesting that response to nilotinib treatment in patients with imatinib resistant or intolerant Ph+ CML-AP and CML-CP is durable for up to 24 months, this needs to be confirmed in the pivotal study in patients with newly diagnosed Ph+ CML-CP. It is possible that resistance to first line nilotinib treatment in patients with newly diagnosed Ph+ CML-CP could arise over time.

Benefit Risk Assessment

Benefits

The pivotal study randomized patients with newly diagnosed CML-CP to imatinib 400 mg qd (n=283), nilotinib 300 mg bd (n=282), and nilotinib 400 mg bd (n=281). The MMR rate at 12 months (primary efficacy endpoint) was 22.3% (63/283) with I400, 44.3% (125/282) with N300 and 42.7% (120/281) with N400 ($p < 0.0001$ for both nilotinib vs imatinib comparisons). The difference in the MMR at 12 months for N300 vs I400 was 22.1% [95%CI: 14.5%, 57.3%] and 20.4% [95%CI: 12.9%, 28.0%] for N400 vs I400. The study was not powered to detect a statistically significant difference between the two doses of nilotinib but the observed MMR rates at 12 months for these two nilotinib

treatments were similar. MMR at 12 months was a surrogate of long term clinical benefit. The RQ-PCR molecular response study indicated that MMR at 12 months (versus no MMR at 12 months) predicts at 84 months improved EFS (91.0% vs 79.4%, p=0.001) and survival free progression to AP/BC (99.0% vs 89.9%, p=0.0004) but not OS (92.5% vs 89.2%, p=0.0197). Overall, based on MMR at 12 months it can be predicted that long term PFS and survival free progression to AP/BC are likely to be superior in patients with newly diagnosed CML-CP treated with N300 or N400 compared with current standard treatment with I400.

The pivotal study also showed that the best CCyR by 12 months (main secondary efficacy endpoint) was statistically significantly greater with both nilotinib doses compared with imatinib. The best CCyR rate at 12 months was 65.0% (184/283) for I400, 80.1% (226/282) for N300 and 77.9% (219/281) for N400 ($p < 0.0001$ for N300 vs I400 and $p < 0.0005$ for N400 vs I400). The difference in best CCyR by 12 months was 15.1% [95%CI: 7.9%, 22.4%] for N300 vs I400 and 12.9% [95%CI: 5.5%, 20.3%] for N400 vs I400. There were a number of other secondary molecular and cytogenetic efficacy endpoints and these generally statistically significantly favoured both nilotinib 300 mg bd and 400 mg bd over imatinib 400 mg bd. However, there was no statistically significant difference in the CHR rate at 12 months between N300 and I400 (89.7% vs 93.3%, respectively) or N400 and I400 (88.6% vs 93.3%, respectively).

The K-M estimated rates of patients free from progression to AP/BC at 12 months were higher with both doses of nilotinib compared with imatinib: 96.5%, 99.3% and 99.6%, for I400, N300 and N400, respectively. There was a statistically significant difference in progression to AP/BC between N400 and I400 (p=0.0037; log rank test) and between N300 and I400 (p=0.0095; log rank test). The K-M estimated rates of EFS at 12 months were higher with both doses of nilotinib compared with placebo, with the difference between N400 and I400 (99.6% vs 95.7% respectively) being statistically significant (p=0.0012; log rank test) and the difference between nilotinib 300 mg qd and I400 (97.6% vs 95.7%, respective) being not statistically significant (p=0.0898; log rank test). The K-M estimated OS rates at 12 months were high for the three treatments (> 99%) and there were no statistically significant differences between N300 and I400 or N400 and I400.

Overall, the 12 month efficacy data from the pivotal study have satisfactorily demonstrated the superiority of both N300 and N400 over standard therapy with I400 for the treatment of newly diagnosed Ph+ CML-CP in adult patients. There appears to be little difference between the efficacy of N300 and N400.

The supportive data suggests that N400 provides a durable response to at least 24 months in patients with imatinib resistant or intolerant Ph+ CML-CP or CML-AP. In 321 patients with CML-CP, the primary efficacy endpoint of MCyR was achieved in 51.4% [95%CI: 45.8%, 57.0%) in the primary ITT population, with CCyR in 36.8% of patients and PCyR in 14.6% of patients. The median time to MCyR was 2.8 [range: 0.9 to 28.2] months, the median duration of MCyR was not reached by the date of data cut-off, and it was estimated that MCyR was maintained at 24 months in 77% of patients who had achieve this endpoint. The MMR for the 24 month follow-up data was 27.9% (82/293) which was lower than the corresponding figure for N400 of 42.7% (120/281) at 12 months in the pivotal study. In 137 patients with CML-AP, the primary efficacy endpoint of confirmed HR was achieved in 50.4% [95%CI: 41.7%, 59%], with CHR in 29.9% of patients, marrow response/NEL in 9.5%, and return to chronic phase in 10.9%. The median time to first confirmed HR was 1 [range: 0.8 to 11.0] month, the median duration of confirmed HR was 24.2 [range: 2.2, 37.2] months and it was estimated that HR was maintained at 24 months in 53% of patients who had achieved this endpoint. The limitations of the supportive data

were the absence of a control group and the doubtful relevance of the results in patients with CML-AP to patients with CML-CP.

Risks

In the pivotal study, nearly all patients in each of the three treatments arms experienced at least one AE (all grades) and just over half were CTC Grade 1 or 2 AEs in the I400 and N300 arms while just over half were CTC Grade 3 or 4 AEs in the N400 arm. However, while most patients in the imatinib and the nilotinib treatment arms experienced at least one AE the pattern was different between the two drugs. The most frequently reported AEs in either of the nilotinib arms and occurring notably more frequently than in the imatinib arm were hepatobiliary abnormalities (increased ALT, AST, and total bilirubin), skin disorders (rash, pruritis, dry skin, and alopecia) and the individual disorders of headache, upper abdominal pain and constipation. The most frequently reported AEs in the imatinib arm and occurring more frequently than in either of the nilotinib arms were gastrointestinal disorders (nausea, vomiting and diarrhoea), haematological disorders (neutropenia and leucopenia), oedema (peripheral, facial and periorbital), and the individual AE of muscle spasm. These different patterns were also observed in the laboratory haematological and biochemical test abnormalities.

The high incidence of AEs in the three treatment arms did not translate into high permanent discontinuation rates. The discontinuation rates for AEs (all grades) were 8.9% (n=25), 6.8% (n=19) and 10.8% (n=30) in the I400, N300 and N400 treatment arms, respectively. About half of the AEs resulting in discontinuations were CTC Grade 3 or 4 events. Most AEs resulting in permanent treatment discontinuation occurred in no more than 2 patients in any treatment group with the exceptions being (N300, N400, I400) thrombocytopenia (2 [0.7%], 3 [1.1%], 7 [2.5%]), hyperbilirubinaemia (4 [1.4%], 2 [0.7%], 1 [0.4%]), neutropenia (3 [1.1%], 2 [0.7%], 1 [1.4%]) and ALT increased (1 [0.4%], 2 [0.7%], 3 [1.1%]). No AE resulting permanent discontinuation in any of the treatment arms occurred in more than 2.5% of patients (that is, no more than 7 patients).

The rates of AE (all grades) leading to dose interruption and/or dose reduction were 43.9% (n=123), 50.5% (n=141) and 59.9% (n=166) in the I400, N300 and N400 treatment arms, respectively. Over half of the AEs leading to dose interruption and/or dose reduction in each of the three treatment groups were CTC Grade 3 or 4 events. The most common AEs (all grades) leading to dose interruption and/or dose discontinuation were (N300, N400, I400) increased ALT (11.5%, 15.2%, 3.2%), thrombocytopenia (9.0%, 11.6%, 8.9%), neutropenia (11.8%, 7.6% 12.5%), rash (3.2%, 6.9%, 0.7%), hyperbilirubinaemia (7.2%, 6.5%, 0.7%), lipase increased (5.4%, 5.8%, 1.4%) and leucopenia (1.4%, 2.2%. 5.7%).

Overall, the data showed that AEs resulting in permanent discontinuation were uncommon in the three treatment arms with about half of the AEs in each arm being manageable by dose interruption and/or reduction and the rest requiring no treatment or possibly symptomatic treatment. None of the safety findings were unexpected and all AEs and clinical laboratory findings for both nilotinib and imatinib have been previously described. Overall, the safety profiles of the two drugs are considered to be acceptable for the treatment of patients with newly diagnosed Ph+ CML-CP. On balance, the safety profile of N300 is superior to N400. The main risks associated with nilotinib and imatinib treatment based on the results from the pivotal study are summarised below.

Liver Function Adverse Events and Laboratory Abnormalities

The AEs of most concern in the nilotinib arms relative to the imatinib arm were liver function abnormalities. The pivotal study excluded patients with total bilirubin levels > 1.5 × ULN and/or ALT and AST levels > 2.5 × ULN. Increased ALT, AST and bilirubin levels were reported more frequently as both AEs and laboratory abnormalities in the nilotinib

arms than in the imatinib arm. The relevant AEs (all grades) occurring ≥ 5% more frequently in either nilotinib arm than in the imatinib arm were (N300, N400, I400): ALT increased (21.5%, 26.0%, 6.1%), AST increased (10.4%, 11.6%, 4.3%), hyperbilirubinaemia (15.1%, 14.8%, 2.1%) and blood bilirubin increased (8.2%, 9.4%, 0.7%). There were no reported SAEs (all grades) occurring in ≥ 2 patients in any treatment group for increased bilirubin, ALT or AST. However, there were 2 patients (0.7%) in the N400 arm with a CTC Grade 3 or 4 SAE defined as "hepatic function abnormal". More than half of all patients in both the N300 (65.9%) and N400 (73.3%) arms had increased laboratory ALT levels and the rates in these two arms was about three times that in the imatinib arm (20.4%). The incidence (I400, N300, N400) of increased laboratory AST was notably higher in the two nilotinib arms than in the imatinib arm (23.2%, 40.1%, 48.4%) as was the incidence of increased laboratory total bilirubin (9.6%, 53.4%, 61.7%). Despite the frequent occurrence of liver function abnormalities, permanent treatment discontinuations resulting from them were uncommon. Overall, there were ≤ 4 patients in each treatment group who discontinued due to an identified liver function abnormality. However, dose interruption and dose reductions due to increased ALT or bilirubin occurred relatively commonly in the two nilotinib groups due predominantly to CTC Grade 1 or 2 events.

Skin Adverse Events

Skin disorders (rash, pruritis, dry skin and alopecia) occurred notably more commonly with nilotinib than with imatinib. The relevant AEs (all grades) occurring ≥ 5% more frequently in either nilotinib arm than in the imatinib arm were (N300, N400, I400): rash (34.4%, 40.8%, 15.4%), alopecia (10.0%, 16.6%, 4.6%), pruritis (17.9%, 5.2%, 6.8%) and dry skin (8.2%, 10.1%, 3.6%). There were no reports of SAEs with ≥ 2 patients in any treatment group for rash, pruritis, dry skin or alopecia. Permanent treatment discontinuations for skin disorders were uncommon and did not differ significantly among the three treatment arms.

Haematological Adverse Events

Haematological AEs of neutropenia and leucopenia were reported more notably with imatinib than with nilotinib. The incidences of the relevant AEs (all grades) occurring ≥ 5% more frequently in the imatinib arm than in either nilotinib arm were (N300, N400, I400): neutropenia (14.7%, 10.5%, 20.4%) and leucopenia (8.2%, 7.6%, 15.4%). Newly occurring or worsening haematological laboratory abnormalities (decreased absolute lymphocyte count, decreased absolute neutrophil count, reduced haemoglobin, decreased total white blood cell count and decreased platelet count) were reported more frequently in the imatinib arm than in either of the nilotinib arms. Newly occurring or worsening CTC Grade 3 or 4 abnormal reductions in absolute lymphocytes, absolute neutrophils, haemoglobin and total white blood cells were reported more frequently in the imatinib arm than in either of the nilotinib arms, while the converse was reported for reductions in the platelet count. Haematological SAEs were reported uncommonly and were almost all CTC Grade 3 or 4 events. The two most common haematological CTC Grade 3 or 4 SAEs were (N300, N400, I400) thrombocytopenia (1.8%, 1.4%, 0.7%) and neutropenia (1.1%, 1.4%, 0.4%). Permanent discontinuations due to haematological events were uncommon while dose interruptions due to thrombocytopenia occurred in about 8.9% to 11.6 % of all patients, neutropenia 7.6% to 12.5% and leucopenia 1.4% to 5.7%.

Gastrointestinal Adverse Events

Gastrointestinal abnormalities (all grades) occurring ≥ 5% more frequently in the imatinib arm than in either of the nilotinib arms were (N300, N400, I400): nausea (17.9%, 24.9%, 35.4%), diarrhoea (13.3%, 14.4%, 33.9%) and vomiting (9.0%, 14.5%, 20.7%). SAEs for

these three conditions were uncommon (≤ 3 patients in any treatment arm) and were predominantly CTC Grade 1 or 2 events. Permanent treatment discontinuations due to these three AEs were uncommon and occurred in a total of 4 patients. Dose interruptions or reductions (≥ 5% in any treatment arm) were not reported for nausea, diarrhoea or vomiting.

Oedema Related Adverse Events

Oedema related AEs (all grades) occurring ≥ 5% more frequently in the imatinib arm than in either of the nilotinib arms were (N300, N400, I400): peripheral oedema (7.5%, 8.3%, 16.1%), facial oedema (1.1%, 1.8%, 13.2%) and periorbital oedema (0.4%, 1.1%, 12.9%). None of the oedema related AEs were reported as a SAE in at least 2 patients in any treatment arm and none resulted in permanent treatment discontinuation, dose interruption or dose reduction in ≥ 5% of patients in any treatment arm.

Other Commonly Occurring Adverse Events

The individual adverse events of headache, upper abdominal pain and constipation occurred notable more commonly with nilotinib than with imatinib. The relevant AEs (any grade) occurring ≥ 5% more frequently in either nilotinib arm than in the imatinib arm were (N300, N400, I400): headache (27.2%, 40.8%, 15.4%), abdominal pain upper (15.1%, 11.9%, 9.3%) and constipation (13.6%, 10.5%, 4.3%). Headache was reported as a SAE (all grades) in 0.7%, 0.4% and 0% of patients in the N300, N400 and I400 arms, respectively. Upper abdominal pain and constipation were not reported as SAEs in ≥ 2 patients in any of the three treatment arms. None of the three AEs (headache, upper abdominal pain or constipation) resulted in permanent treatment discontinuation, dose interruption or dose reduction in ≥ 5% of patients in any treatment arm. The individual adverse event of muscle spasm occurred ≥ 5% more frequently in the imatinib arm than in either of the nilotinib arms (9.7% N300; 9.0% N400; 26.8% I400).

Laboratory Biochemistry Abnormalities (other than Liver Function Tests)

Other than ALT, AST and bilirubin, newly occurring or worsening biochemical abnormalities with an incidence of ≥ 5% in either of the nilotinib arms compared with the imatinib arm were increased amylase, increased total cholesterol, hyperglycaemia and increased lipase. Newly occurring or worsening biochemical abnormalities with an incidence of ≥ 5% in the imatinib arm compared with either of the nilotinib arms were increased serum alkaline phosphatase, hypocalcaemia, increased creatinine, hypophosphataemia and hypokalaemia. None of the most frequently occurring laboratory biochemistry abnormalities (other than LFTs) in the three treatment arms were SAEs in ≥ 2 patients in the three treatment arms. The only frequently occurring laboratory abnormality (other than LFTS) which resulted in permanent treatment discontinuation was increased lipase levels in 1 patient in the N400 arm.

Death and Other SAEs

There were 3 deaths in nilotinib treated patients considered to be unrelated to the study drug and occurring within 28 days of discontinuing the drug. There were no reported deaths occurring within 28 days of discontinuing the study drug in patients treated with imatinib. The most frequent SAEs (≥ 1.0%) occurring in either nilotinib treatment arm and observed more commonly than in the imatinib arm (N300, N400, I400) were CTC Grade 3 or 4 neutropenia (1.1%, 1.4%, 0.4%) and thrombocytopenia (1.8%, 1.4%, 0.7%). No SAEs occurring with a frequency of ≥ 1.0% in the imatinib arm were observed more commonly than in either of the two nilotinib arms.

Vital Signs, ECG and LVEF Abnormalities

There were no significant vital sign changes in the three treatment arms. Clinically significant QTcF interval prolongation occurred uncommonly in the three treatment arms and no cases of torsades de pointes were reported. There were no notable changes in the LVEF in the three treatment arms.

Other Adverse Events of Interest

Other AEs of special interest included cardiac disorders, pancreatitis and diabetes mellitus parameters. Cardiac disorders (all grades) occurred most frequently in the N300 arm (11.5%) than in the N400 (7.9%) and the I400 (5.7%) arms. Most of cardiac disorders in the three treatment arms were CTC Grade 1 or 2 events and individual cardiac AEs occurred in < 4% of patients in any treatment arm. The most frequent cardiac AE in each of the three treatment arms was palpitations (all grades) which occurred in 1.8%, 3.9% and 2.5% of patients in the I400, N300 and N400 arms, respectively. Other cardiac AEs (all grades) occurring with an incidence of ≥ 1% in at least one of the treatment arms were (N300, N400, I300): angina pectoris (0.4%, 1.8%, 0.7%), tachycardia (1.1%, 1.8%, 0.4%), bradycardia (1.4%, 1.1%, 0.4%), atrial fibrillation (1.4%, 0.7%, 0.7%) and A-V block first degree (0%, 0%, 1.4%). The only cardiac SAE was angina pectoris (0.4% N300; 0.7% N400; 0.4% I300) and CTC Grade 1 or 2 angina pectoris was the only cardiac AE which resulted in premature treatment discontinuation (1 patient in the N300 arm).

There were 7 cases of pancreatitis, none of which were CTC Grade 3 or 4. The incidence of pancreatitis was 0.7%, 1.4% and 0.4% in the N300, N400 and I400 arms. Acute pancreatitis resulted in 2 patients discontinuing prematurely (1 in the I400 arm and 1 in the N400 arm). All cases of pancreatitis were considered to be drug related by investigators, apart from 1 case in the N300 arm. In the 57 patients with diabetes mellitus (type II), no notable changes occurred in HbA1c or weight in the three treatment arms over 12 months. However, increases in mean fasting blood glucose at 12 months were reported in patients with diabetes mellitus type II treated with N300 (n=17, 0.86 mmol/L) or N400 (n=13, 1.5 mmol/L) but not with I400 (n=10, -0.22 mmol/L).

Risk Benefit Balance

It was considered that the pivotal 12 month follow up efficacy data have satisfactorily established the superiority of nilotinib (300 mg bd and 400 mg bd) compared with imatinib (400 mg qd) for the treatment of newly diagnosed adult patients with Ph+ CML-CP. Furthermore, the data suggest that there is little difference between the efficacy of N300 and N400 in the target patient population. It was considered that the pivotal 12 month follow up safety data have satisfactorily established the safety of nilotinib (300 mg bd and 400 mg bd) and imatinib (400 mg qd) for the treatment of the target patient population, although there are notable differences in the safety profiles of nilotinib and imatinib. Furthermore, the pivotal safety data suggest that N300 is a safer dose for the target population than N400. Overall, it was considered that the supportive data indicate that the efficacy and safety of N400 are durable for up to 24 months in patients with imatinib resistant or intolerant Ph+ CML-AP and CML-AP.

Conclusions

It was considered that the risk benefit balance for nilotinib 300 mg bd is acceptable for the treatment of newly diagnosed adult patients with Ph+ chronic myeloid leukaemia in the chronic phase. It was recommended that nilotinib 300 mg bd be approved for treatment of this condition.

It should be a condition of registration that the sponsor provide the 24 month efficacy and safety data from the pivotal study [CAMN 107A2303] to the TGA for evaluation as soon as the data become available.

V. Pharmacovigilance Findings

Risk Management Plan

The sponsor submitted a Risk Management Plan version 8, dated 11 December 2009 which was reviewed by the TGA's Office of Product Review (OPR). The sponsor noted that as this document is constantly being revised, some of the risks and pharmacovigilance activities may no longer be applicable.

Safety Specification

The summary of the Ongoing Safety Concerns as specified by the sponsor is shown in Table 15.

Table 15: Summary of ongoing safety concerns

Category	Safety Concern
Important identified risks	QT prolongation Myelosuppression Significant bleeding Severe infections Hepatic transaminase and bilirubin elevations Pancreatitis, lipase and amylase elevations Rash Fluid retention Blood glucose increase Hypophosphataemia
Important potential risks	Sudden death Ischaemic heart disease Cardiac failure Drug induced liver injury Photosensitivity Diabetes mellitus Severe Cutaneous Adverse Reactions Hyperthyroidism
Important identified interactions	Strong CYP3A4 inhibitors Strong CYP3A4 inducers Food
Important potential interactions	P-gp inhibitors Drugs eliminated by CYP3A4, CYP2C8, CYP2C9, CYP2D6 or UGT1A1, and P-gp substrates Drugs that may prolong the QT interval Hormonal contraceptives
Important missing information	Pregnancy Paediatric patients Renal impairment Hepatic impairment Patients with uncontrolled or significant cardiac disease

The clinical reviewer noted that the safety data in the pivotal study were derived from newly diagnosed Ph+ CML-CP patients followed up for 12 months (556 in the nilotinib arms and 280 in the imatinib arm). The safety data in the two supportive studies were derived from 321 Ph+ CML-CP and 137 Ph+ CML-AP imatinib resistant or intolerant patients treated with nilotinib and followed up for 24 months. Overall, the incidence of

AEs, SAEs (including death) and laboratory abnormalities (haematological and biochemical) occurred more frequently with nilotinib in the Ph+ CML-CP and CML-AP supportive studies in imatinib resistant or intolerant patients than with nilotinib in the pivotal study in patients with newly diagnosed Ph+ CML. This is most likely a function of time as patients in the supportive studies were exposed to nilotinib for at least twice as long (24 months) as patients in the pivotal study (12 months). However, there were no new safety signals seen with nilotinib in the 24 month follow up data from the two supportive studies and the toxicities observed in these two studies were consistent with those in the pivotal study.

Pharmacovigilance Plan

The sponsor proposed routine pharmacovigilance activities to monitor all the specified ongoing safety concerns.[14]

In addition the sponsor proposed to further monitor the following important identified or potential risks by following up serious cases of these AEs received from spontaneous and post marketing surveillance and in global clinical trials, using targeted questionnaires/checklists:

- QT prolongation
- Myelosuppression
- Significant bleeding
- Severe infections
- Hepatic transaminase and bilirubin elevations
- Pancreatitis, lipase and amylase elevations
- Fluid retention
- Blood glucose increase
- Sudden death
- Ischaemic heart disease
- Cardiac failure
- Drug induced liver injury
- Diabetes mellitus
- Severe Cutaneous Adverse Reactions

Furthermore targeted safety surveillance to monitor important identified and potential risks and interactions are undertaken in the CML and GIST programs including three ongoing studies.

For the important identified risks 'QT prolongation' and 'Blood glucose increase' this will involve the collection of:

- additional categorical QT safety data in two open label, randomised studies with ongoing monitoring of ECGs and echocardiograms and monitoring of overall safety data through patient disposition, death listings and investigator notifications; and

[14] Routine pharmacovigilance practices involve the following activities:
- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

- additional targeted laboratory data including fasting glucose, HbA1c, insulin levels and C-peptide in a Phase III open label, randomised study of imatinib versus nilotinib respectively.

For the important potential risks 'Sudden death', 'Ischaemic heart disease'/'Cardiac failure' and 'Diabetes mellitus' this will involve the collection of:

- additional categorical QT safety data and monitoring of ECG data as defined for QT prolongation;
- additional cardiac safety data including ECGs and echocardiograms in two open label, randomised studies with ongoing SAE monitoring and monitoring of overall safety data through patient disposition, death listings and investigator notifications ; and
- additional targeted laboratory data including fasting glucose, HbA1c, insulin levels and C-peptide in a Phase III open label, randomised study of imatinib versus nilotinib respectively.

For the important potential interactions 'Drugs eliminated by CYP3A4, CYP2C8, CYP2C9, CYP2D6 or UGT1A1, and Pgp substrates' and 'Hormonal contraceptives', a drug-drug interaction clinical study is planned to evaluate the inductive effect of nilotinib on CYP enzymes.

For the important missing information 'Pregnancy', a global pregnancy registry has been initiated for imatinib and nilotinib.

For the important missing information 'Paediatric patients', the sponsor reported that a paediatric investigation plan has been agreed upon with overseas regulatory authorities. A protocol is being developed for a multiple dose, open label, single agent, non-controlled trial to evaluate pharmacokinetics, pharmacodynamics, safety and activity in paediatric patients from birth to less than 18 years with Philadelphia chromosome positive chronic myeloid leukaemia in chronic or accelerated phase who are imatinib intolerant or in whom the disease is imatinib resistant, or with refractory or relapsed Philadelphia chromosome positive acute lymphoblastic leukaemia. Pending the outcome of this study, a protocol will be developed for a multiple dose, open label, single agent, non-controlled, multicentre trial to evaluate pharmacokinetics, safety and activity in paediatric patients from birth to less than 18 years with Philadelphia chromosome positive chronic myeloid leukaemia in chronic or accelerated phase who are imatinib intolerant or in whom the disease is imatinib resistant or with newly diagnosed Philadelphia chromosome-positive chronic myeloid leukaemia in chronic phase.

In principle the OPR reviewer had no objection to the sponsor implementing additional pharmacovigilance activities to further monitor the specified ongoing safety concerns.

The sponsor should provide copies of the targeted questionnaires/checklists used to follow up serious cases of the specified important identified and potential risks received from spontaneous and post marketing surveillance and in global clinical trials. It was noted that the specified ongoing and initiated studies are not considered to be part of the planned clinical studies in the pharmacovigilance plan, therefore the related study protocols have not been requested for review. Nevertheless an update on the progress/results/analysis of these studies as outlined in the RMP will be expected in future PSURs.

Risk Minimisation Activities

The sponsor proposed routine risk minimisation activities for all the specified ongoing safety concerns and additional risk minimisation activities for the important identified risk 'QT prolongation', the important identified interactions 'Strong CYP3A4 inhibitors'

and 'Food', the important potential interaction 'Drugs that may prolong QT interval' and the important missing information 'Hepatic impairment' and 'Patients with uncontrolled or significant cardiac disease'.[15]

The OPR reviewer noted that the sponsor's justification for such conclusion would appear to be reasonable. Furthermore the sponsor advised that additional risk minimisation activities for implementation only in the EU have been proposed for the important identified risk: 'Fluid retention', the important potential risk: 'Cardiac failure' and the important identified interaction: 'Strong CYP3A4 inducers'. Educational material has been updated to align with the reviewed RMP (Version 8) and the current Australian specific registration details.

The additional risk minimisation activities for above mentioned risks consist of the following:

- Patient/caregivers material will be developed that educates the patient and caregivers. Content will include information on the dosing of nilotinib (timing of doses relative to food and prior dose), as well as possible QT prolongation related side effects, potential drug (prescription and OTC) and food interactions, the need for special monitoring (periodic electrolytes and ECGs), and the need to use with caution in patients with certain medical diseases (patients with hepatic impairment or uncontrolled or significant cardiac disease).
- Physicians/pharmacists/nurses materials will be developed that educates healthcare providers. Content will include the same topics described above for patient/caregivers.

The sponsor will develop a proposal to assess the effectiveness of the risk minimisation activities (educational activities and the provision of educational material). The primary objectives of the proposal will be to quantify awareness and understanding of the risks by the intended audiences. The selection of an appropriate methodology will be made in conjunction with Australian academic research groups with expertise in this field. The sponsor will provide the TGA with the proposal when it becomes available.

The OPR reviewer noted that the sponsor's proposed Risk Minimisation Plan (RMP) would appear to be reasonable. Educational material has been updated to align with the reviewed RMP (Version 8) and the current Australian specific registration details. Final Australian educational materials should be submitted to the TGA for review and evidence that these educational materials have been pre-tested for comprehension and understanding by the intended recipients should also be provided.

In addition the data from spontaneous ADRs are unlikely to be sufficient in measuring the effectiveness of the proposed additional risk minimisation activities. This is due to the underreporting and the lack of reliable exposure (usage) data associated with spontaneous reporting systems, not to mention the information gained from adverse reaction reporting is often incomplete. Consequently the sponsor should consider planning appropriate alternative methods to assess the effectiveness of the education material as a measure to reduce risk. For example drug utilisation studies may be conducted to derive denominator data for use in determining rates of adverse reactions in relation to the specified ongoing safety concerns. Subsequently protocols for any such studies should be submitted to the TGA for assessment.

[15] Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

The data were satisfactory. The 150 mg capsule is a direct scale of the 200 mg capsule.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

Pharmacokinetics

A pharmacokinetic analysis within the first line efficacy study (CAMN107A2303) found non-linearity between the two doses of nilotinib, exposure at 400 mg bd being less than dose proportional to exposure at 300 mg bd.

Efficacy

Two doses of nilotinib, 300 mg bd (N300) and 400 mg bd (N400) and imatinib 400 mg daily (I400) were compared in a randomised, open label, parallel group trial (CAMN107A2303) in patients with newly diagnosed Ph+ CML-CP. Patients were stratified according to their level of risk (low, intermediate, high) using the Sokal risk score. The median age of patients was 47 (range 18-85) years. Major protocol violations occurred in 13% of subjects, balanced across the three treatment arms.

The primary analysis was major molecular response (MMR) at 12 months treatment. The major secondary analysis is to be assessment of the durability of MMR after 24 months treatment. The 24 month analysis is not yet available; however, supplementary data to 18 months were submitted. The supplementary data addressed inconsistencies between the submitted data and the proposed product information which had in part been based on the 18 month data. The median duration of treatment was 18.6 months.

MMR was defined as a ≥ 3-log reduction of BCR-ABL transcript in peripheral blood measured by real time quantitative reverse transcriptase polymerase chain reaction (RQ-PCR). At 12 months, both doses of nilotinib produced significantly greater MMR than imatinib (Table 16). This was the case regardless of Sokal risk.

Table 16: Efficacy Results at 12 months – Trial CAMN107A2303 – ITT

	Imatinib N=283	Nilotinib 300 mg N=282	Nilotinib 400 mg N=281
MMR % Diff [95% CI][1]	22.3	44.3 22.1 [14.5, 29.5]	42.7 20.4 [12.9, 28.0]
CCyR % Diff [95% CI][1]	65.0	80.1 15.1 [7.9, 22.4]	77.9 12.9 [5.5, 20.3]
Not Progressed to AP/BC%[2] log rank p-value vs imatinib	96.5	99.3 p=0.01	99.6 p=0.004
Overall Survival%[2] HR [95% CI]	99.3	99.3 0.78 [0.17, 3.49]	99.2 0.71 [0.30, 1.66]

[1] Difference from imatinib. [2] Kaplan-Meier estimate (excludes follow-up of discontinued patients). AP/BC: Accelerated Phase or Blast Crisis. HR: Hazard Ratio vs imatinib.

Nilotinib also produced significantly greater complete cytogenetic response (CCyR) and lesser progression to accelerated phase or blast crisis (AP/BC) than imatinib. Follow up of

discontinued patients was excluded. CCyR was defined as 0% Ph+ metaphases in bone marrow. There were no significant differences in overall survival.

The benefits in the nilotinib groups were maintained at 18 months. Duration of MMR or CCyR was not assessed. However, the sponsor noted that duration of MMR and CCyR were assessed and reported in both 12 and 18 month analyses

Updated data from two previously submitted uncontrolled second line trials (CAMN107A2101E1 and 2) of N400 in patients with imatinib resistant or intolerant chronic phase and accelerated phase Ph+ CML supported the durability of cytogenetic and haematological responses to 24 months.

Study CSTI571A0106 PCR with imatinib validated the primary efficacy endpoint MMR in the first line efficacy trial. Achievement of MMR at 12 months predicted significant improvement in event free survival at 7 years; however, it did not predict significant improvement in overall survival.

Safety

In the first line trial (CAMN107A2303), there were 836 subjects in the safety set – I400 n=280, N300 n=279 and N400 n=277. The median duration of exposure was 18.6 (range 0-22) months. Skin and hepatobiliary disorders and headache were significantly higher with nilotinib whilst gastrointestinal, musculoskeletal and haematological disorders and oedema were significantly higher with imatinib. The incidence of adverse events was generally lower with the lower nilotinib dose than the higher dose.

Grade 3-4 adverse events occurred at a higher incidence with nilotinib than imatinib – 52% with N400, 46% with N300 and 43% with I400. The pattern of Grade 3-4 events was similar to that for all events with skin, hepatobiliary and headache being significantly greater with nilotinib than imatinib.

In the second line supportive trials (CAMN107A2101E1 and 2), there were 321 CML-CP subjects and 137 CML-AP subjects in the safety set. Median time on treatment was 18 (range 0-36) months for CML-CP and 9 (0-38) months for CML-AP. The incidence of skin disorders and headache were similar, the incidence of hepatobiliary disorders lower and the incidence of neutropenia and thrombocytopenia higher than with nilotinib in the first line trial. The incidence of Grade 3-4 events with nilotinib was also higher in the second line trials (79%) than in the first line trial (46-52%).

Clinical Evaluation

The evaluator recommended approval of the new indication subject to provision of the 24 month efficacy and safety data from the first line trial (CAMN107A2303) when available. The sponsor agreed to provide the 24 month data when available.

Risk Management Plan

The Office of Product Review negotiated a satisfactory RMP (version 8, dated 11 December 2009) with the sponsor.

Based on the new clinical data submitted with this application, the Safety Specification remains adequate. There were no new nonclinical data.

Risk-Benefit Analysis

Delegate Considerations

In the first line trial (CAMN107A2303) in adults with newly diagnosed Ph+ CML-CP, both doses of nilotinib, N300 and N400, significantly increased MMR, the primary endpoint, and CCyR by 12 months compared with I400. Both endpoints are surrogate. The TGA-adopted

EU Guideline does not recognise MMR as a primary endpoint; however, it does recognise CCyR. The sponsor presented a study with imatinib (CSTI571A0106 PCR) which supported MMR as a primary endpoint. MMR at 12 months correlated with event free survival (but not overall survival) at 7 years.

Although nilotinib reduced progression to accelerated phase or blast crisis compared with imatinib, discontinued patients were excluded. Therefore, not much reliance can be placed on these results. Outcomes in discontinued patients will not be included until the 24 month analysis (Saglio et al).[16] There were no significant differences in overall survival.

The nilotinib benefits in MMR and CCyR were maintained at 18 months indicating some durability in these responses. However, longer follow up is needed to confirm the durability of response and if it translates into increased survival. An analysis of the durability of response is due at 24 months. Updated data from previously submitted second line trials supported the durability of molecular and cytogenetic responses to 24 months. The nilotinib dose in these trials was higher (400 mg bd) than the proposed dose.

In general, the lower nilotinib dose (N300) appeared similar in efficacy to the higher dose (N400).

The safety profile of nilotinib and imatinib was similar in the first line trial but with different types of adverse events. Skin and hepatobiliary disorders and headache predominated with nilotinib whilst gastrointestinal, musculoskeletal and haematological disorders and oedema predominated with imatinib. It was noteworthy that there was a higher incidence of haematological disorders with nilotinib in the second line trials than in the first line trial. Otherwise, the safety of nilotinib in the first line trial was consistent with the second line experience. There was a lower incidence of adverse events with the lower nilotinib dose than the higher dose.

The Delegate supported the clinical evaluator's recommendation to approve nilotinib 300 mg twice daily for the treatment of newly diagnosed Ph+ CML-CP. Based on the correlation between 12 month MMR and event free survival with imatinib, a member of the same class as nilotinib, it is likely that the molecular response seen with nilotinib will translate into long term benefit. The 24 month data will clarify the durability of response and impact on disease progression and survival.

The Delegate proposed to approve nilotinib (Tasigna) capsules for the new indication at the dose of 300 mg twice daily:

Treatment of adults with newly diagnosed Philadelphia chromosome positive chronic myeloid leukaemia in chronic phase

The Delegate also proposed to approve the new 150 mg strength of nilotinib (Tasigna) capsules.

Approval will be subject to finalization of the product information and conditional on the implementation of Risk Management Plan, version 8, dated 11 December 2009 and subsequent revisions, and submission of the 24 month analysis of trial CAMN107A2303 and longer term follow up data when available.

Response from Sponsor

The sponsor welcomed the recommendations made by the clinical evaluator and the Delegate to approve Tasigna (nilotinib) for the new indication at the dose of 300 mg bd and to approve the new 150 mg capsule strength:

[16] Saglio et al. Second-generation BCR-ABL kinase inhibitors in CML. N Engl J Med 2010; 363: 1673-4.

Treatment of adults with newly diagnosed Philadelphia chromosome positive chronic myeloid leukaemia in chronic phase.

The recommendations were based upon the 18 month efficacy and safety data from the pivotal study (CAMN107A2303). The Delegate acknowledged that the benefits of Tasigna were maintained at 18 months but that longer term follow up is needed to confirm the durability of response and if it translates to increased survival.

In its pre-ACPM response, the sponsor focused on addressing the Delegate's questions on the durability of the benefits of Tasigna in newly diagnosed patients based on the 18 month data. In addition, the sponsor provided an update on the availability of the 24 month analysis, as requested by the Delegate and reaffirmed its commitment to provide these data to the TGA for review. The sponsor also commented on other points made by the Delegate, specifically on the use of major molecular response (MMR) at 12 months as the primary endpoint and explained why patients who discontinued treatment were excluded from the analysis of the progression to accelerated phase and blast crisis (AP/BC). Finally, for the sake of clarity, the sponsor took the opportunity to address some apparent minor discrepancies in the Delegate's considerations

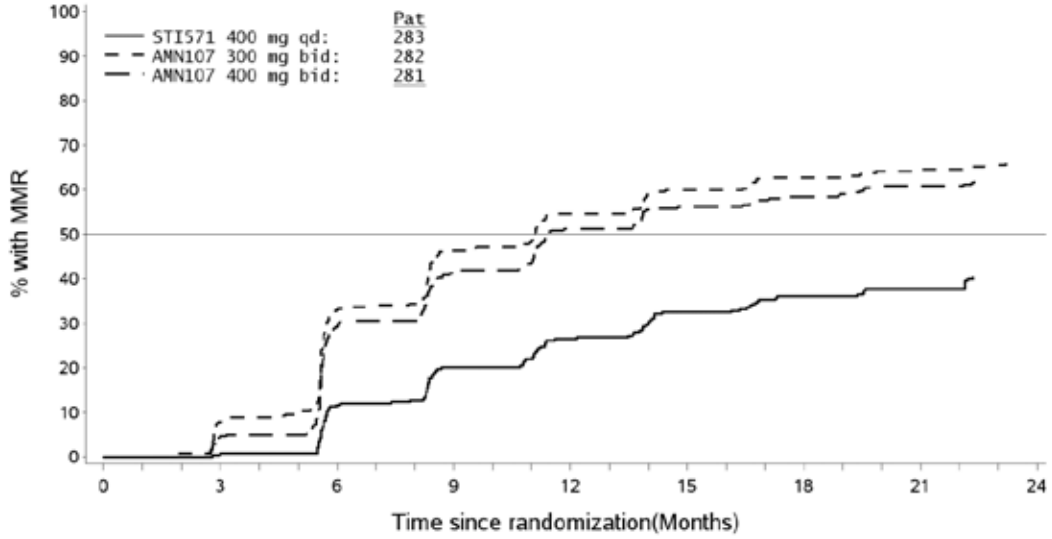
Durability of response

The sponsor noted that the Delegate accepted that the benefits in MMR and complete cytogenetic response (CCyR) were maintained at 18 months indicating some acknowledgement of the durability in these responses. Based on the correlation between 12 month MMR and event free survival with imatinib, the Delegate concluded that it likely that the molecular response seen with nilotinib will translate into long term benefit.

Confidence in the persistence of the long term effect of Tasigna in a first line setting can nonetheless be gained from the 12 and 18 month data from the pivotal trial (CAMN107A2303) in adult patient with newly diagnosed Ph+ CML-CP. The findings from this Phase III pivotal trial indicate consistently superior efficacy outcomes for patients treated with Tasigna when compared with patients treated with imatinib. Tasigna continued to demonstrate higher molecular response rates together with lower rates of treatment failure and reduced risk of progression to AP/BC compared to imatinib over 18 months. The MMR rate at 12 months was double in patients randomised to Tasigna when compared with patients randomised to the imatinib arm and this effect was continued for over 18 months. Results for the other secondary efficacy endpoints, including overall MMR rates, time to MMR and CCyR, continue to support the superiority of Tasigna over imatinib.

The 12 month efficacy data satisfactorily demonstrated the superiority of both Tasigna doses over standard therapy with imatinib for the treatment of newly diagnosed Ph+ CML-CP. The Delegate provided a summary of the efficacy results at 12 months from the pivotal trial. The clinical evaluator noted that with a minimum follow up of 12 months (median 14 months), MMR was achieved by 30.4% of patients in the I400 group, 57.1% of patients in the N300 group and 54.4% of patients in the N400 group. The evaluator noted that the additional follow up data with a minimum follow up of 16 months (median 18 months) showed that MMR increased to 40.3% of patients in the I400 group, 66.0% of patients in the N300 group and 61.9% of patients in the N400 group. The clear superiority of Tasigna over imatinib in terms of MMR rate by 12 months continues for over 18 months (Figure 1).

Figure 1: Cumulative incidence of MMR – Study CAMN107A2303 (FAS)



The superiority of Tasigna over imatinib was also demonstrated for secondary endpoints of cytogenetic response (CCyR, MCyR), as acknowledged by the Delegate. In addition, significantly fewer patients progressed to AP/BC in each Tasigna arm (n=2 in N300 and n=1 in N400) compared to the imatinib arm (n=11) in the 12 month analysis. The updated data indicate that the estimated rates of patients free from progression to AP/BC at 18 months were statistically significantly lower for N300 compared to I400 (99.6% vs 96.4%, p=0.0062) and there were fewer CML related deaths on Tasigna.

The effect of MMR at 12 months is an acceptable surrogate endpoint of long term outcomes. The clinical evaluator accepted that MMR at 12 months can predict long term progression free survival (PFS) and that progression to AP/BC is likely to be superior in patients with newly diagnosed Ph+ CML-CP treated with N300 compared to I400. In a recent publication by Hehlmann R et al, MMR at 12 months has been established as a surrogate for overall survival (independent of treatment approach).[17] Achievement of MMR (vs no MMR) at 12 months predicted superior overall survival at 3 years (99% [95%CI, 97 to 100%] v 95% [95% CI, 93% to 97%]; p=0.0156). When compared with imatinib, the increased proportion of patients who achieved MMR on Tasigna combined with fewer patients progressing to AP/BC on Tasigna firmly supports the notion that a long term survival benefit can be achieved.

Availability of the 24 month data

The 24 month analysis of the results is complete and the results were recently reported at major international meetings, including the European Hematology Association (EHA) Congress in June 2011 and American Society of Clinical Oncology (ASCO) 2011 Meeting in June. Following an agreement with the Delegate, the sponsor included with its pre-ACPM response a copy of the abstract of the 24 month analysis, along with the slides which were presented at the recent EHA Congress.[18] The sponsor reaffirmed its commitment to submit

[17] Hehlmann R, Lauseker M, Jung-Munkwitz, S et al. Tolerability-adapted imatinib 800 mg/d versus 400 mg/d versus 400 mg/d plus interferon-α in newly diagnosed chronic myeloid leukemia.J Clin Oncol. 2011; 29: 1634-1642.

[18] A Hochhaus, G Saglio, P le Coutre et al. Superior efficacy of nilotinib compared with imatinib in newly diagnosed patients with chronic myeloid leukemia in chronic (CML-CP): ENESTnd minimum 24-month follow-up. Abstarct presented at EHA Congress, 2011.

the complete 24 month dataset to the TGA for review and accepted this as a condition of registration, as recommended by the clinical evaluator.

The sponsor maintained the view that the data presented in the initial and supplementary submissions to 18 months were sufficient to support the favourable risk benefit profile of Tasigna in newly diagnosed Ph+ CML-CP and approval in Australia. This view is consistent with the recommendations of the clinical evaluator and the Delegate, as well as the decisions of health authorities in other regulatory jurisdictions. The sponsor commented briefly on the 24 month findings here to reassure the advisory committee that the superior effects of N300 over imatinib seen at 12 months and 18 months were sustained over a minimum follow up of 24 months.

Tasigna continues to show superior molecular responses and significantly fewer progressions to AP/BC compared with imatinib over a minimum 24 month follow up. With longer follow up, the time to progression to AP/BC on treatment was longer on the Tasigna arms (including and excluding clonal evolution) compared with imatinib. The Tasigna arms continue to maintain an advantage in the proportion of patients achieving MMR and the difference between the Tasigna arms and the imatinib arm does not appear to be decreasing over time, unlike earlier trials comparing high dose (800 mg/day) and standard dose (400 mg/day) imatinib therapy where early differences were not evident with longer follow up.[19] The key secondary endpoint of durable MMR at 24 months (proportion of patients who achieved MMR at 12 months and maintained response at 24 months) was evaluated and showed that the responses achieved with Tasigna are durable. In addition, both doses of Tasigna were generally well tolerated and fewer AEs led to discontinuation in the N300 arm compared with the other treatment arms. There were no new safety signals observed with longer follow up.

Other points raised by the Delegate

MMR at 12 months as the primary endpoint

The Delegate noted that the TGA-adopted EU Guideline does not recognise MMR as a primary endpoint although it does recognise complete cytogenetic response (CCyR). It should be noted that MMR and CCyR were used as endpoints in the pivotal trial and that Tasigna demonstrated significantly superior response rates for both N300 and N400 arms compared to the imatinib arm:

• 44.3%, 42.7% and 22.3%, respectively, p-value < 0.0001 for both comparisons

• 80.1%, 77.9% and 65.0% for the N300, N400 and I400, respectively (p < 0.0001 and p=0.0005 for N300 and N400 vs imatinib, respectively).

For the sake of completeness, the sponsor also provided some background on use of MMR at 12 months and its validity as the primary endpoint. The acceptability of MMR at 12 months as the primary endpoint was based on feedback from the US FDA during the development of the study protocol for CAMN107A2303. The EU rapporteur and co-rapporteur were consulted on the utility of the proposed data package and agreed that the proposed application (including MMR as a primary endpoint) was adequate for submission. The new indication and strength were approved in the US and EU based on the 18 month and 12 month data respectively. Significantly, the Delegate acknowledged that Novartis submitted a study with imatinib (Glivec) that supported the use of MMR as the primary endpoint [Study CSTI571A0106PCR]. The clinical evaluator also considered

[19] Cortes JE, Baccarani M, Guilhot F, et al. Phase III, randomized, open-label study of daily imatinib mesylate 400 mg versus 800 mg in patients with newly diagnosed, previously untreated chronic myeloid leukemia in chronic phase using molecular end points: tyrosine kinase inhibitor optimization and selectivity study. J Clin Oncol 2010; 28: 424-430.

the use of MMR at 12 months to be justified on the basis that: (1) nilotinib is not a new chemical entity and is approved for use in imatinib resistant patients, and (2) there are appropriate supportive clinical efficacy data in CML-CP and CML-AP suggesting that haematologic and cytogenetic responses to nilotinib are durable up to at least 24 months.

Exclusion of discontinued patients from analysis of progression to AP and BC

The sponsor noted that the Delegate commented on the reliability of the trial findings in relation to patients who progressed to AP and BC given that discontinued patients were excluded from the analysis. In other large, global Phase III registration studies such as CSTI571A0106 (IRIS)4 and DASISION5 (dasatinib vs imatinib in newly diagnosed Ph+ CPCML), progression events after discontinuation were not prospectively documented.[7,20] Moreover, subsequent treatment(s), dosing, safety and tolerability are not known but are important for evaluating the impact of potential confounding factors. Even so, prospectively collected investigator assessments of progression to AP/BC after discontinuation of treatment are included in the 24 month analysis that will be submitted to the TGA, and were presented at EHA.

When considering progression events of patients after discontinuation of treatment, an additional seven, two, and six progression events (excluding clonal evolution) were observed in the N300, N400, and I400 treatment arms, respectively. Progression within 60 days of discontinuation occurred in one, one and two patients in the N300, N400 and I400 arms, respectively, while the remaining patients progressed at least 60 days after discontinuation. Therefore, a difference is maintained in favour of those patients initially randomised to treatment with N300 over those initially randomised to imatinib even though patients who failed first line treatment with imatinib in the pivotal trial CAMN107A2303 had the opportunity to receive Tasigna or other second line treatments.

Concluding remarks

Tasigna 300 mg bd showed superior efficacy compared with imatinib at 12 and 18 months in patients with newly diagnosed Ph+ CML-CP. The clinical evaluator and the Delegate agreed that the benefits of Tasigna were maintained at 18 months and continue to support the favourable risk/benefit balance for Tasigna 300 mg bd for the treatment of adult patients with newly diagnosed Ph+ CML-CP. The findings at 18 months provide reassurance on the durability of effect and low likelihood of failure and progression over time. Furthermore, analysis of the 24 month follow-up data reaffirms the superiority of Tasigna compared to imatinib for the treatment of adult patients with newly diagnosed Ph+ CML-CP. Tasigna 300 mg bd was shown to be superior to imatinib with higher rates of MMR and CCyR, more durable molecular responses and significantly reduced risk of progression. These results further support the place of Tasigna as an important treatment option for patients with newly diagnosed Ph+ CML-CP. Extending the use of more effective second generation tyrosine kinase inhibitors (TKIs), such as Tasigna, to the treatment of newly diagnosed Ph+ CML-CP potentially enhances patient outcomes. New treatment options that rapidly reduce leukaemic cell burden and inhibits progression, particularly during the early phase can improve the prognosis of the disease. Moreover, first line treatment with a more effective TKIs would not exclude the option of an alternate second generation TKI in patients who are resistant or intolerant to first line treatment.

[20] Kantarjian H. Shah NP, Hochhaus A et al. Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia. NEJM 2010; 362: 2260-2270.

Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, agreed with the Delegate's proposal.

In expressing its view that the submission was suitable to be considered for approval, the ACPM agreed with the Delegate that the evidence of safety and efficacy provided supported a positive risk benefit profile for this product in the indication sought.

The ACPM noted the provision in the pre-ACPM response of an abstract of the 24 month analysis of trial CAMN107A2303 and its apparent confirmation of safety and efficacy. The longer term follow up data should be provided to the TGA. The sponsor should also be encouraged to provide updated paediatric trial data.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Tasigna containing nilotinib for the new indication as described below and the registration of a new strength for Tasigna capsules containing nilotinib 150mg:

Treatment of adult patients with newly diagnosed Philadelphia chromosome positive chronic myeloid leukaemia (CML) in chronic phase

Included among the specific conditions of registration were the following:

- The implementation in Australia of the nilotinib Risk Management Plan (RMP), dated 11 December 2009 (version 8) and any subsequent revisions, as agreed with the TGA and its Office of Product Review.
- The results of the 24 month analysis of trial CAMN107A2303 and longer term follow up data will be submitted to the TGA when available.

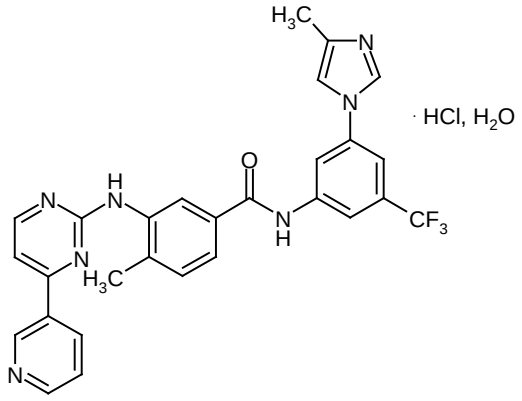
Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

TASIGNA®
(nilotinib)

NAME OF THE DRUG

Active ingredient:	nilotinib.
Chemical name (CAS):	4-Methyl-N-[3-(4-methyl-1H-imidazol-1-yl)-5-(trifluoromethyl) phenyl]-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]-benzamide, monohydrochloride, monohydrate
Molecular formula:	$C_{28}H_{22}F_3N_7O.HCl.H_2O$
CAS number:	Free base - 641571-10-0
Molecular weight:	583.99 (as monohydrate)
Structural formula:	



DESCRIPTION

Each capsule contains 150 mg or 200 mg nilotinib base (as hydrochloride, monohydrate). Nilotinib is a white to slightly yellowish or slightly greenish yellowish powder.

The solubility of nilotinib in aqueous solutions strongly decreases with increasing pH, and it is practically insoluble in buffer solutions of pH 4.5 and higher pH values. It is very soluble in dimethyl sulfoxide, sparingly soluble in ethanol and methanol, very slightly soluble in acetonitrile and n-octanol.

Excipients:
Capsule content: lactose, crospovidone, poloxamer, silica - colloidal anhydrous, magnesium stearate.
Capsule shell: gelatin, titanium dioxide, iron oxide yellow, iron oxide red .
Printing ink: iron oxide red, iron oxide black, shellac glaze - 47.5% (22% esterified) in IMS 74 OP, water-purified,butan-1-ol, methylated spirit – industrial, lecithin, antifoam DC 1510, titanium dioxide, propylene glycol and isopropyl alcohol.

PHARMACOLOGY

Pharmacodynamics

Nilotinib inhibits Bcr-Abl tyrosine kinase activity in the nanomolar range by binding to the ATP-binding site. It also inhibited 32/33 imatinib-resistant mutant forms of Bcr-Abl tyrosine kinase that were tested. As a consequence, nilotinib inhibited the proliferation of cell lines carrying these enzymes. Orally- administered nilotinib, as a single agent, was also effective in reducing tumour burden and prolonging survival in a murine model of CML.

Nilotinib had little or no effect against the majority of other protein kinases examined except for the platelet derived growth factor receptor (PDGFRa and b), and stem cell factor receptor (Kit CSF-1R, DDR) kinases which it inhibited at concentrations within the range achieved following oral administration at therapeutic doses recommended for the treatment of CML.

Pharmacokinetics

Absorption:

Peak concentrations of nilotinib are reached 3 hours after oral administration. Nilotinib absorption following oral administration was approximately 30%.

In healthy volunteers, C_{max} and area under the serum concentration-time curve (AUC) of nilotinib are increased by 112% and 82%, respectively compared to fasting conditions when Tasigna is given with food. Administration of Tasigna 30 minutes or 2 hours after food increased bioavailability of nilotinib by 29% or 15%, respectively (see "DOSAGE AND ADMINISTRATION"). Nilotinib absorption (relative bioavailability) might be reduced by approximately 48% and 22% in patients with total gastrectomy and partial gastrectomy, respectively.

Distribution:

The blood-to-serum ratio of nilotinib is 0.68. Serum protein binding is approximately 98% on the basis of *in vitro* experiments.

Metabolism:

Main metabolic pathways identified in healthy subjects are oxidation and hydroxylation. Nilotinib is the main circulating component in the serum.

Of the nilotinib metabolites, the pyrimidine-N-oxide metabolite (BEJ866) has been found to possess inhibitory activity against the Bcr-Abl kinase in transfected murine hematopoietic cells, albeit at concentrations much higher than those required by the parent drug, nilotinib. The mean serum exposure of BEJ866 is 1.0% of the exposure of nilotinib.

Elimination:

After a single dose of radiolabelled nilotinib in healthy subjects, greater than 90% of the dose was eliminated within 7 days mainly in faeces (93% of the dose). Parent drug accounted for 69% of the dose.

Linearity / non-linearity:

Steady-state nilotinib exposure was dose-dependent with less than dose-proportional increases in systemic exposure at dose levels higher than 400 mg given as once daily dosing. Daily serum exposure to nilotinib of 400 mg twice-daily dosing at steady state was 35% higher than with 800 mg once-daily dosing. Systemic exposure (AUC) of nilotinib at steady state at a dose level of 400 mg twice daily was approximately 13.4% higher than with 300 mg twice daily. The average nilotinib trough and peak concentrations over 12 months were approximately 15.7% and 14.8% higher following 400 mg twice daily dosing compared to 300 mg twice daily. There was no relevant increase in exposure to nilotinib when the dose was increased from 400 mg twice-daily to 600 mg twice-daily.

Other information

Steady state conditions were essentially achieved by day 8. An increase in serum exposure to nilotinib between the first dose and steady state was approximately 2-fold for daily dosing and 3.8-fold for twice-daily dosing. The apparent elimination half-life estimated from the multiple dose pharmacokinetics with daily dosing was approximately 17 hours. Inter-patient variability in nilotinib pharmacokinetics was moderate to high.

Pharmacokinetics in special patient groups:

Age, body weight, or ethnic origin do not affect the pharmacokinetics of nilotinib, whereas there is an effect of gender, with exposure to nilotinib in female patients being approximately 20% greater than in male patients.

CLINICAL TRIALS

Newly diagnosed Philadelphia chromosome positive chronic myeloid leukaemia in chronic phase (Ph+ CML-CP)

An open label, multicenter, randomized Phase III study was conducted to determine the efficacy of TASIGNA versus Glivec (imatinib) in adult patients with cytogenetically confirmed newly diagnosed Ph+ CML-CP. Patients were within six months of diagnosis and were previously untreated for CML-CP, except for hydroxyurea and/or anagrelide, or a maximum of two weeks of imatinib in emergent cases. In addition, patients were stratified according to Sokal risk score at time of diagnosis.

Efficacy was based on a total of 846 patients (283 patients in the imatinib 400 mg once daily group, 282 patients in the nilotinib 300 mg twice daily group, 281 patients in the nilotinib 400 mg twice daily group).

Baseline characteristics were well balanced between the three groups. Median age was 46 years in the imatinib group and 47 years in both nilotinib groups, with 12.4%, 12.8% and 10.0% were ≥65 years of age in imatinib, nilotinib 300 mg twice daily and nilotinib 400 mg twice daily treatment groups, respectively. There were slightly more male than female patients in all groups (55.8%, 56.0% and 62.3% in imatinib, nilotinib 300 mg twice daily and nilotinib 400 mg twice daily, respectively). More than 60% of all patients were Caucasian, and 25% were Asian.

The primary data analysis time point was when all 846 patients completed 12 months of treatment (or discontinued earlier). The median time on treatment is slightly over 18 months in all three treatment groups. In each treatment arm, more than 80% of patients had received treatment for longer than 12 months. The median actual dose intensity was 400 mg/day in the imatinib group, 593 mg/day in the nilotinib 300 mg twice daily group and 779 mg/day in the nilotinib 400 mg twice daily group. This study is on-going.

Major molecular response (MMR)

The primary efficacy variable was MMR at 12 months after the start of study medication. MMR was defined as ≤ 0.1% BCR-ABL/ABL % by international scale measured by RQ-PCR, which corresponds to a ≥ 3 log reduction of BCR-ABL transcript from standardized baseline.

The MMR rate at 12 months was statistically significantly superior in the nilotinib 300 mg twice daily group compared to the imatinib 400 mg once daily group. The rate of MMR at 12 months, was also statistically significantly higher in the nilotinib 400 mg twice daily group compared to the imatinib 400 mg once daily group, Table 1.

In the nilotinib recommended dose of 300 mg twice daily, the rate of MMR at 3, 6, 9 and 12 months were 8.9%, 33.0%, 43.3% and 44.3%. In the nilotinib 400 mg twice daily group, the rate of MMR at 3, 6, 9 and 12 months were 5.0%, 29.5%, 38.1% and 42.7%. In the imatinib 400 mg once daily group, the rate of MMR at 3, 6, 9 and 12 months were 0.7%, 12.0%, 18.0% and 22.3%. Based on a median follow up of approximately 18 months, the best overall MMR rate was 66.0% in the nilotinib 300 mg twice daily group, 61.9% in the nilotinib 400 mg twice daily group and 40.3% in the imatinib group.

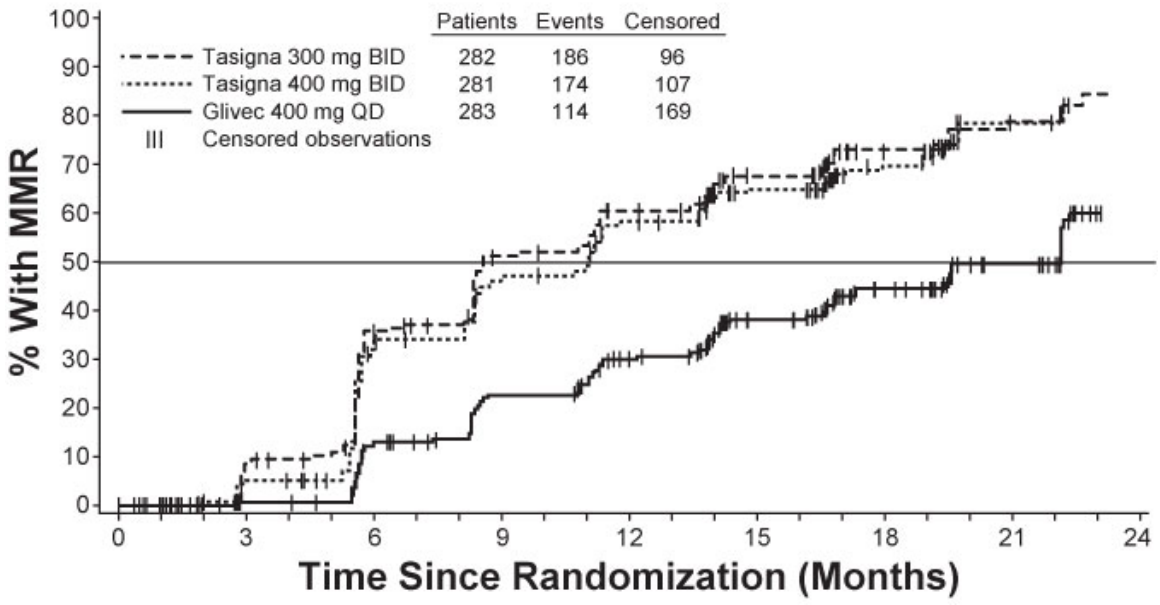
The Kaplan-Meier analyses of time to first MMR among all patients are graphically displayed in Figure 1. The probability of achieving MMR at different time points were higher in both nilotinib groups compared to the imatinib group (HR=2.42 and stratified log-rank p<0.0001 between nilotinib 300 mg twice daily and imatinib, HR=1.52 and stratified log-rank p<0.0001 between nilotinib 400 mg twice daily and imatinib). The proportions of patients who had BCR-ABL ratios falling into categories ≤ 0.01% (4-log reduction) and ≤0.0032% (4.5 log reduction) at 12 months were statistically significantly higher in both the nilotinib groups (11.7%/4.3% and 8.5%/4.6% respectively) compared to the imatinib group (3.9%/0.4%).

For all Sokal risk groups, the MMR rates at 12 months were higher in the two nilotinib groups than in the imatinib group.

Table 1 MMR rate at 12 months

	TASIGNA 300 mg twice daily N=282 n (%)	TASIGNA 400 mg twice daily N=281 n (%)	Glivec 400 mg once daily N=283 N (%)
Major Molecular Response	125(44.3)	120(42.7)	63(22.3)
95% CI for response	[38.4,50.3]	[36.8,48.7]	[17.6, 27.6]
CMH test p-value for response rate (vs. Glivec 400 mg)	<0.0001	<0.0001	
Difference in response rate (vs Glivec 400mg)	22.1	20.4	
95% CI for difference in response rate (%)	[14.5, 29.6]	[12.9, 28.0]	

Figure 1 Kaplan-Meier estimate of time to first MMR [80]



Complete Cytogenetic response (CCyR)

CCyR was defined as 0% Ph+ metaphases in the bone marrow based on a minimum of 20 metaphases evaluated. CCyR rate by 12 months (includes patients who achieved CCyR at or before the 12 month time point as responders) was statistically higher for both the nilotinib 300 mg twice daily and 400 mg twice daily groups compared to imatinib 400 mg once daily group, Table 2.

Table 2 CCyR rate by 12 months

	TASIGNA 300 mg twice daily N=282 n (%)	TASIGNA 400 mg twice daily N=281 n (%)	Glivec 400 mg once daily N=283 N (%)
Complete Cytogenetic Response	226 (80.1)	219 (77.9)	184 (65.0)
95% CI for response	[75.0,84.6]	[72.6,82.6]	[59.2,70.6]
CMH test p-value for response rate (vs. Glivec 400 mg)	<0.0001	0.0005	

18-month Update

At a median follow-up of 18 months, the nilotinib benefits in MMR and CCyR at 12 months were maintained. Progression to accelerated phase or blast crisis will be assessed at 24 months. Longer follow-up is needed to assess the durability of response and if it translates to increased survival.

Overall survival (OS)

A total of 16 patients died during treatment or during the follow-up after discontinuation of treatment. Eight (8) of these 16 deaths were related to CML (1 in the nilotinib 300 mg twice daily group, 1 in the nilotinib 400 mg twice daily group and 6 in the imatinib 400 mg once daily group). The estimated rates of patients alive at 18 months were 98.5%, 99.3% and 96.9%, respectively. There was a statistically significant difference in OS between nilotinib 400 mg twice daily and imatinib (p=0.0331). Considering only CML-related deaths as events, the estimated rates of OS at 18 months were 99.6%, 99.6% and 97.6%, respectively. The Kaplan-Meier p-values for OS for CML-related deaths were 0.0572 between nilotinib 300 mg twice daily and imatinib and 0.0564 between nilotinib 400 mg twice daily and imatinib.

Resistant or intolerant Ph+ CML

An open label uncontrolled multicentre Phase II study was conducted to determine the efficacy of Tasigna (400 mg twice daily) in patients with imatinib resistant or intolerant CML with separate treatment arms for chronic and accelerated phase disease. The study is ongoing. Efficacy was based on 321 chronic phase (CP) patients and 137 accelerated phase (AP) patients enrolled. Median age was 58 years (range 21 – 85 years), with 31% of patients ≥ 65 years of age. There were 48% females and 52% males; 89% caucasian, 4% asian and 5% black patients. Tasigna was administered on a continuous basis (400 mg twice daily at least 2 hours after a meal and with no food for at least one hour after administration) unless there was evidence of inadequate response or disease progression where dose escalation to 600 mg twice daily was allowed.

Table 3 Duration of Exposure with Tasigna®

	Chronic Phase N = 321	Accelerated Phase N = 137
Median duration of therapy in months (25th-75th percentiles)	18.4 (6.4-28.0)	8.7 (3.8-19.6)

The patients' CML disease history is given in Table 4. Resistance to imatinib included failure to achieve a complete haematological response (by 3 months), cytogenetic response (by 6 months) or major cytogenetic response (by 12 months) or progression of disease after a previous cytogenetic or haematological response. Imatinib intolerance included patients who discontinued imatinib because of toxicity and who were not in major cytogenetic response at time of study entry.

The majority of patients had a long history of CML that included extensive prior treatment with other antineoplastic agents including imatinib, hydroxyurea, interferon, and some who had even failed stem cell transplant (Table 4). The median highest prior imatinib dose had been 600 mg/day for both CP and AP patients, and the highest prior imatinib dose was >600 mg/day in 74% of all patients with 40% of patients receiving imatinib doses >800 mg/day.

Table 4 CML Disease History Characteristics

	Chronic Phase (n = 321)	Accelerated Phase (n = 137)
Median time since diagnosis in months (range)	58 (5-275)	71 (2-298)
Imatinib		
Resistant	226 (70%)	109 (80%)
Intolerant without MCyR	95 (30%)	27 (20%)
Median time of imatinib treatment in months (25th-75th percentiles)	32 (17-49)	28 (14-49)
Prior Hydroxyurea	83%	91%
Prior Interferon	58%	50%
Prior non-drug organ transplant	7%	8%

MCyR = major cytogenetic response

The primary endpoint in the CP patients was major cytogenetic response (MCyR), defined as elimination (CCyR, complete cytogenetic response) or significant reduction to <35% Ph+ metaphases (partial cytogenetic response) of Ph+ haematopoietic cells. Complete haematological response (CHR) in CP patients was evaluated as a secondary endpoint. For efficacy assessment, patients needed to have completed 6 months treatment or discontinued the study.

The primary endpoint in the AP patients was overall confirmed haematological response (HR), defined in this trial as either a complete haematological response, no evidence of leukaemia or return to chronic phase. For efficacy assessment, patients needed to have completed 4 months treatment, discontinued the study or achieved a complete haematological response.

Complete Haematologic Response (CHR) criteria: Chronic CML: White Blood Cell Count < 10 x 10^9 /L, no blasts or promyelocytes in peripheral blood, platelets < 450 x 10^9/L, < 5% myelocytes plus metamyelocytes in peripheral blood, basophils < 5% in bone marrow and peripheral blood, and no extramedullary involvement. Accelerated CML: Myeloblasts < 5% in bone marrow & 0 % in peripheral blood, Absolute Neutrophil Count ≥ 1.5 x 10^9/L, platelets ≥ 100 x 10^9/L , basophils < 5% in bone marrow and peripheral blood and no extramedullary involvement.

The rates of response for the Chronic Phase (CP) and Accelerated Phase (AP) treatment arms are reported in Table 5.

Table 5 Response in CML
Interim results of the intent-to-treat (ITT) analysis of patients with at least 24 months follow up

(Best Response Rate)	Chronic Phase			Accelerated Phase
	Intolerant (n = 95)	Resistant (n = 226)	Total (n = 321)	Total (n=137)
Haematologic Response (%)				
Overall (95%CI)	-	-	-	55 (47-64)
Complete	90 (79-97)	72 (64-79)	76[1] (70-82)	31
NEL	-	-	-	12
Return to chronic phase	-		-	12
Median time to HR (months)	-	-	1.0	1.0
Median duration of HR (months)	-	-	Not reached	21.5
Cytogenetic Response (%)				
Major (95%CI)	66 (56-76)	56 (49-63)	59 (54-65)	32 (24-41)
Complete	51	41	44	21
Partial	16	15	15	11
Median time to MCyR (months)	-	-	2.8	2.8
Median duration of MCyR (months)	-	-	Not reached	Not reached
Overall survival				
24 month overall survival rate (%) (Kaplan-Meier estimate)	-	-	87%	70%

NEL = no evidence of leukaemia/ marrow response; MCyR = major cytogenetic response; CHR = Complete Haematologic Response; HR = Haematologic Response
[1]This result is for patients who had not achieved a complete haematological response at study entry (n = 207)

Tasigna was investigated separately in CML-CP and CML-AP patients with extensive previous treatment including a tyrosine kinase inhibitor in addition to imatinib. The majority (83% of CML-CP patients and 85% of CML-AP patients) were imatinib-resistant and the remainder imatinib-intolerant. In the 22 CML-CP patients, (32%) achieved a MCyR with Tasigna. In those without a CHR at baseline (n=16), (50%) achieved a CHR. In the 11 CML-AP patients, (36%) achieved a confirmed HR and one (9%) a MCyR.

INDICATIONS

Tasigna is indicated for the:

- treatment of adult patients with newly diagnosed Philadelphia chromosome positive chronic myeloid leukaemia (CML) in chronic phase.
- treatment of adults with chronic phase and accelerated phase Philadelphia chromosome positive chronic myeloid leukaemia (CML) resistant to or intolerant of prior therapy including imatinib.

CONTRAINDICATIONS

Hypersensitivity to nilotinib or to any of the excipients.

PRECAUTIONS

Myelosuppression:

Treatment with Tasigna is often associated with NCI CTC (National Cancer Institute Common Toxicity Criteria) Grade 3 or 4 thrombocytopenia, neutropenia and anaemia. Occurrence is more frequent in patients with imatinib-resistant or intolerant CML and in particular in patients with CML-AP. Complete blood counts should be performed every two weeks for the first 2 months and then monthly thereafter, or as clinically indicated. Myelosuppression was generally reversible and usually managed by withholding Tasigna temporarily or dose reduction (see "DOSAGE AND ADMINISTRATION").

QT Prolongation:

In vitro data suggest that nilotinib has the potential to prolong cardiac ventricular repolarisation (QT interval).

In the Phase III study in newly diagnosed Ph+ CML-CP patients the change from baseline in mean time-averaged QTcF interval at steady state observed in the nilotinib 300 mg twice daily group was 6 msec. At the recommended dose of 300 mg twice daily no patient had an absolute QTcF of >480 msec and no events of Torsade de Pointes were observed.

In the Phase II study in imatinib-resistant and intolerant CML patients in chronic and accelerated phase, the change from baseline in mean time-averaged QTcF interval at steady state was 6 and 8 msec, respectively. QTcF of >500 msec was observed in 3 patients (<1% of patients in the Phase II study).

In a healthy volunteer study with exposures that were comparable to the exposures observed in patients, the time-averaged mean placebo-subtracted QTcF change from baseline was 7 msec (CI ± 4 msec). No subject had a QTcF >450 msec. In addition, no clinically relevant arrhythmias were observed during the trial. In particular, no episodes of torsade de pointes (either transient or sustained) were observed.

Significant prolongation of the QT interval may occur when Tasigna is inappropriately taken with food, and/or strong CYP3A4 inhibitors and/or medicinal products with a known potential to prolong QT. Therefore, co-administration with food must be avoided and concomitant use with strong CYP3A4 inhibitors and/or medicinal products with a known potential to prolong QT should be avoided (see "Interactions with Other Drugs"). The presence of hypokalaemia and hypomagnesaemia may further enhance this effect (see "DOSAGE AND ADMINISTRATION").

Tasigna should be used with caution in patients who have or who are at significant risk of developing prolongation of QTc, such as those:

- with long QT syndrome,
- with uncontrolled or significant cardiac disease including recent myocardial infarction, congestive heart failure, unstable angina or clinically significant bradycardia.

In clinical studies, patients with uncontrolled or significant cardiac disease including recent myocardial infarction, congestive heart failure, unstable angina, or clinically significant bradycardia were excluded.

Caution should be exercised in patients with relevant cardiac disorders.

Sudden Death

Uncommon cases (0.1 to 1%) of sudden death have been reported in patients in imatinib-resistant or – intolerant CML patients in chronic and accelerated phase receiving Tasigna with a past medical history of cardiac disease or significant cardiac risk factors. Comorbidities in addition to the underlying malignancy were also frequently present as were concomitant medications. Ventricular repolarization abnormalities may have been contributory factors. No cases of sudden deaths have been reported in the newly diagnosed Ph+ CML-CP Phase III study.

Lactose

Since the capsules contain lactose, Tasigna is not recommended for patients with rare hereditary problems of galactose intolerance, severe lactase deficiency or of glucose-galactose malabsorption.

Serum Lipase

Elevation in serum lipase has been observed. Caution is recommended in patients with previous history of pancreatitis. In case lipase elevations are accompanied by abdominal symptoms, doses should be interrupted and appropriate diagnostics should be considered in order to exclude pancreatitis. (see "DOSAGE AND ADMINISTRATION").

Electrolyte Abnormalities

The use of Tasigna can cause electrolyte imbalances commonly (see Adverse effects, Metabolism and Nutrition Disorders). Electrolyte abnormalities must be corrected prior to initiating Tasigna and monitored periodically during therapy.

Hepatotoxicity

Clinical studies showed a risk of increased total bilirubin, ALT and AST levels associated with nilotinib (see "ADVERSE EFFECTS").

Total gastrectomy

The bioavailability of nilotinib might be reduced in patients with total gastrectomy (see "PHARMACOLOGY"). More frequent follow up of these patients should be considered.

Tumour lysis sundrome

Cases of tumour lysis syndrome have been reported in patients treated with Tasigna. For monitoring recommendations please refer to "DOSAGE AND ADMINISTRATION".

Use in patients with hepatic impairment:

Hepatic impairment has a modest effect on the pharmacokinetics of nilotinib. Single dose administration of nilotinib resulted in increases in AUC of 35%, 35% and 19% in subjects with mild, moderate and severe hepatic impairment respectively, compared to a control group of subjects with normal hepatic function. The predicted steady-state C_{max} of nilotinib showed an increase of 29%, 18% and 22% respectively. Pharmacokinetic parameters were subject to high inter-subject variability.

Clinical studies have excluded patients with ALT and/ or AST >2.5 (or >5, if related to disease) times the upper limit of the normal range and/ or total bilirubin >1.5 times the upper limit of the normal range. Metabolism of nilotinib is mainly hepatic. Patients with hepatic impairment might therefore have increased exposure to nilotinib and should be treated with caution (see monitoring recommendations in "DOSAGE AND ADMINISTRATION").

Use in patients with renal impairment:

Clinical studies have not been performed in patients with impaired renal function. Clinical studies have excluded patients with serum creatinine concentration >1.5 times the upper limit of the normal range.

Since nilotinib and its metabolites are not renally excreted, a decrease in total body clearance is not anticipated in patients with renal impairment.

Use in elderly patients:

Approximately 12% and 30% of subjects in the clinical studies (newly diagnosed Ph+ CML-CP and resistant or intolerant Ph+ CML-CP and CML-AP) were 65 or over. No major differences were observed for safety and efficacy in patients ≥ 65 years of age as compared to adults 18 to 65 years.

Use in children:

Clinical studies have not been conducted in children and adolescents.

Effects on ability to drive and use machines

No studies on the effects of nilotinib on the ability to drive and operate machines have been performed. Patients experiencing dizziness, visual impairment or other undesirable effects with a potential impact on the ability to safely drive or use machines should refrain from these activities as long as these undesirable effects persist (see "ADVERSE EFFECTS").

Carcinogenicity

Carcinogenicity studies have not been performed.

Genotoxicity

Genotoxicity studies in bacterial and mammalian *in vitro* systems, with and without metabolic activation, and in a mammalian *in vivo test* did not reveal any evidence for a genotoxic potential of nilotinib.

Reproductive and developmental toxicity

Effect on Fertility

Impairment of fertility

In a fertility study in rats, no effects on sperm count/motility were noted in males and no effects on fertility were noted in males or females. The highest tested dose achieved an exposure (based on plasma AUC) of approximately 5 times that expected in humans at the recommended dose. Sexually active male or female patients taking Tasigna should use adequate contraception.

Use in Pregnancy (Category D)

There are no adequate data on the use of Tasigna in pregnant women. It should not be used during pregnancy. If the drug is used during pregnancy, the patient must be informed of the potential risk to the fetus.

In animal studies, nilotinib induced embryofeto toxicity at doses that also showed maternal toxicity. Increased postimplantation loss was observed in both the fertility study, which involved treatment of both males and females, and in the embryo toxicity study, which involved treatment of females. Embryo-lethality and fetal effects (mainly decreased fetal weights, and increased skeletal changes) in rats and increased resorption of fetuses and skeletal variations in rabbits were observed in the embryofetal toxicity studies. Exposure to nilotinib in females at No-Observed-Adverse-Effect-Levels was generally less than or equal to that in humans at 400 mg/b.i.d.

In a pre- and postnatal study, oral administration of nilotinib to female rats from day 6 of gestation to day 21 or 22 post partum resulted in maternal effects (reduced food consumption and lower body weight gains) and longer gestation period at 60 mg/kg. The maternal dose of 60 mg/kg was associated with decreased pup body weight and changes in some physical development parameters (the mean day for pinna unfolding, tooth eruption and eye opening was earlier). Adverse effects on the reproductive function of pups (lower mating and fertility indices) were also observed at the maternal dose of 60 mg/kg. The No-Observed-Adverse-Effect-Level in maternal animals and offspring was a maternal dose of 20 mg/kg (approximately 1.7 times the plasma AUC in patients at the recommended clinical dose).

Women of childbearing potential must be advised to use effective contraception during treatment with Tasigna.

Use in Lactation

It is not known whether nilotinib is excreted in human milk. Studies in animals demonstrate that it is excreted into milk. Women should therefore not breast-feed while taking Tasigna, as a risk to the infant cannot be excluded.

Interactions with Other Drugs

The administration of Tasigna with agents that are strong CYP3A4-inhibitors and drugs that may prolong the QT interval such as anti-arrhythmic medicines should be avoided (see "DOSAGE AND ADMINISTRATION"). Should treatment with any of these agents be required, it is recommended that therapy with Tasigna be interrupted if possible. If transient interruption of treatment with Tasigna is not possible, close monitoring of the individual for prolongation of the QT interval is indicated.

Concomitant use of Tasigna with medicinal products that are potent inducers of CYP3A4 is likely to reduce exposure to nilotinib to a clinically relevant extent. Therefore, in patients receiving Tasigna, concomitant use of alternative therapeutic agents with less potential for CYP3A4 induction should be selected.

Drugs that may increase nilotinib serum concentration

Nilotinib is mainly metabolised in the liver, and is also a substrate for the multi-drug efflux pump, P-glycoprotein (Pgp). Therefore, absorption and subsequent elimination of systemically absorbed nilotinib may be influenced by drugs that affect CYP3A4 and/or Pgp.

The bioavailability of nilotinib in healthy subjects was increased 3-fold when co-administered with the strong CYP3A4 inhibitor, ketoconazole. Concurrent treatment with strong CYP3A4 inhibitors should therefore be avoided (including but not limited to ketoconazole, itraconazole, voriconazole, ritonavir, clarithromycin, and telithromycin) (see "DOSAGE AND ADMINISTRATION" and "PRECAUTIONS, QT Prolongation"). Alternative concomitant medications with no or minimal CYP3A4 inhibition should be considered.

In a Phase I study of nilotinib given in combination with imatinib (a substrate and moderator of P-gp and CYP3A4), imatinib had a slight inhibitory effect on CYP3A4 and/or PgP. When the two drugs were administered concomitantly, the AUC of nilotinib was increased by 18% to 40%.

Drugs that may decrease nilotinib serum concentration

Inducers of CYP3A4 activity could increase the metabolism of nilotinib and thereby decrease serum concentrations of nilotinib. The concomitant administration of medications that induce CYP3A4 (e.g. phenytoin, rifampicin, carbamazepine, phenobarbital, and St. John's Wort) may reduce exposure to nilotinib. In patients for whom CYP3A4 inducers are indicated, alternative agents with less enzyme induction potential should be considered.

In healthy subjects receiving the CYP3A4 inducer, rifampicin, at 600 mg daily for 12 days, systemic exposure (AUC) to nilotinib was decreased approximately 80%.

Nilotinib has pH-dependent solubility, with lower solubility at higher pH. In healthy subjects receiving esomeprazole at 40 mg once daily for 5 days, gastric pH was markedly increased, but nilotinib absorption was only decreased modestly (27% decrease in C_{max} and 34% decrease in $AUC_{0-\infty}$). TASIGNA may be used concurrently with esomeprazole or other proton pump inhibitors as needed.

Drugs that may have their systemic concentrations altered by nilotinib

Nilotinib is a competitive inhibitor of CYP3A4, CYP2C8, CYP2C9, CYP2D6 and UGT1A1 *in vitro*, with Ki value being lowest for CYP2C9 (Ki=0.13 microM). Caution should be exercised when co-administering Tasigna with drugs with a low therapeutic index which are substrates for the enzymes known to be inhibited by Tasigna (e.g. astemizole, terfenadine, cisapride, cyclosporine, fentanyl, pimozide, quinidine and ergot alkaloids). Some of these drugs also prolong the QT interval, hence ECG monitoring should also be done if alternative drugs cannot be used.

A single-dose drug-drug interaction study in healthy subjects with warfarin 25 mg, a sensitive CYP2C9 substrate, and nilotinib 800 mg did not result in any changes in warfarin pharmacokinetics (C_{max}, $AUC_{0-\infty}$) or warfarin pharmacodynamics (prothrombin time [PT] and international normalised ratio [INR]). The single-dose drug-drug interaction study suggests that Tasigna can be used concurrently with warfarin (up to a dose of 25 mg) without increasing the anti-coagulant effect of warfarin. There are no steady-state pharmacokinetic or pharmacodynamic interaction data for co-administration of nilotinib and warfarin. Consequently, monitoring and control of warfarin pharmacodynamic markers (INR or PT) following initiation of nilotinib therapy (at least during the first 2 weeks) is recommended.

Single-dose administration of nilotinib 600 mg with midazolam 4 mg (a CYP3A substrate) to healthy subjects increased midazolam exposure by 30%. There are no steady-state pharmacokinetic interaction data for co-administration of nilotinib and midazolam. Consequently, it is possible that greater exposure to midazolam might occur with steady –state co-administration of nilotinib and midazolam.

Nilotinib is an inhibitor of P-glycoprotein *in vitro* at clinically relevant concentrations and may potentially influence the absorption/elimination and subsequent serum concentrations of concomitantly-administered drugs that are substrates for this multi-drug efflux pump. Concomitant administration of nilotinib with imatinib, increased the AUC of imatinib by 18% to 39%.

Anti-arrhythmic medicines and other drugs that may prolong QT

Concomitant use of anti-arrhythmic medicines (including, but not limited to amiodarone, disopyramide, procainamide, quinidine and sotalol) and other drugs that may prolong the QT interval (including, but not limited to chloroquine, halofantrine, clarithromycin, haloperidol, methadone, moxifloxacin, bepridil and pimozide) should be avoided (see "PRECAUTIONS").

Other interactions that may affect serum concentrations

The absorption of nilotinib is increased if it is taken with food, resulting in higher serum concentration (see "DOSAGE AND ADMINISTRATION", and "Pharmacokinetics").

Tasigna must not be taken in conjunction with food and should be taken 2 hours after a meal. No food should be consumed for at least one hour after the dose is taken. Grapefruit juice and other foods that are known to inhibit CYP3A4 should be avoided at any time.

Solubility of nilotinib decreases with increasing pH and is practically insoluble in buffer solutions of pH 4.5 or higher. Hence, simultaneous treatment with nilotinib and antacids should be avoided. If antacid therapy is needed, the antacid dose should be administered at least 2 hours prior to or 2 hours after Tasigna dosing. Long-term suppression of gastric acid secretion by proton-pump inhibitors or H2-blockers may reduce nilotinib exposure and so concomitant use of H2-blockers and proton-pump inhibitors should be avoided.

ADVERSE EFFECTS

The data reported in this section reflect exposure to Tasigna in two trials, a randomised controlled trial in newly diagnosed patients with Ph+ CML-CP (n=279) and an uncontrolled trial in patients with Ph+ CML-CP and CML-AP resistant or intolerant to imatinib (n=458). The dose of Tasigna in new patients was 300 mg twice daily and the dose in previously treated patients 400 mg twice daily. The median duration of treatment in new patients was 18.6 months and, in previously treated patients, 18.4 months and 8.7 months respectively in CML-CP and CML-AP.

Haematological, gastrointestinal and skin reactions together with headache, fatigue and myalgia occurred very commonly with Tasigna in both new and previously treated patients. A list of reactions to Tasigna follows.

The following adverse drug reactions were reported in patients in the Tasigna clinical studies at the recommended doses at the following frequency (very common is ≥ 1/10; common is ≥ 1/100 and < 1/10; uncommon is >1/1,000 and <1/100; single events are captured as Unknown in frequency). These adverse reactions are included based on clinical relevance and ranked in order of decreasing seriousness within each category.

Infections and Infestations:

Common: folliculitis
Uncommon: pneumonia, urinary tract infection, gastroenteritis, upper respiratory tract infection (including pharyngitis, nasopharyngitis, rhinitis)
Unknown frequency: sepsis, bronchitis, herpes virus infection, candidiasis, subcutaneous abscess, anal abscess, furuncle, tinea pedis

Neoplasms Benign, Malignant and Unspecified:

Common: skin papilloma
Unknown frequency: papilloma

Blood and Lymphatic System Disorders:

Very Common: neutropenia, thrombocytopenia
Common: febrile neutropenia, pancytopenia lymphopenia, anaemia
Uncommon: haemoglobin decreased
Unknown frequency: thrombocythaemia, leukocytosis

Immune System Disorders:

Unknown frequency: hypersensitivity

Endocrine Disorders:

Uncommon: hyperthyroidism, hypothyroidism
Unknown frequency: hyperparathyroidism secondary, thyroiditis, blood parathyroid hormone increased

Metabolism and Nutrition Disorders:

Common: electrolyte imbalance (including hyperkalaemia, hypokalaemia, hyponatraemia, hypocalcaemia, hypercalcaemia, hypophosphataemia, hyperphosphataemia, hypomagnesaemia), hyperglycaemia, diabetes mellitus, hypercholesterolaemia, hyperlipidaemia

Uncommon: decreased appetite, increased appetite, dehydration, blood glucose decreased
Unknown frequency: hyperuricemia, gout, hypoglycemia, dyslipidemia, blood insulin increased

Psychiatric Disorders:

Common: insomnia, depression
Uncommon: anxiety
Unknown frequency: confusional state, disorientation, amnesia, dysphoria

Nervous System Disorders:

Very common: headache
Common: dizziness, hypoaesthesia, paraesthesia
Uncommon: intracranial haemorrhage, migraine, loss of consciousness (including syncope), tremor, disturbance in attention, hyperaesthesia
Unknown frequency: brain oedema, peripheral neuropathy, optic neuritis, lethargy, dysaesthesia

Eye Disorders:

Common: eye haemorrhage, periorbital oedema, eye pruritus, conjunctivitis, dry eye
Uncommon: vision impairment, vision blurred, visual acuity reduced, eyelid oedema, photopsia, eye irritation
Unknown frequency: papilloedema, diplopia, vision blurred, photophobia, eye swelling, blepharitis, eye pain, chorioretinopathy, conjunctival haemorrhage, conjunctivitis allergic, conjunctival hyperaemia, ocular hyperaemia, ocular surface disease, scleral hyperaemia

Ear and Labyrinth Disorders:

Common: vertigo
Unknown frequency: hearing impaired, ear pain, tinnitus

Cardiac Disorders:

Common: angina pectoris, arrhythmia (including atrioventricular block, cardiac flutter, extrasystoles, atrial fibrillation, bradycardia), palpitations, electrocardiogram QT prolonged
Uncommon: cardiac failure, pericardial effusion, coronary artery disease, cardiomegaly, cyanosis, cardiac murmur,
Unknown frequency: myocardial infarction, pericarditis, ventricular dysfunction, cardiac flutter, ejection fraction decrease, blood pressure increased, troponin increased

Vascular Disorders:

Common: flushing, hypertension,
Uncommon: hypertensive crisis, haematoma, peripheral arterial occlusion disease

Unknown frequency: shock haemorrhagic, hypotension, thrombosis

Respiratory, Thoracic and Mediastinal Disorders:

Common: dyspnoea, dyspnoea exertional, epistaxis, cough, dysphonia
Uncommon: pharyngolaryngeal pain, pleural effusion, interstitial lung disease, pleuric pain, pleurisy, pulmonary oedema, throat irritation
Unknown frequency: pulmonary hypertension, wheezing

Gastrointestinal Disorders:

Very common: nausea, constipation, diarrhoea, lipase increased
Common: abdominal discomfort, dyspepsia, flatulence, vomiting, abdominal pain, abdominal distension, pancreatitis, blood amylase increased
Uncommon: gastroesophageal reflux, gastrointestinal haemorrhage, melaena, mouth ulceration, stomatitis, oesophageal pain, dysgeusia, dry mouth
Unknown frequency: gastric ulcer, gastrointestinal ulcer perforation, retroperitoneal haemorrhage, haematemesis, oesophagitis ulcerative, subileus, gastritis, haemorrhoids, hiatus hernia, rectal haemorrhage, sensitivity of teeth, gingivitis

Hepatobiliary Disorders:

Common : alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased, blood bilirubin increased, blood alkaline phosphatase increased, gamma-glutamyltransferase increased, hepatic function abnormal
Uncommon: hepatitis, jaundice, blood lactate dehydrogenase increased, blood creatinine increased, blood urea increased
Unknown frequency: cholestasis, hepatotoxicity, hepatomegaly, blood bilirubin unconjugated increased, very low density lipoprotein

Skin and Subcutaneous Tissue Disorders:

Very common: rash, pruritus
Common: dry skin, night sweats, hyperhidrosis, eczema, urticaria, erythema, alopecia, dermatitis, contusion, acne
Uncommon: exfoliative rash, drug eruption, pain of skin, swelling face, ecchymosis
Unknown frequency: erythema nodosum, skin ulcer, petechiae, photosensitivity, blister, dermal cyst, sebaceous hyperplasia, skin atrophy, skin discolouration, skin exfoliation, skin hyperpigmentation, skin hypertrophy, palmar-plantar erthrodysaesthesia syndrome

Musculoskeletal and Connective Tissue Disorders:

Common: musculoskeletal chest pain, musculoskeletal pain, flank pain, myalgia, arthralgia, muscle spasms, bone pain , blood creatine kinase (CK) increased
Uncommon: muscular weakness, musculoskeletal stiffness, joint swelling
Unknown frequency: arthritis

Renal and Urinary Disorders:

Common: pollakiuria
Uncommon: dysuria, micturition urgency, nocturia,
Unknown frequency: renal failure, haematuria, urinary incontinence, crematoria

Reproductive System and Breast Disorders:

Uncommon: breast pain, erectile dysfunction, gynaecomastia.
Unknown frequency: breast induration, menorrhagia, nipple swelling

General Disorders and Administration Site Conditions:

Very common: fatigue
Common: pyrexia, chest pain, neck pain, back pain, chest discomfort, asthenia, peripheral oedema, weight decreased, weight increased.
Uncommon: influenza-like illness, face oedema, gravitational oedema, chills, malaise
Unknown frequency: feeling hot, localised oedema

Comparison of Common Non-Laboratory Adverse Reactions in Clinical Trials

Table 6 Most Frequently Reported Non-haematologic Adverse Drug Reactions (≥5% in any TASIGNA Group)

			Newly Diagnosed Ph+ CML-CP						Resistant or Intolerant Ph+ CML-CP and CML-AP			
			TASIGNA 300 mg twice daily	TASIGNA 400 mg twice daily	GLIVEC 400 mg once daily	TASIGNA 300 mg twice daily	TASIGNA 400 mg twice daily	GLIVEC 400 mg once daily	TASIGNA 400 mg twice daily			
			ALL GRADES (%)			GRADE 3 or 4 (%)			ALL GRADES (%)	GRADE 3/4 (%)	CML-CP GRADE 3/4 (%)	CML-AP GRADE 3/4 (%)
System Organ Class	**Frequency**	**Adverse Reaction**	**N=279 %**	**N=277 %**	**N=280 %**	**N=279 %**	**N=277 %**	**N=280 %**	**N=458 %**	**N=458 %**	**N=321 %**	**N=137 %**
Metabolism and nutrition disorders	Common	Anorexia	2	3	2	0	0	0	7	<1	<1	0
Nervous system disorders	Very common	Headache	14	22	8	1	1	0	15	1	2	<1
Gastrointestinal disorders	Very common	Nausea	12	20	33	<1	1	0	20	<1	<1	<1
	Very common	Constipation	9	6	<1	0	<1	0	12	<1	<1	0
	Very common	Diarrhoea	8	7	24	<1	0	1	11	2	2	<1
	Common	Vomiting	5	9	16	0	1	0	10	<1	<1	0
	Common	Abdominal pain upper	9	6	5	<1	0	<1	5	<1	<1	0
	Common	Abdominal pain	5	4	3	0	<1	0	6	<1	<1	<1
	Common	Dyspepsia	4	5	4	0	0	0	3	0	0	0
Skin and subcutaneous tissue disorders	Very common	Rash	32	37	12	<1	3	1	28	1	2	0
	Very common	Pruritus	15	13	5	<1	<1	0	24	<1	<1	0
	Very common	Alopecia	8	13	4	0	0	0	9	0	0	0
	Common	Dry Skin	8	9	3	0	0	0	5	0	0	0
	Common	Erythema	2	5	2	0	0	0	5	<1	<1	0
Musculoskeletal and connective tissue disorders	Very common	Myalgia	10	10	10	<1	0	0	10	<1	<1	<1
	Common	Arthralgia	7	8	8	0	0	0	7	<1	1	0
	Common	Muscle spasms	7	6	26	0	<1	<1	8	<1	<1	0
	Common	Bone pain	4	4	3	0	0	<1	6	<1	<1	0
	Common	Pain in extremity	4	2	7	0	<1	<1	5	<1	<1	<1
General disorders and administration site conditions	Very common	Fatigue	11	9	9	0	<1	<1	17	1	1	<1
	Common	Asthenia	8	5	7	<1	<1	0	6	0	0	0
	Common	Oedema peripheral	5	6	14	0	0	0	6	0	0	0

Comparison of severe Laboratory Abnormalities in Clinical Trials

Table 7 Grade 3/4 Laboratory Abnormalities

	Newly diagnosed Ph+ CML-CP			Resistant or intolerant Ph+	
	TASIGNA 300mg twice daily N=279	**TASIGNA 400mg twice daily N=277**	**GLIVEC 400mg once daily N=280**	**CML-CP N=321 %**	**CML-AP N=137 %**
Haematological Parameters					
Myelosuppression					
-Neutropenia	12%	10%	20%	31%	42%
-Thrombocytopenia	10%	12%	9%	30%	42%
-Anaemia	4%	4%	5%	11%	27%
Biochemistry Parameters					
-Elevated creatinine	0%	0%	<1%	1%	<1%%
-Elevated lipase	7%	7%	3%	18%	18%
-Elevated AST	1%	3%	1%	3%	2%
-Elevated ALT	4%	9%	3%	4%	4%
-Hypophosphatemia	5%	6%	8%	17%	15%
-Elevated Bilirubin (total)	4%	8%	<1%	7%	9%
-Hyperglycemia	6%	4%	0%	12%	6%
-Hyperkalemia	2%	<1%	1%	6%	4%
-Hyponatremia	<1%	<1%	<1%	7%	7%
-Hypokalemia	<1%	1%	1%	2%	9%
-Decreased albumin	0	0	0	4%	3%
-Hypocalccemia	<1%	<1%	0	2%	5%
Elevated alkaline phosphatase	0	0	<1%	<1%	1%

Postmarketing Experience:

The following adverse reactions have been derived from spontaneous case reports literature cases, expanded access programs, and clinical studies other than the global registration trials. Because these reactions are reported from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to nilotinib exposure.

Frequency unknown: cases of tumour lysis syndrome have been reported in patients treated with Tasigna.

DOSAGE AND ADMINISTRATION

Therapy should be initiated by a physician experienced in the treatment of patients with CML and should continue as long as the patient continues to benefit.

Tasigna should be taken twice daily taken approximately 12 hours apart, and must not be taken with food. No food should be consumed for at least 2 hours before and 1 hour after the dose is taken (see "PRECAUTIONS" and "Pharmacokinetics"). The capsules should be swallowed whole with water.

Tasigna may be given in combination with haematopoietic growth factors such as erythropoietin or G-CSF if clinically indicated. Tasigna may be given with hydroxyurea or anagrelide if clinically indicated.

Patients with newly diagnosed Ph+ CML-CP

The recommended dose of Tasigna is 300 mg twice daily (see "Pharmacokinetics").

Patients with Ph+CML –CP and CML-AP resistant to or intolerant to at least one prior therapy including imatinib

The recommended dose of Tasigna is 400 mg twice daily (see "Pharmacokinetics").

Monitoring recommendations and dose adjustments

A baseline ECG is recommended prior to initiating therapy with Tasigna and should be repeated after 7 days and as clinically indicated. Hypokalaemia or hypomagnesaemia must be corrected prior to Tasigna administration and potassium and magnesium blood levels should be monitored periodically during therapy, particularly in patients at risk for these electrolyte abnormalities (see "PRECAUTIONS").

Due to possible occurrence of Tumour Lysis Syndrome (TLS) correction of clinically significant dehydration and treatment of high uric acid levels are recommended prior to initiating therapy with Tasigna (see "ADVERSE EFFECTS").

Tasigna may need to be temporarily withheld and/or dose reduced for haematological toxicities (neutropenia, thrombocytopenia) that are not related to underlying leukaemia (Table 8)

Table 8 Dose Adjustments for Neutropenia and Thrombocytopenia

Newly diagnosed CML in chronic phase at 300 mg twice daily Resistant or intolerant CML in chronic Phase CML at 400 mg twice daily	ANC* < 1.0 x 10^9/L or platelet counts < 50 x 10^9/L	1. Stop Tasigna, and monitor blood counts 2. Resume within 2 weeks at prior dose if ANC > 1.0 x 10^9/L and/or platelets > 50 x 10^9/L 3. If blood counts remain low, a dose reduction to 400 mg once daily may be required
Resistant or intolerant CML in accelerated Phase at 400 mg twice daily	ANC* < 0.5 x 10^9/L and/or platelet counts < 10 x 10^9/L	1. Stop Tasigna, and monitor blood counts 2. Resume within 2 weeks at prior dose if ANC > 1.0 x 10^9/L and/or platelets > 20 x 10^9/L 3. If blood counts remain low, a dose reduction to 400 mg once daily may be required

*ANC = absolute neutrophil count

If clinically significant moderate or severe non-haematological toxicity develops, dosing should be interrupted, and may be resumed at 400 mg once daily once the toxicity has resolved. If clinically appropriate, re-escalation of the dose to 300 mg (newly diagnosed Ph+ CML-CP) or 400 mg (resistant or intolerant Ph+ CML-CP and CML-AP) twice daily should be attempted.

Elevated serum lipase: For Grade 3 or 4 lipase elevations, doses should be reduced to 400 mg once daily or interrupted. Serum lipase levels should be tested monthly or as clinically indicated (see “PRECAUTIONS” and “ADVERSE EFFECTS”).

Elevated bilirubin and hepatic transaminases: For Grade 3 or 4 bilirubin or hepatic transaminase elevations, doses should be reduced to 400 mg once daily or interrupted. Bilirubin and hepatic transaminases levels should be tested monthly or as clinically indicated (see “ADVERSE EFFECTS”).

If a dose is missed the patient should not take an additional dose, but take the usual prescribed next dose.

OVERDOSAGE

Isolated reports of intentional overdose with nilotinib were reported, where an unspecified number of Tasigna capsules were ingested in combination with alcohol and other drugs.

Events included neutropenia, vomiting and drowsiness. No ECG changes or hepatotoxicity were reported. Outcomes were reported as recovered.

In the event of overdose, the patient should be observed and appropriate supportive treatment given.

PRESENTATION AND STORAGE CONDITIONS

Tasigna 150 mg: white to yellowish powder in red opaque hard gelatin capsules, size 1 with black axial imprint "NVR/BCR"

Tasigna 200 mg: white to slightly yellowish powder in light yellow opaque hard gelatin capsules, size 0 with red axial imprint "NVR/TKI"

Tasigna is available in 28's (weekly), 40's, 42's and 112's and 120's (monthly) packs.
The weekly pack contains 2 calendar cards (daytime and night time) of 14 capsules or a carton of 28 capsules.
The monthly pack consists of 4 packs of 28 capsules or 3 packs of 40 capsules.

Storage: Store below 30 degrees Celsius.

POISON SCHEDULE

Poison Schedule: S4

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