SCIENTIFIC DISCUSSION

1. Introduction

Chronic myelogenous leukaemia (CML) is one of several chronic myeloproliferative diseases, a family of clonal disorders of pluripotential hematopoetic stem cells in the marrow. CML has a yearly incidence of 1 in 100 000 in Western countries and its frequency increases steadily with age (Greer JP 2004). It is uncommon in children and accounts for less than 5 % of all childhood leukemias (Rowe and Lichtman 1984). In the population, men are affected more than women (3:2) (Moloney 1977).

A reciprocal chromosome translocation t(9;22), in which the ABL proto-oncogene on chromosome 9 is translocated near the BCR gene on chromosome 22, is the main cause of CML. This genetic alteration, called the Philadelphia chromosome (Ph), results in the formation of a chimeric fusion protein, BCR-ABL (Rowley 1973; Ren 2005). The presence of the Ph chromosome results in an uncontrolled protein phosphorylation of BCR-ABL, rendering it constitutively activated. The BCR-ABL fusion protein is present in more than 90% of CML patients.

CML is characterized by an overproduction of immature myeloid cells and mature granulocytes in the spleen, bone marrow and peripheral blood. These cells have few, if any, morphologic or functional abnormalities. However, if untreated CML progresses and may lead to a disorder associated with bone marrow failure or transformation to acute leukaemia. There are three phases of the disease: a chronic phase (CP), an accelerated phase (AP) and the blast crisis phase (BC). From an initial CP of 4-6 years, CML progresses into the AP marked by the presence of primitive blast cells in the bone marrow and peripheral blood. Finally, the terminal BC phase is characterized by the presence of over 30% of undifferentiated blasts in the bone marrow and peripheral blood (Kantarjian and Talpaz 1988). Usually, patients in the BC phase have a median survival of 18 weeks.

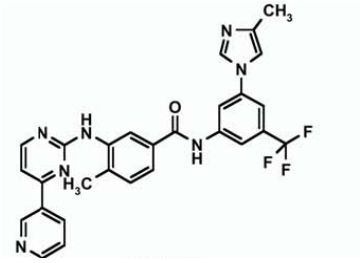
The BCR-ABL inhibitor imatinib mesylate (Glivec) is now the treatment of choice for CML. A high percentage (89%) of newly diagnosed patients with CML are alive after five years of therapy with imatinib (Druker, Guilhot et al. 2006) and the median survival of patients with AP CML is 42.6 months (Silver 2004). The annual rate of progression to AP/BC ranges from 1.5% in the first year, 2.8% in the second year to 0.6% in the fifth year in newly diagnosed patients (Druker, Guilhot et al. 2006). In patients with AP, the estimated rate of progression is 73% at 4 years (Silver 2004). All patients with BC will ultimately progress and die of their disease.

Nilotinib was developed as a second-generation inhibitor of BCR-ABL tyrosine kinase that would be effective in patients with imatinib-resistant or -intolerant CML. Imatinib resistance results from the emergence of point mutations within the kinase domain of BCR-ABL that reduce the binding affinity of the drug (Cowan-Jacob, Guez et al. 2004; Hochhaus and La Rosee 2004). Currently, the only therapy for these patients is dasatinib (Sprycel), a drug recently approved in Europe and US.

Other non-targeted therapeutic options for the management of these patients include hydroxyurea, low dose Ara-C, IFN-α, and multi-agent chemotherapy (usually for advanced phases of the disease). Ultimately, bone marrow transplantation is the most effective therapy for these patients, but its use is limited to young patients who have a suitable donor and can cope with significant toxicities.

About the product

Nilotinib, a synthetic aminopyrimidine, is an ATP-competitive inhibitor for BCR-ABL. Nilotinib is highly selective for BCR-ABL, binding to wild-type BCR-ABL with 20 times the affinity of imatinib, and has *in vitro* activity against many imatinib-resistant mutants. Nilotinib also has increased potency as compared to imatinib, giving it a broader spectrum of activity against BCR-ABL *in vitro* against all but the T315I mutation (also demonstrates resistance to other tyrosine kinase inhibitors). This is expected to result in a clinical benefit for CML-CP and CML-AP patients that are imatinib-resistant or -intolerant.



Nilotinib

2. Quality aspects

Introduction
Nilotinib has been formulated as 200 mg hard capsules for oral administration in the treatment of chronic phase and accelerated phase Philadelphia chromosome positive chronic myelogenous leukemia in patients resistant to or intolerant of at least one prior therapy including imatinib.

Active Substance
The chemical name of nilotinib hydrochloride monohydrate is 4-methyl-N-[3-(4-methyl-1H-imidazol-1-yI)-5-(trifluoromethyl)phenyl]-3-[(4-pyridin-3-ylpyrimidin-2-yl)amino]benzamide hydrochloride monohydrate, and corresponds to the molecular formula: $C_{28}H_{22}F_3N_7O \cdot HCl \cdot H_2O$. It does not contain a chiral centre and no tautomerism is possible. The molecular mass is 583.99 (as monohydrate) and 565.98 (as anhydrate). It appears as a white to slightly yellowish or slightly greenish yellowish powder.
The solubility of nilotinib hydrochloride monohydrate in aqueous solutions at 25°C strongly decreases with increasing pH, and it is practically insoluble in buffer solutions of pH 4.5 and higher pH values. Nilotinib is sparingly soluble in ethanol and methanol.
The pKa_1 for nilotinib hydrochloride monohydrate is 2.1, and pKa_2 is around 5.4.
The distribution coefficient (D) for nilotinib hydrochloride monohydrate in n-octanol / 0.1 N HCl buffer at 37.0 ± 0.5 °C was determined to be 0.08, and the corresponding Log D -1.1.
The active substance has no asymmetric carbons and is, consequently, not optically active.
Several crystal hydrates and solvates of nilotinib hydrochloride monohydrate have been found to date. The different crystalline Forms A, B, C and amorphous have been characterized. Form A corresponds to a dihydrate form. Form B and Form C are monohydrate forms obtained after desolvation of different solvates.
Form B, isolated from the synthetic process and used in the medicinal product, is the most stable form. It shows the least hygroscopic behaviour of all the three crystalline forms A, B, and C. No transformation was observed after storing these three forms at room temperature even for several months.

- Manufacture

The procedure for the manufacture of nilotinib hydrochloride monohydrate involves four synthetic transformations and one sieving step. Reprocessing may take place according to the above procedure, starting at an appropriate stage.
Altogether thirty nine batches of the nilotinib active substance have been manufactured during development and launch. Following the production of the first batch, manufacturing has been transferred to a different site where slight modifications to the synthesis were implemented.
The particle size of the sieved active substance is routinely determined by laser light diffraction. The current particle size requirements for nilotinib hydrochloride monohydrate were set, basically, on technological considerations.

The process validation results show that manufacturing process is reproducible and well controlled within the pre-determined manufacturing acceptance criteria.

- Specification

The specification for the control of the active substance includes tests for Appearance (visual examination), Particle size (laser light diffraction), Clarity and Colour of the solution (Ph. Eur.), Identity (IR, X-ray diffraction), Impurities (HPLC), Residual solvents (GC), Water (Karl Fischer) Sulfated ash (Ph. Eur.), Heavy metals (Ph. Eur.), Microbial limit test (Ph. Eur.), Assay of salt forming agent (potentiometric titration) and Assay (HPLC).
Two different HPLC methods have been developed and are utilised for the determination of the impurities. One of these methods is also used for the Assay test.
The batch analysis results from 39 batches manufactured by the commercial process indicate that the manufacturing process is under control.

- Stability

3 pilot batches manufactured by the commercial process have been stored at -20°C, 5°C, 25°C/60%RH, 30°C/65%RH for 12 months and at 40°C/75%RH for 6 months in the proposed market packaging. Due to the slight hygroscopicity and the slight hydrolysis of the active substance observed, appropriate packaging allowing minimal water permeation is necessary for Nilotinib hydrochloride monohydrate.
Comparative stability tests for up to 6 months have been performed between two packaging materials at different conditions. Both packaging options can be used for the commercial active substance. Additional packaging materials such (for stress testing) have also been tested. The stability studies are planned to continue up to 60 months at -20°C, 5°C and 25°C/60% RH.
No significant changes are observed at ICH conditions when stored in the proposed packaging materials. All quality parameters tested comply with the requirements after storage of the active substance at the given storage conditions.

Stress testing (solid state, forced decomposition and hygroscopicity) and photostability in accordance with ICH conditions have also been performed at different conditions.
After 1 month storage all quality parameters tested comply with the requirements regardless of the storage conditions. Some changes related to water content and to hydrolysis to different extents were observed. However, this observation is in agreement with other stability findings that dictated the use of packaging material with very low water permeability.
The results from photostability studies did not show significant change in stability indicating parameters. The active substance is considered slightly light sensitive.

In conclusion, the stability data provided indicate that the active substance remain stable at different storage conditions and support the proposed retest period and storage conditions.

Medicinal Product

- Pharmaceutical Development

The objective of the development was to develop an immediate release solid dosage form for oral administration by taking the following prerequisites into account:

- High dose to be administered (maximum daily dose = 1200 mg of active substance)
- Active substance is slightly soluble at pH 1 but practically insoluble at pH 6.8
- Tendency of active substance to agglomeration and electrostatic behaviour, low bulk density of active substance

From the existing polymorphic forms, form B, a monohydrate form of nilotinib hydrochloride, has been selected for development and has been used over the toxicity and clinical program. It shows least hygroscopic behaviour among the existing crystalline forms. In development of the active substance no transformation of the polymorphic form has been observed.
Nilotinib hydrochloride monohydrate is characterized as a Class IV compound (low / moderate aqueous solubility and low permeability) according to the Biopharmaceutical Classification System (BCS).

The impact of the particle size on the drug release kinetics has been assessed by testing the dissolution rate of product manufactured with active substance of different particle sizes. It could be observed that the particle size has no impact on the dissolution characteristics of the medicinal product. Based on these results the limits for particle size were set on technological considerations only, i.e. to limit the amount of coarse particles of the active substance and thus to ensure an appropriate content uniformity of the medicinal product and to control the electrostatic behaviour of the active substance resulting in acceptable flow properties of the final blend. The particle size of the sieved active substance is routinely determined by laser light diffraction.

Appropriate compatibility studies have been carried out and it was shown that nilotinib is compatible with all the excipients tested. The finally selected excipients are commonly used for solid oral dosage forms and in compliance with internationally accepted pharmacopoeial standards. There are no known excipient-excipient incompatibilities among the chosen excipients.
Considering the high amount of active substance per dosage unit and its physical characteristics (tendency to agglomeration and electrostatic behaviour, low bulk density), aqueous granulation was the method of choice for the manufacture of the capsule fill mass to allow the use of an acceptable capsule size for the selected dosage strength of 200 mg.
Differences between the clinical formulation and the formulation to be marketed were discussed and the biopharmaceutical equivalence appropriately demonstrated

- Adventitious Agents

Magnesium stearate is of vegetable origin. Lactose monohydrate and gelatin in the capsule shells are of animal origin.
Lactose monohydrate is of pharmaceutical grade derived from bovine milk sourced from healthy animals and under the same conditions as milk collected for human consumption as per the relevant EU Regulation (EC) No 999/2001 of 22 May 2001.
For the gelatin in the capsules valid CEPs have been presented.

- Manufacture of the Product

The manufacturing process of Tasigna is a standard process including aqueous wet granulation, drying, screening, mixing and encapsulation. Therefore manufacturing process development was focused on the evaluation of critical process parameters.
The applicable process parameters were established based on the experiments performed during laboratory, pilot and pre-validation phases. The data gathered during process validation and the provided batch analyses demonstrates that the manufacturing process of Tasigna 200 mg hard capsules is robust and consistently yields medicinal product, which meets the predetermined quality characteristics. The chosen in-process controls have been shown to be suitable for monitoring the manufacturing process.

- Product Specification

The specification for batch release and shelf-life include the following tests: Appearance (visual examination), Identification (UV and HPLC), Mean mass of the capsule content (weighing) , Dissolution (Ph.Eur.), Impurities (HPLC), Microbial limit tests (Ph.Eur.), Uniformity of dosage units (Ph. Eur.), Assay (HPLC). Two different HPLC methods are applied for the determination of the impurities.
Batch analyses for nine batches, manufactured by the commercial manufacturing chain, have been provided. All results meet the specifications and provide evidence that the quality of the finished product is properly controlled by the analytical methods and the set specifications. In addition, they demonstrate the reproducibility of the manufacturing process for the medicinal product.

- Stability of the Product

Three pilot batches and three full scale production batches have been put into stability study. The six batches have been manufactured at the commercial facilities to the final commercial process.
All batches have been placed on long term testing at 25°C/60% RH and 30°C/75% RH, accelerated testing at 40°C/75% RH, as well as testing at other temperatures (e.g. -20°C, 5°C and 50°C) and special tests (e.g. photostability and microbial limit tests).
Up to 12 months of stability data for the pilot batches and up to 6 months for the full scale production batches are presented in this application. Batches stored in the three different blister packaging but

data were presented only for two of them. Parameters investigated: Assay, degradation products, appearance, mean mass, dissolution and microbiological purity.

All results met the requirements at long term storage conditions (25°C/60% RH and 30°C/75% RH). Some gelatin shell cross linking was observed which was always reversible after addition of pepsin to the dissolution medium as recommended according to USP.
At accelerated storage conditions gelatin shell cross linking was also observed. For some samples cross linking could not be reversed by addition of pepsin and thus did not comply with the specifications.
The cross linking of the gelatin shell (i.e. formation of water insoluble membrane during dissolution acting as a barrier restricting drug release) is a well known phenomenon observed when hard gelatin capsules are stressed by high temperature and humidity. The proposed shelf-life and storage conditions take these findings into account.

No change for the chemical results has been observed over 3 months at 50°C. Regarding the physical data, no change has been observed for the appearance and the mean mass.
Two batches have been tested for 6 months at -20°C and no change has occurred except the observation of a gelatin shell cross linking.
In both cases gelatin shell cross linking was observed. However, after the use of dissolution medium with pepsin, the results complied with the requirements in all cases.
The photo stability test conducted at two batches on unprotected capsules (1200 kluxh) demonstrates that the capsules are only very slight sensitive to light. No changes have been observed.

Based on the stability data obtained and their statistical evaluation the proposed shelf-life and storage condition are accepted.

Discussion on chemical, pharmaceutical and biological aspects

The quality of Tasigna hard capsules is adequately established. In general, sufficient chemical and pharmaceutical documentation relating to development, manufacture and control of the active substance and medicinal product has been presented. There are no major deviations from EU and ICH requirements. The results of tests carried out indicate satisfactory consistency and uniformity of all the important product quality characteristics. At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product. The applicant submitted a Letter of Undertaking dated on 19 September 2007 and committed to resolve these as Follow-Up Measures after the opinion, within an agreed timeframe.
It can be safely concluded that the product should have a satisfactory and uniform performance in the clinic.
Stability tests indicate that the product under ICH guidelines conditions is chemically stable for the proposed shelf life.

3. Non-clinical aspects

Introduction

Pivotal non-clinical studies were claimed by the applicant to be conducted in compliance with GLP-regulations. *In vitro* safety pharmacology and the mutagenicity studies for the genotoxic impurities 540-04 and 371-03 were not GLP-compliant.

Pharmacology

Test systems for *in vitro* studies were based on human cancer cell lines or transfected cell lines of different, mostly murine, origin constitutively expressing different types of ligand-dependent tyrosine kinases. Phosphorylation rates could be detected using ELISA techniques and intracellular ATP-concentrations were taken as a marker for cell viability. For the *in vivo* studies CML was modelled using orthotopic mouse systems where haematopoietic or bone marrow cells were retrovirally

transduced to carry the human BCR-ABL gene, and either injected intravenously into athymic mice (acute model) or transplanted into the bone marrow of syngeneic mice (chronic model).

- Primary pharmacodynamics

Nilotinib inhibited native BCR-ABL auto-phosphorylation in cell lines derived from human Philadelphia-positive in CML cells (K-562, KU812F) and from transfected murine haematopoietic cells (32D, Ba/F3), with IC50 values ranging between **20 to 60 nM**. Cells that did not express the BCR-ABL were resistant to nilotinib below 2 μM. Nilotinib was active against many mutant forms of BCR-ABL that proved resistant against imatinib (M237I, M244V, L248V, G250A/E/V, Q252H, E255D, E275K, E276G, E281K, E292K, F311V, F317C/L/V, D325N, S348L, M351T, E355A/G, A380S, M388L, F486S) with IC_{50} values in the range of 30 - 150 nM. Y253H, E255K/R/V, K285N, F359C/V and L387F mutants were less sensitive to nilotinib with IC50 values of 150 - 390 nM, while T351I was resistant up to below 10,000 nM. Using the same cell lines nilotinib inhibited viability and proliferation with IC50 values ranging from **8 to 24 nM**. In summary, nilotinib inhibited autophosphorylation and proliferation of 33 out of 34 BCR-ABL mutants with IC50 values in the concentration range of 20 to 800 nM.

The *in vivo* efficacy of nilotinib was investigated in athymic nude mice i.v. injected with 32D tumour cells, stably transfected with native BCR-ABL (acute model). Tumour growth was measured using a non-invasive imaging system. Following oral administration of either q.d. (18, 45 or 68 mg/kg) or b.i.d. (10, 20 or 30 mg/kg) nilotinib reduced disease burden in a dose-dependent manner. Tumour stasis was observed at 45 mg/kg q.d. and 30 mg/kg b.i.d. Similar anti-tumour efficacy and toxicity (in the form of body weight changes) were obtained with the q.d. and b.i.d. treatment regimens. Following b.i.d. 30 mg/kg treatment for 14 days, nilotinib plasma concentrations were 62, 41, 4.4 μM at 1, 6 and 12 hours following dosing.

To determine if nilotinib treatment would be able to prolonged survival, 75 mg/kg/day nilotinib was orally administered to a larger cohort of mice over a 16-day period, commencing three days after injection of the tumour 32D cells stably transfected with native BCR-ABL (chronic model) (Weisberg, Manley et al. 2005). Vehicle-treated animals (19/20) developed a lethal disease with a median survival of 16 days whereas nilotinib treatment resulted in survival of 15/20 animals when observed over a 105 day observation period.
The effects of nilotinib on survival were also evaluated in a bone marrow transplant model, where bone marrow cells from normal balb-c mice were transduced with BCR-ABL and transferred to mice. Prolonged survival was observed in animals treated p.o. with either imatinib (125 mg/kg/day) or nilotinib (75 mg/kg/day). Vehicle-treated animals exhibited splenomegaly and marked leukocytosis and were sacrificed on day 18 post-transplantation, whereas imatinib and nilotinib-treated animals all were alive at the study end point, 20 days after transplantation. Nilotinib decreased the spleen weight (tumour burden) relative to both vehicle and imatinib-treated animals. Similarly, nilotinib (75 mg/kg/day, p.o.) prolonged survival in the presence of the BCR-ABL mutant E255V and M351T BCR-ABL mutant (Weisberg, Manley et al. 2005).

- Secondary pharmacodynamics

The kinase inhibition profile of nilotinib was evaluated in a panel of cell lines expressing a selection of tyrosine and serine/threonine protein kinases. Several important targets were identified. Nilotinib inhibits the tyrosine kinase activity of the **PDGF-R** with an IC50 of 69 nM. This translates into potent inhibition of PDGF-Rα and PDGF-Rβ-dependent cell proliferation with IC50 values of 2.5-11 nM and 53 nM in Ba/F3 cells, respectively. In a TEL-PDGFRβ mouse model of chronic myelomonocytic leukaemia (CMML), nilotinib administered by gavage at 75 mg/kg/day q.d. significantly prolonged the survival of animals compared to vehicle-treated controls. Furthermore, nilotinib (75 mg/kg/day q.d.) also significantly prolonged animal survival in the FIP1-L1-PDGFRα model of hypereosinophilic syndrome (HES).

In addition, nilotinib was able to potently reduced mutant c-Kit autophosphorylation in GIST cells with a mean IC50 of 210 nM. Consistent with these effects nilotinib strongly inhibited c-Kit dependent cell proliferation. Nilotinib was also a potent inhibitor of the ABL-related tyrosine kinase Arg and it has recently been reported that it inhibits the kinase domain activity of the ephrin receptors, EphB1, EphB2 and EphB4, with IC_{50} values in the low nanomolar range (Melnick, Janes et al. 2006).

Nilotinib did not significantly inhibit (IC_{50}>3 μM) the kinase autophosphorylation and/or cell proliferation of cells expressing any other tested kinases including VEGFR2, EGFR, erbB2, FLT3, Ret, c-Met, c-Src, PKA, PKB, IGF-1R, Insulin receptor, FGF, JAK2, Ras, NPM-Alk, Akt, Pim2. When evaluated in a kinase activity assay, nilotinib was a weak inhibitor of c-Raf-1 (1.2 μM), p38 (1.7 μM), B-Raf-V599E (5.1 μM), Tek/Tie-2 (3.3 μM), KDR/VEGFR-2 (5.3 μM) and c-Src (3.7 μM), and remained inactive (IC_{50} > 10 μM) against a panel of 34 other kinases.

Nilotinib was assessed against a panel of 79 different receptors, ion channels, transporters and enzymes by competitive binding assay. Significant activity was found only against the human recombinant adenosine receptor Ad3 and the human adenosine transporter ENT1 (AdT) with Ki values of 3.2 μM and 1.1 μM, respectively.

- Safety pharmacology programme

1. Cardiovascular effects

A variety of *in vitro* and *in vivo* studies were conducted to explore possible cardiovascular effects of nilotinib (see Table 1).

Table 1: Summary of the cardiovascular safety pharmacology studies conducted with nilotinib.

Study type	Species N/group or cell type	Route	Dose (mg/kg) or concentration (μM)	Major findings
HERG channel	HEK cells	In vitro	0.03, 0.1, 0.3, 1	IC_{50}: 0.13 μM IC_{75}: 0.4 μM
Isolated heart (non GLP)	Rabbit /3♀	In vitro	0.3, 0.9, 3, 9, 18, 30	↑ APD in 1/3 assays at 3 μM and in 2/3 assays at 9 μM, ≥ 3 μM triangulation ≥ 0.9 μM: ↓ in coronary perfusion rate in 1/3 assays
Isolated heart	Rabbit /6♀	In vitro	0.005, 0.015.0.05. 0.15, 0.5	No TRIaD events effects on repolarization process up to 0.5 μM, In the presence of nilotinib, ↓ in coronary perfusion rate at 0.5 μM, one run of ventricular fibrillation in 1/6 hearts (drug precipitation in solution occurred)
Telemetry	Dog / 4 ♂	In vivo Oral (gavage)	30, 100, 300	No effects

N = number; HEK cells = human embryonic kidney cells; IC_{50} = Inhibitory Concentration 50, ↑ = increase; ↓ = decrease, APD = action potential duration, TRIaD = Reference to three primary proarrhythmic properties that are frequently associated with prolongation of APD: Triangulation, Reverse use dependence and Instability. The latter three always lead to Dispersion

2. CNS and respiratory effects

The risk for adverse effects on the CNS and the respiratory system was evaluated following single-dose p.o. administration of nilotinib to male rats (n=10). The animals were evaluated up to 24 hours post-dose. One animal died prematurely during the study, however the cause of death was considered associated to the route of administration. No treatment-related effects were observed on the CNS functions following administration of 300 mg/kg nilotinib. Likewise, nilotinib administration (30 or

300 mg/kg) had no effect on respiratory functions when evaluated using whole body plethysmography.

- Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies were submitted.

Pharmacokinetics

A variety of *in vitro* and *in vivo* pharmacokinetic studies were performed. Plasma, serum and tissue concentrations of nilotinib were determined in mice, rats, rabbits, dogs, and monkeys using validated high pressure liquid chromatography (HPLC) methods coupled to liquid chromatography-mass spectrometry (LC-MS) or radioactivity detection. Plasma protein binding studies used the active substance with ^{3}H label, and tissue distribution studies were conducted with ^{14}C-nilotinib. Limits of quantification in plasma were 2.5 ng/mL (except for rats that were 10 ng/mL).

- Absorption-Bioavailability

The absorption of nilotinib following a single administration was evaluated in mice, rats, rabbits and monkeys. The results are summarised in Table 2.

Table 2. Pharmacokinetic Parameters of nilotinib in Mouse, Rat, Rabbit and Monkey following single dosing.

Species /sex	Route	Dose[c] (mg/kg)	C_{max} (ng/mL)	T_{max} (h)	AUC (ng.h/mL)	$T_{1/2}$ (h)	CL (L/h/kg)	V_{ss} (L/kg)	F (%)
Mouse/♂	I.V.[a]	10	21,200	-	33,800	1.2	0.3	0.52	-
	P.O.[b]	25	7,910	0.5	36,100	0.9	-	-	43
Rat/♂	I.V.[a]	5	10,500	-	19,300	116	0.26	7.9	-
	P.O.[a]	20	1,740	4.0	26,100	41	-	-	34
Rabbit/♀	I.V.[a]	4	5,650	-	5,940	2.0	0.68	0.9	-
	P.O.[b]	30	1,580	1.0	1,580	10	-	-	20
Monkey /♂	I.V.[a]	3	6,380	-	4,770	1.5	0.66	067	-
	P.O.[b]	10	518	2.7	3,880	24	-	-	24

[a] *Solution in cremophor:dimethyl acetamide:5% dextrose = 20:10:70 (v/v/v)*
[b] *Suspension in 0.5% (w/v) hydroxypropyl methylcellulose aqueous solution*
[c] *Dose is given as free base*

Repeated-dose administration of nilotinib to monkeys resulted in a less-than-proportional increase in exposure, as estimated by the AUC, after both single and multiple oral doses. After multiple doses, the inter-animal variability was generally much greater than after a single dose. Evidence of plasma accumulation (up to 5-fold) was observed following repeated dosing. No gender differences were observed with respect to peak concentration or plasma exposure in monkeys. After repeated oral administration to rats, exposure to nilotinib was generally higher in female rats compared to male rats. An increase in dose resulted in a generally proportional increase in exposure after single and multiple doses in male and female rats.

- Distribution

Radioactivity tissue distribution was investigated by quantitative whole-body autoradiography in rats following a single p.o. dose of ^{14}C-nilotinib. Maximal tissue concentrations were generally observed between 2 and 6 hours following ^{14}C-nilotinib administration and radioactivity was higher in the majority of tissues than in the blood. The highest tissue-to-blood ratios were observed in the adrenal cortex (8-9), liver (8-11), uveal tract (8-19) and small intestine (14-40). Substantial radioactivity was detected in the bile. There was minimal passage to the central nervous system with tissue:blood ratios for brain and spinal cord of 0.06 and 0.05 respectively. Ratio for testis was 0.12. At the final time point (168 hours), radioactivity could still be detected in the aorta wall, liver, lung, skin and uveal tract. Nilotinib displayed affinity towards pigmented skin (melanin).

Following a single 20 mg/kg oral dose of ^{14}C-nilotinib in pregnant rats, the highest tissue-to-maternal blood concentration ratios (2 to 10) were observed in the maternal liver, kidney, uterus, heart, and

amnion. The foetus-to-maternal blood ratio at day 10 gestation was 1.5-2.3 (24 h time period post dose). Foetal tissue concentrations at gestation day 17 were all below those observed in maternal blood except 1.6-fold higher in the foetal liver. In pregnant rabbits after oral daily nilotinib dosing, the nilotinib concentration in all foetuses for the dose groups of 30 and 100 mg/kg was below the lower limit of quantification. The mean nilotinib concentration in foetuses in the 300 mg/kg group was 29.8 ng/g tissue, while the mean maternal serum concentration was 372 ng/mL. The relative exposure (foetus-to-maternal serum ratio) was estimated at approximately 8%.

Following an oral dose (20 mg/kg) of ^{14}C-nilotinib in lactating rats, the overall milk:plasma concentration ratio was ~2 based on $AUC_{0-\infty}$ values. Unchanged nilotinib was present at higher concentrations in rat milk compared to that observed in plasma. There were no metabolites detected that were unique to rat milk.

The average nilotinib plasma protein binding was 97.4%, 99.1%, 98.2%, 99.0% and 98.4% in the mouse, rat, dog, monkey and human, respectively. The nilotinib blood-to-plasma concentration ratios were less than one in mice (0.84), rats (0.79), dogs (0.83), monkeys (0.81) and humans (0.68). Heparin did not affect the protein binding of nilotinib in human plasma. Nilotinib is also highly bound (93.4 to 93.9%) to human serum albumin and to α-1 acid glycoprotein (*in vitro*).

- Metabolism

The metabolism of ^{3}H-nilotinib was investigated *in vitro* using rat, dog, monkey, human liver slices and human hepatocytes. The metabolic reactions involved oxidation of the methyl-imidazole ring, degradation of the oxidized imidazole, oxidation of the pyridinyl-pyrimidinyl-amino-methyl-benzamide moiety, amide hydrolysis, glucuronic acid conjugation with parent compound or metabolites, and various combinations of the above reactions. The rates of test substance disappearance at a concentration of 0.7 μM [^{3}H] nilotinib were comparable in all test matrices ranging from 0.89 to 2.7 pmol/h/mg in wet tissue (slices) and approximately 2.7 pmol/h/mg in liver and in human hepatocytes (3.3 pmol/h/10^5 cells). All of the major metabolites found in human liver slices were also detected in rat or monkey liver slices.

Biotransformation of nilotinib was investigated *in vivo* in mouse, rat, rabbit, monkey, and human. The metabolism of nilotinib was extensive and a total of 74 different nilotinib metabolites were detected in plasma, urine and faeces. Unchanged nilotinib was the predominant component in plasma (one hour following i.v. and p.o.). In all the animal species the amount of nilotinib excreted as unchanged drug into the faeces ranged from 18.3% of the dose in the mouse to 57.8% of the dose in monkeys. There were more than thirty metabolites detected in the faeces, however, none contributed greater than 5% of the excreted dose with the majority contributing less than 2% each. Additional metabolites found were unique to rat, all present at levels of less than 3% of the dose.

In humans, unchanged nilotinib was the main circulating component in human serum, accounting for 88% of the AUC_{0-48h}. The two metabolites present at the highest levels in human serum were P36.5 and P41.6 with AUC_{0-48h} values of 6.9% and 5.3% relative to the unchanged drug. These metabolites are formed by a common biotransformation pathway, where the methyl group in the methyl-midazolam moiety of nilotinib is initially hydroxyl Ted (P41.6) and then further oxidized to a carboxylic acid (P36.5). Additional metabolic pathways observed in humans included hydroxylation of the methyl group in the amino-methyl-benzamide moiety (P42.1), N-oxide formation on the pyridine nitrogen (P36), oxidative/ hydrolytic degradation of the midazolam ring leading to multiple products, oxygenation of the pyridinyl-pyrimidinyl-tolyl-amine and methyl-phenyl-imidazole moieties, and cleavage of the amide linkage (P20). P36 and P42.1 were found in human serum with AUC_{0-48h} values of 0.58% and 1.5% relative to unchanged drug. Combinations of these primary biotransformation pathways lead to the observation of twenty distinct human metabolites of nilotinib.

There were numerous metabolites observed in the animal species investigated that were not detected in human. All of the metabolites identified in humans were also detected in one or more of the animal species tested, with the exception of the two minor faecal metabolites (P38 and P40, mono and di-oxygenated nilotinib respectively), which each accounted for ≤ 1.2% of the dose. With respect to plasma metabolites, higher percentages of total AUC were observed in human metabolites P36.5 and P41.6 than in the animal species.

- Excretion

Radiolabelled nilotinib was predominantly excreted via faeces following both i.v. and oral administration (see Table 3). An i.v. excretion study in bile duct cannulated (BDC) rats revealed that the faecal excretion (94.2% of the dose) was the result of both biliary (72.4% of the dose) and GI secretion routes (21.8% of the dose).

Table 3. Summary of the excretion studies conducted for nilotinib.

Species Sex Route	Dose (mg/kg)	Sample collection interval (h)	Excretion of radioactivity (% of dose) Urine	Faeces	Bile	Cage wash	Total recovery
Mouse ♂ i.v.	10	0-168	7.87	76.8	-	0.25	85.1
Mouse ♂ p.o	25	0-168	5.89	91.8	-	0.02	97.7
Rat ♂ i.v.	5	0-168	2.51	93.1	-	0.21	95.9
BDC Rat ♂ i.v.	5	0-72	3.14	21.8	72.4	-	97.3
Rat ♂ p.o.	20	0-168	1.67	84.4	-	0.17	86.3
BDC Rat ♂ p.o.	20	0-72	2.71	55.2	25.4	0.09	83.3
Rabbit ♀ i.v.	4	0-168	18.2	87.4	-	0.06	106
Rabbit ♀ p.o.	30	0-168	28.8	70.9	-	0.26	100
Monkey ♂ i.v.	3	0-168	0.81	91.7	-	9.87	102
Monkey ♂ p.o.	10	0-168	1.63	92.8	-	1.98	96.5

- Pharmacokinetic drug interactions

CYP enzyme inhibition and induction

When tested at concentrations of up to 100 μM in human liver microsomes, nilotinib showed little or no inhibition of CYP1A2 and CYP2E1 enzymes and a moderate inhibition of CYP2C19 (K_i of 3.82 μM) and CYP2D6 (K_i of 1.46 μM). More potent inhibition was observed for CYP2C9 (K_i of 0.132 μM), CYP3A4/5 (K_i of 0.448 μM) and CYP2C8 (K_i of 0.236 μM). Nilotinib also acted as a partial inhibitor for CYP2C8, CYP2C9, CYP2D6 and CYP3A4/5, and it was a fully competitive inhibitor of CYP2C19 activity.

Kinetic experiments performed with pooled human liver microsomes and recombinant human CYP enzymes showed that CYP3A4 and CYP2C8 are expected to be the main contributors to the oxidative metabolism of nilotinib in humans ($CL_{int,CYP2C8} \approx 24\%$ of $CL_{int,CYP3A4}$). CYP3A4 and CYP3A5 demonstrated the highest nilotinib turnover followed by CYP2C8, CYP1A1, CYP1A2 and CYP1B1. Co-incubation with the CYP3A4 inhibitors ketoconazole and troleandomycin reduced nilotinib oxidative metabolism by >95%, with apparent IC_{50} values of 0.012 and 1.2 μM respectively. Minimal inhibition was observed with furafylline (CYP1A2), quercetin (CYP2C8/3A4) or paclitaxal (CYP2C8/3A4). Furthermore, in a clinical study in which 26 healthy subjects were administered a single 200 mg oral dose of nilotinib on day 4 plus ketoconazole on days 1-6, a three-fold increase in the nilotinib serum AUC was observed.

Nilotinib (up to 10 μM) was examined for its potential to induce cytochrome P450 enzymes activities in primary human hepatocytes of three individual donors after 72 h of treatment. The results indicate that nilotinib can be considered to be an *in vitro* inducer of CYP2B6, CYP2C8, and CYP2C9 activities. Induction of CYP1A1 and CYP1A2 mRNA levels and activity constituted less than 40% of the positive control level. UGT1A1 mRNA levels were approximately within 40% of the positive controls. In addition, there was no observed induction of CYP2C19, ABCB1 (Pgp) or ABCC2 (Multidrug resistance-related protein 2, MRP2) mRNA levels.

Inhibition of transporters
The IC_{50} value for inhibition of the Pgp mediated efflux of Rho123 by nilotinib was 1.7 ± 0.11 μM, representing an inhibition of 33%, compared to the positive control 10 μM cyclosporine. The permeability of nilotinib (6 μM) across confluent Caco-2 cell monolayers ranged between an efflux ratio of 3.9-4.1 (determined by dividing the permeability in the basolateral to apical direction by the permeability in the apical to basolateral direction). In the presence of the Pgp inhibitor PSC833, the nilotinib efflux ratio was reduced to near unity (0.80-1.2). However, no effect on the nilotinib efflux ratio was observed in the presence of the MRP inhibitor MK571. The intrinsic permeability of nilotinib (6 μM), estimated from the average permeability values for transport in either direction in the presence of sufficient levels of PSC833 was moderate.

UGT1A1 inhibition
Nilotinib was a potent *in vitro* inhibitor of human uridine diphosphate-glucuronosyltransferase 1A1 (UGT1A1) at clinically relevant concentrations, with an estimated Ki value of 0.19 μM.

Toxicology

- Single dose toxicity

Intravenous single-dose toxicity studies were conducted in rats (see Table 4). The following investigations were performed: mortality, clinical signs, body weight, food consumption, haematology, clinical biochemistry, toxicokinetics measurements, organ weights, macroscopy and microscopy. A 15-day observation period following dosing was included in the study. The no-observed-adverse-effect-level (NOAEL) for the intravenous administration study was 9 mg/kg.

Table 4. Overview of the conducted single-dose toxicity studies.

Species/ Sex/Number/ Group	Dose/Route	$AUC_{0\text{-}24h}$ (ng*h/mL)	Major findings
Rat/2/sex/group	9 mg/kg/I.V. bolus	♂: 76,800 ♀: 110,000	No treatment-related findings
Rat/5/sex/group	9 mg/kg/I.V.	♂: 68,700 ♀: 103,000	No treatment-related findings

- Repeat dose toxicity (with toxicokinetics)

Repeated-dose toxicity studies were conducted in mice, rats, dogs and monkeys. The pivotal studies were performed in rats (26-weeks) and monkeys (39-weeks).

Nilotinib caused toxic effects in animals without a safety margin to clinical use (based on plasma AUC). Reductions in body weight, body weight gain and food consumption were consistently observed and overt body weight reductions caused dose group termination in some cases. In addition, gastrointestinal symptoms in the form of alterations of faecal character and bloody faeces accompanied by abdominal pain (hunched appearance) were observed in monkeys receiving 200 and 600 mg/kg nilotinib, respectively. A number of findings related to hepatobiliary toxicity were made following repeated administration of nilotinib. Liver weight increases were observed in rats (≥30 mg/kg). Liver inflammation, bile stasis, bile inspissation and bile duct proliferation accompanied by increases in ALT and ALP were observed in dogs at ≥45 mg/kg. Moreover, increased plasma cholesterol levels were observed in all species tested except for mice. Bilirubinuria and hyperbilirubinemia was observed in female dogs at 45 mg/kg in the 4-week toxicity study and bilirubinuria was also seen in female dogs at 15 mg/kg. Findings in monkeys administered 30 mg/kg, consisted of mononuclear cell infiltration, bile duct hyperplasia, periportal fibrosis. Additional findings made at higher doses were sinusoidal cell hyperplasia/hypertrophy, cytoplasmic aggregation of sinusoidal cells, enlarged bile duct and an increase in ALT. At the end of the 39-week monkey study, elevated cholesterol values were still observed in the 600 mg/kg recovery female. The single 600 mg/kg recovery male animal showed increased liver weight and altered liver histology that did not show evidence of recovery. Mild haematological changes were observed in mice (reduced red blood

cell counts together with reductions in haemoglobin), rats (increases total leukocyte counts, neutrophil counts, lymphocyte counts and monocyte counts, decreases of erythrocyte counts, haemoglobin concentrations, and haematocrit values) and monkeys (increases in platelet counts, decreases in red cell mass, prolongation in activated partial thromboplastin time APTT) at oral doses > 20 mg/kg for mice and rats and 200 mg/kg for monkeys. Furthermore, increased heart weight, adrenal weight and ovarian weight (including ovarian follicular or luteal cysts) were observed in nilotinib-treated rats.

Toxicokinetics:

Nilotinib was monitored in the large majority of repeat-dose toxicity studies. The animal:human exposure margins at NOAEL (safety margin) obtained from the repeat-dose toxicity studies are given in Table 5.

Table 5. The animal:human exposure margins at NOAEL.

					Exposure multiple [a]	
Species / Study number	**NOAEL[b] (mg/kg)**	**Sex**	**AUC_{0-24h} [c] (ng/mL•h)**	**C_{max} [c] (ng/mL)**	**Based on mean AUC_{0-24h} in humans [a]**	**Based on mean C_{max} in humans [a]**
4-week mice [0580231]	20[d]	Male	20500	-	0.57	-
		Female	21000	-	0.58	-
2-week rat [0370138]	30[d]	Male	45400	3490	1.26	1.54
		Female	103000	7430	2.9	3.29
4-week rat [0370146]	20 [+]	Male	20900	2420	0.58	1.1
		Female	46100	3200	1.3	1.4
26-week rat [0580158]	6 [d]	Male	9200	1590	0.26	0.70
		Female	15300	2370	0.42	1.05
2-week dog [0370139]	20	Male	4680	788	0.13	0.35
		Female	4190	705	0.12	0.31
4-week dog [0370147]	5	Male	1560	370	0.043	0.16
		Female	1780	296	0.049	0.13
4-week cynomolgus [0570038]	600	Male	12000	864	0.33	0.38
		Female	46800	3250	1.3	1.4
39-week cynomolgus [0580157]	30 [d]	Male	9770	632	0.27	0.28
		Female	11600	756	0.32	0.33

[a] based on 800 g/day as 400 mg twice daily (phase II study dose level) in patients with CML, ALL and other hematologic malignancies [CAMN107A2101], C_{max} = 2259 ng/mL, AUC_{0-24} = 36030 ng·h/mL; [b] NOAEL: No Observed Adverse Effect Level; [c] values at the end of the stated treatment-period; [d] since no NOAEL could be defined in the study the lowest administered dose is taken for calculation; [+] NOAEL for females only, not achieved in males

- Genotoxicity

Nilotinib was not genotoxic in a standard battery of *in vitro* and *in vivo* studies. The genotoxic potential of nilotinib was assessed in gene mutations tests in bacteria (Ames test), chromosomal damage in human lymphocytes *in vitro* and in rat bone marrow following oral application. In addition, two non-pivotal studies were submitted: an Ames test and a comet assay for the detection of DNA single strand breaks in the mouse L5178Y cell line. The results of all studies were negative.

- Carcinogenicity

No carcinogenicity studies have been conducted with nilotinib.

- Reproduction Toxicity

All male and female fertility parameters were unaffected by treatment. Due to findings in the repeat-dose toxicity studies, it cannot be fully excluded that long term nilotinib treatment may affect female fertility. Nilotinib treatment caused embryolethality, decreased foetal weights, an increased incidence for skeletal malformations, and skeletal and visceral variations in rats. Overall, the maternal NOAEL was established at 10 mg/kg/day whereas no NOAEL for developmental toxicity could be established. Based on an increase in the incidence of embryo resorption and skeletal variations, the NOAEL for embryo-foetal effects in rabbits was 100 mg/kg/day. The NOAELs established in rats and rabbits corresponded to plasma levels 0.8 and 0.2-fold of the average human nilotinib plasma exposure level (AUC). Consequently, there is no safety margin to human use for the embryo- and foetotoxic effects.

- Local tolerance

Intravenous injection in New Zealand White rabbits was locally well tolerated. Perivenous or intra-arterial injection led to slight to moderate erythema and slight oedema which were recorded at higher severity and incidence at test item injection sites when compared with the control item injection sites. The observed effects are of no relevance for the clinical administration mode.

- Other toxicity studies

Metabolites

In a competitive receptor binding assay, P36.5 displayed Ki values of 6.5 and 0.46 μM against adenosine receptor type 3 and adenosine transporter ENT1, respectively. P36.5 is passively transported in Caco-2 cells and showed permeability lower than 20% of projected absorption in human GI tract. Treatment with P36.5 neither affected the hERG current (at concentrations up to 30 μM) nor did it cause electrophysiological effects in the rabbit isolated heart assay at concentrations up to 2 μM.

Studies on impurities

The impurities are considered qualified up to the following levels: 374-03 (0.34%), 541-04 (0.38%) and 512-05 (0.5%).

The impurities 376-03, 540-04, and 371-03 displayed mutagenic potential when evaluated in Ames tests. 376-03 and 371-03 appeared to be weak mutagens (2-fold increase in the number of revertants when compared to vehicle), whereas 540-04 was more potent (up to 6-fold increase).

Phototoxicity

Nilotinib showed significant absorption within the UV-B and -A range and distribution in the skin after oral administration was observed in rats. In two separate in vitro 3T3 NRU phototoxicity experiments, Photo-Irritation-Factor s (PIF) of 4.7 and 9.6 were detected. No photoallergic potential was detected in the UV-local lymph node assay when skin and eyes were exposed to nilotinib at the highest dose of 400 mg/kg.

Ecotoxicity/environmental risk assessment

Nilotinib is unlikely to pose an appreciable risk to the environment. The Phase I calculation of PEC_{SW} was conservatively based on a market penetration factor (Fpen) of 1%. PEC_{SW} was 6 μg/L. Log K_{ow} was below 4.5 thus further assessment of nilotinib persistence and bioaccumulation is not required. The Phase II – tier A refinement of PEC_{Sw} gives rise to a value of 8.44 ng/L. A Tier B sediment organism toxicity study indicates that nilotinib is unlikely to pose a risk to aquatic organisms and confirm the expected strong sorption to sludge and soil. Based on the results from the activated sludge respiration inhibition study, a $PNEC_{microorg.}$ was established at 3 mg/L. Since the PEC_{Sw}: $PNEC_{microorg.}$ ratio is below 0.1, further evaluations of the effect on microorganisms are not required. It is considered acceptable that a Phase II - Tier B terrestrial assessment may not be conducted given that PEC_{soil} was more than 3500 fold below the action limit (PEC < 100 μg/kg soil) for veterinary medicinal product environmental risk assessment. A $PNEC_{groundwater}$ was not calculated because the substance is highly unlikely to be found in groundwater, due to its physico-chemical and structural properties e.g. low biodegradability and high K_{OC}.

Discussion on the non-clinical aspects

Pharmacology

Nilotinib is a potent inhibitor of native BCR-ABL with an IC_{50} value of 25 nM, thus it is expected to be efficient in patients overexpressing BCR-ABL. Nilotinib was a more potent inhibitor of BCR-ABL than imatinib (around 10-fold). Nilotinib inhibited the autophosphorylation and proliferation of 33 out of 34 BCR-ABL mutants with IC_{50} values in the concentration range of 20 to 800 nM, whereas imatinib was consistently less efficient. T315I mutation was resistant to both nilotinib and imatinib. Based on a clinical C_{max} value of 4.3 μM (400 mg b.i.d.), nilotinib is expected to inhibit the large majority of BCR-ABL mutants at therapeutic plasma levels.
Presently, no clinical safety data indicate an increased risk for congestive heart failure (cardiomyopathy) in patients treated with imatinib, however, there have been recent clinical reports in which imatinib caused cardiotoxicity because of the inhibition of c- ABL (Kerkelä et al. 2006). Considering that nilotinib is a more potent inhibitor of c- ABL than imatinib, the applicant has committed to conduct further non-clinical post-authorisation studies to address these findings.
Nilotinib treatment caused inhibition of the hERG channel with an IC_{50} of 0.13 μM. In accordance with these findings, prolongation of action potential duration was observed at doses ≥3 μM when evaluated in vitro. However, no effects were seen in ECG measurements in dogs or monkeys treated for up to 39 weeks or in a special telemetry study in dogs. Still, QT-prolongation was observed clinically and this safety information has been included in section 5.3 of the SPC.

Pharmacokinetics

Nilotinib was readily absorbed after oral administration (t_{max} 0.5 to 4 h in animals and humans). Bioavailability was moderate and a high tendency for metabolism can be supposed from the single dose animal data. Generally, exposure values in experimental animals were below or equivalent to the human exposure at a dose of 800 mg/day (400 mg bid).

In general, all of the metabolic pathways observed in humans were also observed in the animal species. Accordingly, all of the metabolites identified in humans were also detected in one or more of the animal species tested. The parent drug was the major circulating component (~83%) in rats with an additional 9 minor radioactive components. The metabolite profiles in human liver slices were comparable to those in rat, dog, and monkey.

Toxicology

Studies in dogs and monkeys revealed the liver as the primary target organ for toxicity of nilotinib. Exposures at the lowest dose levels at which the liver effects were seen were lower than the exposure in humans at a dose of 800 mg/day. Alterations included increased alanine aminotransferase and alkaline phosphatase activity and histopathology findings (mainly sinusoidal cell or Kupffer cell hyperplasia/hypertrophy, bile duct hyperplasia and periportal fibrosis). In general the changes in clinical chemistry were fully reversible and only minor liver alterations were seen at longer follow-ups. These results have been included in the wording of section 5.3 of the SPC. Monitoring for hepatic toxicity is included in the ongoing and planned clinical studies and hepatic toxicity is included in the risk-minimisation plan.

Hyperbilirubinaemia could effectively be explained by the effect of nilotinib on UGT1A1. *In vitro* studies showed that nilotinib inhibits activity of UGT1A1. Furthermore pharmacogenetic analysis in patients in Phase I and Phase II trials found a statistically significant association between a specific genotype of the TA repeat polymorphism in the promoter region of UGT1A1 gene ((TA)7/(TA)7) and risk of hyperbilirubinemia. The mechanism is unknown and the possibility of other mechanisms cannot be excluded. Elevated bilirubin is mention as an undesirable effect in section 4.8 of the SPC.

Mild haematological changes were observed in mice. These effects may be a consequence of the pharmacological activity of the compound on c-Kit and PDGF receptors, which play a crucial role in normal haematopoiesis.

Carcinogenicity studies are normally not required for anti-cancer medicinal products due to the short life-expectancy i.e. less than 2 to 3 years (CPMP/SWP/997/96, ICHS1A). However, due to the life-expectancy of CML-CP patients receiving nilotinib (4-6 years), the applicant commits to perform post-authorisation carcinogenicity studies, which results are expected to be submitted by the end of 2010.

There is no safety margin to human use for the embryo- and foetotoxic effects. Consequently, the possibility that pregnant patients in need of nilotinib treatment at different stages of pregnancy cannot be excluded. The potential toxicity of nilotinib on prenatal and postnatal development will be addressed post-approval. As a post-authorisation obligation, the results of the pre- and post-natal study conducted with nilotinib are expected.

Nilotinib did not induce teratogenicity in rats but was embryo- and foetotoxic in rats and rabbits at doses that also showed maternal toxicity. Increased post-implantation loss was observed in both the fertility study, which involved treatment of both males and females, and the embryotoxicity study, which involved treatment of females. Embryo-lethality and foetal effects (mainly decreased foetal weights, skeletal malformations (fused maxilla/zygomatic), visceral and skeletal variations) in rats and increased resorption of foetuses and skeletal variations in rabbits were present in the embryotoxicity studies. Exposure to nilotinib in females at NOAEL was generally less or equal to that in humans at 800 mg/day. These results are adequately reflected in the wording of section 5.3 of the SPC.

Nilotinib was shown to absorb light in the UV-B and UV-A range, distribute into the skin and demonstrated a phototoxic potential *in vitro*, but no effects were observed *in vivo*. The risk that nilotinib causes photosensitisation in patients is considered very low and this was stated in section 5.3 of the SPC. In addition, photosensitivity will be followed as an adverse event in future phase III randomized studies as part of the risk management plan.

4. Clinical aspects

Introduction

Nilotinib is an oral formulation containing 200 mg per capsule developed to treat CML patients in the CP and AP phases that are resistant or intolerant to prior therapy including imatinib.

There were five trials in healthy volunteers and a trial with sub-studies conducted in patients (CML and other haematological malignancies) evaluating the pharmacokinetics of nilotinib. Pharmacokinetics studies were performed following a single or multiple oral doses of 200, 400, 600 or 800 mg of nilotinib. A single study in healthy volunteers and a trial (2101) with 5 sub-studies was conducted in patients to evaluate pharmacodynamics.

The clinical development program for nilotinib consisted of a trial (2101) with a Phase IA dose escalation study and a Phase II dose expansion study. These studies were conducted mainly in CML patients. No data was submitted regarding patients with CML-BC and no indication is claimed for those patients. The data on efficacy was collected up to a data cut-off date of 4 May 2006 for study 2101E2 (CML-CP) and 23 May 2006 for study 2101E1 (CML-AP) and updated in two following cut-offs on 4 September 2006 and 4 January 2007 for CML-CP patients and 23 September 2006 and 23 January 2007 for CML-AP patients.

GCP

5. All clinical trials were performed in accordance with GCP as claimed by the applicant.

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

Pharmacokinetics

The pharmacokinetics of nilotinib was evaluated over a total of 5 trials in healthy volunteers and in one trial with several sub-studies for the target population (patients with chronic phase and accelerated phase Philadelphia chromosome positive CML with resistance or intolerance to prior therapy including imatinib). The pharmacokinetic studies for nilotinib are summarised in table 6 and 7.

Table 6. Summary of clinical pharmacology in healthy subjects

Study No.	Objectives	Nilotinib dose	Nilotinib treatment duration	No. of subjects
2104	Absorption, metabolism, and excretion with [^{14}C]nilotinib	400 mg	Single dose	4
2106	Food effect	400 mg	3 single doses	48
2108	Drug-drug interaction with midazolam, CYP3A4 substrate	600 mg	2 single doses	18
2110	Drug-drug interaction with ketoconazole, CYP3A4 inhibitor	200 mg	2 single doses	26
2119	Cardiac Safety (QT/QTc) [a)]	400-800 mg/day	Single dose, q.d. for up to 8 days, b.i.d. for 3 days	102

Table 7. Summary of clinical pharmacology in target patient population

Phase	Objectives	Nilotinib dose	No. of patients
Phase IA Study 2101 PhI PK	Basic pharmacokinetics, exposure-response relationship	50-1200 mg/day	119
Phase IA	Pilot food effect	400-600 mg b.i.d	10
Phase IA/II	Exposure-safety relationship	50-1200 mg/day	308
Phase IA/II Trial 2101 PopPK	Population pharmacokinetics	50-1200 mg/day	253
Phase II Study 2101 PhII_PK	Relative bioavailability of the CSF and FMI	400 mg b.i.d	54

The analytical method used to determine the concentration of nilotinib and the minor pharmacological active metabolite (BEJ866) in human serum was high performance liquid chromatography - tandem mass spectrometry (HPLC-MS/MS). The lower limit of quantification was 2.50 ng/ml and 1.00 ng/ml, respectively. Full validation reports were submitted.

Standard statistical analyses were used for PK analysis.

- Absorption

Bioavailability
The absolute bioavailability of nilotinib was not assessed, as this formulation has a low aqueous solubility and was administered orally. Therefore, the extent of absorption was estimated based on excreted radioactive [^{14}C]nilotinib in healthy subjects. The estimated absorption was approximately 30%, where the Tmax was reached approximately 3 hours following administration.

Bioequivalence
Two formulation of nilotinib were used, the clinical service formulation (CSF), which was used in study 2101 and the final market image (FMI), which was introduced in study 2101E1 and 2101E2. The FMI differs from the CSF by a reduction in capsule size. Only minor quantitative, and no qualitative modifications were made between the CSF and the FMI and no bioequivalence study in humans was conducted. Pharmacokinetic parameters, C_{max}, C_{min}, and the ratio of C_{max}/C_{min} were studied and no relevant differences were detected between the two formulations.

Influence of food
The effect of food on the pharmacokinetic parameters of 400 mg oral dose of nilotinib (FMI formulation) was evaluated (Study 2106). The subjects received 3 treatments of single dose of nilotinib under fasting, high fat meal and light meal conditions. The concomitant administration of nilotinib with food significantly increased subjects exposure to nilotinib, especially in high fat meals. The increase in the total exposure (AUC_{0-t}) was 82% and C_{max} was 112% after a high fat breakfast whereas the increase in AUC_{0-t} was 29% and C_{max} was 55% after a light breakfast given 30 minutes prior to dosing.

- Distribution

Study 2104 evaluated the distribution of nilotinib in the plasma. The mean apparent volume distribution (Vz/f) was calculated as 579 litres. The fraction of nilotinib distributed to red blood cells (fBC) ranged from 0.09 to 0.23 in humans. It was demonstrated that α_1-acid glycoprotein was the main plasma protein binding to nilotinib (99.1%).

- Elimination

Unchanged nilotinib was the predominant circulating component detected in the serum, accounting for 87.5 ± 9.2% of the total nilotinib-related radioactivity from 0-48 h. The apparent plasma clearance (CL/f) was determined as 29.1 l/h. The plasma half-life of nilotinib was not influenced by the intake of food. Nilotinib administered orally was excreted primarily into the faeces as unchanged drug (69% of the dose), with an additional 21% of the excreted dose in the faeces being distributed between 18 different faecal metabolites, accounting for a total of 90% of the administered dose. Only 4.5% of the dose was excreted by the kidneys.

A total of 74 distinct metabolites of nilotinib were observed. Based on the analysis of nilotinib and its metabolites found in faeces and urine, the major metabolic pathway was found to be hydroxylation of the methyl group in the methyl-imidazole ring (metabolite P41.6, resulting in 6.7% of total drug exposure in serum), with further oxidation of the hydroxyl group to carboxylic acid (metabolite P36.5, resulting in 4.7% of total drug exposure in serum). Although these metabolites were present at high levels in human serum, 88% of the total drug-related exposure was still due to unchanged nilotinib. Studies in human liver microsomes and recombinant CYP enzymes have shown that nilotinib is primarily metabolised by CYP3A4, with additional contribution from CYP2C8.

In studies of Caco-2 cells, nilotinib was a weak substrate for P-gp.

- Dose proportionality and time dependencies

Single-dose exposure relationship in healthy subjects is summarized in table 8.

Table 8. Pharmacokinetics of nilotinib after a single-dose in healthy subjects

Study No.	Dose (mg)	N	C_{max} (ng/mL)	AUC_{0-inf} (ng·h/mL)
2110	200	26	356 (142)	8590 (4753)
2106	400	44	508 (175)	14656 (5066)
2108	600	18	453 (204)	14576 (5109)

Dose proportionality was measured in the range between 50 to 1200 mg q.d. in the Phase IA (Study 2101PhI_PK). There was a nilotinib dose-dependent correlation with C_{max} and AUC where increase C_{max} and AUC was observed with nilotinib doses between 50 mg to 400 mg. However, C_{max} and AUC appeared to plateau for doses above 400 mg, remaining relatively constant over the dose range between 400 mg and 1200 mg.

Once daily doses of nilotinib, 400 mg or 800 mg, showed no appreciable differences in serum exposure to drug. Twice daily dosing of 400 mg schedule resulted in a 35% greater than with 800 mg

once daily dose. There was no further increase in exposure to nilotinib when given 600 mg dose with the twice daily schedule (1200 mg/day).

Nilotinib was shown to accumulate with prolonged exposure. At the clinical dose of 400 mg b.i.d., accumulation index is about 3.8 for C_{max}. A 600 mg b.i.d. dose showed no significant increase in exposure over 400 mg b.i.d. To evaluate the Phase II stage of the study, 400 mg b.i.d. dose regimen was selected based on the relevant pharmacokinetic properties, as well as based on satisfactory safety and preliminary efficacy data reported.

- Intra- and inter-individual variability

Over the dose range of 50-1200 mg/day, the inter-patient variability (coefficient of variation) was 34 to 72 % for C_{max} and 32 to 64% for AUC_{0-t}. The inter-patient variability on clearance was 33%, and the inter-occasion variability on the bioavailability was 44%. The intra-subject variability estimated from data in healthy subjects was 31% for Cmax and 30% for AUC_{0-inf}.

- Pharmacokinetics in target population

Comparable exposure in healthy volunteers and the target population has been demonstrated.

- Special populations

Based on the population pharmacokinetic evaluation in 253 patients in the Phases IA/II Study 2101, exposure to nilotinib in female patients was approximately 20% greater than in male patients. Race, weight and age had no effect on the pharmacokinetic of nilotinib.

Nilotinib was not studied in a paediatric population.

Nilotinib has not been studied in patients with a renal or hepatic impairment.

- Pharmacokinetic interaction studies

In vitro studies revealed that CYP3A4 may be the primary enzyme responsible for metabolizing nilotinib. In addition, nilotinib was shown to inhibit the metabolic clearance of other CYP3A4 substrates, suggesting that there may be drug interactions between nilotinib and other compounds utilizing this metabolic pathway. The potential of nilotinib to inhibit the activity of cytochrome P450 (CYP) enzymes was investigated using pooled human liver microsomes and enzyme-specific probe substrates. K_i values of 0.24, 0.13, 3.8, 1.5, and 0.45 μM were determined for CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5, respectively. These results suggest that nilotinib is a moderately potent inhibitor of CYP2C19 and CYP2D6 and a potent inhibitor of CYP2C8, CYP2C9, and CYP3A4/5. Based on the steady-state nilotinib serum C_{max} of 4.3 μM (2260 ng/ml) observed in patients receiving twice daily doses of 400 mg, it is likely that nilotinib could act as an inhibitor of CYP2C8, CYP2C9, CYP2D6, and CYP3A4/5 activity in clinical settings, but less likely for CYP2C19. Preincubation experiments using human liver microsomes and nilotinib showed no potential for time-dependent inhibition (i.e., no mechanism-based inactivation) of CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5.
To further investigate and characterize the drug-drug interaction, nilotinib was studied in combination with midazolam (study 2108), a CYP3A4 substrate, and ketoconazole (study 2110), a CYP3A4 inhibitor.

Study 2108 was an open-label, single center, randomized, three-way crossover study that showed that co-administration of midazolam and nilotinib did not have a significant effect on the pharmacokinetics of nilotinib. There were no significant differences observed in any of the different treatment sequences. Therefore, there are no statistically significant differences in pharmacokinetic parameters of nilotinib when administered in conjunction with midazolam. However, in the presence of nilotinib, the AUC and C_{max} of midazolam increased by 30% and 20%, respectively. Given that nilotinib is a weak inhibitor of CYP3A4, it is still recommended to avoid co-administration of nilotinib and other medication that are CYP3A4 substrates.

Study 2110 was an open-label, single center, two-period, single sequence crossover study that showed that co-administration of ketoconazole with nilotinib increased AUC and C_{max} of nilotinib. The

summary of pharmacokinetic parameters comparing nilotinib alone and co-administered with ketoconazole is shown in table 9.

Table 9 Summary of nilotinib pharmacokinetic parameters comparing nilotinib alone and co-administered with ketoconazole.

Parameter	Nilotinib (n=25)	Nilotinib+Ketoconazole (n=25)
t_{max} (h)	4.0 (2.0-8.0)	4.0 (2.0-8.0)
C_{max} (ng/mL)	356 (142)	673 (279)
AUC_{0-t} (ng·h/mL)	8793 (4769)	27757 (13183)
AUC_{0-inf} (ng·h/mL)	8590 (4753)	26682 (13703)
CL/f (L/h)	31.0 (17.0)	12.3 (13.9)
Vz/f (L)	587 (385)	333 (219)
$t_{1/2}$ (h)	15.2 (9.3)	32.7 (17.9)

As shown in table 9, the half-life of nilotinib was prolonged by approximately 115%, C_{max} was increased by 84% and AUC was increased by approximately 3 fold. Inversely, there were no effects of nilotinib on the pharmacokinetics of ketoconazole (data not shown). The effect of inhibition of CYP3A4 by ketoconazole on nilotinib pharmacokinetics was statistically significant.

The potential of nilotinib to act as an inhibitor of human UGT1A1 was investigated by examining the effect of increasing drug concentrations on bilirubin and estradiol glucuronidation activity in *in vitro* assay systems. Inhibition of UGT1A1 activity by nilotinib was apparent using either probe reaction with an estimated IC_{50} <1 µM. A follow-up kinetic study estimated a K_i value of 0.19 µM for inhibition of estradiol glucuronidation, suggesting that nilotinib could inhibit the activity of UGT1A1 in a clinical settings.
Nilotinib was found to be a weak substrate for P-gp mediated efflux (efflux ratio: 3.9-4.1 at a nilotinib concentration of 6 µM). The relatively small P-gp mediated efflux ratios for nilotinib coupled with its moderate intrinsic permeability suggest that nilotinib should be sufficiently absorbed following oral administration. Additional experiments indicated that nilotinib inhibits the P-gp mediated efflux of Rhodamine 123, a known P-gp substrate, with an IC_{50} of 1.7 µM. Based on this IC_{50} and the steady-state nilotinib C_{max} of 4.3 µM. The interaction between nilotinib and P-gp was not investigated *in vivo*.

In addition, the effect of neutralizing agents, such as antacids and proton pumps inhibitor (PPIs) or antiemitics on nilotinib pharmacokinetics were not investigated. Given that the solubility of nilotinib is poor in environments with pH values of >1, absorption of nilotinib may be compromised.

Pharmacodynamics

There was one pharmacodynamic study in healthy volunteers(2119), 3 PD studies in patients as part of a Phase I study (BMD CAMN107A 2101, 2101-01, 2101-02) and 2 PD studies in patients as part of phase II studies (BMD CAMN107A 2101-04, 2101-05).

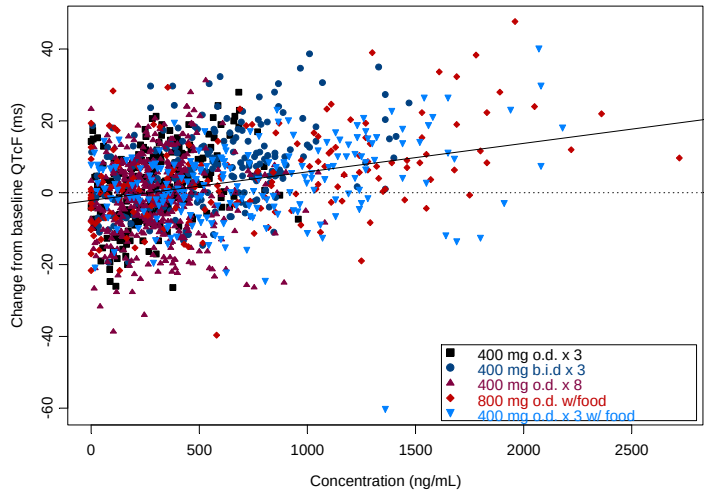
- Mechanism of action

No studies have been submitted.

- Primary and Secondary pharmacology

Studies measuring QTc prolongation was investigated in healthy volunteers and in the target population. Volunteers received either nilotinib or a placebo in one of the following regimens: 1)once daily doses of 400 mg for a total of 3 doses, 2) twice daily doses of 400 mg for a total of 5 doses, 3) once daily doses of 400 mg for a total of 8 doses, 4) a single dose of 800 mg with a high fat meal, and 5) once daily doses of 400 mg with a high fat meal for a total of 3 doses. The nilotinib concentration versus QTcF change from baseline in healthy subjects in shown in Figure 1:

Figure 1: Nilotinib concentration against change form baseline QTcF



Nilotinib at doses of 400 mg administered under fasting conditions on once daily schedule for 3 to 8 days had no consistent effects on the QTcF interval. When nilotinib was administered after a high fat meal as a single dose of 800 mg (C_{max} of 1669 ng/mL) or 400 mg once daily dose after a high fat meal for 3 days (day 3 C_{max} of 1532 ng/mL), the drug produced modest, but statistically significant increases in QTcF. The time averaged QTcF change was 6.4 msec (90% CI: 2.1-11 msec) for 400 mg once daily dose for 3 days with a high fat meal, and 7.4 msec (90% CI: 3.2-12 msec) for a single 800 mg dose with a high fat meal.

Studies measuring QTc prolongation was explored in the target population. In Phase IA of study 2101, the relationship between dose or serum concentration and changes in QTcF interval was measured. Table 10 shows the mean time-averaged change from baseline in QTcF by dose level.

Table 10: Dose level versus QTc mean change from baseline

Total daily dose (mg)	Regimen	Mean change from baseline (msec)	90% CI
200	o.d.	1.2	-2.5 - 5.0
400	o.d.	2.1	-1.0 - 5.2
800	o.d.	2.5	-0.8 - 5.9
1200	o.d.	1.8	-3.4 - 6.9
800	400 mg b.i.d.	6.2	3.3 - 9.1
1200	600 mg b.i.d.	7.6	3.4 – 12

A relationship between plasma concentration and effect was established. There was an association between nilotinib AUC and white blood count (WBC) reduction. Age and gender did not show a significant influence.

The promoter polymorphism of the UGT1A1 gene was investigated by DNA sequencing to identify an association between genetic variation and hyperbilirubinemia. The TA(7)/TA(7) genotype was identified to be associated with a statistically significant increase in risk of hyperbilirubinemia.

- Overall discussion and conclusion

Pharmacokinetics of nilotinib was reasonably well studied in healthy volunteers and in the target population. Nilotinib was not studied in a paediatric population and, thus, is not recommended to be used in children at this time, as stated in section 4.2 of the SPC.

Administration of nilotinib with food significantly increased AUC exposure, especially in high fat meals. Therefore, it is recommended that nilotinib not be taken with a meal in order to minimize the

effect of food on nilotinib bioavailability. A statement in this regard is included in sections 4.2, 4.4 and 4.5 of the SPC.

The dose-proportionality study of nilotinib demonstrated that nilotinib was not dose-proportional. The AUC and C_{max} exposure increased in a dose-dependent manner until a maximum dose of 400 mg q.d. was reached. A dose-limiting exposure was apparent above this dose, since increases above this level resulted in significantly less exposure to nilotinib than expected. This limitation is overcome to some extent by increasing the daily dose in two separate dosing steps; administering 400 mg nilotinib b.i.d. instead of 800 mg q.d. This dosing regimen was shown to increase nilotinib AUC exposure by 35%, where the mean maximum plasma concentration reached approximately 2260 ng/mL (SD 800).

A pharmacokinetic study based on the stratification of population was performed to identify extrinsic factors influencing the pharmacokinetic of nilotinib. There were no significant influences of weight, age and race on the pharmacokinetic properties of nilotinib, though data are insufficient for the latter. However, exposure in female patients appears to be increased by approximately 20%.
Pharmacokinetics in a paediatric population was not studied

The pharmacokinetic of nilotinib was not studied in patients with renal or hepatic impairment. Given the metabolism and excretion profile of nilotinib, pharmacokinetics of nilotinib are likely to be affected in patients with hepatic impairment but unlikely in patients with renal impairment. A warning statement regarding patients with renal and hepatic impairment was included in section 4.2 of the SPC and the company has committed to study PK in hepatic impaired patient as a post-authorization study.

Given that the solubility of nilotinib is poor in environments with pH values of >1, absorption of nilotinib may be compromised. Effects of neutralizing agents or antiemitics should be further investigated. The applicant has committed to perform a drug-drug interaction study with PPIs in healthy subjects as a follow-up measure. A special statement warning of these potential interactions has been included in the SPC, sections 4.4 and 4.5.

In vitro studies suggested that nilotinib may have the potential to inhibit several CYP enzymes, as well as inhibition of P-gp and UGT1A1. The applicant demonstrated a clinically significant increase in nilotinib exposure following co-administration with ketoconazole, a potent CYP3A4 inhibitor. Therefore, it is recommended that co-administration of nilotinib with other compounds that are inhibitors of CYP3A4 should be avoided. A warning statement stating the risks of co-administration of nilotinib with other CYP3A4 subtrates is included in sections 4.4 and 4.5 of the SPC. The effect of nilotinib on midazolam, a model substrate and inducer of CYP3A4, was moderate and does not suggest that nilotinib inhibition of CYP3A4 may be a clinically relevant issue. However, the applicant will provide the final report on a drug-drug interaction study with a CYP3A4 inducer like rifampicin as a post-authorization follow-up measure, as this may have important safety implications. The applicant also commits to provide post-authorization studies to quantify the possible effect of nilotinib on CYP2C8, CYP2C19, CYP2D6, p-glycoprotein and UGT1A1.

Results from pharmacodynamic studies measuring QTc prolongation in healthy volunteers and target population show a significant increase in the mean time-averaged change from baseline in QTcF associated with nilotinib treatment. Therefore, nilotinib should be used with caution in patients who have or may develop prolongation of QTc, including co-treatment with other drugs that may prolong QTc. An appropriate warning to the effect was included in sections 4.2, 4.4, 4.5 and 4.8 of the SPC. In addition an educational material addressing the cardiac risks associated with nilotinib will be provided to prescribers and pharmacists prior to launch.

Clinical efficacy

The clinical efficacy program of nilotinib in imatinib-resistant/intolerant Ph+ CML in CP or AP was based on study 2101, an uncontrolled unblinded, non-randomised, multi-centre Phase IA/II trial which contained several treatment arms, two of which provided the CML patient cohorts: Study 2101E2 (Phase II) for the indication in patients with CML-Chronic Phase (CML-CP) and study 2101E1 (Phase II) for the indication in patients with CML-Accelerated Phase (CML-AP). In addition, some supportive efficacy was provided in the Phase I part of the study.

- Dose response study(ies)

The dose-escalation Phase IA component of study 2101 evaluated the safety, tolerability, biologic activity, and pharmacokinetic (PK) profile of nilotinib. Eligibility criteria included age ≥ 18 years with imatinib-resistant Ph+ CML in CP, AP or BC; or relapsed/refractory Ph+ ALL, adequate performance status (WHO ≤ 2), and normal hepatic, renal, and cardiac functions. 119 patients were enrolled and analyzed.

Nilotinib hard gelatin capsules were administered orally and dose strengths of 50mg and 200mg were supplied. The starting dose was a flat dose of 50 mg administered continuously on a once-daily schedule, repeated as a 28-day cycle. A second schedule evaluated twice-daily dosing, starting at 400 mg orally. Following completion of cycle 1 (28 days), treatment with nilotinib continued until the patient experienced unacceptable toxicity or disease progression.

The two-sample MCRM model determined that 600 mg b.i.d was the maximum tolerated dose (MTD). The criteria for selection of a dose regimen included the PK profile, the hematologic and cytogenetic responses observed, and safety data of patients in the CML-AP cohort (see Table 11). The 400 mg b.i.d. dose regimen was selected for evaluation in the Phase II component of the study.

Table 11: Study 2101PhI_PK

Nilotinib				**Steady-state (day 15) AUC0-24h (ng·h/mL)**	
Group	**Initial dose (mg)**	**HR (%)**	**Time to first HR (days)**	**All patients [a)]**	**CML-AP patients [b]**
1	50-200 o.d	13	76	6880 (4750)	6110(2350-14600)
2	400-1200 o.d.	41	87	26000 (13800)	24900 (5770-65900)
3	400 b.i.d	64	43	36000 (11800)	35200 (14600-61000)
4	600 b.i.d.	78	29	32800 (13800)	28900 (16000-61500)

a) Mean (SD) of dose group
b) Median (range) of dose group

- Main studies

a) Study 2101 E2: For patients who are resistant to or intolerant of imatinib with CML-Chronic phase (CML-CP)

METHODS

Study Participants

The study population included adult patients with CML-CP who were imatinib-resistant or imatinib-intolerant under the following criteria:

Imatinib resistance for CML-CP patients included:
1. Any of the following occurring during imatinib therapy:
• Patients who have failed to achieve CHR after 3 months of imatinib therapy or have lost a CHR.
• Loss of CHR defined as any of the following documented 2 times, at least 2 weeks apart:
    1. WBC ≥ 20.0 x 109/L and not attributable to other causes (e.g. infection)
    2. Platelet count ≥ 600 x 109/L
    3. Appearance of ≥ 5% myelocytes + metamyelocytes in the peripheral blood
    4. Appearance of blasts or promyelocytes in the peripheral blood
    5. Splenomegaly to a size ≥ 5 cm below the left costal margin
• Patients who had failed to achieve at least a minimal cytogenetic response after 6 months of imatinib therapy or patients who had lost a minimal cytogenetic response documented on 2 separate occasions.
• Patients who had failed to achieve a major cytogenetic response after 12 months of imatinib therapy or patients who had lost a major cytogenetic response documented on 2 separate occasions.
• Cytogenetic relapse, defined by ≥ 30% increase in bone marrow Ph+ metaphase cells, documented on 2 separate occasions.

• Clonal evolution, defined by the presence of additional chromosomal abnormalities in the Ph-positive cells, excluding variant Ph translocations, loss of chromosome Y, or constitutional abnormalities.
2. Patients otherwise eligible for study receiving < 600 mg imatinib per day must have been treated with ≥ 600 mg per day for a minimum of 3 months, unless they met the criteria outlined below for the definition of imatinib intolerance, or unless there was a disease progression defined as any of the following:
• Doubling of any of the following: total peripheral WBC, basophils, blasts or platelets, documented on 2 separate occasions at least 1 week apart
• Development of grade 3/4 disease-related symptoms (bone pain, fever, weight loss, anorexia)
• The presence of one of the following amino acid mutations detected by direct sequencing:
• L248, G250, Q252, Y253, E255, T315, F317, H396

Imatinib intolerance (at any dose and/or duration) included patients who did not have a major cytogenetic response to imatinib, and had discontinued imatinib therapy due to the following: Grade 3 or 4 adverse events that persisted in spite of optimal supportive care measures, for example: skin rash, fluid retention, cardiopulmonary events, thrombocytopenia, liver function abnormalities, peripheral neuropathy and diarrhea; or Grade 2 adverse events related to imatinib therapy, in spite of optimal supportive care measures, that persisted for ≥ 1 month or that recurred for more than 3 times whether dose was reduced or discontinued.

Eligibility criteria included patients age ≥ 18 years with imatinib resistant or intolerant CML-CP, with adequate performance status (WHO ≤ 2), and normal hepatic, renal, and cardiac functions. Inclusion criteria required <15% blasts in peripheral blood and bone marrow, < 30% blasts plus promyelocytes in peripheral blood and bone marrow, < 20% basophiles in the peripheral blood, ≥ 100 x 10^9/L (≥ 100,000/mm^3) platelets, no evidence of extramedullary leukemic involvement, with the exception of liver or spleen and no prior treatment with an investigational TKI other than imatinib. Exclusion criteria included patient undertaking medication that have the potential to prolong the QT interval or are CYP3A4 inhibitors or any treatment with hematopoietic colony-stimulating growth factors (e.g., G-CSF, GMCSF) ≤ 1 week prior to starting study drug. Erythropoietin was allowed.

Treatments

The dose for Phase II was 400 mg nilotinib b.i.d. (total daily dose of 800 mg). Patients may have had a dose escalation to 600 mg b.i.d. according to escalation criteria.

Objectives

Primary objective:

- To evaluate the efficacy and safety of nilotinib in patients with imatinib-resistant or intolerant CML-CP

Secondary objectives included:

- To detect of BCR-ABL transcripts by Q-RT-PCR, to detect Crk-L protein by western blot and to perform a mutational analysis of the BCR-ABL kinase domain during and after therapy in malignant cells taken from the bone marrow and/or blood
- To evaluate the population pharmacokinetics of nilotinib
- To examine whether individual genetic variation in genes relating to drug metabolism, CML and the drug pathway confer differential response to nilotinib
- To identify gene expression patterns in tumor cells that are associated with treatment response to nilotinib or that correlate with the severity or progression of CML

Outcomes/endpoints

The primary efficacy variable for CML-CP was major (complete + partial) cytogenetic response (MCyR).

The secondary efficacy variables included: loss of MCyR, duration of MCyR, rate of CHR, loss of CHR, duration of CHR, time to treatment failure (TTF), time to AP or BC, major molecular response (MMR), number (and percent) of patients who received stem cell transplants (HSCT), and overall survival (OS). Additional efficacy variables included: time to MCyR, time to CHR, time to progression (TTP). Baseline mutations and gene expression patterns during and after therapy were also investigated.

Sample size

The protocol-specified efficacy analysis for CML-CP is defined for the time when the first 132 patients either completed 12 months of treatment, discontinued the study, or a confirmed hematologic response had been observed. The sample size was calculated assuming a true response rate of $p \geq 20\%$, based on a one-sided level of significance of 2.5% and a power of 90%.

An interim analysis was scheduled when the first 132 patients either completed 6 months of treatment or discontinued study. The interim analysis took place with a data cut-off from the 04 May 2006 and is the basis of this MAA. Additional cut-off dates for follow-up data collection were performed on 04 Sep 2006 and 04 Jan 2007.

Randomisation and blinding (masking)

There was no randomisation or blinding in this open and uncontrolled phase II study.

Statistical methods

The study was designed to evaluate the major (complete + partial) cytogenetic response rate using Fleming's single-stage, single-arm test procedure to test H_0: $p \leq 10\%$ where p is the major cytogenetic response rate.

Assuming a true response rate of $p \geq 20\%$, with $\alpha = 2.5\%$ (one-sided) and power = 90%, the required number of responders were 21/132 in the CML-CP patient group. Response rate was calculated and 95% confidence interval (CI) was provided using Pearson-Clopper limits. Time-to-event variables were analyzed using Kaplan-Meier method.

Safety variables were analyzed by frequency counts of adverse events, newly-occurring or worsening grade 3-4 laboratory abnormalities along with shift table analysis and of QT prolongation.

Patients who discontinued before any cytogenetic assessment were considered as non-assessable (NA) in terms of efficacy evaluation, except for patients who discontinued due to progression (PD) or death without any cytogenetic assessment, in which case patients were considered as 'PD' or 'Death'. For patients who discontinued the study, any assessment after the discontinuation was not used for efficacy evaluation. Date of study discontinuation was considered as the date of study completion visit or date of last dose of nilotinib.

Subgroup analysis was performed in the ITT primary population concerning the matter of resistance or intolerance on demographic and disease factors and with regard to the item dose escalation.

RESULTS

Participant flow and Recruitment

The originally planned and required sample size of 132 patients (primary enrolment) was recruited between 21 April 2005 and 17 October 2005. Patients from North America (N=35), Europe (N=93) Australia (N=2) and Asia (=2) from 63 centres in 10 participating countries (USA, Belgium, Germany, Spain, France, Italy, Netherlands, UK, South Korea and Australia) were enrolled. The cut-off date at the time of the initial MAA was on 4 May 2006 for this primary population. Additional patients were enrolled according to protocol, in order to provide continued patient access to nilotinib. Later cut-off

dates for collection of efficacy and safety data were performed on 04 Sep 2006 and 04-Jan-2007 from total of 280 and 320 patients respectively (overall populations).

The majority of treatment discontinuations in the overall population were because of adverse events (15.9%) or disease progression (15.9%) (cut-off 4 Jan 2007).

Conduct of the study

Ten amendments were made to the original protocol. The most important was amendment 8 (dated Feb 2006) which included modifications regarding cardiac safety:

- Contraindication, unless absolutely necessary, of concomitant administration of agents that prolonged the QT interval and CYP3A4 inhibitors. In cases where unavoidable, a strong recommendation that ECG be obtained 24 to 48 hours and one week after initiating the concomitant therapy
- Revision of criteria for discontinuation or dose reduction of nilotinib based on ECG QTc prolongation
- Lowering of the maximal QTcF for inclusion: from 480 to 450 msec
- Exclusion of patients diagnosed with or treated for unstable angina during the past 12 months

Protocol violations occurred in 51.5 % (68/132) of all ITT primary patients (cut-off 4 May 2006): 28 were considered major violations and led to exclusion of patients from per-protocol efficacy analyses.

Baseline data

The median time since first diagnosis of CML was 4.6 years with a range from 0.4 to 22.9 years. Approximately half of all patients (48.2%) were diagnosed with CML ≥ 5 years prior to study entry. The majority of patients (57.4%) had achieved prior cytogenetic response. In approximately one third of all patients, a complete haematologic response (CHR) was the best response achieved and about 9% never reached CHR. In the ITT primary population, 68.9% of the patients were imatinib resistant. The majority (58.3%) of these patients had received ≥600 mg of imatinib per day for at least 3 months. Of the remaining patients, 4.5% had not received ≥600 mg of imatinib per day for at least 3 months and had evidence of disease progression, and 6.1% of all patients had not received ≥600 mg of imatinib per day for at least 3 months and did not have evidence of disease progression. Overall, less than one third (31.1%) of the ITT primary patients were imatinib-intolerant.

Baseline and disease characteristics of CML-CP patients are summarized in Table 12:

Table 12: Demographics and disease characteristics at baseline, CML-CP patients in Study 2101E2 (ITT primary population).

Demographic variable	No prior TKI except imatinib N=132	Disease history	No prior TKI except imatinib N=132
Age (years)		Baseline CHR	
Mean ± SD	56.4±13.10	Yes	46 (34.8)
Median	58.0	No	86 (65.2)
min - max	26.0-85.0	Time since first diagnosis of CML (Median months)	56.5
Age category (n(%))		Number (%) of patients	
<35 years	9 (6.8)	Imatinib-resistant	91 (68.9)
≥ 35 - < 55 years	42 (31.8)	Imatinib-intolerant	41 (31.1)
≥ 55 - < 65 years	45 (34.1)		
≥ 65 years	36 (27.3)	Prior highest imatinib dose (n (%))≥ 600 mg	97 (73.5)
Sex (n (%))		Prior stem cell transplant	1(0.8)
Male	72 (54.5)		
Female	60 (45.5)	Prior interferon	53 (40.2)
Race (n (%))		Baseline BM blasts ≥50%	0
Asian (Oriental)	2 (1.5)	BCR-ABL mutations	
Black	3 (2.3)	N*	34
Caucasian	127 (96.2)	n (%)	21 (61.8)
Other	0 (0.0)	Prior TKI	0
Weight (kg)			
n	130		
Mean ± SD	77.6 ±14.71		
Median	76.8		
min - max	43.0-117.5		
WHO performance status (n (%))			
Grade 0	95 (72.0)		
Grade 1	36 (27.3)		
Grade 2	1 (0.8)		

Numbers analysed

Efficacy populations were defined as follows:

ITT primary population includes the first 132 CML-CP patients who have either completed 6 months of treatment or discontinued study. Patients with major protocol violations were considered non responders regardless of whether or not they experienced a response.

Conventional ITT population consisted of all patients in the ITT primary population who were assessed for their response irrespective of any major protocol violation. In the ITT primary population, patients with major protocol violations were considered non responders. In the revised ITT population, actual observed responses of these major protocol violators were considered.

Per-protocol (PP) population consisted of all patients in the ITT primary population who had no major protocol violations. The list of patients eligible for the PP population was finalized prior to database lock.

In addition, two categories of patients were distinguished based on the time of their enrolment:

Primary enrolment consists of the first 132 consecutively enrolled CML-CP patients. This is the patient population as specified in the statistical analysis plan of the original MAA.

Overall enrolment includes all 320 patients in the study, including the first primary enrolled 132 patients mentioned above.

All efficacy analyses were based on the ITT primary population. In addition, cytogenetic and haematologic responses were analyzed using per-protocol populations. Populations analysed (cut-off 04 May 2006) were as follows:

ITT primary population	**N = 132**
Baseline CHR	46 (34.8%)
Baseline not CHR	86 (65.2%)
Per-protocol (hematologic response)	115 (87.1%)
Per-protocol (cytogenetic response)	105 (79.5%)

The median duration of exposure for the different updates is summarized in Table 13:

Table 13: Duration of exposure in CML-CP patients

	Primary enrollment			Overall enrollment	
	N = 132			N=280	N = 320
Cut-off date	4 May 2006	4 Sept 2006	4 Jan 2007	4 Sept 2006	4 Jan 2007
Mean exposure (days ±SD)	**211 (106)**	**288 (157)**	**353 (209)**	**250 (133)**	**316 (169)**
Median exposure (days)	**235**	**355.0**	**460**	**261**	**341**
Exposure range (days)	**3 - 379**	**3 - 502**	**3 - 624**	**1 - 502**	**1 – 624**

Outcomes and estimation

Primary Endpoint:
The primary efficacy endpoint for CML-CP patients was the overall major cytogenetic response rate (MCyR = complete + partial cytogenetic response) (see Tables 14 and 15).

Table 14: Response rates in CML-CP patients

Best response, n (%)	**ITT primary**		**Conventional ITT**	
	Primary enrolment N = 132	Overall enrolment N = 320	Primary enrolment N = 132	Overall enrolment N = 320
Major Cytogenetic Response	59 (44.7)	156 (48.8)	68 (51.5)	180 (56.3)
Complete Cytogenetic Response	39 (29.5)	110 (34.4)	45 (34.1)	128 (40.0)
Partial Cytogenetic Response	20 (15.2)	46 (14.4)	23 (17.4)	52 (16.3)
	N=86	N=206	N=86	N=206
Complete Hematologic Response (patients not in CHR at baseline)	62 (72.1)	144 (69.9)	66 (76.7)	157 (76.2)

The response data for imatinib resistant and imatinib intolerant CML-CP patients are presented in Table 15. Only imatinib intolerant patients who had not previously achieved a major cytogenetic response with imatinib were eligible.

Table 15: Response rate in imatinib-resistant and –intolerant CML-CP patients (primary ITT)

Best response, n (%)	**Primary enrolment**		**Overall enrolment**	
	Resistant N = 91	Intolerant N = 41	Resistant N = 226	Intolerant N = 94
Major Cytogenetic Response	41 (45.1)	18 (43.9)	107 (47.3)	49 (52.1)
	N = 64	N = 22	N = 154	N= 52
Complete Hematologic Response (patients not in CHR at baseline)	44 (68.8)	18 (81.8)	99 (64.3)	45 (86.5)

Secondary Endpoints:

Table 15 presents the rates of patients in continuous MCyR at 3, 6 and 12 months. The duration of response was defined conservatively as the time from the date of first occurrence of the response to the earliest date of the following: loss of response, progression to next disease phase, discontinuation due to AE, lab abnormality, progressive disease, or death.

Table 15: Estimated duration of major cytogenetic response in CML-CP patients (primary ITT)

Estimated response duration	Primary enrolment Patients with MCyR N = 59	Overall enrolment Patients with MCyR N = 156
3 month rate of continuing MCyR	86.1%	86.6%
6 month rate of continuing MCyR	69.7%	72.4%
12 month rate of continuing MCyR	56.6%	60.6%

Table 16 presents the time to progression (defined as the time from the date of first study drug to the earliest date of loss of response, progression, discontinuation due to progression of disease or death). As the median time to progression has not yet been reached, only 3, 6 and 12 month estimates are presented below.

Table 16: Estimated time to progression in CML-CP patients (primary ITT)

Estimated time to progression	Primary enrolment N = 132	Overall enrolment N = 320
3 month of no progression	92.6%	93.6%
6 month of no progression	89.7%	87.8%
12 month of no progression	79.2%	76.5%

Table 17 presents the overall survival for the overall CML-CP patient population which also includes survival follow-up data after patients discontinued the study. As the median overall survival has not yet been reached, only 3, 6 and 12 month estimates are presented below.

Table 17: Estimated survival rate in CML-CP patients

Estimated survival rate	Overall enrolment N = 320
3 month	99.4%
6 month	99.1%
12 month	95.5%

b) Study 2101 E1: For patients who are resistant to or intolerant of imatinib with CML-Accelerated phase (CML-AP)

METHODS:

Study Participants

The study population was defined as including adult patients with CML-AP who were imatinib-resistant / intolerant under the following criteria:

Imatinib resistance for CML-AP patients included:
1. Any of the following during imatinib therapy with at least 600 mg per day (unless they met the criteria outlined below for the definition of imatinib intolerance):
    - Disease progression from CP to AP occurring during imatinib therapy.
    - Disease progression defined as ≥ 50% increase in peripheral white blood cell count, blast count, basophils, or platelets during imatinib therapy for AP.
    - Lack of hematologic response in the bone marrow following a minimum of 4 weeks of imatinib therapy for AP.
2. Patients otherwise eligible for study receiving < 600 mg per day were eligible if the presence of one of the following amino acid mutations was detected by direct sequencing:
    - L248, G250, Q252, Y253, E255, T315, F317, H396 CML-AP patients who became resistant during chronic phase and met the definition of imatinib resistant in the CML-chronic phase were eligible for entry.

Imatinib intolerance included patients who did not have a major cytogenetic response to imatinib, and had discontinued imatinib therapy due to the following: Grade 3 or 4 adverse events that persisted in spite of optimal supportive care measures, for example: skin rash, fluid retention, cardiopulmonary events, thrombocytopenia, liver function abnormalities, peripheral neuropathy and diarrhea; or Grade 2 adverse events related to imatinib therapy, in spite of optimal supportive care measures, that persisted for ≥ 1 month or that recurred for more than 3 times whether dose was reduced or discontinued.

Eligibility criteria included patients with imatinib resistant or intolerant CML-AP, defined as never in blast crisis before starting treatment, age ≥ 18 years, with adequate performance status (WHO ≤ 2), and normal hepatic, renal, and cardiac functions. One or more of the following criteria had to be present within 4 weeks prior to beginning treatment: 1. ≥ 15% but < 30% blasts in blood or bone marrow, 2. ≥ 30% blasts plus promyelocytes in peripheral blood or bone marrow (providing that < 30% blasts present in bone marrow), 3. Peripheral basophils ≥ 20%, 4. Thrombocytopenia < 100 X 109/L unrelated to therapy. The same exclusion criteria as in patients with chronic phase CML were applied including no prior treatment with an investigational TKI other than imatinib.

Treatments

The dose for Phase II was 400 mg nilotinib b.i.d. (total daily dose of 800 mg). Patients may have had a dose escalation to 600 mg b.i.d. according to escalation criteria.

Objectives

The primary objective was to evaluate the efficacy and safety of nilotinib in patients with imatinib-resistant or intolerant CML-AP.

Secondary objectives were the same as for patients with chronic phase CML.

Outcomes/endpoints

The primary efficacy variable for CML-AP was confirmed overall hematologic response (HR).

The secondary efficacy variables included: loss of HR, loss of complete hematologic response (CHR), duration of HR, time to HR, time to progression, time to treatment failure (TTF), cytogenetic response (CyR), loss of major cytogenetic response (MCyR), loss of complete cytogenetic response (CCyR), duration of MCyR/CCyR, time to MCyR/CCyR, major molecular response (MMR), number (and percent) of patients who received stem cell transplants, and overall survival (OS). Additional efficacy variables included: time to CHR, time to MCyR, time to progression (TTP). Baseline mutations and gene expression patterns during and after therapy were also investigated.

Sample size and statistical methods

The protocol-specified Group A efficacy analysis for CML-AP was to be performed after the first 132 CML-AP patients either completed 24 weeks of treatment, discontinued the study, or a confirmed hematologic response had been observed. However, the Phase-IA results demonstrated that the majority of patients achieved a hematologic response well before 24 weeks of treatment. The median time to best hematologic response for CML-AP patients was 28 days and the observed rate of hematologic response (76%) achieved in Phase IA was much higher than anticipated (20%). Based on this observations, the claim of efficacy for CML-AP patients was modified to the first 64 patients included in the study who have completed 4 months of treatment or discontinued study.

Randomization/blinding (masking)

There was no randomisation or blinding in this open and uncontrolled phase II study.

Statistical methods
The study was designed to evaluate the confirmed overall hematologic response rate using Fleming's single-stage, single-arm test procedure to test H0: $p \leq 10\%$ where p is the hematologic response rate. Assuming a true response rate of $p \geq 25\%$, with $\alpha = 2.5\%$ (one-sided) and power = 90%, the required number of responders were 12/64 in the CML-AP patient group. Response rate was calculated and 95% confidence interval (CI) was provided using Pearson-Clopper limits. Time to event variables was analyzed using Kaplan-Meier method.

RESULTS

Participant flow and Recruitment

The originally planned and required sample size of 64 patients (primary enrolment) was recruited between 9 May 2005 and 18 January 2006. The cut-off date at the time of the initial MAA was on 23 May 2006 for this primary population. Additional patients were enrolled according to protocol, in order to provide continued patient access to nilotinib. Later cut-off dates for collection of efficacy and safety data were performed on 23 Sep 2006 and 23 Jan 2007 from total of 96 and 119 patients respectively (overall populations).

The majority of treatment discontinuations in the overall population were because of adverse events (15 patients, 12.6%) or disease progression (35 patients, 29.4%) (cut-off 23 Jan 2007).

Conduct of the study

The conduct of the study was the same as in patients with chronic phase CML. The same ten substantial amendments also apply for accelerated phase CML patients.

Protocol violations occurred in 76.6% (49/64) of all ITT primary patients (cut-off 4 May 2006). 28 were considered major violations and led to exclusion of patients from per-protocol efficacy analyses.

Baseline data

Baseline and disease characteristics of CML-CP patients are summarized in Table 18:

Table 18: Demographics and disease characteristics at baseline, CML-AP patients in Study 2101E1 (ITT primary population).

Demographic variable	**No prior TKI except imatinib N=64**	**Disease history**	**No prior TKI except imatinib N=64**
Age (years)			
Mean ± SD	58.8 ± 12.89	Time since first diagnosis of CML (median months)	73.6
Median	61.0	mini - max	2.2 - 298.2
min - max	24 - 79		
Age category (n(%))		Number (%) of patients	
<35 years	4 (6.3)	Imatinib-resistant	52 (81.3)
≥ 35 - < 55 years	13 (20.3)	Imatinib-intolerant	12 (18.8)
≥ 55 - < 65 years	25 (39.1)		
≥ 65 years	22 (34.4)	Prior highest imatinib dose (n (%))≥ 600 mg	53 (82.9)
Sex (n (%))		Prior stem cell transplant	1
Male	34 (53.1)		
Female	30 (46.9)	Prior interferon	23 (35.9)
Weight (kg)		Baseline BM blasts ≥50%	0
n	130	BCR-ABL mutations	
Mean ± SD	77.6 ±14.71	N*	14
Median	76.8	n (%)	11 (79)
min - max	43.0-117.5	Prior TKI	0
WHO performance status (n (%))			
Grade 0	28 (43.8)		
Grade 1	30 (46.9)		
Grade 2	5 (7.8)		
Grade >2	1 (1.6)		

Numbers analysed

All efficacy analyses were based on the ITT primary population. In addition, cytogenetic and hematologic responses were analyzed using per-protocol populations. For the definitions of the populations please refer to the respective bullet point in the chronic phase CML arm above.

Populations analysed (cut-off 23 May 2006) are as follows:

ITT primary population	**N = 64**
Per-protocol (hematologic response)	45 (70.3%)
Per-protocol (cytogenetic response)	55 (85.9%)

In addition the two categories of patients based on the time of their enrolment were:

Primary enrolment: the first 64 consecutively enrolled CML-AP patients. This is the patient population as specified in the statistical analysis plan of the original MAA.

Overall enrolment: Since the study was still enrolling at the time of data cut-off, out of the 127 patients enrolled at the cut-off date, the efficacy population included the 119 patients who have either completed 6 months of treatment or discontinued from the study for progressive disease, including the first primary enrolled 64 patients mentioned above.

Outcomes and estimations

Primary Endpoint:

Table 19 presents the rates of hematologic response (primary efficacy endpoint) as well as for MCyR in CML-AP patients.

Table 19: Response rates in CML-AP patients

Best response, n (%)	**ITT primary**		**Conventional ITT**	
	Primary enrolment N = 64	Overall enrolment N = 119	Primary enrolment N = 64	Overall enrolment N = 119
Hematologic Response	33 (51.6)	50 (42.0)	39 (60.9)	56 (47.1)
Complete Hematologic Response	19 (29.7)	30 (25.2)	20 (31.3)	31 (26.1)
Marrow response/No evidence of leukemia	5 (7.8)	8 (6.7)	8 (12.5)	11 (9.2)
Return to chronic phase	9 (14.1)	12 (10.1)	11 (17.2)	14 (11.8)
Major Cytogenetic Response (complete + partial)	19 (29.7)	32 (26.9)	22 (34.4)	35 (29.4)

The response data for imatinib resistant and imatinib intolerant CML-AP patients are presented in Table 20. Only imatinib intolerant patients who had not previously achieved a major cytogenetic response with imatinib were eligible.

Table 20: Response rate in imatinib-resistant and –intolerant CML-AP patients (primary ITT)

Best response, n (%)	Primary enrolment		Overall enrolment	
	Resistant N = 53	Intolerant N = 11	Resistant N = 96	Intolerant N = 23
Confirmed Hematologic Response	29 (54.7)	4 (36.4)	41 (42.7)	9 (39.1)
Major Cytogenetic Response (complete + partial)	16 (30.2)	3 (27.3)	25 (26.0)	7 (30.4)

Secondary Endpoints:

Table 21 presents the duration of confirmed HR. The duration of response was defined conservatively as the time from the date of first occurrence of the response to the earliest date of the following: loss of response, progression to next disease phase, discontinuation due to AE, lab abnormality, progressive disease, or death. As the median duration has not yet been reached, only 3, 6 and 12 months response rates are presented below.

Table 21: Estimated duration of first hematologic response in CML-AP patients (primary ITT)

Estimated response duration	Primary enrolment Patients with HR N = 33	Overall enrolment Patients with HR N = 50
3 month rate of continuing HR	93.9%	94.0%
6 month rate of continuing HR	77.4%	78.0%
12 month rate of continuing HR	69.7%	70.4%

Table 22 presents the time to progression (defined as the time from the date of first study drug to the earliest date of loss of response, progression, discontinuation due to progression of disease or death). As the median time to progression has not yet been reached, only 3, 6 and 12 month estimates are presented below.

Table 22: Estimated time to progression in CML-AP patients (primary ITT)

Estimated time to progression	Primary enrolment N = 64	Overall enrolment N = 119
3 month of no progression	84.9%	84.9%
6 month of no progression	66.2%	69.5%
12 month of no progression	55.9%	57.8%

Table 23 presents the overall survival for the overall CML-AP patient population which also includes survival follow-up data after patients discontinued the study. As the median overall survival has not yet been reached, only 3, 6 and 12 month estimates are presented below.

Table 23: Estimated survival rate in CML-AP patients

Estimated survival rate	Overall enrolment N = 119
3 month	97.5%
6 month	92.4%
12 month	78.5%

Ancillary analyses

- Analysis performed across trials (pooled analyses and meta-analysis)

Analyses across trials were not performed.

- Clinical studies in special populations

Clinical studies in special populations were not performed.

- Supportive studies

Supportive studies were not performed.

- Discussion on clinical efficacy

An open-label, uncontrolled, multicentre Phase II study was conducted to determine the efficacy of Tasigna 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 320 CP patients and 119 AP patients enrolled. Overall, 73% of patients were imatinib-resistant, while 27% were imatinib-intolerant. Median duration of treatment was 341 days for CP patients and 202 days for AP patients. Tasigna was administered on a continuous basis (twice daily 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. Dose escalation to 600 mg twice daily was allowed.

Efficacy data was updated by changing the cut-off date for the CML-CP study to 04-Jan-2007 and for the CML-AP study to 23-Jan-2007. This adds 8 months compared to the original submission resulting in a minimum follow-up of 14 months in the CML-CP study and 12 months in the CML-AP study. The efficacy data was confirmed in the updated cut-off. The MCyR and CHR are both convincing for the CML-CP population and CML-AP population respectively. Efficacy data in patients with CML-BC are not available. At present only dasatinib, which was approved in November 2006 after submission of the Tasigna application, is indicated in these patients. The efficacy of nilotinib appears to be similar to dasatinib, however not head to head comparison is available.

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 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 had even failed organ transplant. The median highest prior imatinib dose had been 600 mg/day for CP patients and 800 mg/day for AP patients. The highest prior imatinib dose was ≥600 mg/day in 75% of all patients, with 41% of patients receiving imatinib doses ≥800 mg/day.

Separate treatment arms were also included in the Phase II study to investigate Tasigna in a group of CP and AP patients who had been extensively pre-treated with multiple therapies including a tyrosine kinase inhibitor agent in addition to imatinib. The study is ongoing. Of these patients 30/36 (83%) were treatment resistant not intolerant. In 22 CP patients evaluated for efficacy Tasigna induced a 32% MCyR rate and a 50% CHR rate. In 11 AP patients, evaluated for efficacy, treatment induced a 36%

overall HR rate.
After imatinib failure, 24 different Bcr-Abl mutations were noted in 45% of chronic phase and 57% of accelerated phase CML patients who were evaluated for mutations. Tasigna demonstrated efficacy in patients harbouring a variety of Bcr-Abl mutations associated with imatinib resistance, except T315I.

Clinical safety

The primary safety population included 438 imatinib-resistant/intolerant patients with CML-CP or CML-AP (318 patients with CML-CP/120 patients with CML-AP) treated with 400 mg b.i.d. of nilotinib during the two pivotal phase II treatment arms of study 2101 (2101E2 in CML-CP and 2101E1 in CML-AP). Dose escalation to 600 mg b.i.d. was performed only in a small number of patients (12.9% and 21.7%). Additional supportive safety data was presented from the Phase I of Study 2101 and some other small studies. Overall the safety information derived from these studies is in line with the findings in the pivotal studies.

- Patient exposure

The median duration of exposure for the CML-CP and CML-AP patients is summarized in Table 24:

Table 24: Duration of exposure for safety analyses in CML-CP and CML-AP patients

Duration of exposure	CML-CP N = 320	CML-AP N = 127
Mean exposure (±SD) – days	315.8 (168.7)	225.9 (156.4)
Median exposure – days	341.0	190.0
25^{th} -75^{th} percentiles	196.0 – 437.0	113.0 – 349.0
Exposure range – days	1 – 624	2 – 611
< 3 months	52 (16.3%)	24 (18.9%)
≥ 3 months - < 6 months	25 (7.8%)	36 (28.3%)
≥ 6 months - < 12 months	99 (30.9%)	38 (29.9%)
≥ 12 months	144 (45.0%)	29 (22.8%)

The mean dose intensity was roughly 700 mg/day (± 202 mg/day), comparable for both indications and corresponded to 400 mg b.i.d dosing.

- Adverse events

The most frequently observed adverse events (AEs) in patients with CML-CP or CML-AP (Phase II of Study 2101) are shown for each disease stage in Table 25. Overall, haematological and myelosuppressive toxicity was noted as the most frequent cause of AEs, followed by gastrointestinal and skin related AEs. Due to short duration of treatment, especially in CML-CP patients, no assessment concerning changes of AEs after long term exposure was possible.

Table 25: Frequent adverse events (more than 5%, cut-off 4 May 2006) – Studies 2101E2 and 2101E1

Preferred term	CML-CP (2101E2) N = 282 n (%)	CML-AP (2101E1) N = 89 n (%)	Total N = 371 n (%)
Patients with AE(s)	270 (95.7)	88 (98.9)	358 (96.5)
Thrombocytopenia	71 (25.2)	34 (38.2)	105 (28.3)
Rash	74 (26.2)	26 (29.2)	100 (27.0)
Nausea	83 (29.4)	14 (15.7)	97 (26.1)
Headache	78 (27.7)	17 (19.1)	95 (25.6)
Pruritus	75 (26.6)	18 (20.2)	93 (25.1)
Diarrhea	58 (20.6)	16 (18.0)	74 (19.9)
Anemia	47 (16.7)	26 (29.2)	73 (19.7)
Fatigue	59 (20.9)	14 (15.7)	73 (19.7)
Constipation	53 (18.8)	19 (21.3)	72 (19.4)
Neutropenia	41 (14.5)	23 (25.8)	64 (17.3)
Vomiting	53 (18.8)	9 (10.1)	62 (16.7)
Arthralgia	43 (15.2)	14 (15.7)	57 (15.4)
Cough	39 (13.8)	16 (18.0)	55 (14.8)
Myalgia	37 (13.1)	15 (16.9)	52 (14.0)
Nasopharyngitis	43 (15.2)	8 (9.0)	51 (13.7)
Pyrexia	32 (11.3)	17 (19.1)	49 (13.2)
Pain in extremity	34 (12.1)	12 (13.5)	46 (12.4)
Asthenia	33 (11.7)	9 (10.1)	42 (11.3)
Bone pain	29 (10.3)	13 (14.6)	42 (11.3)
Abdominal pain	26 (9.2)	14 (15.7)	40 (10.8)
Lipase increased	29 (10.3)	8 (9.0)	37 (10.0)
Muscle spasms	24 (8.5)	13 (14.6)	37 (10.0)
Edema peripheral	28 (9.9)	7 (7.9)	35 (9.4)
Anorexia	23 (8.2)	11 (12.4)	34 (9.2)
Back pain	23 (8.2)	11 (12.4)	34 (9.2)
Abdominal pain upper	24 (8.5)	7 (7.9)	31 (8.4)
Alopecia	22 (7.8)	8 (9.0)	30 (8.1)
Dyspnea	26 (9.2)	4 (4.5)	30 (8.1)
Alanine aminotransferase increased	24 (8.5)	5 (5.6)	29 (7.8)
Insomnia	23 (8.2)	6 (6.7)	29 (7.8)
Night sweats	23 (8.2)	5 (5.6)	28 (7.5)
Blood bilirubin increased	19 (6.7)	6 (6.7)	25 (6.7)
Erythema	22 (7.8)	3 (3.4)	25 (6.7)
Upper respiratory tract infection	21 (7.4)	4 (4.5)	25 (6.7)
Weight decreased	21 (7.4)	4 (4.5)	25 (6.7)
Dry skin	20 (7.1)	3 (3.4)	23 (6.2)
Hyperbilirubinemia	17 (6.0)	6 (6.7)	23 (6.2)
Dyspepsia	19 (6.7)	2 (2.2)	21 (5.7)
Pharyngolaryngeal pain	15 (5.3)	6 (6.7)	21 (5.7)
Dizziness	19 (6.7)	1 (1.1)	20 (5.4)
Hyperhidrosis	17 (6.0)	2 (2.2)	19 (5.1)

Updated results from the 4 January 2007 cut-off confirm that the overall incidence of AEs was 99.1% in CML-CP patients and 96.7% in CML-AP patients. The most frequent study drug-related AEs in the overall population and in the CML-CP patients were thrombocytopenia (25.8%), rash (28.3%), pruritus (23.6%), nausea (22.3%), fatigue (19.8%), headache (17.6%), neutropenia (13.8%) and diarrhoea (10.4%). In CML-AP patients, the most frequent study drug-related AEs were thrombocytopenia (31.7%), neutropenia (20%), rash (20.8%), pruritus (17.5%), anaemia (15%) and constipation (10.8%). Lipase was increased in 11.6% of patients and bilirubin in 5,7% of patients.

Pancreatitis was reported in 3 CML-CP patients (0.7%) all grade 1-2 and 1 CML-AP patient (0.8%) – grade 2.

- Serious adverse event/deaths/other significant events

The most frequently observed CTC grade 3 or 4 AEs in patients with imatinib resistant or intolerant CML-CP or CML-AP are shown for each disease stage in Table 26:

Table 26: Frequent CTC grade 3 or 4 adverse events (more than 1%, cut-off 4 May 2006) – Studies 2101E2 and 2101E1

Preferred term	CML-CP (2101E2) N = 282 n (%)	CML-AP (2101E1) N = 89 n (%)	Total N = 371 n (%)
Any CTC grade 3 or 4 event	168 (59.6)	58 (65.2)	226 (60.9)
Thrombocytopenia	56 (19.9)	27 (30.3)	83 (22.4)
Neutropenia	37 (13.1)	21 (23.6)	58 (15.6)
Anemia	15 (5.3)	12 (13.5)	27 (7.3)
Lipase increased	14 (5.0)	6 (6.7)	20 (5.4)
Leucopenia	5 (1.8)	5 (5.6)	10 (2.7)
Diarrhea	6 (2.1)	2 (2.2)	8 (2.2)
Platelet count decreased	5 (1.8)	3 (3.4)	8 (2.2)
Arthralgia	7 (2.5)	0	7 (1.9)
Pneumonia	2 (0.7)	5 (5.6)	7 (1.9)
Abdominal pain	3 (1.1)	3 (3.4)	6 (1.6)
Blood bilirubin increased	5 (1.8)	1 (1.1)	6 (1.6)
Febrile neutropenia	3 (1.1)	3 (3.4)	6 (1.6)
Hyperbilirubinemia	5 (1.8)	1 (1.1)	6 (1.6)
Myalgia	5 (1.8)	1 (1.1)	6 (1.6)
Neutrophil count decreased	3 (1.1)	3 (3.4)	6 (1.6)
Thrombocythemia	4 (1.4)	2 (2.2)	6 (1.6)
Alanine aminotransferase increased	5 (1.8)	0	5 (1.3)
Angina pectoris	4 (1.4)	1 (1.1)	5 (1.3)
Blood amylase increased	3 (1.1)	2 (2.2)	5 (1.3)
Fatigue	4 (1.4)	1 (1.1)	5 (1.3)
Hemoglobin decreased	0	5 (5.6)	5 (1.3)
Headache	4 (1.4)	1 (1.1)	5 (1.3)
Myocardial infarction	4 (1.4)	1 (1.1)	5 (1.3)
Rash	5 (1.8)	0	5 (1.3)
Hyperglycemia	4 (1.4)	0	4 (1.1)
Pain in extremity	3 (1.1)	1 (1.1)	4 (1.1)

Updated results from the 4 January 2007 cut-off confirm that a majority of CML patients experienced severe AEs (SAE) during the course of the study, with 69.5% of CML-CP patients and 67.5% of CML-AP patients presenting CTC grade 3 or 4 AEs. The most frequently reported CTC grade 3 or 4 AEs overall included thrombocytopenia (25.3%), neutropenia (16.7%), anaemia (8.7%) and increased lipase (7.5%). In CML-CP patients, the most frequently reported CTC grade 3 or 4 AEs were identical to above (22%, 15.4%, 6.9% and 6.9% for thrombocytopenia, neutropenia, anaemia and increased lipase, respectively). In CML-AP patients, additional frequently reported CTC grade 3 or 4 AEs included leucopenia (6.7%), pneumonia (4.2%) and decreased haemoglobin (4.2%).

The most frequent SAEs overall were related to blood and lymphatic system disorders (7.3%), followed by those of cardiac disorders (5.7%), gastrointestinal disorders (4.6%), general disorders (5.3%), and infections and infestations (5.5%). In CML-CP patients, the most frequent SAEs were thrombocytopenia (2.8%), neutropenia (1.9%), and myocardial infarction (1.3%). In CML-AP patients, the most frequent SAEs were thrombocytopenia (7.5%), neutropenia (6.7%) and pneumonia (5.0%). 3 Patients (0,8%) were reported with pancreatitis as SAE.

Blood and lymphatic disorders

Myelosuppression was a common finding. Thrombocytopenia, neutropenia, and anaemia were the most frequently reported grade 3 and 4 laboratory abnormalities in CML-CP and CML-AP patients.

- The incidences of treatment-emergent CTC grade 3-4 thrombocytopenia in CML-CP and CML-AP patients were 22% and 34.2%, respectively.
- The incidences of treatment-emergent CTC grade 3-4 neutropenia in CML-CP and CML-AP patients were 15.7% and 30%, respectively.
- The incidences of treatment-emergent CTC grade 3-4 anaemia in CML-CP and CML-AP patients were 6.9% and 13.3%, respectively.

In the CML-CP population, the most frequent CTC grade 3-4 haematological abnormalities concerned absolute lymphocytes (24%), neutrophils (28.3%), white blood count (17.1%) and platelet counts (11.2%). The median time to first grade 3 or 4 neutropenia, thrombocytopenia, anaemia and leucopenia was 49.5, 39, 46 and 50.5 days, respectively. The median duration of grade 3 or 4 neutropenia, thrombocytopenia, anaemia and leucopenia was 15, 22, 8 and 15 days, respectively (cut-off date 4 May 2006).

In the CML-AP population, the findings were similar: the most frequent CTC grade 3-4 haematological abnormalities concerned absolute lymphocytes (35.1%), haemoglobin (22.9%), white blood count (30.5%), neutrophils (37.1%) and platelet counts (37.4%). The median time to first grade 3 or 4 neutropenia, thrombocytopenia, anaemia and leucopenia was 19, 14, 13.0 and 28 days, respectively. The median duration of grade 3 or 4 neutropenia, thrombocytopenia, anaemia and leucopenia was 15, 26, 8 and 14 days, respectively (cut-off date 4 May 2006).

Bleeding

Severe bleeding events were rare in both phase II CML-CP and CML-AP studies. In CML-CP patient in phase II of Study 2101 (n = 341), all grades and grade 3-4 gastrointestinal haemorrhages occurred in 9 (2.6%) and 4 (1.3%) patients only. In CML-AP patient in phase II of Study 2101 (n = 120), all grades and grade 3-4 gastrointestinal haemorrhages occurred in 5 (3.8%) and 2 (1.5%). Intracranial bleeding occurred in 1 (0.3%) and 3 (3%) CML-CP and CML-AP patients, respectively. One case of cerebral haemorrhage lead to death. Haematological toxicity was reversible after 2-3 weeks of study drug discontinuation. Haematological toxicity was more pronounced in CML-AP patients compared to CML-CP patients.

Cardiac Adverse Events

The number and percentage of CML-CP or CML-AP patients with selected cardiac adverse events are shown in Table 27.

Table 27: Number of patients with selected cardiac preferred terms (cut-off 4 January 2007)

Cardiac terms groupings	CML-CP N=320 n (%)	CML-AP N=127 n (%)	Total N=447 n (%)
Number of patients with cardiac AEs	48 (15.0)	11 (8.7)	59 (13.2)
Number of patients with Grade 3/4 cardiac AEs	24 (7.5)	6 (4.7)	30 (6.7)
Atrial arrhythmia Preferred Terms 1			
Number of patients with ≥ 1 AE	7 (2.2)	4 (3.1)	11 (2.5)
Number of AEs regardless of causality	12	4	16
AEs related to study drug	3	1	4
CTC grade 3 or 4 AEs	2	1	3
SAEs	4	2	6
Discontinuation	0	1	1
Ventricular arrhythmia Preferred Terms 2			
Number of patients with ≥ 1 AE	2 (0.6)	0	2 (0.4)
Number of AEs regardless of causality	3	0	3
AEs related to study drug	0	0	0
CTC grade 3 or 4 AEs	0	0	0
SAEs	1	0	1
Discontinuation	0	0	0
Other arrhythmias Preferred Terms 3			
Number of patients with ≥ 1 AE	18 (5.6)	1 (0.8)	19 (4.3)
Number of AEs regardless of causality	20	1	21
AEs related to study drug	5	0	5
CTC grade 3 or 4 AEs	3	0	3
SAEs	4	0	4
Discontinuation	0	0	0
Cardiac Failure Preferred Terms 4			
Number of patients with ≥ 1 AE	5 (1.6)	2 (1.6)	7 (1.6)
Number of AEs regardless of causality	6	3	9
AEs related to study drug	2	2	4
CTC grade 3 or 4 AEs	3	3	6
SAEs	3	3	6
Discontinuation	0	0	0
Myocardial ischemia Preferred Terms 5			
Number of patients with ≥ 1 AE	20 (6.3)	3 (2.4)	23 (5.1)
Number of AEs regardless of causality	37	3	40
AEs related to study drug	5	1	6
CTC grade 3 or 4 AEs	16	2	18
SAEs	14	2	16
Discontinuation	2	0	2
Myocardial Infarction Preferred Terms 6			
Number of patients with ≥ 1 AE	6 (1.9)	2 (1.6)	8 (1.8)
Number of AEs regardless of causality	6	2	8
AEs related to study drug	1	0	1
CTC grade 3 or 4 AEs	6	1	7
SAEs	6	2	8
Discontinuation	2	1	3
Seizures High Level Terms 7			
Number of patients with ≥ 1 AE	1 (0.3)	1 (0.8)	2 (0.4)
Number of AEs regardless of causality	1	5	6
AEs related to study drug	0	0	0
CTC grade 3 or 4 AEs	0	3	3
SAEs	0	5	5
Discontinuation	0	0	0
Syncope Preferred Terms 8			
Number of patients with ≥ 1 AE	7 (2.2)	3 (2.4)	10 (2.2)

Cardiac terms groupings	CML-CP N=320 n (%)	CML-AP N=127 n (%)	Total N=447 n (%)
Number of AEs regardless of causality	8	3	11
AEs related to study drug	2	0	2
CTC grade 3 or 4 AEs	4	1	5
SAEs	3	1	4
Discontinuation	0	0	0

[1] Atrial fibrillation, Atrial flutter, Supraventricular, tachycardia, Arrhythmia supraventricular, Supraventricular tachyarrhythmia, Supraventricular extrasystoles
[2] Ventricular tachyarrhythmia, Ventricular flutter, Ventricular extrasystoles
[3] Bradycardia, Tachycardia, Cardiac flutter, Sinus bradycardia, Tachyarrhythmia, Atrioventricular block first degree, Bundle branch block right, Electrocardiogram T wave inversion, Heart rate irregular
[4] Cardiac failure, Cardiac failure congestive, Pulmonary oedema, Left ventricular dysfunction, Ejection fraction decreased
[5] Angina pectoris, myocardial ischemia, coronary artery stenosis, Coronary artery disease, Arteriosclerosis coronary artery
[6] Myocardial infarction, Acute myocardial infarction
[7] Seizures and seizure disorders NEC, Generalised tonic-clonic seizures, Absence seizures, Partial complex seizures, Partial simple seizures NEC
[8] Loss of consciousness, syncope, syncope vasovagal

QT interval changes
The number and percentage of CML-CP or CML-AP patients with notable values in QTcF intervals are shown in Table 28.

Table 28: Patients with QTcF abnormalities (Safety population)

QTc category	CML-CP N = 320 N (%)	CML-AP N = 127 n (%)	Total N = 447 n (%)
Absolute QTcF > 480 ms	5 (1.6)	0	5 (1.1)
Absolute QTcF > 500 ms	3 (0.9)	0	3 (0.7)
QTcF increase from baseline > 30 ms	119 (37.2)	58 (45.7)	177 (39.6)
QTcF increase from baseline > 60 ms	7 (2.2)	6 (4.7)	13 (2.9)

Table 29 summarizes the estimated probability of having QTcF increases (from baseline) in each of the three-month intervals for patients who are still on treatment at start of the respective interval. Patients with multiple events in an interval are only counted once for that interval.

Table 29: Estimated conditional probability of having QTcF increases from baseline

QTc category	N at start of interval	Number of events	Conditional probability	95% CI
QTcF increase from baseline > 30 ms				
< 3 months	447	124	0.297	0.253 – 0.341
≥ 3 months - < 6 months	371	65	0.188	0.147 – 0.229
≥ 6 months - < 9 months	310	49	0.171	0.127 – 0.215
≥ 9 months - < 12 months	248	39	0.182	0.130 – 0.233
≥ 12 months - < 15 months	173	19	0.146	0.085 – 0.207
≥ 15 months - < 18 months	77	10	0.180*	0.079 – 0.281
QTcF increase from baseline > 60 ms				
< 3 months	447	6	0.015	0.003 – 0.026
≥ 3 months - < 6 months	371	1	0.003	0.000 – 0.009
≥ 6 months - < 9 months	310	2	0.007	0.000 – 0.017
≥ 9 months - < 12 months	248	4	0.019	0.001 – 0.037
≥ 12 months - < 15 months	173	2	0.016	0.000 – 0.038
≥ 15 months - < 18 months	77	2	0.037*	0.000 – 0.087

* Due to low number of patients, these values need to be considered with caution.

Clinical chemistry

Elevation in serum lipase (CTC grade 4) was found in 2.7% of the target population. Pancreatitis occurred in 5 (0.8%) of 622 patients treated in phase II of Study 2101 and in 2 (0.7%) and 1 (1.1%) of CML-CP and CML-AP patients. It resulted in treatment discontinuation in all 3 cases in the CML-CP and CML-AP population

Deaths

In the original studies, three deaths occurred in CML-CP and 7 in CML-AP. Out of these, the investigators suspected that two deaths in CML-CP patients and two deaths in CML-AP population had a suspected cause of death related to the study drug. These patients died from sequelae related to the haematological toxicity (sepsis, bleeding) and cardiac disorder (cardiac failure, coronary heart disease). In the complete phase II program 47 deaths occurred in 622 patients. Most of these deaths were due to the underlying disease (25/47), deaths to infection or sepsis were observed in 9/47 patients, death as a consequence of an intra-cerebral bleeding was seen in 7/47 patients and cardiac reason was reported in 4 patients.

As of July 25, 2007 approximately 2,740 patients received nilotinib in Novartis sponsored clinical studies and investigator-initiated clinical trials for CML, GIST, and other hematologic malignancies and the Compassionate use program. From the total safety population of 2,740 nilotinib patients, 10 cases of sudden cardiac deaths have been identified. Overall, the investigator causality assessment for nilotinib was considered suspected in 5, not suspected in 4 and not provided in 1 case. Based on a review of these 10 cases by an external expert cardiologist, a causality assessment of not related or unlikely was made in 5 cases and for the remaining 5 cases a causal role for nilotinib could not be ruled out. This means the frequency is 0.18-0.36%.

- Laboratory findings

Laboratory abnormalities are summarized in Table 30.

Table 30: Grade 3-4 laboratory abnormalities

	CML-CP n=318 %	**CML-AP n=120 %**
	Grade 3-4	**Grade 3-4**
Haematological parameters		
- Neutropenia	28%	37%
- Thrombocytopenia	28%	37%
- Anaemia	8%	23%
Biochemistry parameters		
- Elevated creatinine	<1%	0%
- Elevated lipase	15%	17%
- Elevated SGOT (AST)	1%	<1%
- Elevated SGPT (ALT)	4%	2%
- Hypophosphataemia	10%	10%
- Elevated bilirubin (total)	9%	10%

- Safety in special populations

Pregnancy
No pregnancies have been reported during the nilotinib clinical development program.

Children and adolescents
Tasigna was not investigated in children and adolescents below 18 years of age.

Elderly patients
Approximately 30% of subjects in clinical studies were 65 years of age or over. No major differences were observed for safety and efficacy in patients ≥ 65 years of age as compared to adults aged 18 to 65 years.

Patients with renal impairment
Clinical studies have not been performed in patients with impaired renal function.

Patients with hepatic impairment
Tasigna has not been investigated in patients with hepatic impairment.

- Safety related to drug-drug interactions and other interactions

Interactions resulting from CYP3A4 interference of nilotinib have been investigated in two studies in healthy volunteers using midazolam as substrate and ketoconazole as an inhibitor of the CYP3A4. Co-administration of ketoconazole with nilotinib increased nilotinib C_{max} by 84% and AUC by 3-fold. No change in ketoconazole pharmacokinetic was observed. Nilotinib decreased the apparent clearance of midazolam resulting in increases of C_{max} and AUC by 20% and 31%, respectively. Studies with CYP3A4 inducers like Rifampicin were not performed.

The potential of nilotinib to act as an inhibitor of human UGT1A1 was investigated by examining the effect of increasing drug concentrations on bilirubin and estradiol glucuronidation activity in in-vitro assay systems. Inhibition of UGT1A1 activity by nilotinib was apparent therefore it could inhibit the activity of UGT1A1 in clinical settings.

Food influence
Food factors affecting the serum concentration of nilotinib have been identified in the pharmacokinetic studies in phase I and II. The serum concentration of nilotinib is increased when it is taken with or immediately after food, and particularly when it is taken with or after a high fat meal.

A high-fat meal increases the QTcF by 10 msec from baseline. If the patient at the same time takes a CYP 3A4 inhibitor the predicted prolongation is 18 msec.

- Discontinuation due to adverse events

Discontinuation due to AEs was seen in both studies in 68 of 438 (15.5 %) patients who develop AEs (98.4%). The most frequent reason for discontinuation due to AEs was haematological toxicity (26/438; 5.9%) with neutropenia or thrombocytopenia. Cardiac (6/438; 1.4%), gastrointestinal (7/438, 1.6%) and cutaneous (6/438, 1.4%) AEs were the other important reasons for discontinuation.

- Post marketing experience

No post marketing experience was available at the time of submission of the application.

- Discussion on clinical safety

The main focus of the assessment of safety results is the data of the pivotal phase II CML-CP and CML-AP patient population. Overall, from the result presented in the interim analysis, nilotinib seems to be tolerated relatively well in both populations. A mean dose intensity of approx 700 mg/day (±202 mg/day) was observed at date of cut-off, with short median duration of exposures of 341 days for CML-CP patients and 202 days for CML-AP patients.

The overall incidence of adverse events was 99.1% in CML-CP patients (phase II study) and 96.7% in CML-AP patients (phase II study). Nearly all patients included in the pivotal studies some AEs were observed during the treatment, however the toxicity is manageable and it has been adequately stated in section 4.8 of the SPC. Overall, haematological and myelosuppressive toxicity and cardiac events were noted as the most frequent cause of AEs.

Treatment with nilotinib is associated with thrombocytopenia, neutropenia and anaemia (National Cancer Institute Common Toxicity Criteria grade 3-4). Thrombocytosis is often seen in CML-CP.I In more advanced stages of the disease, thrombocytopenia is a common finding. Occurrence is more frequent 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 nilotinib temporarily or dose reduction (see section 4.2)

Nilotinib was shown to prolong cardiac ventricular repolarisation as measured by the QT interval on the surface ECG in a concentration-dependent manner. Therefore, nilotinib must be used with caution in patients who are at a significant risk of developing prolongation of QTc. Close monitoring for an effect on the QTc interval is advisable and a baseline ECG is recommended prior to initiating therapy with nilotinib as clinically indicated. Moreover, significant prolongation of the QT interval may occur when nilotinib is inappropriately taken with strong CYP3A4 inhibitors and/or medicinal products with a known potential to prolong QT, and/or food. The presence of hypokalaemia and hypomagnesaemia may further enhance this effect. These concerns have been adequately stated in sections 4.2 and 4.4 of the SPC. In addition, educational material addressing the cardiac risks associated with nilotinib will be provided to prescribers and pharmacists prior to launch.

The incidences of QTcF change from baseline > 60 ms and QTcF > 500 ms do not increase with cumulative exposure to nilotinib. Thus the two analyses are consistent and confirm that the risk from QT prolongation does not increase with duration of exposure.

Bleeding-related events are not uncommon in a bone marrow disorder like CML. Gastrointestinal tract bleedings and CNS bleedings are also well recognized complication in this severely ill population. Haematologic toxicity is known from other tyrosine kinase inhibitors (TKIs: imatinib, dasatinib) and was reversible after 2-3 weeks of study drug discontinuation. As expected and partly caused by the progressing underlying disease, haematological toxicity was more pronounced in CML-AP patients compared to CML-CP patients.

Elevation in serum lipase, not observed in preclinical toxicology studies, was an unexpected safety finding in the target population and was observed in an overall 2.7% CTC grade 4. However it was

clinically manageable in the majority of CML-CP and CML-AP patients. Caution is recommended in patients with previous history of pancreatitis and a warning has been included in sections 4.2 and 4.4 of the SPC. Additionally bilirubin and hepatic transaminases levels should be tested monthly or as clinically indicated. For Grade 3-4 bilirubin elevations, doses should be reduced to 400 mg once daily or interrupted as specified in section 4.2 of the SPC.

Clinical studies were not performed in patients with impaired renal function. Clinical studies 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. A warning has been included in sections 4.2 and 4.4 of the SPC.

Nilotinib was not investigated in patients with hepatic impairment. Caution is recommended in these patients and a warning has been included in sections 4.2 and 4.4. The applicant has committed to perform a post-authorization study in patients with hepatic impairment.

There are no adequate data on the use of nilotinib in pregnant women. Studies in animals show that nilotinib while not genotoxic or teratogenic, was embryolethal and produced foetotoxicity in embryo-foetal development studies in rats and rabbits at doses that also produced maternal toxicity. Thus, nilotinib should not be used during pregnancy unless clearly necessary. If the drug is used during pregnancy, the patient must be informed of the potential risk to the foetus and women of childbearing potential must be advised to use effective contraception during treatment. In addition, it is not known whether nilotinib is excreted in human milk. Studies in animals demonstrate that it is excreted into breast milk. Women should therefore not breastfeed while taking nilotinib. A warning regarding pregnancy and lactation has been included in section 4.6 of the SPC.
Nilotinib is not recommended for use in children and adolescents below 18 years of age due to a lack of data on safety and efficacy. A warning has been included in section 4.2 of the SPC.

Approximately 30% of subjects in clinical studies were 65 years of age or over. No major differences were observed for safety and efficacy in patients ≥ 65 years of age as compared to adults aged 18 to 65 years.

6. Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan, which included a risk minimisation plan.

Table Summary of the risk management plan

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimisation activities
QT prolongation	Collect additional categorical QT safety data in two Phase III open-label, randomized studies of imatinib versus nilotinib with DMC oversight. Monthly line listing to be provided to Health Authorities. All other routine pharmacovigilance activities.	Special warnings and precautions on risk of QT prolongation are discussed in Section 4.4 of the SPC or Section 5.2 and 5.3 of the PI Additional information regarding QT prolongation is also contained in the interaction and undesirable effects sections of the labelling (i.e. Sections 4.5 and 4.8 of the SPC and Sections 5.2 and 6.1 of the PI). Educational material

Myelosuppression	Monitoring of laboratory data for ongoing clinical trials. All other routine pharmacovigilance activities.	Special warnings and precautions on risk of myelosuppression and dose adjustment information in case of Neutropenia and Thrombocytopenia in Sections 4.2 and 4.4 of the SPC or Sections 2 and 5.1 of the PI. Relevant preferred terms reported as adverse events in Section 4.8 of the SPC or Section 6 of the PI. Educational material
Severe haemorrhage	Routine pharmacovigilance activities.	Special warnings and precautions on risk of myelosuppression and dose adjustment information in case of Thrombocytopenia in Sections 4.2 and 4.4 of the SPC or Sections 2 and 5.1 of the PI. Relevant preferred terms reported as adverse events in Section 4.8 of the SPC or Section 6 of the PI. Educational material
Severe infections	Routine pharmacovigilance activities.	Special warnings and precautions on risk of myelosuppression and dose adjustment information in case of Neutropenia in Sections 4.2 and 4.4 of the SPC or Sections 2 and 5.1 of the PI. Relevant preferred terms reported as adverse events in Section 4.8 of the SPC or Section 6 of the PI. Educational material
Hepatic transaminase and bilirubin elevations	Monitoring of laboratory data for ongoing clinical trials. Additional monitoring as defined for Drug induced liver injury.	Relevant preferred terms reported as adverse events in Section 4.8 of the SPC or Section 6 of the PI. Dose adjustment information is in Section 4.2 of the SPC and Section 2 of the PI. Educational material
Lipase and amylase elevations	Monitoring of laboratory data for ongoing clinical trials. Additional monitoring as defined for Pancreatitis.	Relevant preferred terms reported as adverse events in Section 4.8 of the SPC or Section 6 of the PI. Dose adjustment information is in Section 4.2 of the SPC and Section 2 of the PI. Educational material
Rash	Routine pharmacovigilance activities.	Relevant preferred terms reported as adverse events in Section 4.8 of the SPC or Section 6 of the PI. Educational material
Fluid retention	Routine pharmacovigilance activities.	Relevant preferred terms reported as adverse events in Section 4.8 of the SPC or Section 6 of the PI. Educational material
Blood glucose increase	Blood glucose increase	Collect additional targeted laboratory data including fasting glucose, HbA1c, insulin levels and C-peptide in Phase III open-label, randomized studies of imatinib versus nilotinib. Monitoring of laboratory data for ongoing clinical trials. Additional monitoring as defined for Diabetes mellitus.
Hypophosphataemia	Monitoring of laboratory data for ongoing clinical trials.	Relevant preferred terms reported as adverse events in Section 4.8 of the SPC

	All other routine pharmacovigilance activities.	or Section 6 of the PI. Educational material
Important potential risks		
Sudden death	Monthly line listing to be provided to Health Authorities. Additional monitoring as defined for QT prolongation.	As may pertain to QT prolongation: Special warnings and precautions on the potential risk of QT prolongation is discussed in Section 4.4 of the SPC or Section 5.2 and 5.3 of the PI. Additional information regarding QT prolongation is also contained in the interaction and undesirable effects sections of the labeling (i.e. Sections 4.5 and 4.8 of the SPC and Sections 5.2 and 6.1 of the PI).
Ischemic heart disease	Collect additional cardiac safety data including ECGs, echocardiograms and cardiac enzymes in two Phase III open-label, randomized studies of imatinib versus nilotinib with DMC oversight. Monthly line listing to be provided to Health Authorities. All other routine pharmacovigilance activities.	Relevant preferred terms reported as adverse events in Section 4.8 of the SPC or Section 6 of the PI. Educational material
Cardiac failure	Collect additional cardiac safety data including ECGs, echocardiograms and cardiac enzymes in two Phase III open-label, randomized studies of imatinib versus nilotinib with DMC oversight. All other routine pharmacovigilance activities.	Relevant preferred terms reported as adverse events in Section 4.8 of the SPC or Section 6 of the PI. Educational material
Drug induced liver injury	Routine pharmacovigilance activities.	Special warnings and precautions for use and relevant preferred terms reported as adverse events in Sections 4.4 and 4.8 of the SPC or Sections 5 and 6 of the PI. Educational material
Pancreatitis	Routine pharmacovigilance activities.	Special warnings and precautions for use and relevant preferred terms reported as adverse events in Sections 4.4 and 4.8 of the SPC or Sections 5 and 6 of the PI. Educational material
Photosensitivity	Routine pharmacovigilance activities.	Relevant preferred terms reported as adverse events in Section 4.8 of the SPC or Section 6 of the PI. Educational material
Diabetes Mellitus	Collect additional targeted laboratory data including fasting glucose, HbA1c, insulin and C-peptide in Phase III open-label, randomized studies of imatinib versus nilotinib. All other routine pharmacovigilance activities.	Relevant preferred terms reported as adverse events in Section 4.8 of the SPC or Section 6 of the PI. Educational material

Important identified interactions		
Strong CYP3A4 inhibitors	Routine pharmacovigilance activities.	Special warnings and precautions on risk of drug interaction and description of the interaction in Sections 4.4 and 4.5 of the SPC or Sections 5.3 and 7 of the PI. Educational material
P-gp inhibitors	Routine pharmacovigilance activities.	Description of the interaction in Section 4.5 of the SPC or Sections 5.3 and 7 of the PI.
Food	Routine pharmacovigilance activities.	Special warnings and precautions on risk of food interaction in Section 4.2 of the SPC or Section 5.4 of the PI. Educational material
Important potential interactions		
Strong CYP3A4 Inducers	A drug interaction study is currently ongoing. All other routine pharmacovigilance activities.	Special warnings and precautions on risk of drug interaction and description of the interaction in Sections 4.4 and 4.5 of the SPC or Sections 5.3 and 7 of the PI. Educational material
Proton Pump Inhibitors	Proton Pump Inhibitors	A drug-drug interaction study is planned. All other routine pharmacovigilance activities
Drugs Eliminated by CYP3A4, CYP2C8, CYP2C9, CYP2D6 or UGT1A1 and P-gp Substrates	Routine pharmacovigilance activities.	Description of the interaction in Section 4.5 of the SPC or Sections 5.3 and 7 of the PI.
Drugs that may prolong the QT interval	Routine pharmacovigilance activities.	Special warnings and precautions on risk of drug interaction and description of the interaction in Sections 4.4 and 4.5 of the SPC or Sections 5.3 and 7 of the PI. Educational material
Hormonal contraceptives	Routine pharmacovigilance activities.	Warning on risk of drug interaction and description of the interaction in Sections 4.4 and 4.5 of the SPC or Sections 5.3 and 7 of the PI as they pertain to drugs eliminated by CYP3A4; based on available literature, there is no indication that a loss of contraceptive efficacy would be expected to occur.
Important missing information		
Pregnancy	An oral pre- and post-natal study in rats in ongoing. All other routine pharmacovigilance activities	The risks in case of pregnancy are described in Section 4.6 of the SPC or Section 5.5 of the PI. Educational material
Paediatric patients	A paediatric study is planned. All other routine pharmacovigilance activities	Paediatric use discussed in Section 4.2 of the SPC or Section 8.4 of the PI. Educational material
Renal impairment patients	Routine pharmacovigilance activities.	Use in renal impairment patients discussed in Section 4.2 of the SPC or Section 8.7 of the PI.
Hepatic impairment	A study in hepatically-impaired patients is ongoing. All other routine	Warning on risk of use in hepatic impairment patients and description of use in Section 4.4 of the SPC or Sections 5.7

	pharmacovigilance activities	and 8.6 of the PI. Dose adjustment information is in Section 4.2 of the SPC and Section 2 of the PI. Educational material
Patients with uncontrolled or significant cardiac disease	Routine pharmacovigilance activities.	Information on the use in patients with uncontrolled or significant cardiac disease in Section 4.2 and 4.4 of the SPC or Section 8.8 of the PI. Educational material

The CHMP, having considered the data submitted in the application is of the opinion that the following risk minimisation activities are necessary for the safe and effective use of the medicinal product: See as detailed in section 2.3

6. Overall conclusions, risk/benefit assessment and recommendation

Quality

The quality of the product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product were investigated and are controlled in a satisfactory way. There are no unresolved quality issues, which have a negative impact on the Benefit Risk balance of the product.

Non-clinical pharmacology and toxicology

Nilotinib is a potent inhibitor of the ABL tyrosine kinase activity of the BCR-ABL oncoprotein both in cell lines and in primary Philadelphia-chromosome positive leukaemia cells. The substance binds with high affinity to the ATP-binding site in such a manner that it is a potent inhibitor of wild-type BCR-ABL and maintains activity against 32/33 imatinib-resistant mutant forms of BCR-ABL. As a consequence of this biochemical activity, nilotinib selectively inhibits the proliferation and induces apoptosis in cell lines and in primary Philadelphia-chromosome positive leukaemia cells from CML patients. In murine models of CML, as a single agent nilotinib reduces tumour burden and prolongs survival following oral administration.

Nilotinib has little or no effect against the majority of other protein kinases examined, including Src, except for the PDGF, Kit and Ephrin receptor kinases, which it inhibits at concentrations within the range achieved following oral administration at therapeutic doses recommended for the treatment of CML

Nilotinib did not have effects on CNS or respiratory functions. *In vitro* cardiac safety studies demonstrated a preclinical signal for QT prolongation, based upon block of hERG currents and prolongation of the action potential duration in isolated rabbit hearts by nilotinib. No effects were seen in ECG measurements in dogs or monkeys treated for up to 39 weeks or in a special telemetry study in dogs.

Repeated-dose toxicity studies in dogs of up to 4 weeks' duration and in cynomolgus monkeys of up to 9 months' duration revealed the liver as the primary target organ of toxicity of nilotinib. Alterations included increased alanine aminotransferase and alkaline phosphatase activity and histopathology findings (mainly sinusoidal cell or Kupffer cell hyperplasia/hypertrophy, bile duct hyperplasia and periportal fibrosis). In general the changes in clinical chemistry were fully reversible after a four-week recovery period and the histological alterations showed partial reversibility. Exposures at the lowest dose levels at which the liver effects were seen were lower than the exposure in humans at a dose of 800 mg/day. Only minor liver alterations were seen in mice or rats treated for up to 26 weeks. Mainly reversible increases in cholesterol levels were seen in rats, dogs and monkeys.

Genotoxicity studies in bacterial *in vitro* systems and in mammalian *in vitro* and *in vivo* systems with

and without metabolic activation did not reveal any evidence for a mutagenic potential of nilotinib. Carcinogenicity studies with nilotinib have not been performed.
Nilotinib did not induce teratogenicity, but did show embryo- and foetotoxicity at doses that also showed maternal toxicity. Increased post-implantation loss was observed in both the fertility study, which involved treatment of both males and females, and the embryotoxicity study, which involved treatment of females. Embryo-lethality and foetal effects (mainly decreased foetal weights, skeletal malformations (fused maxilla/zygomatic) visceral and skeletal variations) in rats and increased resorption of foetuses and skeletal variations in rabbits were present in the embryotoxicity studies. Exposure to nilotinib in females at No-Observed-Adverse-Effect-Levels was generally less or equal to that in humans at 800 mg/day. No effects on sperm count/motility or on fertility were noted in male and female rats up to the highest tested dose, approximately 5 times the recommended dosage for humans.

Nilotinib was shown to absorb light in the UV-B and UV-A range, is distributed into the skin and showed a phototoxic potential *in vitro*, but no effects have been observed *in vivo*. Therefore the risk that nilotinib causes photosensitisation in patients is considered very low.

Efficacy

Efficacy claimed for nilotinib in adult patients for the orphan indications: CML-Chronic Phase (CML-CP) and CML-Accelerated Phase (CML-AP) in patients who are resistant to or intolerant to imatinib was based on the basis of two pivotal phase II studies (study 2101E2, study 2101E1). This application is made on the basis of updated interim analyses in both studies and the final analysis reports.
The primary endpoint for patients with CML-CP was major cytogenetic response (complete or partial) (MCyR). The efficacy data of the pivotal study arm of patients (n=132) and the overall enrolment (n=320) were based on a mean nilotinib exposure of 460 and 341 days respectively. The best MCyR response was 44.7% (59/132), 95% CI 36.0-53.6 for the primary enrolment population and 48.8% (156/320), 95% CI 43.2-54.4 for the overall enrolment population. The complete haematologic response (CHR) rate was 70.9% for CML-CP patients without CHR at baseline.
The primary endpoint for patients with CML-AP was CHR. The efficacy data of the pivotal study arm of patients (n=64) and the overall enrolment (n=119) were based on a mean nilotinib exposure of 211 and 202 days respectively. The best CHR was 51.6% (33/64), 95% CI 38.7-64.2 for the primary enrolment population and 42.0% (50/119), 95% CI 33.0-51.4 for the overall enrolment population. The MCyR rate was 31.3% (95% CI: 20.2% - 44.1%) for patients with CML-AP.

Safety

The present review refers to a total of 438 patients who were exposed to nilotinib. The most frequent study drug-related AEs in the overall population and in the CML-CP patients were thrombocytopenia (25.8%), rash (28.3%), pruritus (23.6%), nausea (22.3%), fatigue (19.8%), headache (17.6%), neutropenia (13.8%) and diarrhoea (10.4%). In CML-AP patients, the most frequent study drug-related AEs were thrombocytopenia (31.7%), neutropenia (20%), rash (20.8%), pruritus (17.5%), anaemia (15%) and constipation (10.8%). Lipase was increased in 11.6% of patients and bilirubin in 5.7% of patients.

A majority of CML patients experienced severe AEs during the course of the study with 69.5% of CML-CP patients and 67.5% of CML-AP patients presenting CTC grade 3 or 4 AEs. The most frequently reported CTC grade 3 or 4 AEs overall included thrombocytopenia (25.3%), neutropenia (16.7%), anaemia (8.7%) and increased lipase (7.5%). In CML-CP patients, the most frequent SAEs were thrombocytopenia (2.8%), neutropenia (1.9%), and myocardial infarction (1.3%). In CML-AP patients, the most frequent SAEs were thrombocytopenia (7.5%), neutropenia (6.7%) and pneumonia (5.0%). 3 Patients (0,8%) were reported with pancreatitis as SAE.

A high number of patients in the phase II study experienced QTc prolongations from baseline of > 30 msec (39.6%). QTcF increases of > 60 msec were reported in 2.9%. The risk of sudden deaths observed in patients receiving nilotinib is 0.36%.

From the safety database, all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these.

- User consultation

The Applicant performed a readability testing ("user consultation") and a satisfactory report has been provided.

Risk-benefit assessment

The efficacy of nilotinib in CML-CP and CML-AP has been sufficiently documented as regards to generally accepted surrogate endpoints and durability of the response.

The risk of sudden cardiac death was assessed in CML patients taking nilotinib. Results from PD studies and clinical trials showed that the risk over time for patients on nilotinib for a baseline increase in QTcF of > 30 msec is 15-30% and for a > 60 msec increase is 0.3-3%, without a cumulative trend. The present risk benefit assessment includes a total of 2,740 patients who were exposed to nilotinib. This includes all patient enrolled in clinical studies and compassionate use. In this population, 10 cases of sudden cardiac death were reported. Following a review from an external expert cardiologist, 5/10 cases were classified as 'possible' while the remaining 5/10 were considered 'not related'. The risk of sudden cardiac death is then 0.18% if 'possible' cases are included, or 0.36% if all the cases are included. Although the cardiac risk is of concern, the precautionary measures proposed by the applicant indicate that this risk was decreased over time and is manageable.

Recently the tyrosine kinase inhibitor dasatinib (Sprycel) has been approved for the treatment of adults with chronic, accelerated or blast phase chronic myeloid leukaemia (CML) with resistance or intolerance to prior therapy including imatinib mesilate. No data are available for a direct comparison of the efficacy and safety profiles of the two agents. However, broadly speaking, the efficacy of nilotinib in chronic and accelerated phases appears to be in the range of what described for dasatinib in these disease stages. Concerning safety, the cardiac risk of nilotinib was of concern. The applicant showed that this risk seems to decrease over time and that precautionary measures may make this risk acceptable.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- Pharmacovigilance activities, in addition to the use of routine pharmacovigilance, are needed to investigate further some of the safety concerns

- Additional risk minimisation activities are required, (see as detailed in section 2.3)

Similarity with authorised orphan medicinal products

The CHMP is of the opinion that Tasigna is similar to Glivec within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 5.1. Tasigna and Glivec share the same principal molecular structural features, both containing a N-(2-methylphenyl)-4(3-pyridinyl)-2-pyrimidinamine part, rendering half of the molecules identical. In addition, due to the flexibility and reversibility of amide bridges, the common part may be extended to include the phenyl group linked to the amide bridge. If a molecule is 50% identical with the possibility of even more additional similarity it is enough to conclude structural similarity.

The CHMP is of the opinion that Tasigna is not similar to Sprycel within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 5.2. Tasigna and Sprycel do not share the same principal molecular structural features and the only major common element is the aniline-amide

portion of the molecules, which corresponds to 22% of Tasigna and to 24% of Sprycel as assessed by molecular weight.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Tasigna in the "treatment of adults with chronic and accelerated phase Philadelphia chromosome positive chronic myelogenous leukaemia (CML) with resistance or intolerance to prior therapy including imatinib. Efficacy data in patients with CML in blast crisis are not available." was favourable and therefore recommended the granting of the marketing authorisation.

In addition, the CHMP, with reference to Article 8 of Regulation EC No 141/2000, considers Tasigna not to be similar (as defined in Article 3 of Commission Regulation EC No. 847/2000) to Sprycel for the same therapeutic indication.

In addition, the CHMP, with reference to Article 8 of Regulation EC No 141/2000, considers Tasigna to be similar (as defined in Article 3 of Commission Regulation EC No. 847/2000) to Glivec for the same therapeutic indication. However, the holder of the marketing authorisation for Glivec has given his consent to the applicant.

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