

Tasigna®

Antineoplastic agents - Protein-tyrosine kinase inhibitor

DESCRIPTION AND COMPOSITION**Pharmaceutical form**

Hard capsules

50 mg hard capsules

White to yellowish powder in gelatin capsule with red opaque cap and light yellow opaque body, size 4 with black radial imprint “NVR/ABL” on cap

150 mg hard capsules

White to yellowish powder in red opaque hard gelatin capsules, size 1 with black axial imprint “NVR/BCR”.

200 mg hard capsules

White to yellowish powder in light yellow opaque hard gelatin capsules, size 0 with red axial imprint “NVR/TKI”.

Active substance**50 mg hard capsules**

One hard capsule contains 50 mg nilotinib base (as hydrochloride monohydrate)

150 mg hard capsules

Each capsule contains 150 mg nilotinib base (as hydrochloride, monohydrate).

200 mg hard capsules

Each capsule contains 200 mg nilotinib base (as hydrochloride, monohydrate)

Excipients**50 mg hard capsules**

Capsule content: Lactose monohydrate; Crospovidone; Poloxamer; Silica colloidal, anhydrous/Colloidal silicon dioxide; Magnesium stearate

Capsule shell: Gelatin; Titanium dioxide (E 171); Iron oxide, red (E 172), Iron oxide, yellow (E 172)

Printing ink: Shellac; Iron oxide, black (E 172); Propylene glycol; Ammonium hydroxide

150 mg hard capsules

Capsule content: Lactose monohydrate; Crospovidone; Poloxamer; Silica colloidal, anhydrous/Colloidal silicon dioxide; Magnesium stearate

Capsule shell: Gelatin; Titanium dioxide (E 171); Iron oxide, red (E 172), Iron oxide, yellow (E 172)

Printing ink: Shellac; Iron oxide, black (E 172); n-Butyl alcohol; Propylene glycol; Dehydrated ethanol; Isopropyl alcohol; Ammonium hydroxide

200 mg hard capsules

Capsule content: Lactose monohydrate; Crospovidone; Poloxamer; Silica colloidal, anhydrous/Colloidal silicon dioxide; Magnesium stearate

Capsule shell: Gelatin; Titanium dioxide (E 171); Iron oxide, yellow (E 172)

Printing ink: Shellac; Dehydrated alcohol; Isopropyl alcohol; Butyl alcohol; Propylene glycol; Strong ammonia solution; Potassium hydroxide; Iron oxide, red (E 172)

INDICATIONS

Tasigna hard capsules are indicated for the:

- treatment of adult and paediatric patients with newly diagnosed Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase. The effectiveness of Tasigna is based on major molecular response and cytogenetic response rates.
- treatment of chronic phase and accelerated phase Philadelphia chromosome positive chronic myelogenous leukemia (Ph+ CML) in adult patients resistant to or intolerant to at least one prior therapy including imatinib. The effectiveness of Tasigna is based on hematologic and cytogenetic response rates.
- treatment of paediatric patients with chronic phase Philadelphia chromosome positive CML with resistance or intolerance to prior therapy including imatinib.

DOSAGE REGIMEN AND ADMINISTRATION

Tasigna is available in three dosage strengths (50 mg, 150 mg and 200 mg).

Treatment with Tasigna should be initiated by a physician experienced in the treatment of patients with CML.

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

Monitoring of response to Tasigna therapy in Ph+ CML patients should be performed both routinely and when therapy is modified, to identify suboptimal response, loss of response to therapy, poor patient compliance, or possible drug-drug interaction. Results of monitoring should guide appropriate CML management.

General target population

Dosage in adult patients with newly diagnosed Ph+ CML- Chronic Phase (CP)

The recommended dose of Tasigna is 300 mg twice daily (see section CLINICAL STUDIES). Treatment should be continued as long as the patient continues to benefit.

Dosage 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 $230 \text{ mg}/\text{m}^2$ twice daily, rounded to the nearest 50 mg dose (to a maximum single dose of 400 mg) (see Table 1-1). Different strengths of Tasigna 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 1-1 Dosing scheme of nilotinib 230 mg/m² 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

Dosage in adult patients with Ph+ CML-CP and CML- Accelerated Phase (AP) resistant to or intolerant to at least one prior therapy including imatinib

The recommended dose of Tasigna is 400 mg twice daily (see section CLINICAL STUDIES). Treatment should be continued as long as the patient continues to benefit.

Monitoring recommendations and dose adjustments

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

QT interval prolongation

Table 1 Dose Adjustments for QT prolongation

ECG with a QTc > 480 msec	<ol style="list-style-type: none"> 1. Withhold Tasigna, and perform an analysis of serum potassium and magnesium, and if below lower limit of normal, correct with supplements to within normal limits. Concomitant medication usage must be reviewed. 2. Resume within 2 weeks at prior dose if QTcF returns to <450 msec and to within 20 msec of baseline. 3. If QTcF is between 450 msec and 480 msec after 2 weeks reduce the dose to 400 mg once daily. 4. If, following dose-reduction to 400 mg once daily, QTcF returns to >480 msec, Tasigna should be discontinued. 5. An ECG should be repeated approximately 7 days after any dose adjustment.
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Increases in total serum cholesterol levels have been reported with Tasigna therapy (see Section WARNINGS AND PRECAUTIONS). Lipid profiles should be determined prior to initiating Tasigna 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 Tasigna therapy (see section WARNINGS AND PRECAUTIONS). Blood glucose levels should be assessed prior to initiating Tasigna therapy and monitored during treatment.

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

Tasigna may need to be temporarily withheld and/or dose reduced for hematological toxicities (neutropenia, thrombocytopenia) that are not related to underlying leukemia (see Table 2).

Table 2 Dose Adjustments for Neutropenia and Thrombocytopenia

<p>Adult patients with: Newly diagnosed CML in chronic phase at 300 mg twice daily</p> <p>Resistant or intolerant CML in chronic phase at 400 mg twice daily</p>	<p>ANC* <1 x 10⁹/L and/or platelet counts <50 x 10⁹/L</p>	<ol style="list-style-type: none"> 1. Stop Tasigna, and monitor blood counts 2. Resume within 2 weeks at prior dose if ANC >1 x 10⁹/L and/or platelets >50 x 10⁹/L 3. If blood counts remain low, a dose reduction to 400 mg once daily may be required.
<p>Adult patients with resistant or intolerant CML in accelerated phase at 400 mg twice daily</p>	<p>ANC* <0.5 x 10⁹/L and/or platelet counts <10 x 10⁹/L</p>	<ol style="list-style-type: none"> 1. Stop Tasigna, and monitor blood counts. 2. Resume within 2 weeks at prior dose if ANC >1.0 x 10⁹/L and/or platelets >20 x 10⁹/L. 3. If blood counts remain low, a dose reduction to 400 mg once daily may be required.

<p>Paediatric patients with:</p> <ul style="list-style-type: none"> - Newly diagnosed CML in chronic phase at 230 mg/m² twice daily - Resistant or intolerant CML in chronic phase at 230 mg/m² twice daily 	<p>ANC* <1 x 10⁹/L and/or platelet counts <50 x 10⁹/L</p>	<ol style="list-style-type: none"> 1. Stop TASIGNA and monitor blood counts 2. Resume within 2 weeks at prior dose if ANC > 1.5 x 10⁹/L and/or platelets > 75 x 10⁹/L. 3. If blood counts remain low, a dose reduction to 230 mg/m² once daily may be required. 4. If event occurs after dose reduction, consider discontinuing treatment.
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*ANC = absolute neutrophil count

If clinically significant moderate or severe non-hematologic 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 newly diagnosed patients with CML-CP or 400 mg twice daily in adult patients with resistant or intolerant CML-CP and CML-AP or 230 mg/m² twice daily in paediatric patients, dosing may be resumed at 400 mg once daily once the toxicity has resolved. If the prior dose was 400 mg once daily in adult patients or 230 mg/m² once daily in paediatric patients, treatment should be discontinued. If clinically appropriate, re-escalation of the dose in adult patients to 300 mg (newly diagnosed Ph⁺ CML-CP) or 400 mg (resistant or intolerant Ph⁺ CML-CP and CML-AP) twice daily or 230 mg/m² twice daily in paediatric patients should be attempted.

Elevated serum lipase: For Grade 3 to 4 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/m² once daily treatment can be resumed at 230 mg/m² once daily. If the prior dose was 230 mg/m² once daily, and recovery to Grade ≤1 takes longer than 28 days, treatment should be discontinued. Serum lipase levels should be tested monthly or as clinically indicated (see sections WARNINGS AND PRECAUTIONS and ADVERSE DRUG REACTIONS).

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

Special populations

Paediatric patients (below 18 years)

The safety and efficacy of Tasigna 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.

Geriatric patients (65 years or above)

Approximately 12% and 30% of subjects in the clinical studies (newly diagnosed Ph⁺ CML-CP and resistant or intolerant Ph⁺ CML-CP and CML-AP) were 65 years of age or older. No

major differences were observed for safety and efficacy in patients ≥ 65 years of age as compared to adults 18 to 65 years of age.

Renal impairment

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

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

Hepatic impairment

Hepatic impairment has a modest effect on the pharmacokinetics of nilotinib. Dose adjustment is not considered necessary in hepatically impaired patients. Patients with hepatic impairment should be treated with caution (see section WARNINGS AND PRECAUTIONS).

Cardiac disorders

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

Caution should be exercised in patients with relevant cardiac disorders (see section WARNINGS AND PRECAUTIONS).

Method of administration

Tasigna should be taken twice daily, at approximately 12 hour intervals, and must not be taken with food. The capsules should be swallowed whole with water. No food should be consumed for at least two hours before the dose is taken and no additional food should be consumed for at least one hour after the dose is taken (see section WARNINGS AND PRECAUTIONS and section INTERACTIONS).

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

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

CONTRAINDICATIONS

Tasigna is contraindicated in patients with known hypersensitivity to nilotinib or to any of the excipients.

WARNINGS AND PRECAUTIONS

Myelosuppression

Treatment with Tasigna is often associated with thrombocytopenia, neutropenia and anemia (NCI CTC Grade 3/4). The occurrence is more frequent in patients with imatinib-resistant or intolerant CML and in particular in patients with accelerated-phase (CML AP). Complete blood counts should be performed every two weeks for the first 2 months and then monthly thereafter, or as clinically indicated. Myelosuppression was generally reversible and usually managed by withholding Tasigna temporarily or reducing the dose (see section DOSAGE REGIMEN AND ADMINISTRATION).

QT Prolongation

Tasigna has been shown to prolong cardiac ventricular repolarization as measured by the QT interval on the surface ECG in a concentration-dependent manner.

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

In the Phase II study in imatinib-resistant or intolerant CML patients in chronic and accelerated phase, treated with nilotinib 400 mg twice daily, the change from baseline in mean time-averaged QTcF interval at steady-state was 5 msec and 8 msec, respectively. QTcF of >500 msec was observed in 4 patients (<1% of these patients).

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

Clinically meaningful prolongation of the QT interval may occur when Tasigna is inappropriately taken with food, and/or strong CYP3A4 inhibitors and/or medicinal products with a known potential to prolong QT interval; therefore, concomitant administration should be avoided (see section WARNINGS AND PRECAUTIONS: Food-Effects and section INTERACTIONS).

The presence of hypokalemia and hypomagnesemia may place patients at risk of developing QT prolongation (see section DOSAGE REGIMEN AND ADMINISTRATION).

Prolongation of the QT interval may expose patients to the risk of fatal outcome.

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

- with 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 therapy with Tasigna and should be repeated after 7 days and as clinically indicated. Hypokalemia or hypomagnesemia must be corrected prior to Tasigna administration and should be monitored periodically during therapy.

Sudden Death

In clinical trials, uncommon cases (0.1 to 1%) of sudden death have been reported in patients in imatinib-resistant or -intolerant CML patients in chronic and accelerated phase receiving Tasigna with a past medical history of cardiac disease or significant cardiac risk factors. Comorbidities in addition to the underlying malignancy were also frequently present as were concomitant medications. Ventricular repolarization abnormalities may have been contributory factors. Based on post-marketing exposure in patient-years, the estimated reporting rate for spontaneous reports of sudden death is 0.02% per patient-year. No cases of sudden deaths have been reported in the newly diagnosed Ph+ CML-CP Phase III study.

Cardiovascular events

Cardiovascular events were reported in a randomized, Phase III nilotinib trial in newly diagnosed CML patients and observed in the post-marketing reports. With a median time on therapy of 60.5 months in the clinical trial, Grade 3 / 4 cardiovascular events included peripheral arterial occlusive disease (1.4% and 1.1% at 300 mg and 400 mg twice a day respectively), ischemic heart disease (2.2% and 6.1% at 300 mg and 400 mg twice a day respectively) and ischemic cerebrovascular events (1.1% and 2.2% at 300 mg and 400 mg twice a day respectively). If acute signs or symptoms of cardiovascular events occur, advise patients to seek immediate medical attention. The cardiovascular status of patients should be evaluated and cardiovascular risk factors should be monitored and actively managed during TASIGNA therapy according to standard guidelines (see section DOSAGE REGIMEN AND ADMINISTRATION).

Fluid retention

Severe forms of drug related fluid retention such as pleural effusion, pulmonary edema, 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 etiology should be evaluated and patients treated accordingly (see section DOSAGE REGIMEN AND ADMINISTRATION).

Hepatitis B reactivation

Reactivation of hepatitis B can occur in patients who are chronic carriers of this virus after receiving a BCR-ABL tyrosine kinase inhibitor (TKI), such as nilotinib. Some cases involving drugs of the BCR-ABL TKI class resulted in acute hepatic failure or fulminant hepatitis leading to liver transplantation or a fatal outcome (see section ADVERSE DRUG REACTIONS).

Patients should be tested for hepatitis B infection before initiating treatment with nilotinib. Patients currently on nilotinib should have baseline testing for hepatitis B infection in order to identify chronic carriers of the virus. 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 hepatitis B infection during treatment. Carriers of hepatitis B virus who require treatment with nilotinib should be closely monitored for signs and symptoms of active hepatitis B infection throughout therapy and for several months following termination of therapy.

Special monitoring of Ph+ CML-CP patients 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 levels, evaluation of the depth of molecular response, and determination of a possible loss of molecular remission after Tasigna treatment discontinuation.

Newly diagnosed Ph+ CML-CP patients who have achieved a sustained deep molecular response (MR 4.5)

Discontinuation of treatment may be considered in eligible Ph+ CML-CP patients who have been treated with TASIGNA 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 Tasigna should be initiated by a physician experienced in the treatment of patients with CML.

Patients who lose MMR must re-initiate treatment within 4 weeks of when loss of remission is known to have occurred. Tasigna 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 Tasigna therapy should have their BCR-ABL transcript levels monitored monthly until MMR is re-established and every 12 weeks thereafter (see CLINICAL STUDIES).

Ph+ CML-CP patients who have achieved a sustained deep molecular response (MR 4.5) on Tasigna following prior imatinib therapy

Discontinuation of treatment may be considered in eligible Ph+ CML-CP patients who have been treated with Tasigna 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 Tasigna should be initiated by a physician experienced in the treatment of patients with CML (see CLINICAL STUDIES)

Patients with confirmed loss of MR4.0 (two consecutive measures separated by at least 4 weeks showing loss of MR4.0) or loss of MMR must re-initiate treatment within 4 weeks of when loss of remission is known to have occurred. Tasigna therapy should be re-initiated at either 300 mg or 400 mg twice daily. Patients who re-initiate Tasigna therapy should have their BCR-ABL transcript levels monitored monthly until previous MMR or MR4.0 is re-established and every 12 weeks thereafter (see CLINICAL STUDIES).

Monitoring of Patients who have discontinued therapy

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 transcript levels must be assessed prior to and during treatment discontinuation (see CLINICAL STUDIES).

Patients who are eligible to discontinue Tasigna 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.

For patients who lose MR4.0 ($MR4 = BCR-ABL/ABL \leq 0.01\%$ IS) but not Major Molecular Response (MMR) ($MMR = BCR-ABL/ABL \leq 0.1\%$ 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 MR4.0 and MR4.5. Patients who maintain BCR-ABL levels between MMR and MR4.0 for a minimum of 4 consecutive measurements can return to the original monitoring schedule.

Loss of MMR or confirmed loss of MR4.0 (two consecutive measures separated by at least 4 weeks showing loss of MR4.0) 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 is required to detect possible loss of remission (see CLINICAL STUDIES). For patients who fail to achieve MMR after three months of treatment re-initiation, BCR-ABL kinase domain mutation testing should be performed.

Discontinuation of Tasigna should only be performed if the potential benefit justifies the potential risk to the patient.

Special Populations

Pediatric patients (below 18 years)

The long-term effects of prolonged treatment with TASIGNA in pediatric patients are unknown. There have been case reports of growth retardation in pediatric patients treated with TASIGNA. Close monitoring of growth in pediatric patients under TASIGNA treatment is recommended.

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 a day had a grade 3/4 elevation in total cholesterol; however, there were no Grade 3/4 elevations in the 300 mg twice a day dose group (see section ADVERSE DRUG REACTIONS). It is recommended that the lipid profiles be determined before initiating treatment with Tasigna, assessed at month 3 and 6 after initiating therapy, and at least yearly during chronic therapy (see section DOSAGE REGIMEN AND ADMINISTRATION). If a HMG CoA reductase inhibitor (a lipid lowering agent) is needed, please refer to section INTERACTIONS, before starting treatment since certain HMG CoA reductase inhibitors are metabolized by the CYP3A4 pathway.

Blood glucose

In a Phase III study in newly diagnosed CML patients, 6.9% of the patients treated with 400 mg nilotinib twice a day had a Grade 3/4 elevation in blood glucose; and 7.2% of the patients treated with 300 mg nilotinib twice a day had a Grade 3/4 elevation in blood glucose. It is

recommended that the glucose levels should be assessed before initiating treatment with Tasigna and monitored during treatment as clinically indicated (see section DOSAGE REGIMEN AND ADMINISTRATION). If test results warrant therapy, physicians should follow their local standards of practice and treatment guidelines.

Interactions

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

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

Food-Effects

The bioavailability of nilotinib is increased by food. Tasigna must not be taken in conjunction with food (see sections DOSAGE REGIMEN AND ADMINISTRATION and INTERACTIONS) and should be taken 2 hours after a meal. No food should be consumed for at least one hour after the dose is taken.

Grapefruit juice and other foods that are known to inhibit CYP3A4 should be avoided at any time.

Hepatic Impairment

Metabolism of nilotinib is mainly hepatic. Hepatic impairment has a modest effect on the pharmacokinetics of nilotinib. Single dose administration of nilotinib resulted in increases in AUC of 35%, 35% and 19% in subjects with mild, moderate and severe hepatic impairment respectively, compared to a control group of subjects with normal hepatic function. The predicted steady-state C_{max} of nilotinib showed an increase of 29%, 18% and 22% respectively. The mean $T_{1/2}$ of nilotinib was found to be similar between the mild impairment group (about 15.1 hours) and control group (about 16.0 hours), but prolonged to 21.6 hours in the moderate impairment group and 32.4 hours in the severe impairment group. Caution is recommended in patients with hepatic impairment (see monitoring recommendations in section DOSAGE REGIMEN AND ADMINISTRATION).

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 children and adolescents are unknown.

Serum Lipase

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

Total gastrectomy

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

Tumor lysis syndrome

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

INTERACTIONS

Nilotinib is mainly metabolized 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 drugs that affect CYP3A4 and/or P-gp.

Drugs that may increase nilotinib serum concentrations

In a Phase I study of nilotinib given in combination with imatinib (a substrate and moderator of P-gp and CYP3A4), both drugs had a slight inhibitory effect on CYP3A4 and/or Pgp.

When the two drugs were administered concomitantly, the AUC of imatinib was increased by 18% to 39%, and the AUC of nilotinib was increased by 18% to 40%.

The exposure of nilotinib in healthy subjects was increased by 3-fold when co-administered with the strong CYP3A4 inhibitor ketoconazole. Concomitant treatment with strong CYP3A4 inhibitors including ketoconazole, itraconazole, voriconazole, ritonavir, moxifloxacin, clarithromycin, and telithromycin, should therefore be avoided (see sections DOSAGE REGIMEN AND ADMINISTRATION and WARNINGS AND PRECAUTIONS regarding QT prolongation). Increased exposure to nilotinib might also be expected with moderate CYP3A4 inhibitors. Alternative concomitant medications with no or minimal CYP3A4 inhibition should be considered.

Drugs that may decrease nilotinib serum concentrations

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

Potent inducers of CYP3A4 activity could increase the metabolism of nilotinib and thereby decrease plasma concentrations of nilotinib. The concomitant administration of medicinal

products that induce CYP3A4 (e.g. phenytoin, rifampicin, carbamazepine, phenobarbital, and St. John's Wort) is 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, therefore absorption of nilotinib might be reduced by substances that suppress gastric acid secretion. The concomitant use of antacids, H₂ blockers, or proton pump inhibitors with Tasigna is not recommended.

Nilotinib has pH-dependent solubility, with lower solubility at higher pH. In healthy subjects receiving esomeprazole at 40 mg once daily for 5 days, gastric pH was markedly increased, but nilotinib absorption was only decreased modestly (27% decrease in C_{max} and 34% decrease in AUC_{0-∞}). Tasigna 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 Tasigna was administered 10 hours after and 2 hours before famotidine. Therefore, when the concurrent use of an H₂ blocker is necessary, it may be administered approximately 10 hours before and approximately 2 hours after the dose of Tasigna.

In the same study as above, administration of an antacid (aluminum hydroxide/magnesium hydroxide/simethicone) 2 hours before or after a single 400 mg dose of Tasigna 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 Tasigna.

Drugs that may have their systemic concentration altered by nilotinib

In vitro nilotinib is identified as a competitive inhibitor of CYP3A4, CYP2C8, CYP2C9, CYP2D6 and UGT1A1 with Ki value being lowest for CYP2C9 (Ki=0.13 microM). Enzyme induction studies indicate that nilotinib can be considered to be an *in vitro* inducer of CYP2B6, CYP2C8 and CYP2C9 activities.

In CML patients, nilotinib administered at 400 mg twice daily for 12 days increased the systemic exposure of oral midazolam (a substrate of CYP3A4) 2.6-fold. Nilotinib is a moderate CYP3A4 inhibitor. As a result, the systemic exposure of other drugs primarily metabolized 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 drugs 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. (See section WARNINGS and PRECAUTIONS).

In healthy subjects, nilotinib at clinically relevant concentrations was not found to alter the pharmacokinetics or pharmacodynamics of warfarin, a sensitive CYP2C9 substrate. Tasigna can be used concurrently with warfarin without increasing the anticoagulant effect.

Anti-arrhythmic medicines and other drugs that may prolong the QT interval

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

Food interactions

The absorption and the bioavailability of nilotinib are increased if it is taken with food, resulting in higher serum concentration (see section DOSAGE REGIMEN AND ADMINISTRATION, WARNINGS AND PRECAUTIONS and CLINICAL PHARMACOLOGY).

Grapefruit juice and other foods that are known to inhibit CYP3A4 should be avoided at any time.

PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Pregnancy

Risk Summary

Tasigna can cause fetal harm when administered to a pregnant woman. There are no adequate data on the use of Tasigna in pregnant women. Reproductive studies in rats and rabbits have demonstrated that nilotinib induced embryo-toxicity and/or fetotoxicity (following prenatal exposure to nilotinib) at exposures equal to the one achieved in humans at the maximum recommended human dose of 400 mg twice daily. The potential risk for humans is unknown. Tasigna should not be used during pregnancy unless necessary. If the drug is used during pregnancy or if the patient becomes pregnant while taking Tasigna, the patient must be informed of the potential risk to the fetus.

If a woman who is being treated with Tasigna 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 Tasigna treatment during pregnancy (see sections DOSAGE REGIMEN AND ADMINISTRATION AND WARNINGS AND PRECAUTIONS)

Animal Data

Nilotinib did not induce teratogenicity, but did show embryo- and fetotoxicity at doses which also showed maternal toxicity. Increased post implantation loss was observed in both the fertility study, with treatment of both males and females, and in the embryotoxicity study with the treatment of females. Embryo-lethality and fetal effects (mainly decreased fetal weights, visceral and skeletal variations) in rats and increased resorption of fetuses and skeletal variations in rabbits were present in the embryo toxicity studies. Exposure to nilotinib in females at No-Observed-Adverse-Effect-Levels (NOAEL) was generally less or equal to that in humans at 800 mg/day.

In a pre- and postnatal study, the oral administration of nilotinib to female rats from day 6 of gestation to day 21 or 22 postpartum resulted in maternal effects (reduced food consumption and lower body weight gains) and longer gestation period at 60 mg/kg. The maternal dose of 60 mg/kg was associated with decreased pup body weight and changes in some physical development parameters (the mean day for pinna unfolding, tooth eruption and eye opening was

earlier). The NOAEL in maternal animals and offspring was a maternal dose of 20 mg/kg.

Lactation

Risk Summary

It is not known whether nilotinib is excreted in human milk. Studies in animals demonstrate that nilotinib is excreted into breast milk. Lactating women should not breast-feed while taking Tasigna and for 2 weeks after the last dose, as a risk to the infant cannot be excluded.

Females and males of reproductive potential

Contraception

Females

Females of reproductive potential must be advised to use effective method of contraception (methods that result in less than 1% pregnancy rates) while receiving Tasigna and for up to 2 weeks after ending treatment with Tasigna.

Infertility

The effect of nilotinib on male and female fertility is not known. In animal studies no effects on sperm count/motility, and on fertility were noted in male and female rats up to the highest tested dose of approximately 5-fold greater than the recommended dosage for human.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

ADVERSE DRUG REACTIONS

Summary of the safety profile

The nilotinib safety profile described below is based on data from adult patients with newly diagnosed Ph+ CML-CP in a randomized, open label, active comparator-controlled phase-III trial and adult patients with resistant or intolerant Ph+ CML-CP and CML-AP which served as a basis for the listed indications (see Table 3 and section INDICATIONS). Safety information from two Tasigna treatment discontinuation studies in adult patients and from a Phase III study in adult patients with Ph+ CML in chronic phase with suboptimal response to imatinib is also provided.

In adult patients with newly diagnosed Ph+ CML-CP

The data reported below reflect exposure to Tasigna from a randomized phase III study in adult patients with newly diagnosed Ph+ CML in chronic phase treated at the recommended dose of 300 mg twice daily (n=279). The median time on treatment was 60.5 months (range

0.1 to 70.8 months).

Non-hematologic adverse drug reactions (ADRs) reported with very common frequency ($\geq 10\%$) were rash, pruritus, headache, nausea, fatigue, alopecia, myalgia, and upper abdominal pain. Most of these ADRs were mild to moderate in severity (Grade 1 or 2). Constipation, diarrhoea, dry skin, muscle spasms, arthralgia, abdominal pain, peripheral oedema, vomiting and asthenia were observed less commonly ($<10\%$ and $\geq 5\%$) and have been of mild to moderate severity, manageable and generally did not require dose reduction.

Pleural and pericardial effusions, regardless of causality, occurred in 2% and $<1\%$ of patients, respectively, receiving Tasigna 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 in the nilotinib recommended dose of 300 mg twice daily was 6 msec. In the nilotinib 400 mg twice daily group and the imatinib 400 mg once daily group the change from baseline in mean time-averaged QTcF interval at steady state was 6 msec and 3 msec respectively. No patient had an absolute QTcF of >500 msec while on study drug in any of the Tasigna treatment groups and no events of Torsades de Pointes were observed. QTcF increase from baseline that exceeds 60 msec was observed in 5 patients while on Tasigna (one in the 300 mg twice daily treatment group and four in the 400 mg twice daily treatment group).

No patients in any treatment group had a LVEF $<45\%$ during treatment. Also, there were no patients with 15% or greater decrease from baseline in LVEF.

No sudden deaths have been reported in any treatment group.

In the nilotinib 300 mg twice daily group, haematologic ADRs include myelosuppression: thrombocytopenia (18%), neutropenia (15%), and anaemia (8%). Biochemistry ADRs include alanine aminotransferase increased (24%), hyperbilirubinaemia (16%), aspartate aminotransferase increased (12%), lipase increased (11%), blood bilirubin increased (10%), hyperglycaemia (4%), hypercholesterolaemia (3%), and hypertriglyceridaemia ($<1\%$). See Table 5 for Grade 3/4 laboratory abnormalities.

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

In adult patients with resistant or intolerant Ph+ CML-CP and CML-AP

The data reported below reflect exposure to Tasigna in 458 adult patients with Ph+ CML-CP (n=321) and CML-AP (n=137) resistant to or intolerant to at least one prior therapy including imatinib in an open-label multicenter study treated at the recommended dose of 400 mg twice daily.

Non-haematologic ADRs reported with very common frequency ($\geq 10\%$ in the combined CML-CP and CML-AP patient populations) were rash, pruritus, nausea, fatigue, headache, constipation, diarrhoea, vomiting and myalgia. Most of these ADRs were mild to moderate in severity. Alopecia, muscle spasms, decreased appetite, arthralgia, bone pain, abdominal pain, peripheral oedema and asthenia were observed less frequently ($<10\%$ and $>5\%$) and have been of mild to moderate severity (Grade 1 or 2).

Pleural and pericardial effusions as well as complications of fluid retention occurred in $<1\%$ of patients receiving Tasigna. Cardiac failure was observed in $<1\%$ of patients. Gastrointestinal and central nervous system (CNS) haemorrhage was reported in 1% and $<1\%$ of

patients, respectively.

QTcF exceeding 500 msec was observed in this study in 4 patients (<1%). No episodes of Torsades de Pointes (transient or sustained) were observed.

Haematologic ADRs include myelosuppression: thrombocytopenia (31%), neutropenia (17%), and anaemia (14%). See Table 5 for grade 3/4 laboratory abnormalities.

Discontinuation due to adverse drug reactions was observed in 16% of CP and 10% of AP patients.

In adult patients with Ph+ CML-CP who have not achieved a molecular response greater than or equal to a 4.5 log reduction with imatinib treatment

The data reported below were generated in a randomized, open-label, Phase III study where adult male and female patients diagnosed with Ph+ CML-CP and after two years of imatinib therapy were exposed to Tasigna 400 mg twice daily versus imatinib 400 mg or 600 mg once daily for 48 months. Patients randomized to the imatinib arm received the same dose of imatinib as prior to randomization. The median duration of exposure was 47.2 months in the Tasigna arm and 37.0 months and 26.7 months in the 400 mg and 600 mg dose cohorts of the imatinib arm, respectively.

The adverse drug reactions reported by at least 20% of the patients in the Tasigna group and more frequently compared to the imatinib group were headache, rash, and pruritus. A greater proportion of patients in the TASIGNA group reported adverse events (AEs) leading to discontinuation and AEs requiring dose adjustment/interruption compared to those in the imatinib group. Increases in bilirubin and transaminases were commonly reported following Tasigna treatment.

Up to the 48-month cut-off date, three on-treatment deaths have been observed (two in the Tasigna arm and one in the imatinib arm). Three patients died more than 28 days after study drug discontinuation (one in the Tasigna arm and two in the imatinib arm).

QTc intervals >450 ms were observed in 4 patients receiving Tasigna therapy on Day 8. No patient had a QTc interval >480 ms. Increases in QTc interval from baseline of >30 ms were reported for 8 patients (7.9%). No patient experienced QTc prolongation >60 ms in the Tasigna group.

Most Frequently Reported Adverse Drug Reactions

Non-haematologic ADRs (excluding laboratory abnormalities) that were reported in at least 5% of the adult patients in any of the Tasigna clinical studies that serve as a basis for the listed indications are shown in Table 3. These are ranked under heading of frequency, the most frequent first. Within each frequency grouping adverse drug reactions are presented in order of decreasing seriousness. In addition the corresponding frequency category for each adverse drug reaction is based on the following (CIOMS III) convention: very common ($\geq 1/10$) or common ($\geq 1/100$ to $< 1/10$). The frequency is based on the highest for any Tasigna group in the two studies, using one decimal precision for percentages.

Table 3 Most Frequently Reported Non-haematologic Adverse Drug Reactions (≥5% in any Tasigna Group)

			Newly Diagnosed Ph+ CML-CP						Resistant or Intolerant Ph+ CML-CP and CML-AP			
			60-month analysis						24-month analysis			
			Tasigna 300 mg twice daily	Tasigna 400 mg twice daily	Imatinib 400 mg once daily	Tasigna 300 mg twice daily	Tasigna 400 mg twice daily	Imatinib 400 mg once daily	Tasigna 400 mg twice daily			
			ALL GRADES (%)			GRADE 3 or 4 (%)			ALL GRADES (%)	GRADE 3/4 (%)	CML-CP GRADE 3/4 (%)	CML-AP GRADE 3/4 (%)
System Organ Class	Frequency	Adverse Drug Reaction	N=279 %	N=277 %	N=280 %	N=279 %	N=277 %	N=280 %	N=458 %	N=458 %	N=321 %	N=137 %
Metabolism and nutrition disorders	Common	Decreased appetite ¹	4	4	3	0	0	0	8	<1	<1	0
Nervous system disorders	Very common	Headache	16	22	10	2	1	<1	15	1	2	<1
Gastrointestinal disorders	Very common	Nausea	14	21	35	<1	1	<1	20	<1	<1	<1
	Very common	Constipation	10	7	3	0	<1	0	12	<1	<1	0
	Very common	Diarrhoea	9	7	31	<1	0	3	11	2	2	<1
	Very common	Vomiting	6	9	19	0	1	0	10	<1	<1	0
	Very common	Abdominal pain upper	10	9	8	1	0	<1	5	<1	<1	0
	Common	Abdominal pain	6	6	4	0	<1	0	6	<1	<1	<1
	Common	Dyspepsia	5	5	6	0	<1	0	3	0	0	0
Skin and subcutaneous tissue disorders	Very common	Rash	33	38	14	<1	3	2	28	1	2	0
	Very common	Pruritus	18	16	5	<1	<1	0	24	<1	<1	0
	Very common	Alopecia	10	14	6	0	0	0	9	0	0	0
	Very Common	Dry Skin	10	12	5	0	0	0	5	0	0	0
	Common	Erythema	3	6	3	0	0	0	5	<1	<1	0

			Newly Diagnosed Ph+ CML-CP						Resistant or Intolerant Ph+ CML-CP and CML-AP			
			60-month analysis						24-month analysis			
			Tasigna 300 mg twice daily	Tasigna 400 mg twice daily	Imatinib 400 mg once daily	Tasigna 300 mg twice daily	Tasigna 400 mg twice daily	Imatinib 400 mg once daily	Tasigna 400 mg twice daily			
			ALL GRADES (%)			GRADE 3 or 4 (%)			ALL GRADES (%)	GRADE 3/4 (%)	CML-CP GRADE 3/4 (%)	CML-AP GRADE 3/4 (%)
System Organ Class	Frequency	Adverse Drug Reaction	N=279 %	N=277 %	N=280 %	N=279 %	N=277 %	N=280 %	N=458 %	N=458 %	N=321 %	N=137 %
Musculoskeletal and connective tissue disorders	Very common	Myalgia	10	12	13	<1	<1	<1	10	<1	<1	<1
	Common	Arthralgia	8	10	8	<1	0	<1	7	<1	1	0
	Common	Muscle spasms	9	9	30	0	<1	1	8	<1	<1	0
	Common	Bone pain	4	5	4	0	<1	<1	6	<1	<1	0
	Common	Pain in extremity	5	3	8	<1	<1	<1	5	<1	<1	<1
General disorders and administration site conditions	Very common	Fatigue	12	11	13	0	<1	1	17	1	1	<1
	Common	Asthenia	9	5	9	<1	<1	0	6	0	0	0
	Common	Edema peripheral	5	7	18	<1	0	0	6	0	0	0

¹ Also includes preferred term anorexia

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

Additional Data from Clinical Trials

The following adverse drug reactions were reported in adult patients in the Tasigna clinical studies which serve as a basis for the listed indications at the recommended doses at a frequency of less than 5% (common is $\geq 1/100$ to $< 1/10$; uncommon is $\geq 1/1,000$ to $< 1/100$; single events are captured as frequency not known) (Table 4). For laboratory abnormalities, very common events ($\geq 1/10$) not included in Table 3 are also reported. These adverse reactions are included based on clinical relevance and ranked in decreasing order of seriousness within each category, obtained from two clinical studies: 1. Newly diagnosed Ph+ CML-CP 60 months' analysis and 2. Resistant or intolerant Ph+ CML- CP and CML-AP 24 months' analysis.

Table 4 Adverse drug reactions reported in clinical studies in adult patients

Infections and infestations	
Common:	Folliculitis, upper respiratory tract infection (including pharyngitis, nasopharyngitis, rhinitis)
Uncommon:	Pneumonia, bronchitis, urinary tract infection, herpes virus infection, candidiasis (including oral candidiasis), gastroenteritis
Not known:	Sepsis, subcutaneous abscess, anal abscess, furuncle, tinea pedis, hepatitis B reactivation
Neoplasms Benign, Malignant and Unspecified	
Common:	Skin papilloma
Not known:	Oral papilloma, paraproteinaemia
Blood and lymphatic system disorders	
Common:	Leukopenia, eosinophilia, febrile neutropenia, pancytopenia, lymphopenia
Not known:	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:	Gout, dehydration, increased appetite, 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, basilar artery stenosis, brain oedema, optic neuritis, lethargy, dysaesthesia, restless legs syndrome
Eye disorders	
Common:	Eye haemorrhage, periorbital oedema, eye pruritus, conjunctivitis, dry eye (including xerophthalmia)

Uncommon:	Vision impairment, vision blurred, visual acuity reduced, eyelid oedema, photopsia, hyperaemia (scleral, conjunctival, ocular), eye irritation, conjunctival haemorrhage
Not known:	Papilloedema, diplopia, photophobia, eye swelling, blepharitis, eye pain, chorioretinopathy, 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 atrioventricular block, cardiac flutter, extrasystoles, atrial fibrillation, tachycardia, 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 decrease

Vascular disorders

Common:	Hypertension, flushing
Uncommon:	Hypertensive crisis, peripheral arterial occlusive disease, intermittent claudication, arterial stenosis limb, haematoma, arteriosclerosis
Not known:	Shock haemorrhagic, hypotension, thrombosis, peripheral artery stenosis

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, dyspepsia, dysgeusia, flatulence
Uncommon:	Gastrointestinal haemorrhage, melena, 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, pain of skin, ecchymosis, swelling face
Not known:	Psoriasis, erythema multiforme, erythema nodosum, skin ulcer, palmar-plantar erythrodysesthesia syndrome, petechiae, photosensitivity, blister, dermal cyst, sebaceous hyperplasia, skin atrophy, skin discolouration, skin exfoliation, skin hyperpigmentation, skin hypertrophy, hyperkeratosis

Musculoskeletal and connective tissue disorders

Common:	Musculoskeletal chest pain, musculoskeletal pain, back pain, neck pain, flank 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, hematuria, 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:	Pyrexia, chest pain (including non-cardiac chest pain), pain, chest discomfort, malaise
Uncommon:	Face oedema, gravitational oedema, influenza-like illness, chills, feeling body temperature change (including feeling hot, feeling cold)
Not known:	Localized oedema
Investigations	
Very common:	Alanine aminotransferase increased, aspartate amino-transferase increased, lipase increased, lipoprotein cholesterol (including low density and high density) increased, total cholesterol increased, blood triglycerides increased
Common:	Haemoglobin decreased, blood amylase increased, gamma-glutamyltransferase increased, blood creatine phosphokinase increased, blood alkaline phosphatase increased, blood insulin increased, weight decreased, weight increased, globulins decreased
Uncommon:	Blood lactate dehydrogenase increased, blood urea increased
Not known:	Troponin increased, blood bilirubin unconjugated increased, blood insulin decreased, insulin C-peptide decreased, blood parathyroid hormone increased

Laboratory abnormalities

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

Table 5 Grade 3/4 Laboratory Abnormalities

	Newly diagnosed Ph+ CML-CP			Resistant or intolerant Ph+	
	Tasigna 300 mg twice daily N=279	Tasigna 400 mg twice daily N=277	Imatinib 400 mg once daily N=280	Tasigna 400mg twice daily CML-CP N=321	Tasigna 400mg twice daily CML- AP N=137
Haematologic Parameters					
Myelosuppression					
-Neutropenia	12%	11%	22%	31%	42%
-Thrombocytopenia	10%	12%	9%	30%	42%
-Anaemia	4%	5%	6%	11%	27%
Biochemistry Parameters					
-Elevated creatinine	0%	0%	<1%	1%	<1%
-Elevated lipase	9%	10%	4%	18%	18%
-Elevated SGOT (AST)	1%	3%	1%	3%	2%
-Elevated SGPT (ALT)	4%	9%	3%	4%	4%
-Hypophosphatemia	8%	10%	10%	17%	15%
-Elevated Bilirubin (total)	4%	9%	<1%	7%	9%
-Elevated glucose	7%	7%	<1%	12%	6%
-Elevated Cholesterol	0%	1%	0%	*	*

(total)						
-Elevated tri- glycerides		0%	<1%	0		*

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

* parameter not collected

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

After discontinuation of Tasigna therapy within the framework of attempting treatment-free remission (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 patients with Ph+ CML-CP (N=190), musculoskeletal symptoms within a year of Tasigna discontinuation were reported in 24.7% vs. 16.3% within the previous year on Tasigna treatment.

In a Phase II clinical study with patients with Ph+ CML-CP on Tasigna and previously treated with imatinib (N=126), musculoskeletal symptoms within a year of discontinuation were reported in 42.1% vs. 14.3% within the previous year on Tasigna treatment.

Adverse drug reactions from spontaneous reports and literature cases (frequency not known)

The following adverse drug reactions have been derived from post-marketing experience with Tasigna via spontaneous case reports, literature cases, expanded access programs, and clinical studies other than the global registration trials. Because 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 not known: Tumour lysis syndrome, facial paralysis

Paediatric population

The safety of nilotinib in paediatric patients (from 2 to <18 years of age) with Ph+ CML-CP (n=69) has been investigated in two studies. In paediatric patients with Ph+ CML-CP, 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 of 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 (see Dosage regimen and administration)

Growth retardation in pediatric population

In a Phase II (n=58) pediatric study, with a median exposure of 33 months in each cohort (newly diagnosed and resistant or intolerant Ph+ CML-CP), adverse drug reactions of mild and moderate severity associated with growth and deceleration of growth in regard to the height were reported in 3 patients (5.2%) including growth retardation in 2 adolescent patients and growth hormone deficiency with body height below normal in the remaining patient (age category: child). No negative effects were observed in relation to the bone age or bone biomarkers and no delayed puberty was observed. Close monitoring of growth in pediatric patients under TASIGNA treatment is recommended (see Warnings and Precautions)

OVERDOSAGE

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

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

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION (MOA)

Tasigna is a potent and selective inhibitor of the ABL tyrosine kinase activity of the BCR- ABL oncoprotein both in cell lines and in primary Philadelphia-chromosome positive leukemia cells. The drug binds strongly within 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 BCR-ABL dependent cell lines and in primary Philadelphia-chromosome positive leukemia cells derived from CML patients. In murine models of CML, as a single agent nilotinib reduces tumor burden and prolongs survival following oral administration.

PHARMACODYNAMICS (PD)

Tasigna has little or no effect against the majority of other protein kinases examined, including SRC, except for the PDGF, KIT, CSF-1R, DDR 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 (see Table 6).

Table 6 Kinase Profile of Nilotinib (Phosphorylation IC₅₀ nM)

BCR-ABL	PDGFR	KIT
20	69	210

PHARMACOKINETICS (PK)

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 Tasigna is given with food. Administration of Tasigna 30 minutes or 2 hours after food increased bioavailability of nilotinib by 29% or 15%, respectively (see section DOSAGE REGIMEN AND ADMINISTRATION, WARNINGS AND PRECAUTIONS and INTERACTIONS).

Nilotinib absorption (relative bioavailability) might be reduced by approximately 48% and

22% in patients with total gastrectomy and partial gastrectomy, respectively.

Distribution

Blood-to-plasma ratio of nilotinib is 0.68. Plasma protein binding is approximately 98% on the basis of *in vitro* experiments.

Biotransformation/Metabolism

Main metabolic pathways identified in healthy subjects are oxidation and hydroxylation. Nilotinib is the main circulating component in the serum, primarily metabolized by CYP3A4. None of the metabolites contribute significantly to the pharmacological activity of nilotinib.

Elimination

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

The apparent elimination half-life estimated from the multiple dose PK with daily dosing was approximately 17 hours. Inter-patient variability in nilotinib PK was moderate to high (AUC: 32% to 64%).

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

Steady state conditions were essentially achieved by day 8. An increase in systemic exposure to nilotinib between the first dose and steady state was approximately 2-fold for the 400 mg once daily dosing and 3.8-fold for the 400 mg twice-daily dosing.

Bioavailability/bioequivalence studies

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

Paediatric population

Following administration of nilotinib in paediatric patients at 230 mg/m² 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 single or multiple doses appeared to be comparable between paediatric patients from 2 years to <10 years and from ≥10 years to <18 years

CLINICAL STUDIES

Newly diagnosed Ph+ CML-CP

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

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

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

The primary data analysis time point was when all 846 patients completed 12 months of treatment (or discontinued earlier). Subsequent analyses reflect when patients completed 24, 36, 48 and 60 months of treatment (or discontinued earlier). The median time on treatment was approximately 60 months in all three treatment groups. The median actual dose intensity was 400 mg/day in the imatinib group, 593 mg/day in the nilotinib 300 mg twice daily group and 773 mg/day in the nilotinib 400 mg twice daily group. This study is on-going.

Major molecular response (MMR)

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

The primary efficacy endpoint, MMR rate at 12 months was statistically significantly superior in the nilotinib 300 mg twice daily group compared to the imatinib 400 mg once daily group (44.3% vs 22.3%, $p < 0.0001$). The rate of MMR at 12 months, was also statistically significantly higher in the nilotinib 400 mg twice daily group compared to the imatinib 400 mg once daily group (42.7% vs 22.3%, $p < 0.0001$), Table 7.

At the nilotinib recommended dose of 300 mg twice daily, the rates of MMR at 3, 6, 9 and 12 months were 8.9%, 33.0%, 43.3% and 44.3%. In the nilotinib 400 mg twice daily group, the rates of MMR at 3, 6, 9 and 12 months were 5.0%, 29.5%, 38.1% and 42.7%. In the imatinib 400 mg once daily group, the rates of MMR at 3, 6, 9 and 12 months were 0.7%, 12.0%, 18.0% and 22.3%.

The MMR rates at 12, 24, 36, 48 and 60 months is presented in Table 7.

Table 7 MMR rate

	Tasigna 300 mg twice daily N=282 n (%)	Tasigna 400 mg twice daily N=281 n (%)	Imatinib 400 mg once daily N=283 n (%)
MMR at 12 months 95% CI for response	125(44.3) ¹ [38.4,50.3]	120(42.7) ¹ [36.8,48.7]	63(22.3) [17.6, 27.6]
MMR at 24 months 95% CI for response	174 (61.7) ¹ [55.8,67.4]	166 (59.1) ¹ [53.1,64.9]	106 (37.5) [31.8,43.4]
MMR at 36 months² 95% CI for response	165 (58.5) ¹ [52.5,64.3]	161 (57.3) ¹ [51.3,63.2]	109 (38.5) [32.8,44.5]
MMR at 48 months³ 95% CI for response	169 (59.9) ¹ [54.0,65.7]	155 (55.2) [49.1,61.1]	124 (43.8) [38.0,49.8]
MMR at 60 months⁴ 95% CI for response	177 (62.8) [56.8,68.4]	172 (61.2) [55.2,66.9]	139 (49.1) [43.2,55.1]

¹ 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 BID 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).

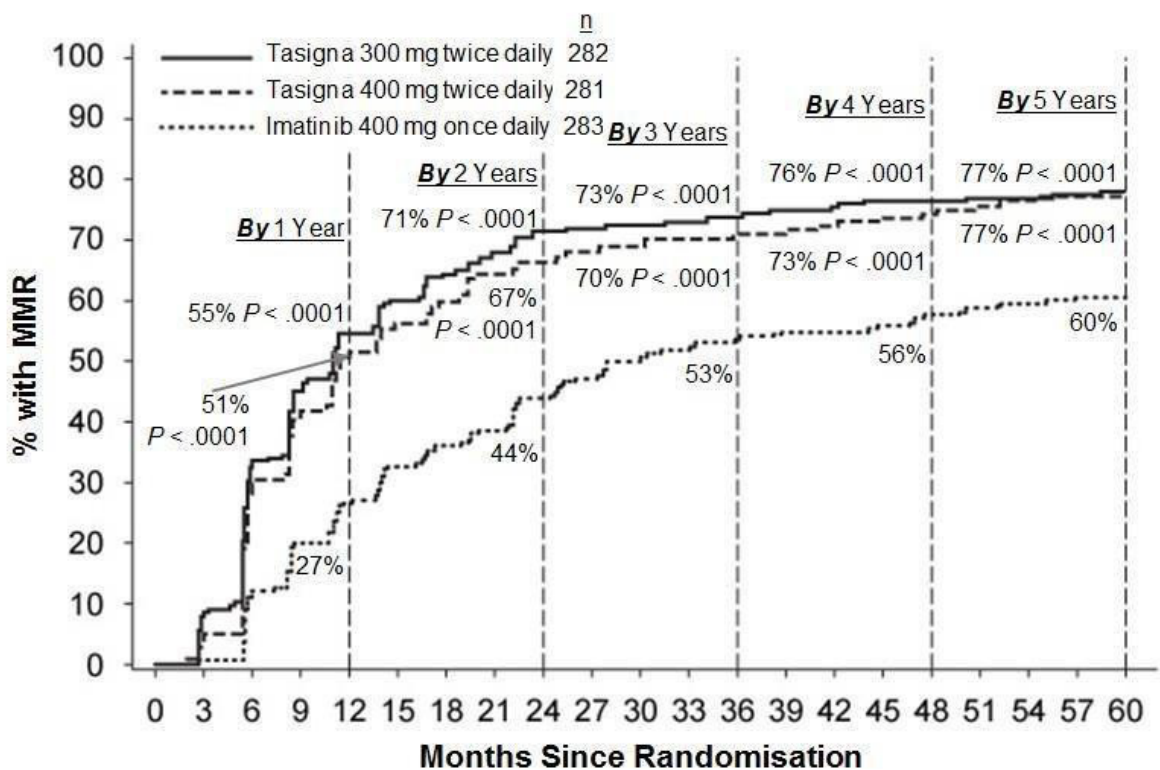
³ Only patients who were in MMR at a specific time point are included as responders for that time point. A total of 305 (36.1%) of all patients were not evaluable for MMR at 48 months (98 in the nilotinib 300 mg BID group, 88 in the nilotinib 400 mg BID group and 119 in the imatinib group) due to missing/unevaluable 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 BID group, 93 in the nilotinib 400 mg BID 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).

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)

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 $\leq 10\%$ at 3 months of treatment compared to 67% (176/264) of patients on imatinib 400 mg once daily. Patients with BCR-ABL levels $\leq 10\%$ at 3 months of treatment show a greater overall survival at 60 months compared to those who did not achieve this molecular response level (96% vs. 82% respectively [$p=0.0116$]).

Based on the Kaplan-Meier analyses of time to first MMR among all patients the probability of achieving MMR at different time points were higher in both nilotinib groups compared to the imatinib group (HR=2.20 and stratified log-rank $p<0.0001$ between nilotinib 300 mg twice daily and imatinib, HR=1.90 and stratified log-rank $p<0.0001$).

between nilotinib 400 mg twice daily and imatinib).

The proportions of patients who had a molecular response of $\leq 0.01\%$ and $\leq 0.0032\%$ by International Scale (IS) at different time-points is presented in Table 8 and the proportion of patients who had a molecular response of $\leq 0.01\%$ and $\leq 0.0032\%$ by IS by different time- points are presented in Figure 2 and 3. Molecular response of $\leq 0.01\%$ and $\leq 0.0032\%$ by IS corresponds to a ≥ 4 log reduction and ≥ 4.5 log reduction, respectively, of BCR-ABL transcripts from a standardized baseline.

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

	Tasigna 300 mg twice daily N=282 (%)		Tasigna 400 mg twice daily N=281 (%)		Imatinib 400 mg once daily N=283 (%)	
	$\leq 0.01\%$	$\leq 0.0032\%$	$\leq 0.01\%$	$\leq 0.0032\%$	$\leq 0.01\%$	$\leq 0.0032\%$
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

Figure 2 Cumulative incidence of molecular response of $\leq 0.01\%$ (4-log reduction)

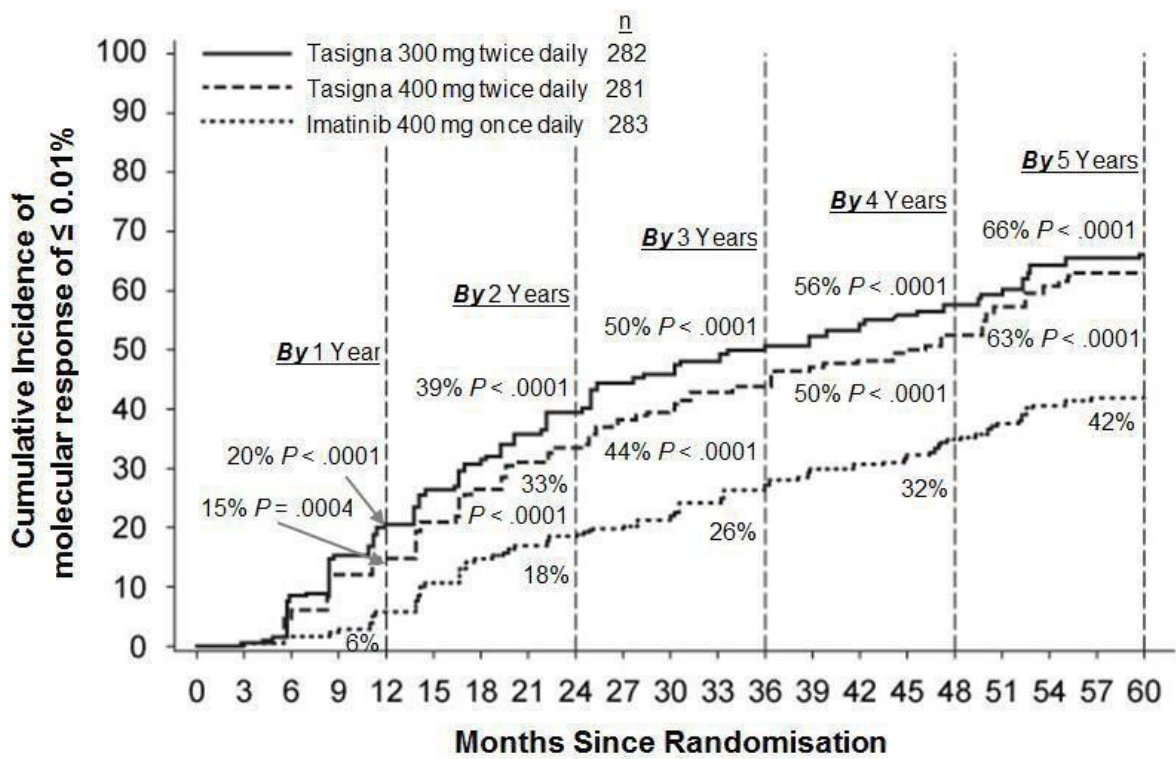
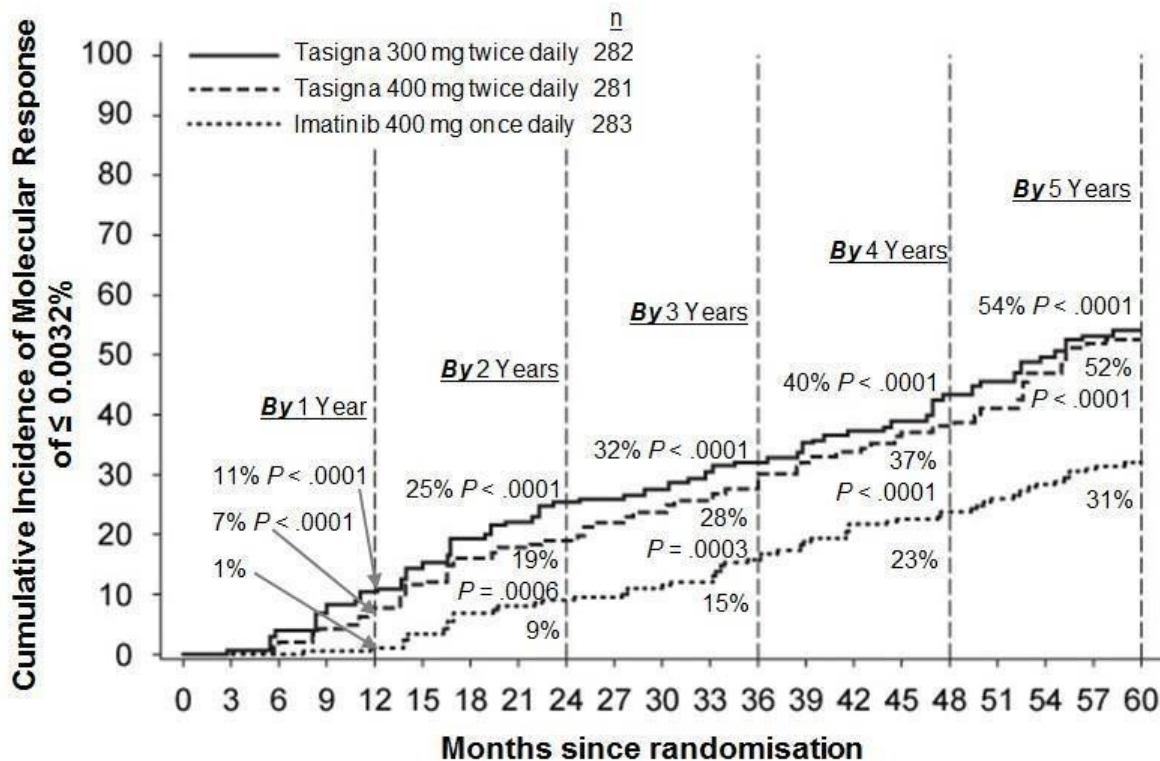


Figure 3 Cumulative incidence of molecular response of $\leq 0.0032\%$ (4.5 log reduction)



Duration of MMR

Based on Kaplan-Meier estimates of the duration of first MMR, the proportions of patients who were maintaining response after 60 months among patients who achieved MMR were 93.4% (95% CI: 89.9% to 96.9% in the nilotinib 300 mg twice daily group, 92.0% (95% CI: 88.2% to 95.8%) in the nilotinib 400 mg twice daily group and 89.1% (95% CI: 84.2% to 94.0%) in the imatinib 400 mg once daily group.

Complete Cytogenetic response (CCyR)

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

Table 9 CCyR rate

	Tasigna 300 mg twice daily N=282 n (%)	Tasigna 400 mg twice daily N=281 n (%)	Imatinib 400 mg once daily N=283 N (%)
By 12 months			
Complete Cytogenetic Response 95% CI for response	226(80.1) [75.0,84.6]	219(77.9) [72.6,82.6]	184(65.0) [59.2,70.6]
CMH test p-value for response rate (vs. Imatinib 400 mg)	<0.0001	0.0005	
By 24 months			
Complete Cytogenetic Response 95% CI for response	245(86.9%) [82.4,90.6]	238(84.7%) [79.9,88.7]	218(77.0%) [71.7,81.8]
CMH test p-value for response rate (vs. Imatinib 400 mg)	0.0018	0.0160	

Duration of CCyR

Based on Kaplan-Meier estimates, the proportions of patients who were maintaining response after 60 months among patients who achieved CCyR were 99.1% (95% CI: 97.9% to 100%) in the nilotinib 300 mg twice daily group, 98.7% (95% CI: 97.1% to 100%) in the nilotinib 400 mg twice daily group and 97.0% (95% CI: 94.7% to 99.4%) in the imatinib 400 mg once daily group.

Progression to AP/BC on treatment

Progression to AP/BC on treatment is defined as the time from the date of randomization to the first documented disease progression to AP/BC or CML-related death. Overall by the cut-off date, 17 patients progressed to AP or BC on treatment (2 in the nilotinib 300 mg twice daily group, 3 in the nilotinib 400 mg twice daily group and 12 in the imatinib 400 mg once daily group). The estimated rates of patients free from progression to AP or BC at 60 months were 99.3%, 98.7% and 95.2%, respectively (HR=0.1599 and stratified log-rank p=0.0059 between nilotinib 300 mg BID and imatinib, HR=0.2457 and stratified log-rank p=0.0185 between nilotinib 400 mg BID and imatinib). No new events of progression to AP/BC were reported on-treatment since the 2-year analysis.

Including clonal evolution as a criterion for progression, a total of 24 patients progressed to AP or BC 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 AP or BC including clonal evolution at 60 months were 98.7%, 97.9% and 93.2%, respectively

(HR=0.1626 and stratified log-rank p=0.0009 between nilotinib 300 mg BID and imatinib, HR = 0.2848 and stratified log-rank p=0.0085 between nilotinib 400 mg BID and imatinib).

Overall survival (OS)

A total of 50 patients died during treatment or during the follow-up after discontinuation of treatment (18 in the nilotinib 300 mg twice daily group, 10 in the nilotinib 400 mg twice daily group and 22 in the imatinib 400 mg once daily group). Twenty-six (26) of these 50 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 60 months were 93.7%, 96.2% and 91.7%, respectively (HR=0.8026 and stratified log-rank p = 0.4881 between nilotinib 300 mg twice daily and imatinib, HR=0.4395 and stratified log-rank p = 0.0266 between nilotinib 400 mg twice daily and imatinib). Considering only CML-related deaths as events, the estimated rates of OS at 60 months were 97.7%, 98.5% and 93.8%, respectively (HR=0.3673 and stratified log-rank p = 0.0292 between nilotinib 300 mg twice daily and imatinib, HR=0.2411 and stratified log-rank p = 0.0057 between nilotinib 400 mg twice daily and imatinib).

Switch to Tasigna treatment in adult patients with Ph+ CML-CP who have not achieved a molecular response greater than or equal to a 4.5-log reduction with imatinib treatment

In an open-label, multicenter, randomized Phase III study, 207 adult patients with Ph+ CML- CP who received treatment with imatinib for at least 2 years, with no permanent imatinib dose adjustment within 6 months and no major toxicity within 3 months of study entry were enrolled in the study. Patients were randomized 1:1 either to receive Tasigna 400 mg twice daily (n=104) or to continue treatment with imatinib at the same dose (400 mg or 600 mg once daily) as administered prior to randomization (n=103). Randomization was stratified by duration of prior treatment with imatinib and duration of prior interferon use. The median time on treatment (from first day of treatment to last day of randomized treatment) at cut-off was 47.2 months in the Tasigna treatment arm, and 37.0 months and 26.7 months in the 400 mg and 600 mg dose cohorts of the imatinib arm, respectively.

The two treatment arms were well balanced with respect to demographic and baseline characteristics (including BCR-ABL transcript levels at study entry). Median age was 46 years in the Tasigna arm and 52 years in the imatinib arm, with 13.5% and 13.6% of patients aged ≥ 65 years in the Tasigna and imatinib treatment arms, respectively. There were more male (68.3% in the Tasigna treatment arm and 63.1% in the imatinib treatment arm) than female patients. More than 80% of all patients were Caucasians. Up to the cut-off date, the median actual dose intensity was 775.7 mg/day in the Tasigna treatment arm and 400 mg/day and 600 mg/day in the two dose cohorts of the imatinib treatment arm, respectively.

The primary endpoint of the study was the rate of confirmed best cumulative complete molecular response (CMR) within the first year of study therapy with Tasigna or imatinib. The rate of confirmed best cumulative CMR during the first 12 months was 12.5% in the Tasigna arm and 5.8% in the imatinib arm. The primary endpoint did not

reach statistical significance at the early 12-month time point (p=0.1083), with an odds ratio (OR) of 2.096 in favor of Tasigna.

Resistant or intolerant Ph+ CML

An open-label, uncontrolled multicenter Phase II study was conducted to determine the efficacy of Tasigna (400 mg twice daily) in patients with imatinib resistant or intolerant CML with separate treatment arms for chronic and accelerated phase disease. Efficacy was based on 321 CP patients and 137 AP patients enrolled. Median duration of treatment was 561 days and 264 days, respectively (see Table 10). Tasigna was administered on a continuous basis, (twice daily 2 hours after a meal and no additional food for at least one hour) unless there was evidence of inadequate response or disease progression. Dose escalation to 600 mg twice daily was allowed.

Table 10 **Duration of Exposure with Tasigna**

	Chronic Phase N = 321	AcceleratedPhase N = 137
Median duration of therapy in days (25 th – 75 th percentiles)	561 (196-852)	264 (115-595)

Resistance to imatinib included failure to achieve a complete hematologic 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 hematologic 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 such as imatinib, hydroxyurea, interferon, and some that had even failed organ transplant (Table 11). The median highest prior imatinib dose had been 600 mg/day for CP and AP patients, and the highest prior imatinib dose was ≥600 mg/day in 74% of all patients with 40% of patients receiving imatinib doses ≥800 mg/day.

Table 11 **CML Disease History Characteristics**

	Chronic Phase (n = 321)	AcceleratedPhase (n = 137)*
Median time since diagnosis in months (range)	58 (5-275)	71 (2-298)
Imatinib		
Resistant	226 (70%)	109 (80%)
Intolerant without MCyR	95 (30%)	27 (20%)

Median time of imatinib treatment in days (25 th – 75 th percentiles)	976 (519 - 1,488)	857 (424 - 1,497)
Prior Hydroxyurea	83%	91%
Prior Interferon	58%	50%
Prior organ transplant	7%	8%

*One patient had missing information for imatinib-resistant/intolerant status

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+ hematopoietic cells. Complete hematologic response (CHR) in CP patients was evaluated as a secondary endpoint. The primary endpoint in the AP patients was overall confirmed hematologic response (HR), defined as either a complete hematologic response, no evidence of leukemia 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 Tasigna 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% to 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% to 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 vs. 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 55%. Most responders achieved a HR early with Tasigna treatment (median 1.0 months) and these have been durable (median duration of confirmed HR was 21.5 months). Of the patients who achieved HR, 49% (95% CI: 35% to 62%) were maintaining response at 24 months. MCyR rate was 32% with a median time to response of 2.8 months. Of the patients who achieved MCyR, 66% (95% CI: 50% to 82%) were maintaining response at 24 months. Median duration of MCyR has not been reached. The rates of response for the two treatment arms are reported in Table 12.

The estimated 24-month overall survival rate in CML -AP patients was 70%.

Table 12 Response rate 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)
Haematologic Response (%)						
Overall (95%CI)	-	-	-	56 (35-75)	55 (45-65)	55 (47-64)
Complete	87 (74-94)	65 (56-72)	70 ¹ (63-76)	37	30	31
NEL	-	-	-	15	11	12
Return to CP	-	-	-	4	14	12

Cytogenetic Response (%)

Major (95%CI)	57 (46-67)	49 (42-56)	51 (46-57)	41 (22-61)	30 (22-40)	32 (24-41)
Complete	41	35	37	30	19	21
Partial	16	14	15	11	11	11

NEL = no evidence of leukaemia/marrow response

¹

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

* One patient had missing information for imatinib-resistant/tolerant status

Separate treatment arms were also included in the Phase II study to study 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. 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 42% of chronic phase and 54% of accelerated phase CML patients who were evaluated for mutations. Tasigna demonstrated efficacy in patients harboring a variety of BCR-ABL mutations associated with imatinib resistance, except T315I.

Treatment discontinuation in newly diagnosed Ph+ CML-CP patients who have achieved a sustained deep molecular response

In an open-label, multicenter, single-arm study, 215 adult patients with Ph+ CML-CP treated with TASIGNA in first-line for ≥ 2 years who achieved MR4.5 as measured with the MolecularMD MRDx™ BCR-ABL Test were enrolled to continue TASIGNA treatment for an additional 52 weeks (Tasigna consolidation phase). Of the 215 patients, 190 patients (88.4%) entered the “Treatment-free Remission” (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 $\leq 0.01\%$ IS), and maintained for 1 year
- The last assessment being MR4.5 (BCR-ABL / ABL $\leq 0.0032\%$ IS)
- No more than two assessments falling between MR4.0 and MR4.5 (0.0032% IS $<$ BCR- ABL / ABL $\leq 0.01\%$ IS).

In the set of patients who entered the TFR phase, the median age was 55 years. The proportion of female patients was 49.5%, and 21.1% of the patients were ≥ 65 years of age. The median actual dose intensity during the 52-week Tasigna consolidation phase was 600.0 mg/day.

BCR-ABL levels were monitored every 4 weeks during the first 48 weeks of the TFR phase. Monitoring frequency was intensified to every 2 weeks upon the loss of MR4.0.

Biweekly monitoring ended at one of the following time points:

- Loss of MMR requiring patient to re-initiate Tasigna treatment
- When the BCR-ABL levels returned to a range between MR4.0 and MR4.5
- When the BCR-ABL levels remained lower than MMR for 4 consecutive measurements (8 weeks from initial loss of MR4.0).

Any patient with loss of MMR during the TFR phase re-initiated Tasigna treatment at 300

mg twice daily or at a reduced dose level of 400 mg once daily if required from the perspective of tolerance, within 5 weeks after the collection date of the blood sample demonstrating loss of MMR. Patients who required re-initiation of Tasigna treatment were monitored for BCR-ABL levels every 4 weeks for the first 24 weeks and then every 12 weeks thereafter in patients who regained MMR.

The primary endpoint was the percentage of patients who were 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 in the TFR phase at 48 weeks.

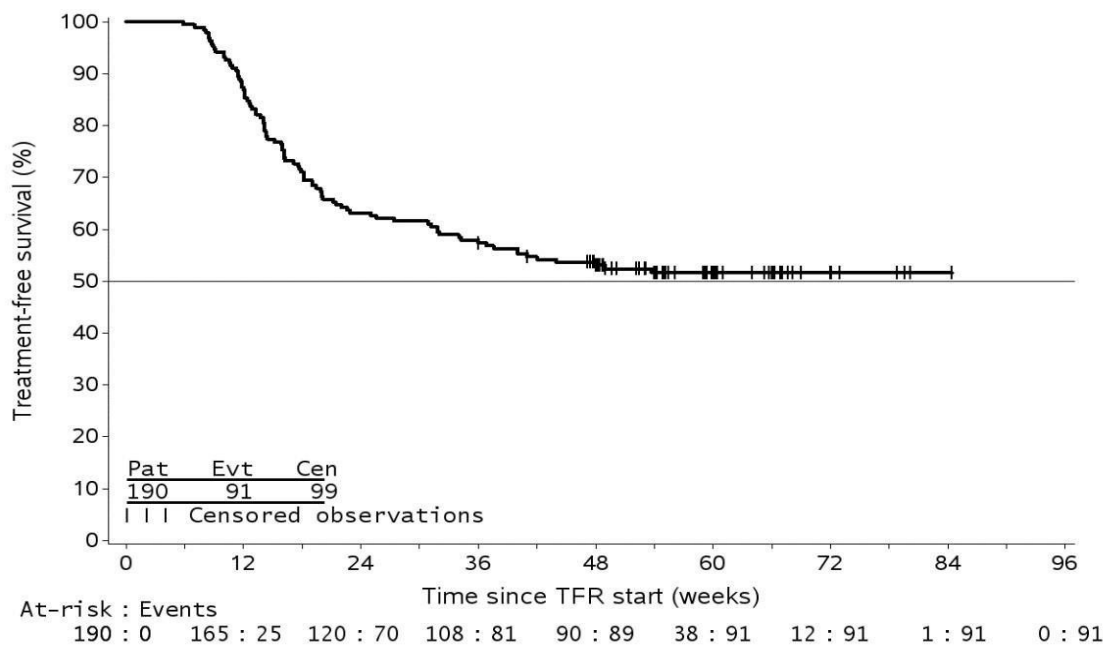
Eighty-eight patients (46.3%) discontinued from the TFR phase due to loss of MMR, and 1 (0.5%), 1 (0.5%), and 3 patients (1.6%) due to death from unknown cause, physician decision, and subject decision, respectively. Among the 88 patients who discontinued the TFR phase due to loss of MMR, 86 patients restarted TASIGNA treatment and 2 patients permanently discontinued from the study.

Of the 86 patients who restarted treatment due to loss of MMR in the TFR phase, 85 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 TASIGNA 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 rate at 24 weeks of re-initiation was 98.8% (95% CI: 94.2, 99.9). The KM estimated MR4.5 rate at 24 weeks of re-initiation was 90.9% (95% CI: 83.2, 96.0).

Among the 190 patients in the TFR phase, 99 patients (52.1%) did not have a treatment-free survival (TFS) event on or before the 48 month cut off date, and were censored at the date of their last assessment prior to cut-off. The KM estimate of median TFS has not yet been reached (Figure 4).

Figure 4 Kaplan-Meier estimate of treatment-free survival after start of TFR (Full Analysis Set)



Treatment discontinuation in Ph+ CML-CP adult patients who have achieved a sustained deep molecular response on Tasigna following prior imatinib therapy

In an open-label, multicenter, single-arm study, 163 adult patients with Ph+ CML-CP 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 Tasigna, then switched to Tasigna for at least two years), and who achieved MR4.5 on Tasigna treatment as measured with the MolecularMD MRDx™ BCR-ABL Test were enrolled to continue TASIGNA treatment for an additional 52 weeks (Tasigna consolidation phase). Of the 163 patients, 126 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 $\leq 0.0032\%$ IS) during 1 year.

The median age of the patients who entered the TFR phase was 56 years. The proportion of female patients was 55.6%, and 27.8% of the patients were ≥ 65 years of age. The median actual dose intensity during the 52-week Tasigna consolidation phase was 771.8 mg/day with 52.4% and 29.4% of patients receiving a daily Tasigna dose of 800 mg and 600 mg just before entry into the TFR phase, respectively.

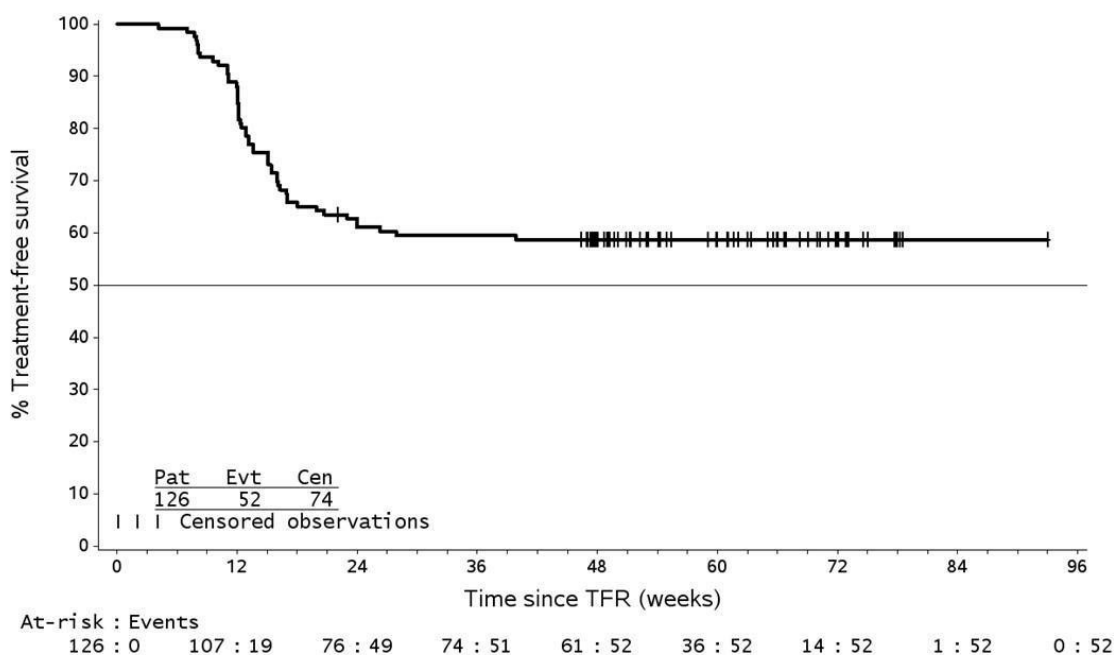
Patients who entered the TFR phase but experienced two consecutive measurements of BCR-ABL/ABL $>0.01\%$ IS were considered having a confirmed loss of MR4.0, triggering re-initiation of Tasigna treatment. Patients with loss of MMR in the TFR phase immediately restarted Tasigna treatment without confirmation. All patients who restarted Tasigna therapy had BCR-ABL transcript levels monitored every 4 weeks for the first 24 weeks, then once every 12 weeks. The primary endpoint was defined as the proportion of patients without confirmed loss of MR4.0 or loss of MMR within 48 weeks following discontinuation of Tasigna therapy. 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 Tasigna therapy within 48 weeks after the start of the TFR phase.

Among the 53 patients who discontinued from the TFR phase due to confirmed loss of MR4.0 or loss of MMR, 51 patients restarted Tasigna therapy and 2 patients permanently discontinued from the study. Of the 51 patients who restarted Tasigna treatment due to confirmed loss of MR4.0 or loss of MMR in the TFR phase, 48 patients (94.1%) regained MR4.0 and 3 patients (5.9%) did not regain MR4.0. Forty-seven patients (92.2%) regained MR4.5 and 4 patients (7.8%) did not regain MR4.5 by the time of the cut-off date.

The Kaplan-Meier (KM) estimated median time on Tasigna 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 rate of MR4.0 at 48 weeks of re-initiation was 100.0%. (95% CI: not estimated). The KM estimated rate of MR4.5 at 48 weeks of re-initiation was 94.8% (95% CI: 85.1, 99.0).

Among the 126 patients in the TFR phase, 74 patients (58.7%) did not have a treatment-free survival (TFS) event on or before the 48-month cut off date, and were censored at the date of their last assessment prior to cut-off. The other 52 patients had a TFS event (18 patients had confirmed loss of MR4.0, and 34 patients lost MMR). The median TFS has not yet been reached (Figure 5).

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



Paediatric patients

The safety and efficacy of nilotinib in paediatric patients with Ph+ CML-CP 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-CP (n=25) or imatinib/dasatinib resistant or intolerant Ph+ CML-CP (n=44) received nilotinib treatment at a dose of 230 mg/m² 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/m²/day (range: 149 to 517 mg/m²/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 to 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.

NON-CLINICAL SAFETY DATA

Nilotinib has been evaluated in safety pharmacology, repeated dose toxicity, genotoxicity, reproductive toxicity (see section PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL), phototoxicity and carcinogenicity (rat and mice) studies.

Safety pharmacology and repeated dose toxicity

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 up to 39 weeks or in a special telemetry study in dogs.

Repeated dose toxicity studies in dogs up to 4 weeks duration and in cynomolgus monkeys 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, the histological alterations only showed partial reversibility. Exposures at the lowest dose levels where 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 up to 26 weeks. Mainly reversible increases in cholesterol levels were seen in rats, dogs and monkeys.

Carcinogenicity and mutagenicity

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.

In the 2-year rat carcinogenicity study, 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 were representing approximately 2× to 3× human daily steady state exposure (based on AUC) to nilotinib at the dose of 800 mg/day. The major target organ for non-neoplastic lesions was the uterus (dilatation, vascular ectasia, hyperplasia endothelial cell, inflammation and/or epithelial hyperplasia).

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).

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 postpartum through young adult (day 70 postpartum) at doses of 2, 6 and 20 mg/kg/day. Effects were limited to the dose of 20 mg/kg/day and consisted of reductions in body weight parameters and food consumption with recovery after dosing ceased. The No-Observed-Effect-level in juvenile rats was considered to be 6 mg/kg/day. Overall, the toxicity profile in juvenile rats was comparable to that observed in adult rats.

Phototoxicity

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*. However, no phototoxicity has been observed *in vivo*. Therefore the risk that nilotinib causes photosensitization in patients is considered very low.

INCOMPATIBILITIES

Not applicable.

STORAGE

See folding box.

Tasigna should not be used after the date marked “EXP” on the pack.

Tasigna must be kept out of the reach and sight of children.

Manufacturer:

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