Summary of Product Characteristics

1. Name of the Drug Product

Nilonix 200 Capsule

2. Qualitative and Quantitative Composition

FORMULATION PER CAPSULE

Product Name: Nilonix 200 Capsule

(Each Capsule Contains Nilotinib Hydrochloride Monohydrate INN eqv. to Nilotinib 200 mg

Filled Weight per Capsule: 310.00 mg

Sl. No.	Name of Materials	Specification	Quantity/ Capsule (mg)	Used As
ACTIVE SUBSTANCE:				
01	Nilotinib Hydrochloride Monohydrate	INN	*220.60 mg (Equivalent. to Nilotinib 200 mg)	Active Material
EXCIPIENTS:				
02	Crospovidone	BP	12.40	Disintegrant
03	Sodium Starch Glycolate (Primojel)	BP	18.60	Disintegrant
04	Polacrilin Potassium (Kyron-T 314)	USP-NF	31.00	Dissolution enhancer
05	Sodium Stearyl Fumarate	BP	3.10	Lubricant
06	Colloidal Anhydrous Silica (Aerosil 200)	BP	3.10	Glidant
07	Anhydrous Lactose	BP	9.30	Moisture Controlling Agent.
08	Microcrystalline Cellulose (Avicel PH 102)	BP	**11.90	Diluent
09	Empty Hard Gelatin Capsule Shell, Size # 0 Cap: Maroon (OP) Body: White (OP)	Ph. Grade	01 Piece	Capsule Shell

Note:

* Based on 100% potency

** Calculated amount of material

Prepared By:	Checked By:	Approved By:
04.11.19	04.11.19	04.11.19
Farhana Sharmin	Hasina Pervin	Dr. Parimal Talukder
Executive, R & D	Deputy Manager, R & D	Sr. Manager, R & D

3. Pharmaceutical Form

Hard Gelatin Capsule

White to slightly yellowish powder is encapsulated in hard gelatin capsule shell, size# 0 (White OP Body & Marron OP Cap).

4. Clinical particulars

4.1 Therapeutic indications

Nilotinib is indicated for the treatment of:

- Adult and paediatric patients with newly diagnosed Philadelphia chromosome positive chronic myelogenous leukaemia (CML) in the chronic phase,

- Paediatric patients with Philadelphia chromosome positive CML in chronic phase with resistance or intolerance to prior therapy including imatinib.

4.2 Posology and method of administration

Therapy should be initiated by a physician experienced in the diagnosis and the treatment of patients with CML.

Posology

Treatment should be continued as long as clinical benefit is observed or until unacceptable toxicity occurs.

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

Posology for Philadelphia chromosome positive CML adult patients

The recommended dose is:

- 300 mg twice daily in newly diagnosed patients with CML in the chronic phase,
- 400 mg twice daily in patients with chronic or accelerated phase CML with resistance or intolerance to prior therapy.

For a dose of 300 mg twice daily, 150 mg hard capsules are available.

Posology for Philadelphia chromosome positive CML paediatric patients

Dosing in paediatric patients is individualised and is based on body surface area (mg/m^2). The recommended dose of nilotinib is 230 mg/m^2 twice daily, rounded to the nearest 50 mg dose (to a maximum single dose of 400 mg) (see Table 1). Different strengths of Nilotinib hard capsules can be combined to attain the desired dose.

There is no experience with treatment of paediatric patients below 2 years of age. There are no data in newly diagnosed paediatric patients below 10 years of age and limited data in imatinib-resistant or intolerant paediatric patients below 6 years of age.

Table 1 Paediatric dosing scheme of nilotinib 230 mg/m^2 twice daily

Body Surface Area (BSA)	Dose in mg (twice daily)

Up to 0.32 m^2	50 mg
0.33 – 0.54 m^2	100 mg
0.55 – 0.76 m^2	150 mg
0.77 – 0.97 m^2	200 mg
0.98 – 1.19 m^2	250 mg
1.20 – 1.41 m^2	300 mg
1.42 – 1.63 m^2	350 mg
≥1.64 m^2	400 mg

Adult Philadelphia chromosome positive CML patients in chronic phase who have been treated with nilotinib as first-line therapy and who achieved a sustained deep molecular response (MR4.5)

Discontinuation of treatment may be considered in eligible adult Philadelphia chromosome positive (Ph+) CML patients in chronic phase who have been treated with nilotinib at 300 mg twice daily for a minimum of 3 years if a deep molecular response is sustained for a minimum of one year immediately prior to discontinuation of therapy. Discontinuation of nilotinib therapy should be initiated by a physician experienced in the treatment of patients with CML.

Eligible patients who discontinue nilotinib therapy must have their BCR-ABL transcript levels and complete blood count with differential monitored monthly for one year, then every 6 weeks for the second year, and every 12 weeks thereafter. Monitoring of BCR-ABL transcript levels must be performed with a quantitative diagnostic test validated to measure molecular response levels on the International Scale (IS) with a sensitivity of at least MR4.5 (BCR-ABL/ABL ≤0.0032% IS).

For patients who lose MR4 (MR4=BCR-ABL/ABL ≤0.01%IS) but not MMR (MMR=BCR-ABL/ABL ≤0.1%IS) during the treatment-free phase, BCR-ABL transcript levels should be monitored every 2 weeks until BCR-ABL levels return to a range between MR4 and MR4.5. Patients who maintain BCR-ABL levels between MMR and MR4 for a minimum of 4 consecutive measurements can return to the original monitoring schedule.

Patients who lose MMR must re-initiate treatment within 4 weeks of when loss of remission is known to have occurred. Nilotinib therapy should be re-initiated at 300 mg twice daily or at a reduced dose level of 400 mg once daily if the patient had a dose reduction prior to discontinuation of therapy. Patients who re-initiate nilotinib therapy should have their BCR-ABL transcript levels monitored monthly until MMR is re-established and every 12 weeks thereafter.

Dose adjustments or modifications

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

Table 2 Dose adjustments for neutropenia and thrombocytopenia

Adult patients with newly diagnosed chronic phase CML at 300 mg twice daily and imatinib-resistant or intolerant CML in chronic phase at 400 mg twice daily	ANC* <1.0 x 10^9/l and/or platelet counts <50 x 10^9/l	1. Treatment with nilotinib must be interrupted and blood count monitored. 2. Treatment must be resumed within 2 weeks at prior dose if ANC >1.0 x 10^9/l and/or platelets >50 x 10^9/l. 3. If blood counts remain low, a dose reduction to 400 mg once daily may be required.
Adult patients with imatinib-resistant or intolerant CML in accelerated phase at 400 mg twice daily	ANC* <0.5 x 10^9/l and/or platelet counts <10 x 10^9/l	1. Treatment with nilotinib must be interrupted and blood count monitored. 2. Treatment must be resumed within 2 weeks at prior dose if ANC >1.0 x 10^9/l and/or platelets >20 x 10^9/l. 3. If blood counts remain low, a dose reduction to 400 mg once daily may be required.
Paediatric patients with newly diagnosed CML in chronic phase at 230 mg/m^2 twice daily and imatinib-resistant or intolerant CML in chronic phase at 230 mg/m^2 twice daily	ANC* <1.0 x 10^9/l and/or platelet counts <50 x 10^9/l	1. Treatment with nilotinib must be interrupted and blood count monitored. 2. Treatment must be resumed within 2 weeks at prior dose if ANC >1.5 x 10^9/l and/or platelets >75 x 10^9/l. 3. If blood counts remain low, a dose reduction to 230 mg/m^2 once daily may be required. 4. If event occurs after dose reduction, consider discontinuing treatment.

*ANC = absolute neutrophil count

If clinically significant moderate or severe non-haematological toxicity develops, dosing should be interrupted, and patients should be monitored and treated accordingly. If the prior dose was 300 mg twice daily in adult patients or 230 mg/m^2 twice daily in paediatric patients, dosing may be resumed at 400 mg once daily in adult patients and at 230 mg/m^2 once daily in paediatric patients once the toxicity has resolved. If the prior dose was 400 mg once daily in adult patients or 230 mg/m^2 once daily in paediatric patients, treatment should be discontinued. If clinically appropriate, re-escalation of the dose to 300 mg twice daily in adult patients or to 230 mg/m^2 twice daily in paediatric patients should be considered.

Elevated serum lipase: For Grade 3-4 serum lipase elevations, doses in adult patients should be reduced to 400 mg once daily or interrupted. In paediatric patients, treatment must be interrupted until the event returns to Grade ≤1. Thereafter, if the prior dose was 230 mg/m^2 twice daily, treatment can be resumed at 230 mg/m^2 once daily. If the prior dose was 230 mg/m^2 once daily, treatment should be discontinued. Serum lipase levels should be tested monthly or as clinically indicated.

Elevated bilirubin and hepatic transaminases: For Grade 3-4 bilirubin and hepatic transaminase elevations in adult patients, doses should be reduced to 400 mg once daily or interrupted. For Grade ≥2 bilirubin elevations or Grade ≥3 hepatic transaminase elevations in paediatric patients, treatment must be interrupted until the levels return to Grade ≤1. Thereafter, if the prior dose was 230 mg/m^2 twice daily, treatment can be resumed at 230 mg/m^2 once daily. If the prior dose was 230 mg/m^2 once daily, and recovery to Grade ≤1 takes longer than 28 days, treatment should be discontinued. Bilirubin and hepatic transaminases levels should be tested monthly or as clinically indicated.

Special populations

Elderly

Approximately 12% of subjects in the clinical study 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.

Renal impairment

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

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

Hepatic impairment

Hepatic impairment has a modest effect on the pharmacokinetics of nilotinib. Dose adjustment is not considered necessary in patients with hepatic impairment. However, patients with hepatic impairment should be treated with caution.

Cardiac disorders

In clinical studies, patients with uncontrolled or significant cardiac disease (e.g., recent myocardial infarction, congestive heart failure, unstable angina or clinically significant bradycardia) were excluded. Caution should be exercised in patients with relevant cardiac disorders.

Increases in total serum cholesterol levels have been reported with nilotinib therapy. Lipid profiles should be determined prior to initiating nilotinib therapy, assessed at month 3 and 6 after initiating therapy and at least yearly during chronic therapy.

Increases in blood glucose levels have been reported with nilotinib therapy. Blood glucose levels should be assessed prior to initiating nilotinib therapy and monitored during treatment.

Paediatric population

The safety and efficacy of Nilotinib in paediatric patients with Philadelphia chromosome positive CML in chronic phase from 2 to less than 18 years of age have been established. There is no experience in paediatric patients below 2 years of age or in paediatric patients with Philadelphia chromosome positive CML in accelerated phase or blast crisis. There are no data in newly diagnosed paediatric patients below 10 years of age and limited data in imatinib-resistant or intolerant paediatric patients below 6 years of age.

Method of administration

Nilotinib should be taken twice daily approximately 12 hours apart and must not be taken with food. The hard capsules should be swallowed whole with water. No food should be consumed for 2 hours before the dose is taken and for at least one hour after.

For patients who are unable to swallow hard capsules, the content of each hard capsule may be dispersed in one teaspoon of apple sauce (puréed apple) and should be taken immediately. Not more than one teaspoon of apple sauce and no food other than apple sauce must be used.

4.3 Contraindications

Hypersensitivity to active substance or to any of the excipients listed in section 6.1

4.4 Special warnings and precautions for use

Myelosuppression

Treatment with nilotinib is associated with (National Cancer Institute Common Toxicity Criteria grade 3-4) thrombocytopenia, neutropenia and anaemia. 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.

QT prolongation

Nilotinib has been shown to prolong cardiac ventricular repolarisation as measured by the QT interval on the surface ECG in a concentration-dependent manner in adult and paediatric patients.

In the Phase III study in patients with newly diagnosed CML in chronic phase receiving 300 mg nilotinib twice daily, the change from baseline in mean time-averaged QTcF interval at steady state was 6 msec. No patient had a QTcF >480 msec. No episodes of torsade de pointes were observed.

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

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 the QT interval, and/or food. The presence of hypokalaemia and hypomagnesaemia may further enhance this effect. Prolongation of the QT interval may expose patients to the risk of fatal outcome.

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

- With congenital long QT prolongation.

- With uncontrolled or significant cardiac disease including recent myocardial infarction, congestive heart failure, unstable angina or clinically significant bradycardia.

- Taking anti-arrhythmic medicinal products or other substances that lead to QT prolongation.

Close monitoring for an effect on the QTc interval is advisable and a baseline ECG is recommended prior to initiating nilotinib therapy and as clinically indicated. Hypokalaemia or hypomagnesaemia must be corrected prior to Nilotinib administration and should be monitored periodically during therapy.

Sudden death
Uncommon cases (0.1 to 1%) of sudden deaths have been reported in patients with imatinib-resistant or intolerant CML in chronic phase or accelerated phase with a past medical history of cardiac disease or significant cardiac risk factors. Co-morbidities in addition to the underlying malignancy were also frequently present as were concomitant medicinal products. Ventricular repolarisation abnormalities may have been contributory factors. No cases of sudden death were reported in the Phase III study in newly diagnosed patients with CML in chronic phase.

Fluid retention and oedema
Severe forms of drug-related fluid retention such as pleural effusion, pulmonary oedema, and pericardial effusion were uncommonly (0.1 to 1%) observed in a Phase III study of newly diagnosed CML patients. Similar events were observed in post-marketing reports. Unexpected, rapid weight gain should be carefully investigated. If signs of severe fluid retention appear during treatment with nilotinib, the aetiology should be evaluated and patients treated accordingly.

Cardiovascular events
Cardiovascular events were reported in a randomised Phase III study in newly diagnosed CML patients and observed in post-marketing reports. In this clinical study with a median on-therapy time of 60.5 months, Grade 3-4 cardiovascular events included peripheral arterial occlusive disease (1.4% and 1.1% at 300 mg and 400 mg nilotinib twice daily, respectively), ischaemic heart disease (2.2% and 6.1% at 300 mg and 400 mg nilotinib twice daily, respectively) and ischaemic cerebrovascular events (1.1% and 2.2% at 300 mg and 400 mg nilotinib twice daily, respectively). Patients should be advised to seek immediate medical attention if they experience acute signs or symptoms of cardiovascular events. The cardiovascular status of patients should be evaluated and cardiovascular risk factors monitored and actively managed during nilotinib therapy according to standard guidelines. Appropriate therapy should be prescribed to manage cardiovascular risk factors.

Hepatitis B reactivation
Reactivation of hepatitis B in patients who are chronic carriers of this virus has occurred after these patients received BCR-ABL tyrosine kinase inhibitors. Some cases resulted in acute hepatic failure or fulminant hepatitis leading to liver transplantation or a fatal outcome.

Patients should be tested for HBV infection before initiating treatment with nilotinib. Experts in liver disease and in the treatment of hepatitis B should be consulted before treatment is initiated in patients with positive hepatitis B serology (including those with active disease) and

for patients who test positive for HBV infection during treatment. Carriers of HBV who require treatment with nilotinib should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy.

Special monitoring of adult Ph+ CML patients in chronic phase who have achieved a sustained deep molecular response.

Eligibility for discontinuation of treatment

Eligible patients who are confirmed to express the typical BCR-ABL transcripts, e13a2/b2a2 or e14a2/b3a2, can be considered for treatment discontinuation. Patients must have typical BCR-ABL transcripts to allow quantitation of BCR-ABL, evaluation of the depth of molecular response, and determination of a possible loss of molecular remission after discontinuation of treatment with nilotinib.

Monitoring of patients who have discontinued therapy

Frequent monitoring of BCR-ABL transcript levels in patients eligible for treatment discontinuation must be performed with a quantitative diagnostic test validated to measure molecular response levels with a sensitivity of at least MR4.5 (BCR-ABL/ABL ≤0.0032% IS). BCR-ABL transcript levels must be assessed prior to and during treatment discontinuation.

Loss of major molecular response (MMR=BCR-ABL/ABL ≤0.1%IS) will trigger treatment re-initiation within 4 weeks of when loss of remission is known to have occurred. Molecular relapse can occur during the treatment-free phase, and long-term outcome data are not yet available. It is therefore crucial to perform frequent monitoring of BCR-ABL transcript levels and complete blood count with differential in order to detect possible loss of remission. For patients who fail to achieve MMR after three months of treatment re-initiation, BCR-ABL kinase domain mutation testing should be performed.

Laboratory tests and monitoring

Blood lipids

In a Phase III study in newly diagnosed CML patients, 1.1% of the patients treated with 400 mg nilotinib twice daily showed a Grade 3-4 elevation in total cholesterol; no Grade 3-4 elevations were however observed in the 300 mg twice daily dose group. It is recommended that the lipid profiles be determined before initiating treatment with nilotinib, assessed at month 3 and 6 after initiating therapy and at least yearly during chronic therapy. If a HMG-CoA reductase inhibitor (a lipid-lowering agent) is required before initiating treatment since certain HMG-CoA reductase inhibitors are also metabolised by the CYP3A4 pathway.

Blood glucose

In a Phase III study in newly diagnosed CML patients, 6.9% and 7.2% of the patients treated with 400 mg nilotinib and 300 mg nilotinib twice daily, respectively, showed a Grade 3-4 elevation in blood glucose. It is recommended that the glucose levels be assessed before initiating treatment with Nilotinib and monitored during treatment, as clinically indicated. If test results warrant therapy, physicians should follow their local standards of practice and treatment guidelines.

Interactions with other medicinal products

The administration of Nilotinib with agents that are strong CYP3A4 inhibitors (including, but not limited to, ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin, ritonavir) should be avoided. Should treatment with any of these agents be required, it is recommended that nilotinib therapy be interrupted if possible. If transient interruption of treatment is not possible, close monitoring of the individual for prolongation of the QT interval is indicated.

Concomitant use of nilotinib with medicinal products that are potent inducers of CYP3A4 (e.g., phenytoin, rifampicin, carbamazepine, phenobarbital and St. John's Wort) is likely to reduce exposure to nilotinib to a clinically relevant extent. Therefore, in patients receiving nilotinib, co-administration of alternative therapeutic agents with less potential for CYP3A4 induction should be selected.

Food effect

The bioavailability of nilotinib is increased by food. Nilotinib must not be taken in conjunction with food and should be taken 2 hours after a meal. No food should be consumed for at least one hour after the dose is taken. Grapefruit juice and other foods that are known to inhibit CYP3A4 should be avoided. For patients who are unable to swallow hard capsules, the content of each hard capsule may be dispersed in one teaspoon of apple sauce and should be taken immediately. Not more than one teaspoon of apple sauce and no food other than apple sauce must be used.

Hepatic impairment

Hepatic impairment has a modest effect on the pharmacokinetics of nilotinib. Single dose administration of 200 mg of nilotinib resulted in increases in AUC of 35%, 35% and 19% in subjects with mild, moderate and severe hepatic impairment, respectively, compared to a control group of subjects with normal hepatic function. The predicted steady-state C_{max} of nilotinib showed an increase of 29%, 18% and 22%, respectively. Clinical studies have excluded patients with alanine transaminase (ALT) and/or aspartate transaminase (AST) >2.5 (or >5, if related to disease) times the upper limit of the normal range and/or total bilirubin >1.5 times the upper limit of the normal range. Metabolism of nilotinib is mainly hepatic. Patients with hepatic impairment might therefore have increased exposure to nilotinib and should be treated with caution.

Serum lipase

Elevation in serum lipase has been observed. Caution is recommended in patients with previous history of pancreatitis. In case lipase elevations are accompanied by abdominal symptoms, nilotinib therapy should be interrupted and appropriate diagnostic measures considered to exclude pancreatitis.

Total gastrectomy

The bioavailability of nilotinib might be reduced in patients with total gastrectomy. More frequent follow-up of these patients should be considered.

Tumour lysis syndrome

Due to possible occurrence of tumour lysis syndrome (TLS) correction of clinically significant dehydration and treatment of high uric acid levels are recommended prior to initiating nilotinib therapy.

Lactose

Nilotinib hard capsules contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Paediatric population

Laboratory abnormalities of mild to moderate transient elevations of aminotransferases and total bilirubin have been observed in children at a higher frequency than in adults, indicating a higher risk of hepatotoxicity in the paediatric population. Liver function (bilirubin and hepatic transaminases levels) should be monitored monthly or as clinically indicated. Elevations of bilirubin and hepatic transaminases should be managed by withholding nilotinib temporarily, dose reduction and/or discontinuation of nilotinib. The long-term effects of prolonged treatment with nilotinib in paediatric patients are unknown. In a study in the CML paediatric population, growth retardation has been documented in patients treated with nilotinib. Close monitoring of growth in paediatric patients under nilotinib treatment is recommended.

4.5 Interaction with other medicinal products and other forms of interaction

Nilotinib may be given in combination with haematopoietic growth factors such as erythropoietin or granulocyte colony-stimulating factor (G-CSF) if clinically indicated. It may be given with hydroxyurea or anagrelide if clinically indicated.

Nilotinib is mainly metabolised in the liver with CYP3A4 expected to be the main contributor to the oxidative metabolism. Nilotinib is also a substrate for the multi-drug efflux pump, P-glycoprotein (P-gp). Therefore, absorption and subsequent elimination of systemically absorbed nilotinib may be influenced by substances that affect CYP3A4 and/or P-gp.

Substances that may increase nilotinib serum concentrations

Concomitant administration of nilotinib with imatinib (a substrate and moderator of P-gp and CYP3A4), had a slight inhibitory effect on CYP3A4 and/or P-gp. The AUC of imatinib was increased by 18% to 39%, and the AUC of nilotinib was increased by 18% to 40%. These changes are unlikely to be clinically important.

The exposure to nilotinib in healthy subjects was increased 3-fold when co-administered with the strong CYP3A4 inhibitor ketoconazole. Concomitant treatment with strong CYP3A4 inhibitors, including ketoconazole, itraconazole, voriconazole, ritonavir, clarithromycin, and telithromycin, should therefore be avoided. Increased exposure to nilotinib might also be expected with moderate CYP3A4 inhibitors. Alternative concomitant medicinal products with no or minimal CYP3A4 inhibition should be considered.

Substances that may decrease nilotinib serum concentrations

Rifampicin, a potent CYP3A4 inducer, decreases nilotinib C_{max} by 64% and reduces nilotinib AUC by 80%. Rifampicin and nilotinib should not be used concomitantly.

The concomitant administration of other medicinal products that induce CYP3A4 (e.g., phenytoin, carbamazepine, phenobarbital and St. John's Wort) is likewise likely to reduce exposure to nilotinib to a clinically relevant extent. In patients for whom CYP3A4 inducers are indicated, alternative agents with less enzyme induction potential should be selected.

Nilotinib has pH dependent solubility, with lower solubility at higher pH. In healthy subjects receiving esomeprazole at 40 mg once daily for 5 days, gastric pH was markedly increased, but nilotinib absorption was only decreased modestly (27% decrease in C_{max} and 34% decrease in AUC0-∞). Nilotinib may be used concurrently with esomeprazole or other proton pump inhibitors as needed.

In a healthy subjects study, no significant change in nilotinib pharmacokinetics was observed when a single 400 mg dose of nilotinib was administered 10 hours after and 2 hours before famotidine. Therefore, when the concurrent use of a H2 blocker is necessary, it may be administered approximately 10 hours before and approximately 2 hours after the dose of Nilotinib.

In the same study as above, administration of an antacid (aluminium hydroxide/magnesium hydroxide/simethicone) 2 hours before or after a single 400 mg dose of nilotinib also did not alter nilotinib pharmacokinetics. Therefore, if necessary, an antacid may be administered approximately 2 hours before or approximately 2 hours after the dose of Nilotinib.

Substances that may have their systemic concentration altered by nilotinib
In vitro, nilotinib is a relatively strong inhibitor of CYP3A4, CYP2C8, CYP2C9, CYP2D6 and UGT1A1, with Ki value being lowest for CYP2C9 (Ki=0.13 microM).

A single-dose drug-drug interaction study in healthy volunteers with 25 mg warfarin, a sensitive CYP2C9 substrate, and 800 mg nilotinib did not result in any changes in warfarin pharmacokinetic parameters or warfarin pharmacodynamics measured as prothrombin time (PT) and international normalised ratio (INR). There are no steady-state data. This study suggests that a clinically meaningful drug-drug interaction between nilotinib and warfarin is less likely up to a dose of 25 mg of warfarin. Due to lack of steady-state data, control of warfarin pharmacodynamic markers (INR or PT) following initiation of nilotinib therapy (at least during the first 2 weeks) is recommended.

In CML patients, nilotinib administered at 400 mg twice daily for 12 days increased the systemic exposure (AUC and C_{max}) of oral midazolam (a substrate of CYP3A4) 2.6-fold and 2.0-fold, respectively. Nilotinib is a moderate CYP3A4 inhibitor. As a result, the systemic exposure of other medicinal products primarily metabolised by CYP3A4 (e.g., certain HMG-CoA reductase inhibitors) may be increased when co-administered with nilotinib. Appropriate monitoring and dose adjustment may be necessary for medicinal products that are CYP3A4 substrates and have a narrow therapeutic index (including but not limited to alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, sirolimus and tacrolimus) when co-administered with nilotinib.

Anti-arrhythmic medicinal products and other substances that may prolong the QT interval

Nilotinib should be used with caution in patients who have or may develop prolongation of the QT interval, including those patients taking anti-arrhythmic medicinal products such as amiodarone, disopyramide, procainamide, quinidine and sotalol or other medicinal products that may lead to QT prolongation such as chloroquine, halofantrine, clarithromycin, haloperidol, methadone and moxifloxacin.

Food interactions

The absorption and bioavailability of nilotinib are increased if it is taken with food, resulting in a higher serum concentration. Grapefruit juice and other foods that are known to inhibit CYP3A4 should be avoided.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception

Women of childbearing potential have to use highly effective contraception during treatment with nilotinib and for up to two weeks after ending treatment.

Pregnancy

There are no or limited amount of data from the use of nilotinib in pregnant women. Studies in animals have shown reproductive toxicity. Nilotinib should not be used during pregnancy unless the clinical condition of the woman requires treatment with nilotinib. If it is used during pregnancy, the patient must be informed of the potential risk to the fetus.

If a woman who is being treated with nilotinib is considering pregnancy, treatment discontinuation may be considered based on the eligibility criteria for discontinuing treatment. There is a limited amount of data on pregnancies in patients while attempting treatment-free remission (TFR). If pregnancy is planned during the TFR phase, the patient must be informed of a potential need to re-initiate nilotinib treatment during pregnancy.

Breast-feeding

It is unknown whether nilotinib is excreted in human milk. Available toxicological data in animals have shown excretion of nilotinib in milk. Since a risk to the newborns/infants cannot be excluded, women should not breast-feed during Nilotinib treatment and for 2 weeks after the last dose.

Fertility

Animal studies did not show an effect on fertility in male and female rats.

4.7 Effects on ability to drive and use machines

Nilotinib has no or negligible influence on the ability to drive and use machines. However, it is recommended that patients experiencing dizziness, fatigue, visual impairment or other undesirable effects with a potential impact on the ability to drive or use machines safely should refrain from these activities as long as the undesirable effects persist.

4.8 Undesirable effects

Summary of the safety profile

The data described below reflect exposure to nilotinib in 279 adult patients from a randomised Phase III study in patients with newly diagnosed Ph+ CML in chronic phase treated with 300 mg of nilotinib twice daily. Safety information from a Nilotinib treatment discontinuation study in CML patients who have been treated with nilotinib as first-line therapy is also provided.

In adult patients with newly diagnosed CML in chronic phase

The median duration of exposure was 60.5 months (range 0.1-70.8 months).

The most frequent (≥10%) non-haematological adverse reactions were rash, pruritus, headache, nausea, fatigue, alopecia, myalgia and upper abdominal pain. Most of these adverse reactions were mild to moderate in severity. Constipation, dry skin, asthenia, muscle spasms, diarrhoea, arthralgia, abdominal pain, vomiting and peripheral oedema were observed less commonly (<10% and ≥5%) were of mild to moderate severity, manageable and generally did not require dose reduction.

Treatment-emergent haematological toxicities include myelosuppression: thrombocytopenia (18%), neutropenia (15%) and anaemia (8%). Biochemical adverse drug reactions include alanine aminotransferase increased (24%), hyperbilirubinaemia (16%), aspartate aminotransferase increased (12%), lipase increased (11%), blood bilirubin increased (10%), hyperglycaemia (4%), hypercholesterolaemia (3%) and hypertriglyceridaemia (<1%). Pleural and pericardial effusions, regardless of causality, occurred in 2% and <1% of patients, respectively, receiving nilotinib 300 mg twice daily. Gastrointestinal haemorrhage, regardless of causality, was reported in 3% of these patients.

The change from baseline in mean time-averaged QTcF interval at steady state was 6 msec. No patient had an absolute QTcF >500 msec while on the study medicinal product. QTcF increase from baseline exceeding 60 msec was observed in <1% of patients while on the study medicinal product. No sudden deaths or episodes of torsade de pointes (transient or sustained) were observed. No decrease from baseline in mean left ventricular ejection fraction (LVEF) was observed at any time during treatment. No patient had a LVEF of <45% during treatment nor an absolute reduction in LVEF of more than 15%.

Discontinuation due to adverse drug reactions was observed in 10% of patients.

In adult patients with imatinib-resistant or intolerant CML in chronic phase and accelerated phase

The data described below reflect exposure to nilotinib in 458 adult patients in an open-label multicentre Phase II study in patients with imatinib-resistant or intolerant CML in chronic phase (n=321) and accelerated phase (n=137) treated at the recommended dose of 400 mg twice daily.

The most frequent (≥10%) non-haematological drug-related adverse events were rash, pruritus, nausea, fatigue, headache, vomiting, myalgia, constipation and diarrhoea. Most of these

adverse events were mild to moderate in severity. Alopecia, muscle spasms, decreased appetite, arthralgia, abdominal pain, bone pain, peripheral oedema, asthenia, upper abdominal pain, dry skin, erythema and pain in extremity were observed less commonly (<10% and ≥5%) and have been of mild to moderate severity (Grade 1 or 2). Discontinuation due to adverse drug reactions was observed in 16% of chronic phase and 10% of accelerated phase patients.
Treatment-emergent haematological toxicities include myelosuppression: thrombocytopenia (31%), neutropenia (17%) and anaemia (14%). Pleural and pericardial effusions as well as complications of fluid retention occurred in <1% of patients receiving Nilotinib. Cardiac failure was observed in <1% of patients. Gastrointestinal and CNS haemorrhage were reported in 1% and <1% of patients, respectively.

QTcF exceeding 500 msec was observed in <1% of patients. No episodes of torsade de pointes (transient or sustained) were observed.

Tabulated list of adverse reactions

The adverse reactions are ranked under heading of frequency using the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Most frequently reported adverse reactions in Nilotinib clinical studies
Non-haematological adverse reactions (excluding laboratory abnormalities) that are reported in at least 5% of the adult patients treated with 300 mg of nilotinib twice daily in the randomised Phase III study are shown in Table 3.

Table 3 Non-haematological adverse reactions (≥5% of all patients)*

	Newly diagnosed CML-CP 300 mg twice daily n=279			**Imatinib-resistant or intolerant CML-CP and CML-AP 400 mg twice daily n=458**				
	60-month analysis			**24-month analysis**				
System organ class/Adverse reaction	**Frequency**	**All grades**	**Grade 3-4**	**Frequency**	**All grades**	**Grade 3-4**	**CML-CP n=321 Grade 3-4**	**CML-AP n=137 Grade 3-4**
		%	**%**		**%**	**%**	**%**	**%**
Metabolism and nutrition disorders								
Decreased appetite **	Common	4	0	Common	8	<1	<1	0
Nervous system disorders								
Headache	Very common	16	2	Very common	15	1	2	<1
Gastrointestinal disorders								

Nausea	Very common	14	<1	Very common	20	<1	<1	<1
Constipation	Common	10	0	Very common	12	<1	<1	0
Diarrhoea	Common	9	<1	Very common	11	2	2	<1
Vomiting	Common	6	0	Very common	10	<1	<1	0
Upper abdominal pain	Very common	10	1	Common	5	<1	<1	0
Abdominal pain	Common	6	0	Common	6	<1	<1	<1
Dyspepsia	Common	5	0	Common	3	0	0	0
Skin and subcutaneous tissue disorders								
Rash	Very common	33	<1	Very common	28	1	2	0
Pruritus	Very common	18	<1	Very common	24	<1	<1	0
Alopecia	Very common	10	0	Common	9	0	0	0
Dry skin	Common	10	0	Common	5	0	0	0
Erythema	Common	3	0	Common	5	<1	<1	0
Musculoskeletal and connective tissue disorders								
Myalgia	Very common	10	<1	Very common	10	<1	<1	<1
Muscle spasms	Common	9	0	Common	8	<1	<1	0
Arthralgia	Common	8	<1	Common	7	<1	1	0
Bone pain	Common	4	0	Common	6	<1	<1	0
Pain in extremity	Common	5	<1	Common	5	<1	<1	<1
General disorders and administration site conditions								
Fatigue	Very common	12	0	Very common	17	1	1	<1
Asthenia	Common	9	<1	Common	6	0	0	0
Oedema peripheral	Common	5	<1	Common	6	0	0	0

* Percentages are rounded to integer for presentation in this table. However, percentages with one decimal precision are used to identify terms with a frequency of at least 5% and to classify terms according to frequency categories.

**Also includes preferred term anorexia

Adverse reactions that were reported in adult patients in the Nilotinib clinical studies which serve as a basis for the approved indications at a frequency of less than 5% are shown in Table 4. For laboratory abnormalities, very common adverse reactions not included in Table 3 are also reported. These adverse reactions are included based on clinical relevance.

Table 4 Adverse reactions in adult patients in the Nilotinib Phase III study (<5% of all patients)

Infections and infestations	
Common:	Folliculitis, upper respiratory tract infection (including pharyngitis, nasopharyngitis, rhinitis)
Uncommon:	Pneumonia, urinary tract infection, gastroenteritis, bronchitis, herpes virus infection, candidiasis (including oral candidiasis)
Not known:	Sepsis, subcutaneous abscess, anal abscess, furuncle, tinea pedis, hepatitis B reactivation
Neoplasms benign, malignant and unspecified (including cysts and polyps)	
Common:	Skin papilloma
Not known:	Oral papilloma, paraproteinaemia
Blood and lymphatic system disorders	
Common:	Leukopenia, eosinophilia, febrile neutropenia, pancytopenia, lymphopenia
Uncommon:	Thrombocythaemia, leukocytosis
Immune system disorders	
Not known:	Hypersensitivity
Endocrine disorders	
Uncommon:	Hyperthyroidism, hypothyroidism
Not known:	Hyperparathyroidism secondary, thyroiditis
Metabolism and nutrition disorders	
Very common:	Hypophosphataemia (including blood phosphorus decreased)
Common:	Electrolyte imbalance (including hypomagnesaemia, hyperkalaemia, hypokalaemia, hyponatraemia, hypocalcaemia, hypercalcaemia, hyperphosphataemia), diabetes mellitus, hyperglycaemia, hypercholesterolaemia, hyperlipidaemia, hypertriglyceridaemia
Uncommon:	Dehydration, increased appetite, gout, dyslipidaemia
Not known:	Hyperuricaemia, hypoglycaemia
Psychiatric disorders	
Common:	Depression, insomnia, anxiety
Not known:	Disorientation, confusional state, amnesia, dysphoria
Nervous system disorders	
Common:	Dizziness, peripheral neuropathy, hypoaesthesia, paraesthesia
Uncommon:	Intracranial haemorrhage, ischaemic stroke, transient ischaemic attack, cerebral infarction, migraine, loss of consciousness (including syncope), tremor, disturbance in attention, hyperaesthesia

Not known:	Cerebrovascular accident, brain oedema, optic neuritis, lethargy, dysaesthesia, restless legs syndrome
Eye disorders	
Common:	Eye haemorrhage, periorbital oedema, eye pruritus, conjunctivitis, dry eye (including xerophthalmia)
Uncommon:	Visual impairment, vision blurred, conjunctival haemorrhage, visual acuity reduced, eyelid oedema, photopsia, hyperaemia (scleral, conjunctival, ocular), eye irritation
Not known:	Papilloedema, chorioretinopathy, diplopia, photophobia, eye swelling, blepharitis, eye pain, conjunctivitis allergic, ocular surface disease
Ear and labyrinth disorders	
Common:	Vertigo
Not known:	Hearing impaired, ear pain, tinnitus
Cardiac disorders	
Common:	Angina pectoris, arrhythmia (including atroventricular block, cardiac flutter, extrasystoles, tachycardia, atrial fibrillation, bradycardia), palpitations, electrocardiogram QT prolonged
Uncommon:	Cardiac failure, myocardial infarction, coronary artery disease, cardiac murmur, pericardial effusion, cyanosis
Not known:	Ventricular dysfunction, pericarditis, ejection fraction decreased
Vascular disorders	
Common:	Hypertension, flushing, peripheral artery stenosis
Uncommon:	Hypertensive crisis, peripheral arterial occlusive disease, intermittent claudication, arterial stenosis limb, haematoma, arteriosclerosis
Not known:	Shock haemorrhagic, hypotension, thrombosis
Respiratory, thoracic and mediastinal disorders	
Common:	Dyspnoea, dyspnoea exertional, epistaxis, cough, dysphonia
Uncommon:	Pulmonary oedema, pleural effusion, interstitial lung disease, pleuritic pain, pleurisy, pharyngolaryngeal pain, throat irritation
Not known:	Pulmonary hypertension, wheezing, oropharyngeal pain
Gastrointestinal disorders	
Common:	Pancreatitis, abdominal discomfort, abdominal distension, dysgeusia, flatulence
Uncommon:	Gastrointestinal haemorrhage, melaena, mouth ulceration, gastroesophageal reflux, stomatitis, oesophageal pain, dry mouth, gastritis, sensitivity of teeth
Not known:	Gastrointestinal ulcer perforation, retroperitoneal haemorrhage, haematemesis, gastric ulcer, oesophagitis ulcerative, subileus, enterocolitis, haemorrhoids, hiatus hernia, rectal haemorrhage, gingivitis
Hepatobiliary disorders	
Very common:	Hyperbilirubinaemia (including blood bilirubin increased)
Common:	Hepatic function abnormal
Uncommon:	Hepatotoxicity, toxic hepatitis, jaundice

Not known:	Cholestasis, hepatomegaly
Skin and subcutaneous tissue disorders	
Common:	Night sweats, eczema, urticaria, hyperhidrosis, contusion, acne, dermatitis (including allergic, exfoliative and acneiform)
Uncommon:	Exfoliative rash, drug eruption, skin pain, ecchymosis, swelling face
Not known:	Erythema multiforme, erythema nodosum, skin ulcer, palmar-plantar erythrodysaesthesia syndrome, petechiae, photosensitivity, blister, dermal cysts, sebaceous hyperplasia, skin atrophy, skin discolouration, skin exfoliation, skin hyperpigmentation, skin hypertrophy, hyperkeratosis, psoriasis
Musculoskeletal and connective tissue disorders	
Common:	Musculoskeletal chest pain, musculoskeletal pain, back pain, flank pain, neck pain, muscular weakness
Uncommon:	Musculoskeletal stiffness, joint swelling
Not known:	Arthritis
Renal and urinary disorders	
Common:	Pollakiuria
Uncommon:	Dysuria, micturition urgency, nocturia
Not known:	Renal failure, haematuria, urinary incontinence, chromaturia
Reproductive system and breast disorders	
Uncommon:	Breast pain, gynaecomastia, erectile dysfunction
Not known:	Breast induration, menorrhagia, nipple swelling
General disorders and administration site conditions	
Common:	Chest pain (including non-cardiac chest pain), pain, pyrexia, chest discomfort, malaise
Uncommon:	Face oedema, gravitational oedema, influenza-like illness, chills, feeling body temperature change (including feeling hot, feeling cold)
Not known:	Localised oedema
Investigations	
Very common:	Alanine aminotransferase increased, aspartate aminotransferase increased, lipase increased, lipoprotein cholesterol (including low density and high density) increased, total cholesterol increased, blood triglycerides increased
Common:	Haemoglobin decreased, blood amylase increased, blood alkaline phosphatase increased, gamma-glutamyltransferase increased, blood creatinine phosphokinase increased, weight decreased, weight increased, blood insulin increased, globulins decreased
Uncommon:	Blood lactate dehydrogenase increased, blood glucose decreased, blood urea increased
Not known:	Troponin increased, blood bilirubin unconjugated increased, blood insulin decreased, insulin C-peptide decreased, blood parathyroid hormone increased

Clinically relevant or severe abnormalities of routine haematological or biochemistry laboratory values in adult patients are presented in Table 5.

Table 5 Grade 3-4 laboratory abnormalities*

	Newly diagnosed CML-CP 300 mg twice daily	**Imatinib-resistant or intolerant CML-CP and CML-AP 400 mg twice daily**	
	n=279 (%)	**CML-CP n=321 (%)**	**CML-AP n=137 (%)**
Haematological parameters			
Myelosuppression			
- Neutropenia	12	31	42
- Thrombocytopenia	10	30	42
- Anaemia	4	11	27
Biochemistry parameters			
- Elevated creatinine	0	1	<1
- Elevated lipase	9	18	18
- Elevated SGOT (AST)	1	3	2
- Elevated SGPT (ALT)	4	4	4
- Hypophosphataemia	8	17	15
- Elevated bilirubin (total)	4	7	9
- Elevated glucose	7	12	6
- Elevated cholesterol (total)	0	**	**
- Elevated triglycerides	0	**	**

*Percentages with one decimal precision are used and rounded to integer for presentation in this table

**Parameters not collected

Treatment discontinuation in adult Ph+ CML patients in chronic phase who have achieved a sustained deep molecular response

After discontinuation of nilotinib therapy within the framework of attempting TFR, patients may experience musculoskeletal symptoms more frequently than before treatment discontinuation, e.g., myalgia, pain in extremity, arthralgia, bone pain, spinal pain or musculoskeletal pain.

In a Phase II clinical study with newly diagnosed adult patients with Ph+ CML in chronic phase (N=190), musculoskeletal symptoms were reported within a year of Nilotinib discontinuation in 24.7% versus 16.3% within the previous year on nilotinib treatment.

In a Phase II clinical study with adult patients with Ph+ CML in chronic phase on nilotinib treatment and previously treated with imatinib (N=126), musculoskeletal symptoms were

reported within a year of discontinuation in 42.1% versus 14.3% within the previous year on nilotinib treatment.

Description of selected adverse reactions

Sudden death

Uncommon cases (0.1 to 1%) of sudden deaths have been reported in Nilotinib clinical trials and/or compassionate use programs in patients with imatinib-resistant or intolerant CML in chronic phase or accelerated phase with a past medical history of cardiac disease or significant cardiac risk factors.

Hepatitis B reactivation

Hepatitis B reactivation has been reported in association with BCR-ABL TKIs. Some cases resulted in acute hepatic failure or fulminant hepatitis leading to liver transplantation or a fatal outcome.

Post-marketing experience

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

Frequency very common: Growth retardation has been documented in paediatric patients treated with nilotinib.

Frequency rare: Cases of tumour lysis syndrome have been reported in patients treated with nilotinib.

Paediatric population

The safety of nilotinib in paediatric patients (from 2 to <18 years of age) with Philadelphia chromosome positive CML in chronic phase (n=69) has been investigated in two studies (see section 5.1). In paediatric patients, the frequency, type and severity of adverse reactions observed have been generally consistent with those observed in adults, with the exception of the laboratory abnormalities hyperbilirubinaemia (Grade 3/4: 13.0%) and transaminase elevation (AST Grade 3/4: 1.4%, ALT Grade 3/4: 8.7%) which were reported at a higher frequency than in adult patients. Bilirubin and hepatic transaminase levels should be monitored during treatment.

Growth retardation in paediatric population

In an interim analysis in a study in the CML paediatric population, with a median exposure of 33 months in each cohort (newly diagnosed and resistant or intolerant Ph+ CML-CP), growth retardation (crossing two main percentile lines from baseline) has been documented in 12.1%. Close monitoring of growth in paediatric patients under nilotinib treatment is recommended.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Isolated reports of intentional overdose with nilotinib were reported, where an unspecified number of Nilotinib hard capsules were ingested in combination with alcohol and other medicinal products. Events included neutropenia, vomiting and drowsiness. No ECG changes or hepatotoxicity were reported. Outcomes were reported as recovered.

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

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors

ATC code: L01XE08

Mechanism of action

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.

Pharmacodynamic effects

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.

Table 6 Kinase profile of nilotinib (phosphorylation IC_{50} nM)

BCR-ABL	PDGFR	KIT
20	69	210

Clinical efficacy

Clinical studies in newly diagnosed CML in chronic phase

An open-label, multicentre, randomised Phase III study was conducted to determine the efficacy of nilotinib versus imatinib in 846 adult patients with cytogenetically confirmed newly diagnosed Philadelphia chromosome positive CML in the chronic phase. Patients were within

six months of diagnosis and were previously untreated, with the exception of hydroxyurea and/or anagrelide. Patients were randomised 1:1:1 to receive either nilotinib 300 mg twice daily (n=282), nilotinib 400 mg twice daily (n=281) or imatinib 400 mg once daily (n=283). Randomisation was stratified by Sokal risk score at the time of diagnosis.

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

The primary data analysis time point was when all 846 patients completed 12 months of treatment (or discontinued earlier). Subsequent analyses reflect when patients completed 24, 36, 48, 60 and 72 months of treatment (or discontinued earlier). The median time on treatment was approximately 70 months in the nilotinib treatment groups and 64 months in the imatinib group. The median actual dose intensity was 593 mg/day for nilotinib 300 mg twice daily, 772 mg/day for nilotinib 400 mg twice daily and 400 mg/day for imatinib 400 mg once daily. This study is ongoing.

The primary efficacy endpoint was major molecular response (MMR) at 12 months. MMR was defined as ≤0.1% BCR-ABL/ABL% by international scale (IS) measured by RQvPCR, which corresponds to a ≥3 log reduction of BCR-ABL transcript from standardised baseline. The MMR rate at 12 months was statistically significantly higher for nilotinib 300 mg twice daily compared to imatinib 400 mg once daily (44.3% versus 22.3%, p<0.0001). The rate of MMR at 12 months, was also statistically significantly higher for nilotinib 400 mg twice daily compared to imatinib 400 mg once daily (42.7% versus 22.3%, p<0.0001).

The rates of MMR at 3, 6, 9 and 12 months were 8.9%, 33.0%, 43.3% and 44.3% for nilotinib 300 mg twice daily, 5.0%, 29.5%, 38.1% and 42.7% for nilotinib 400 mg twice daily and 0.7%, 12.0%, 18.0% and 22.3% for imatinib 400 mg once daily.
The MMR rate at 12, 24, 36, 48, 60 and 72 months is presented in Table 7.

Table 7 MMR rate

	Nilotinib 300 mg twice daily n=282 (%)	Nilotinib 400 mg twice daily n=281 (%)	Imatinib 400 mg once daily n=283 (%)
MMR at 12 months			
Response (95% CI)	44.3[1] (38.4; 50.3)	42.7[1] (36.8; 48.7)	22.3 (17.6; 27.6)
MMR at 24 months			
Response (95% CI)	61.7[1] (55.8; 67.4)	59.1[1] (53.1; 64.9)	37.5 (31.8; 43.4)
MMR at 36 months[2]			

Response (95% CI)	58.5[1] (52.5; 64.3)	57.3[1] (51.3; 63.2)	38.5 (32.8; 44.5)
MMR at 48 months[3]			
Response (95% CI)	59.9[1] (54.0; 65.7)	55.2 (49.1; 61.1)	43.8 (38.0; 49.8)
MMR at 60 months[4]			
Response (95% CI)	62.8 (56.8; 68.4)	61.2 (55.2; 66.9)	49.1 (43.2; 55.1)
MMR at 72 months[5]			
Response (95% CI)	52.5 (46.5; 58.4)	57.7 (51.6; 63.5)	41.7 (35.9; 47.7)

[1] Cochran-Mantel-Haenszel (CMH) test p-value for response rate (vs. imatinib 400 mg) <0.0001

[2] Only patients who were in MMR at a specific time point are included as responders for that time point. A total of 199 (35.2%) of all patients were not evaluable for MMR at 36 months (87 in the nilotinib 300 mg twice daily group and 112 in the imatinib group) due to missing/unevaluable PCR assessments (n=17), atypical transcripts at baseline (n=7), or discontinuation prior to the 36-month time point (n=175).

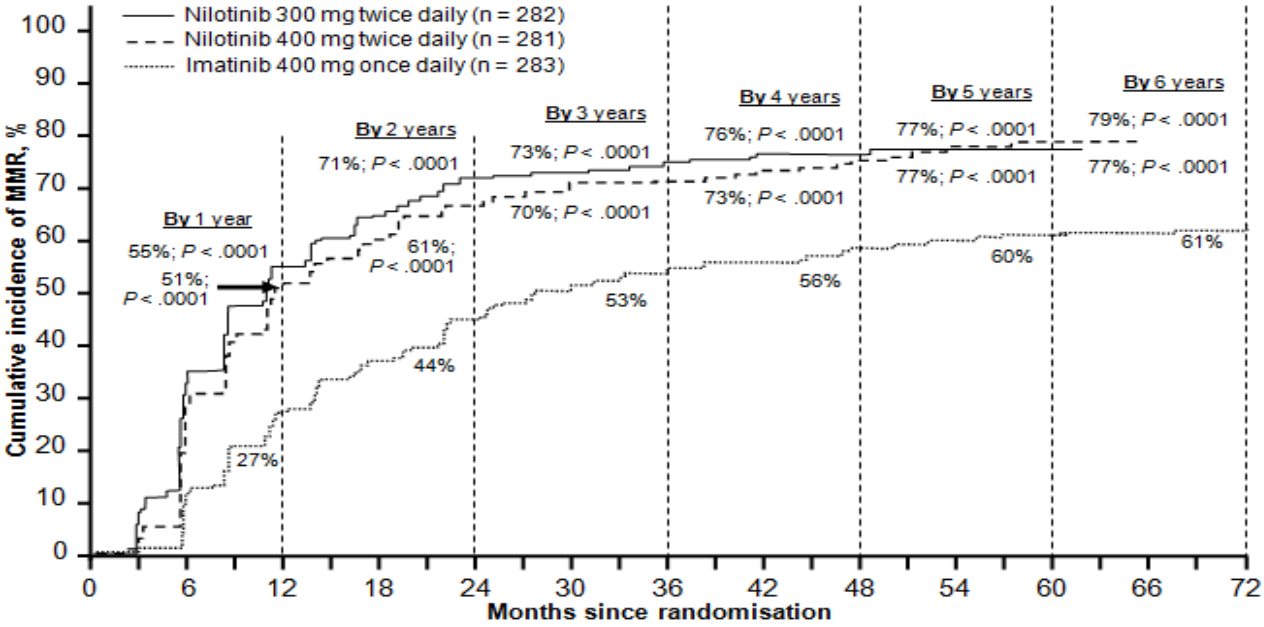
[3] Only patients who were in MMR at a specific time point are included as responders for that time point. A total of 305 (36.1%) of all patients were not evaluable for MMR at 48 months (98 in the nilotinib 300 mg twice daily group, 88 in the nilotinib 400 mg twice daily group and 119 in the imatinib group) due to missing/unevaluable PCR assessments (n=18), atypical transcripts at baseline (n=8), or discontinuation prior to the 48-month time point (n=279).

[4] Only patients who were in MMR at a specific time point are included as responders for that time point. A total of 322 (38.1%) of all patients were not evaluable for MMR at 60 months (99 in the nilotinib 300 mg twice daily group, 93 in the nilotinib 400 mg twice daily group and 130 in the imatinib group) due to missing/unevaluable PCR assessments (n=9), atypical transcripts at baseline (n=8) or discontinuation prior to the 60-month time point (n=305).

[5] Only patients who were in MMR at a specific time point are included as responders for that time point. A total of 395 (46.7%) of all patients were not evaluable for MMR at 72 months (130 in the nilotinib 300 mg twice daily group, 110 in the nilotinib 400 mg twice daily group and 155 in the imatinib group) due to missing/unevaluable PCR assessments (n=25), atypical transcripts at baseline (n=8) or discontinuation prior to the 72-month time point (n=362).

MMR rates by different time points (including patients who achieved MMR at or before those time points as responders) are presented in the cumulative incidence of MMR.

Figure 1 Cumulative incidence of MMR



For all Sokal risk groups, the MMR rates at all time points remained consistently higher in the two nilotinib groups than in the imatinib group.

In a retrospective analysis, 91% (234/258) of patients on nilotinib 300 mg twice daily achieved BCR-ABL levels ≤10% at 3 months of treatment compared to 67% (176/264) of patients on imatinib 400 mg once daily. Patients with BCR-ABL levels ≤10% at 3 months of treatment show a greater overall survival at 72 months compared to those who did not achieve this molecular response level (94.5% vs. 77.1% respectively [p=0.0005]).

Based on the Kaplan-Meier analysis of time to first MMR the probability of achieving MMR at different time points was higher for both nilotinib at 300 mg and 400 mg twice daily compared to imatinib 400 mg once daily (HR=2.17 and stratified log-rank p<0.0001 between nilotinib 300 mg twice daily and imatinib 400 mg once daily, HR=1.88 and stratified log-rank p<0.0001 between nilotinib 400 mg twice daily and imatinib 400 mg once daily).

The proportion of patients who had a molecular response of ≤0.01% and ≤0.0032% by IS at different time points are presented in Table 8 and the proportion of patients who had a molecular response of ≤0.01% and ≤0.0032% by IS by different time points are presented in Figures 2 and 3. Molecular responses of ≤0.01% and ≤0.0032% by IS correspond to a ≥4 log reduction and ≥4.5 log reduction, respectively, of BCR-ABL transcripts from a standardised baseline.

Table 8 Proportions of patients who had molecular response of ≤0.01% (4 log reduction) and ≤0.0032% (4.5 log reduction)

	Nilotinib 300 mg twice daily n=282 (%)		Nilotinib 400 mg twice daily n=281 (%)		Imatinib 400 mg once daily n=283 (%)	
	≤0.01%	**≤0.0032%**	**≤0.01%**	**≤ 0.0032%**	**≤0.01%**	**≤0.0032%**

At 12 months	11.7	4.3	8.5	4.6	3.9	0.4
At 24 months	24.5	12.4	22.1	7.8	10.2	2.8
At 36 months	29.4	13.8	23.8	12.1	14.1	8.1
At 48 months	33.0	16.3	29.9	17.1	19.8	10.2
At 60 months	47.9	32.3	43.4	29.5	31.1	19.8
At 72 months	44.3	31.2	45.2	28.8	27.2	18.0

Figure 2 Cumulative incidence of molecular response of ≤0.01% (4-log reduction)

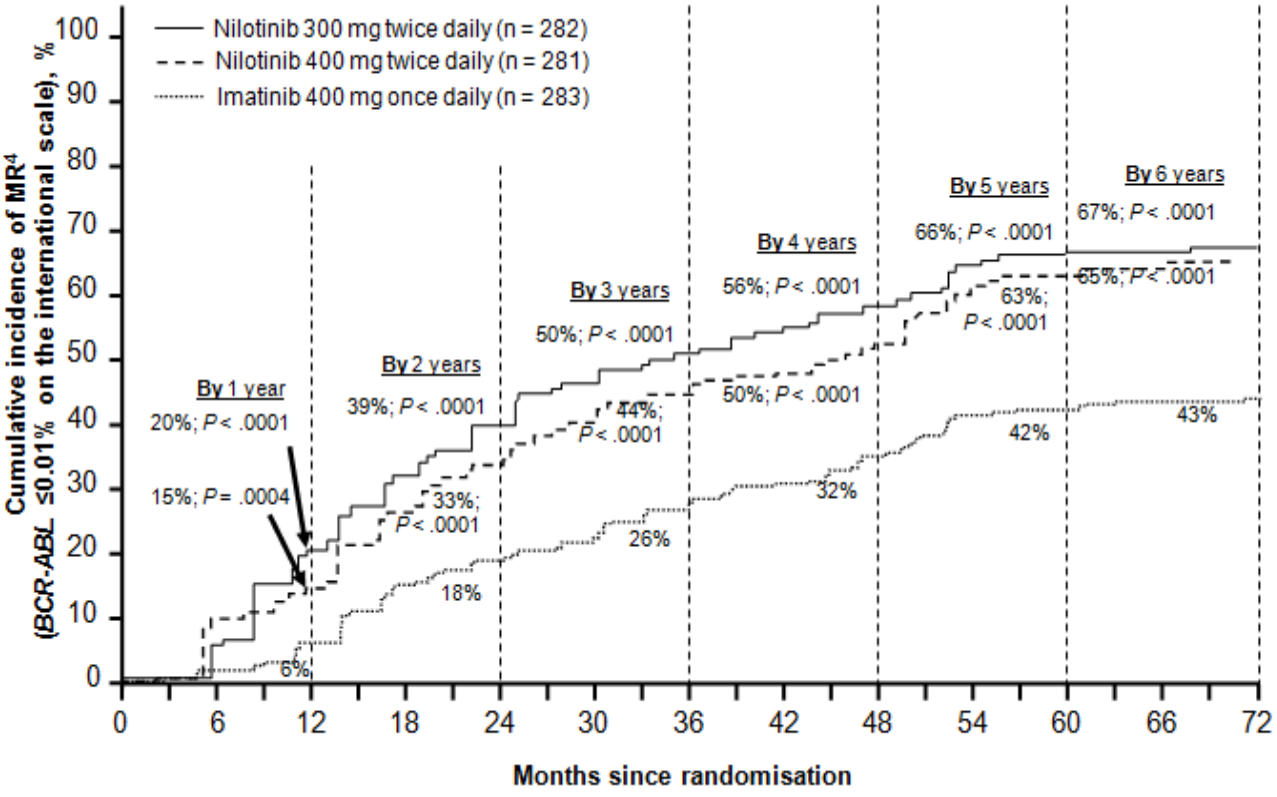
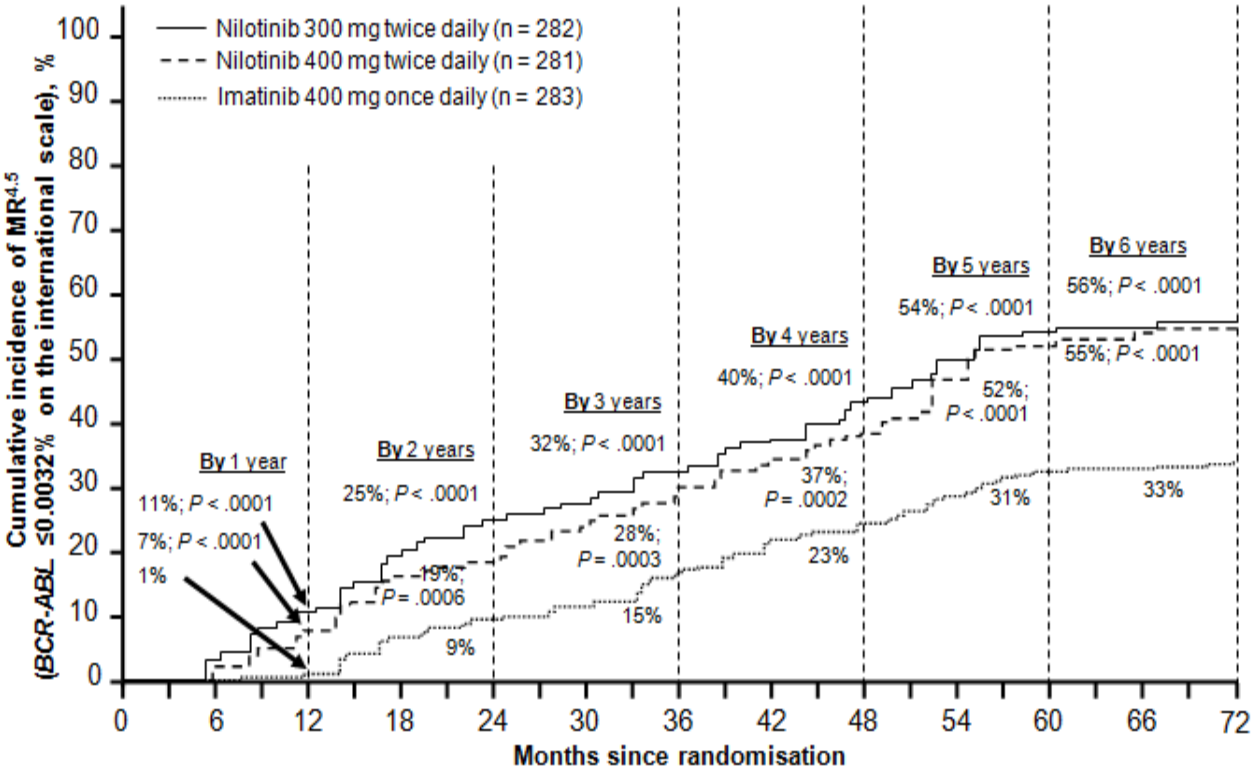


Figure 3 Cumulative incidence of molecular response of ≤0.0032% (4.5 log reduction)



Based on Kaplan-Meier estimates of the duration of first MMR, the proportions of patients who were maintaining response for 72 months among patients who achieved MMR were 92.5% (95% CI: 88.6-96.4%) in the nilotinib 300 mg twice daily group, 92.2% (95% CI: 88.5-95.9%) in the nilotinib 400 mg twice daily group and 88.0% (95% CI: 83.0-93.1%) in the imatinib 400 mg once daily group.

Complete cytogenetic response (CCyR) was defined as 0% Ph+ metaphases in the bone marrow based on a minimum of 20 metaphases evaluated. Best CCyR rate by 12 months (including patients who achieved CCyR at or before the 12 month time point as responders) was statistically higher for both nilotinib 300 mg and 400 mg twice daily compared to imatinib 400 mg once daily, see Table 9.

CCyR rate by 24 months (includes patients who achieved CCyR at or before the 24 month time point as responders) was statistically higher for both the nilotinib 300 mg twice daily and 400 mg twice daily groups compared to the imatinib 400 mg once daily group.

Table 9 Best CCyR rate

	Nilotinib 300 mg twice daily n=282 (%)	Nilotinib 400 mg twice daily n=281 (%)	Imatinib 400 mg once daily n=283 (%)
By 12 months			
Response (95% CI)	80.1 (75.0; 84.6)	77.9 (72.6; 82.6)	65.0 (59.2; 70.6)

No response	19.9	22.1	35.0
CMH test p-value for response rate (versus imatinib 400 mg once daily)	<0.0001	0.0005	
By 24 months			
Response (95% CI)	86.9 (82.4; 90.6)	84.7 (79.9; 88.7)	77.0 (71.7; 81.8)
No response	13.1	15.3	23.0
CMH test p-value for response rate (versus imatinib 400 mg once daily)	0.0018	0.0160	

Based on Kaplan-Meier estimates, the proportions of patients who were maintaining response for 72 months among patients who achieved CCyR were 99.1% (95% CI: 97.9-100%) in the nilotinib 300 mg twice daily group, 98.7% (95% CI: 97.1-100%) in the nilotinib 400 mg twice daily group and 97.0% (95% CI: 94.7-99.4%) in the imatinib 400 mg once daily group.

Progression to accelerated phase (AP) or blast crisis (BC) on treatment is defined as the time from the date of randomisation to the first documented disease progression to accelerated phase or blast crisis or CML-related death. Progression to accelerated phase or blast crisis on treatment was observed in a total of 17 patients: 2 patients on nilotinib 300 mg twice daily, 3 patients on nilotinib 400 mg twice daily and 12 patients on imatinib 400 mg once daily. The estimated rates of patients free from progression to accelerated phase or blast crisis at 72 months were 99.3%, 98.7% and 95.2%, respectively (HR=0.1599 and stratified log-rank p=0.0059 between nilotinib 300 mg twice daily and imatinib once daily, HR=0.2457 and stratified log-rank p=0.0185 between nilotinib 400 mg twice daily and imatinib once daily). No new events of progressions to AP/BC were reported on-treatment since the 2-year analysis.

Including clonal evolution as a criterion for progression, a total of 25 patients progressed to accelerated phase or blast crisis on treatment by the cut-off date (3 in the nilotinib 300 mg twice daily group, 5 in the nilotinib 400 mg twice daily group and 17 in the imatinib 400 mg once daily group). The estimated rates of patients free from progression to accelerated phase or blast crisis including clonal evolution at 72 months were 98.7%, 97.9% and 93.2%, respectively (HR=0.1626 and stratified log-rank p=0.0009 between nilotinib 300 mg twice daily and imatinib once daily, HR=0.2848 and stratified log-rank p=0.0085 between nilotinib 400 mg twice daily and imatinib once daily).

A total of 55 patients died during treatment or during the follow-up after discontinuation of treatment. (21 in the nilotinib 300 mg twice daily group, 11 in the nilotinib 400 mg twice daily group and 23 in the imatinib 400 mg once daily group). Twenty-six (26) of these 55 deaths were related to CML (6 in the nilotinib 300 mg twice daily group, 4 in the nilotinib 400 mg twice daily group and 16 in the imatinib 400 mg once daily group). The estimated rates of patients alive at 72 months were 91.6%, 95.8% and 91.4%, respectively (HR=0.8934 and stratified log-rank p=0.7085 between nilotinib 300 mg twice daily and imatinib, HR=0.4632 and stratified log-rank p=0.0314 between nilotinib 400 mg twice daily and imatinib).

Considering only CML-related deaths as events, the estimated rates of overall survival at 72 months were 97.7%, 98.5% and 93.9%, respectively (HR=0.3694 and stratified log-rank p=0.0302 between nilotinib 300 mg twice daily and imatinib, HR=0.2433 and stratified log-rank p=0.0061 between nilotinib 400 mg twice daily and imatinib).

Clinical studies in imatinib-resistant or intolerant CML in chronic phase and accelerated phase

An open-label, uncontrolled, multicentre Phase II study was conducted to determine the efficacy of nilotinib in adult patients with imatinib resistant or intolerant CML with separate treatment arms for chronic and accelerated phase disease. Efficacy was based on 321 CP patients and 137 AP patients enrolled. Median duration of treatment was 561 days for CP patients and 264 days for AP patients (see Table 10). Nilotinib 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. The dose was 400 mg twice daily and dose escalation to 600 mg twice daily was allowed.

Table 10 Duration of exposure with nilotinib

	Chronic phase n=321	Accelerated phase n=137
Median duration of therapy in days (25th-75th percentiles)	561 (196-852)	264 (115-595)

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.

Overall, 73% of patients were imatinib-resistant, while 27% were imatinib-intolerant. 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 (Table 11). The median highest prior imatinib dose had been 600 mg/day. The highest prior imatinib dose was ≥600 mg/day in 74% of all patients, with 40% of patients receiving imatinib doses ≥800 mg/day.

Table 11 CML disease history characteristics

	Chronic phase (n=321)	Accelerated phase (n=137)*
Median time since diagnosis in months (range)	58 (5–275)	71 (2–298)
Imatinib Resistant Intolerant without MCyR	 226 (70%) 95 (30%)	 109 (80%) 27 (20%)
Median time of imatinib treatment in days (25^{th}-75^{th} percentiles)	975 (519-1,488)	857 (424-1,497)
Prior hydroxyurea	83%	91%

Prior interferon	58%	50%
Prior bone marrow transplant	7%	8%
* Missing information on imatinib-resistant/intolerant status for one patient.		

The primary endpoint in the CP patients was major cytogenetic response (MCyR), defined as elimination (CCyR, complete cytogenetic response) or significant reduction to <35% Ph+ metaphases (partial cytogenetic response) of Ph+ haematopoietic cells. Complete haematological response (CHR) in CP patients was evaluated as a secondary endpoint. The primary endpoint in the AP patients was overall confirmed haematological response (HR), defined as either a complete haematological response, no evidence of leukaemia or return to chronic phase.

Chronic phase

The MCyR rate in 321 CP patients was 51%. Most responders achieved their MCyR rapidly within 3 months (median 2.8 months) of starting nilotinib treatment and these were sustained. The median time to achieve CCyR was just past 3 months (median 3.4 months). Of the patients who achieved MCyR, 77% (95% CI: 70% - 84%) were maintaining response at 24 months. Median duration of MCyR has not been reached. Of the patients who achieved CCyR, 85% (95% CI: 78% - 93%) were maintaining response at 24 months. Median duration of CCyR has not been reached. Patients with a CHR at baseline achieved a MCyR faster (1.9 versus 2.8 months). Of CP patients without a baseline CHR, 70% achieved a CHR, median time to CHR was 1 month and median duration of CHR was 32.8 months. The estimated 24-month overall survival rate in CML-CP patients was 87%.

Accelerated phase

The overall confirmed HR rate in 137 AP patients was 50%. Most responders achieved a HR early with nilotinib treatment (median 1.0 months) and these have been durable (median duration of confirmed HR was 24.2 months). Of the patients who achieved HR, 53% (95% CI: 39% - 67%) were maintaining response at 24 months. MCyR rate was 30% with a median time to response of 2.8 months. Of the patients who achieved MCyR, 63% (95% CI: 45% - 80%) were maintaining response at 24 months. Median duration of MCyR was 32.7 months. The estimated 24-month overall survival rate in CML-AP patients was 70%.

The rates of response for the two treatment arms are reported in Table 12.

Table 12 Response in CML

(Best response rate)	**Chronic phase**			**Accelerated phase**		
	Intolerant (n=95)	**Resistant (n=226)**	**Total (n=321)**	**Intolerant (n=27)**	**Resistant (n=109)**	**Total* (n=137)**
Haematological Response (%)						
Overall (95%CI) Complete NEL Return to CP	- 87 (74-94) - -	- 65 (56-72) - -	- 70[1] (63-76) - 	48 (29-68) 37 7 4	51 (42-61) 28 10 13	50 (42-59) 30 9 11
Cytogenetic Response (%)						
Major (95%CI) Complete Partial	57 (46-67) 41 16	49 (42-56) 35 14	51 (46-57) 37 15	33 (17-54) 22 11	29 (21-39) 19 10	30 (22-38) 20 10

NEL = no evidence of leukaemia/marrow response

114 CP patients had a CHR at baseline and were therefore not assessable for complete haematological response

* Missing information on imatinib-resistant/intolerant status for one patient.

Efficacy data in patients with CML-BC are not yet available. Separate treatment arms were also included in the Phase II study to investigate Nilotinib 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. Of these patients 30/36 (83%) were treatment resistant not intolerant. In 22 CP patients evaluated for efficacy nilotinib 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 42% of chronic phase and 54% of accelerated phase CML patients who were evaluated for mutations. Nilotinib demonstrated efficacy in patients harboring a variety of BCR-ABL mutations associated with imatinib resistance, except T315I.

Treatment discontinuation in adult Ph+ CML patients in chronic phase who have been treated with nilotinib as first-line therapy and who have achieved a sustained deep molecular response

In an open-label, single-arm study, 215 adult patients with Ph+ CML in chronic phase treated with nilotinib in first-line for ≥2 years who achieved MR4.5 as measured with the MolecularMD MRDx BCR-ABL test were enrolled to continue nilotinib treatment for additional 52 weeks (nilotinib consolidation phase). 190 of 215 patients (88.4%) entered the TFR phase after achieving a sustained deep molecular response during the consolidation phase, defined by the following criteria:

- the 4 last quarterly assessments (taken every 12 weeks) were at least MR4.0 (BCR-ABL/ABL ≤0.01% IS), and maintained for one year
- the last assessment being MR4.5 (BCR-ABL/ABL ≤0.0032% IS)

- no more than two assessments falling between MR4.0 and MR4.5 (0.0032% IS < BCR-ABL/ABL ≤0.01% IS).

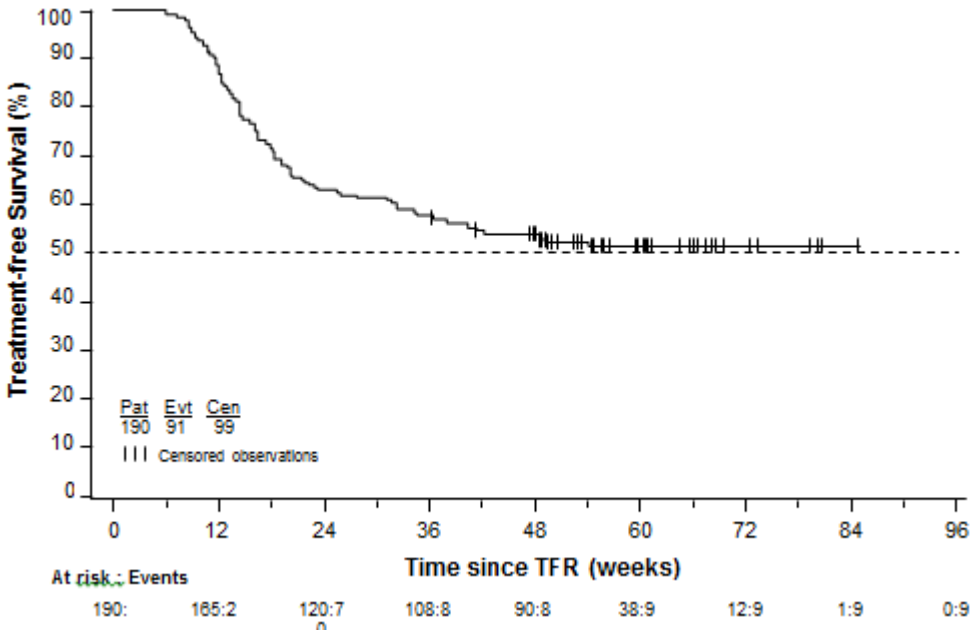
The primary endpoint was the percentage of patients in MMR at 48 weeks after starting the TFR phase (considering any patient who required re-initiation of treatment as non-responder). Of the 190 patients who entered the TFR phase, 98 patients (51.6% [95% CI: 44.2, 58.9]) were in MMR at 48 weeks.

Eighty-eight patients (46.3%) discontinued the TFR phase due to loss of MMR, and 1 (0.5%), 1 (0.5%), and 3 patients (1.6%) due to death from unknown cause, physician decision and subject decision, respectively. Among these 88 patients, 86 patients restarted nilotinib treatment and 2 patients permanently discontinued the study. Eighty-five of these 86 patients (98.8%) regained MMR, (one patient discontinued study permanently due to subject decision) and 76 patients (88.4%) regained MR4.5 by the time of the cut-off date.

The Kaplan-Meier (KM) estimated median time on nilotinib treatment to regain MMR and MR4.5 was 7.9 weeks (95% CI: 5.1, 8.0) and 13.1 weeks (95% CI: 12.3, 15.7), respectively. The KM estimated MMR and MR4.5 rates at 24 weeks of re-initiation were 98.8 % (95% CI: 94.2, 99.9) and 90.9 % (95% CI: 83.2, 96.0), respectively.

The KM estimate of median treatment-free survival (TFS) has not yet been reached (Figure 4); 99 of 190 patients (52.1%) did not have a TFS event.

Figure 4 Kaplan-Meier estimate of treatment-free survival after start of TFR (full analysis set)



Treatment discontinuation in adult CML patients in chronic phase who have achieved a sustained deep molecular response on nilotinib treatment following prior imatinib therapy

In an open-label, single-arm study, 163 adult patients with Ph+ CML in chronic phase taking tyrosine kinase inhibitors (TKIs) for ≥3 years (imatinib as initial TKI therapy for more than 4 weeks without documented MR4.5 on imatinib at the time of switch to nilotinib, then switched to nilotinib for at least two years), and who achieved MR4.5 on nilotinib treatment as measured with the MolecularMD MRDx BCR-ABL test were enrolled to continue nilotinib treatment for

additional 52 weeks (nilotinib consolidation phase). 126 of 163 patients (77.3%) entered the TFR phase after achieving a sustained deep molecular response during the consolidation phase, defined by the following criterion:

- The 4 last quarterly assessments (taken every 12 weeks) showed no confirmed loss of MR4.5 (BCR-ABL/ABL ≤0.0032% IS) during one year.

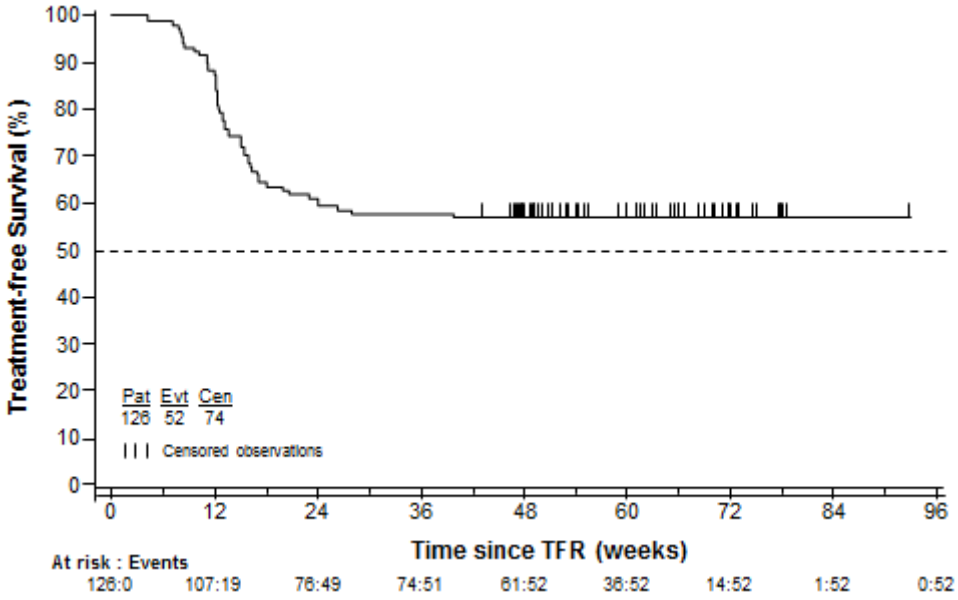
The primary endpoint was the proportion of patients without confirmed loss of MR4.0 or loss of MMR within 48 weeks following treatment discontinuation. Of the 126 patients who entered the TFR phase, 73 patients (57.9%, [95% CI: 48.8, 66.7]) had no loss of MMR, no confirmed loss of MR4.0, and no re-initiation of nilotinib within 48 weeks.

Among the 53 patients who discontinued the TFR phase due to confirmed loss of MR4.0 or loss of MMR, 51 patients restarted nilotinib and 2 patients discontinued the study. Forty-eight of these 51 patients (94.1%) regained MR4.0 and 47 patients (92.2%) regained MR4.5 by the time of the cut-off date.

The Kaplan-Meier (KM) estimated median time on nilotinib to regain MR4.0 and MR4.5 was 12.0 weeks (95% CI: 8.3, 12.7) and 13.1 weeks (95% CI: 12.4, 16.1), respectively. The KM estimated MR4.0 and MR4.5 rates at 48 weeks of re-initiation were 100.0% (95% CI: not estimated) and 94.8% (95% CI: 85.1, 99.0), respectively.

The median TFS has not yet been reached (Figure 5); 74 of 126 patients (58.7%) did not have a TFS event.

Figure 5 Kaplan-Meier estimate of treatment-free survival after start of TFR (full analysis set)



Paediatric population

The safety and efficacy of nilotinib in paediatric patients with Ph+ CML in chronic phase have been investigated in two studies. A total of 69 paediatric patients (from 2 to <18 years of age) with either newly diagnosed Ph+ CML in chronic phase (n=25) or imatinib/dasatinib resistant or imatinib-intolerant Ph+ CML in chronic phase (n=44) received nilotinib treatment at a dose of 230 mg/m^2 twice daily, rounded to the nearest 50 mg dose (to a maximum single dose of 400 mg).

In the pooled CML patient population, the median actual dose intensity was 435.5 mg/m^2/day (range: 149 to 517 mg/m^2/day), and the median relative dose intensity was 94.7% (range: 32 to 112%). Forty patients (58.0%) had relative dose intensity superior to 90%. The median time on treatment with nilotinib was 13.80 months (range: 0.7-30.9 months).

In the resistant or intolerant CML patients, the major molecular response (MMR; BCR-ABL/ABL ≤0.1% IS) rate was 40.9% (95% CI: 26.3, 56.8) at 12 cycles, with 18 patients being in MMR. In the newly diagnosed CML patients, the MMR rate was 60.0% (95% CI: 38.7, 78.9) at 12 cycles, with 15 patients achieving MMR. In resistant or intolerant CML patients, the cumulative MMR rate was 47.7% by cycle 12. In newly diagnosed CML patients, the cumulative MMR rate was 64.0% by cycle 12.

Among the 21 resistant or intolerant CML patients who were in MMR at any time on treatment, the median time to first MMR was 2.76 months (95% CI: 0.03, 5.55). For the 17 newly diagnosed CML patients who achieved MMR, the median time to first MMR was 5.55 months (95% CI: 5.52, 5.75).

Among resistant or intolerant CML patients, the percentage of patients who achieved BCR-ABL/ABL ≤0.01% IS (MR4.0) by the cut-off date was 11.4%, while 4.5% of the patients achieved BCR-ABL/ABL ≤0.0032% IS (MR4.5). Among newly diagnosed patients, the percentage of patients who achieved MR4.0 was 32%, while 28.0% achieved MR4.5.

None of the 21 resistant or intolerant CML patients who were in MMR on treatment had confirmed loss of MMR. Among the 17 newly diagnosed CML patients who achieved MMR, one patient had confirmed loss of MMR (the patient lost CHR due to an increase in basophil count, however did not progress to AP/BC).

One resistant or intolerant CML patient progressed to AP/BC after about 10 months on treatment.

No deaths were reported on treatment or after treatment discontinuation in both studies.

5.2 Pharmacokinetic properties

Absorption

Peak concentrations of nilotinib are reached 3 hours after oral administration. Nilotinib absorption following oral administration was approximately 30%. The absolute bioavailability of nilotinib has not been determined. As compared to an oral drink solution (pH of 1.2 to 1.3), relative bioavailability of nilotinib capsule is approximately 50%. In healthy volunteers, C_{max} and area under the serum concentration-time curve (AUC) of nilotinib are increased by 112% and 82%, respectively, compared to fasting conditions when Nilotinib is given with food. Administration of Nilotinib 30 minutes or 2 hours after food increased bioavailability of nilotinib by 29% or 15%, respectively.

Nilotinib absorption (relative bioavailability) might be reduced by approximately 48% and 22% in patients with total gastrectomy and partial gastrectomy, respectively.

Distribution
The blood-to-plasma ratio of nilotinib is 0.71. Plasma protein binding is approximately 98% on the basis of *in vitro* experiments.

Biotransformation
Main metabolic pathways identified in healthy subjects are oxidation and hydroxylation. Nilotinib is the main circulating component in the serum. None of the metabolites contribute significantly to the pharmacological activity of nilotinib. Nilotinib is primarily metabolised by CYP3A4, with possible minor contribution from CYP2C8.

Elimination
After a single dose of radiolabelled nilotinib in healthy subjects, more than 90% of the dose was eliminated within 7 days, mainly in faeces (94% of the dose). Unchanged nilotinib accounted for 69% of the dose.

The apparent elimination half-life estimated from the multiple-dose pharmacokinetics with daily dosing was approximately 17 hours. Inter-patient variability in nilotinib pharmacokinetics was moderate to high.

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

Steady-state conditions were essentially achieved by day 8. An increase in serum exposure to nilotinib between the first dose and steady state was approximately 2-fold for daily dosing and 3.8-fold for twice-daily dosing.

Bioavailability/bioequivalence studies
Single-dose administration of 400 mg nilotinib, using 2 hard capsules of 200 mg whereby the content of each hard capsule was dispersed in one teaspoon of apple sauce, was shown to be bioequivalent with a single-dose administration of 2 intact hard capsules of 200 mg.

Paediatric population
Following administration of nilotinib in paediatric patients at 230 mg/m^2 twice daily, rounded to the nearest 50 mg dose (to a maximum single dose of 400 mg), steady-state exposure and clearance of nilotinib were found to be similar (within 2-fold) to adult patients treated with 400 mg twice daily. The pharmacokinetic exposure of nilotinib following a single or multiple doses appeared to be comparable between paediatric patients from 2 years to <10 years and from ≥10 years to <18 years.

5.3 Preclinical safety data

Nilotinib has been evaluated in safety pharmacology, repeated dose toxicity, genotoxicity, reproductive toxicity, phototoxicity and carcinogenicity (rats and mice) studies.

Safety pharmacology studies

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

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

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

In the 2-year rat carcinogenicity study, the major target organ for non-neoplastic lesions was the uterus (dilatation, vascular ectasia, endothelial cell hyperplasia, inflammation and/or epithelial hyperplasia). There was no evidence of carcinogenicity upon administration of nilotinib at 5, 15 and 40 mg/kg/day. Exposures (in terms of AUC) at the highest dose level represented approximately 2x to 3x human daily steady-state exposure (based on AUC) to nilotinib at the dose of 800 mg/day.

In the 26-week Tg.rasH2 mouse carcinogenicity study, in which nilotinib was administered at 30, 100 and 300 mg/kg/day, skin papillomas/carcinomas were detected at 300 mg/kg, representing approximately 30 to 40 times (based on AUC) the human exposure at the maximum approved dose of 800 mg/day (administered as 400 mg twice daily). The No-Observed-Effect-Level for the skin neoplastic lesions was 100 mg/kg/day, representing approximately 10 to 20 times the human exposure at the maximum approved dose of 800 mg/day (administered as 400 mg twice daily). The major target organs for non-neoplastic lesions were the skin (epidermal hyperplasia), the growing teeth (degeneration/atrophy of the enamel organ of upper incisors and inflammation of the gingiva/odontogenic epithelium of incisors) and the thymus (increased incidence and/or severity of decreased lymphocytes).

Reproductive toxicity and fertility studies

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, premature fusion of the facial bones (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. In a pre- and postnatal development study in rats, maternal exposure to nilotinib caused reduced pup body weight with associated changes in physical development parameters as well as reduced mating and fertility indices in the offspring. 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.

Juvenile animal studies

In a juvenile development study, nilotinib was administered via oral gavage to juvenile rats from the first week post-partum through young adult (day 70 post-partum) at doses of 2, 6 and 20 mg/kg/day. Besides standard study parameters, evaluations of developmental landmarks, CNS effects, mating and fertility were performed. Based on a reduction in body weight in both genders and a delayed preputial separation in males (which may be associated with the reduction in weight), the No-Observed-Effect-Level in juvenile rats was considered to be 6 mg/kg/day. The juvenile animals did not exert increased sensitivity to nilotinib relative to adults. In addition, the toxicity profile in juvenile rats was comparable to that observed in adult rats.

Phototoxicity studies

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.

6. Pharmaceutical particulars

6.1 List of excipients

Crospovidone

Sodium Starch Glycolate

Polacrillin Potasium (Kyron-T 314)

Sodium Stearyl Fumarate

Colloidal Anhydrous Silica

Anhydrous Lactose

Empty Hard Gelatin Capsule Shell, Size# 0 (Maroon OP Body & White OP Cap)

6.2 Incompatibilities
Not applicable

6.3 Shelf life
2 years

6.4 Special precautions for storage
Store below 30ºC and dry place, away from light and mointure. Keep out of the each of children

6.5 Nature and contents of container
Primary Packaging: HDPE bottle

Secondary Packaging: Paper board carton

Pack size: 120 Capsules in a Box

6.6 Special precautions for disposal and other handling
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorization holder

CORPORATE OFFICE
Beacon Business Center
9/B/2, Toyenbee Circular Road, Motijheel, Dhaka- 1223, Bangladesh

Tel: +880-2-5716371-76,

Fax: 880-2-57165379

E-mail: beacon@beaconpharma.com.bd

Website: www. beaconpharma.com.bd

FACTORY
Bhaluka, Mymensingh, Bangladesh

8. Marketing authorization Number:
DAR No. 341-389-010

9. Date of first authorization/renewal of the authorization
08.08.2019/07.08.2024

10. Date of revision of the text
14.11.2019