1. NAME OF THE MEDICINAL PRODUCT

Tasigna 150 mg capsules
Tasigna 200 mg capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Tasigna 150 mg capsules

One capsule contains 150 mg nilotinib (as hydrochloride monohydrate).

Excipient with known effect
One capsule contains 117.08 mg lactose monohydrate.

Tasigna 200 mg capsules

One capsule contains 200 mg nilotinib (as hydrochloride monohydrate).

Excipient with known effect
One capsule contains 156.11 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsule

Tasigna 150mg capsules

White to yellowish powder in red opaque capsules, size 1 with black axial imprint "NVR/BCR".

Tasigna 200mg capsules

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Tasigna 150mg and 200mg are indicated for the treatment of adult patients with newly diagnosed Philadelphia chromosome positive chronic Myelogenous leukaemia (CML) in the chronic phase.

Tasigna 200mg **only** is indicated also for the treatment of Philadelphia chromosome positive chronic myeloid leukaemia (Ph+CML) in chronic phase or accelerated phase in patients resistant to or experiencing significant toxicity during treatment with imatinib.

4.2 Posology and method of administration

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

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

occurs.

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

Posology for Philadelphia chromosome positive CML adult patients
The recommended dose of Tasigna is:

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

For a dose of 300 mg twice daily, 150 mg capsules are available.
For a dose of 400 mg once daily (see dose adjustments below), 200 mg capsules are available.

Philadelphia chromosome positive CML patients in chronic phase who have been treated with nilotinib as first-line therapy and who achieved a sustained deep molecular response (MR4.5)
Discontinuation of treatment may be considered in eligible Philadelphia chromosome positive (Ph+) CML patients in chronic phase who have been treated with nilotinib at 300 mg twice daily for a minimum of 3 years if a deep molecular response is sustained for a minimum of one year immediately prior to discontinuation of therapy. Discontinuation of nilotinib therapy should be initiated by a physician experienced in the treatment of patients with CML (see sections 4.4 and 5.1).

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

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

Patients who lose MMR must re-initiate treatment within 4 weeks of when loss of remission is known to have occurred. Nilotinib therapy should be re-initiated at 300 mg twice daily or at a reduced dose level of 400 mg once daily if the patient had a dose reduction prior to discontinuation of therapy. Patients who re-initiate nilotinib therapy should have their BCR-ABL transcript levels monitored monthly until MMR is re-established and every 12 weeks thereafter (see section 4.4).

Philadelphia chromosome positive CML patients in chronic phase who have achieved a sustained deep molecular response (MR 4.5) on nilotinib following prior imatinib therapy
Discontinuation of treatment may be considered in eligible Philadelphia chromosome positive (Ph+) CML patients in chronic phase who have been treated with nilotinib for a minimum of 3 years if a deep molecular response is sustained for a minimum of one year immediately prior to discontinuation of therapy. Discontinuation of nilotinib therapy should be initiated by a physician experienced in the treatment of patients with CML (see sections 4.4 and 5.1).

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

Patients with confirmed loss of MR4 (MR4= BCR-ABL/ABL ≤0.01%IS) during the treatment-free phase (two consecutive measures separated by at least 4 weeks showing loss of MR4) or loss of major molecular response (MMR=BCR-ABL/ABL ≤0.1%IS) must re-initiate treatment within 4 weeks of when loss of remission is known to have occurred. Nilotinib therapy should be re-initiated at either 300 mg or 400 mg twice daily. Patients who re-initiate nilotinib therapy should have their BCR-ABL transcript levels monitored monthly until previous major molecular response or MR4 level is re-established and every 12 weeks thereafter (see section 4.4).

Dose adjustments or modifications
Tasigna may need to be temporarily withheld and/or dose reduced for haematological toxicities (neutropenia, thrombocytopenia) that are not related to the underlying leukaemia (see Table 1).

Table 1 Dose adjustments for neutropenia and thrombocytopenia

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

*ANC = absolute neutrophil count

If clinically significant moderate or severe non-haematological toxicity develops, dosing should be interrupted, and patients should be monitored and treated accordingly. If the prior dose was 300 mg twice daily in adult newly diagnosed patients with CML in the chronic phase, or 400 mg twice daily in adult patients with imatinib-resistant or intolerant CML in chronic or accelerated phase, dosing may be resumed at 400 mg once daily in adult patients once the toxicity has resolved. If the prior dose was 400 mg once daily in adult patients, treatment should be discontinued. If clinically appropriate, re-escalation of the dose to the starting dose of 300 mg twice daily in adult newly diagnosed patients with CML in the chronic phase or to 400 mg twice daily in adult patients with imatinib-resistant or intolerant CML in chronic or accelerated phase should be considered.

Elevated serum lipase: For Grade 3-4 serum lipase elevations, doses in adult patients should be reduced to 400 mg once daily or interrupted. Serum lipase levels should be tested monthly or as clinically indicated (see section 4.4).

Elevated bilirubin and hepatic transaminases: For Grade 3-4 bilirubin and hepatic transaminase elevations in adult patients, doses should be reduced to 400 mg once daily or interrupted. Bilirubin and hepatic transaminases levels should be tested monthly or as clinically indicated.

Special populations

Elderly
Approximately 12% of subjects in the Phase III study in patients with newly diagnosed CML in chronic phase and approximately 30% of subjects in the Phase II study in patients with imatinib-resistant or intolerant CML in chronic phase and accelerated phase were 65 years of age or over. No major differences were observed for safety and efficacy in patients ≥65 years of age as compared to adults aged 18 to 65 years.

Renal impairment
Clinical studies have not been performed in patients with impaired renal function.
Since nilotinib and its metabolites are not renally excreted, a decrease in total body clearance is not anticipated in patients with renal impairment.

Hepatic impairment
Hepatic impairment has a modest effect on the pharmacokinetics of nilotinib. Dose adjustment is not considered necessary in patients with hepatic impairment. However, patients with hepatic impairment should be treated with caution (see section 4.4).

Cardiac disorders
In clinical studies, patients with uncontrolled or significant cardiac disease (e.g., recent myocardial infarction, congestive heart failure, unstable angina or clinically significant bradycardia) were excluded. Caution should be exercised in patients with relevant cardiac disorders (see section 4.4).

Increases in total serum cholesterol levels have been reported with nilotinib therapy (see section 4.4). Lipid profiles should be determined prior to initiating nilotinib therapy, assessed at month 3 and 6 after initiating therapy and at least yearly during chronic therapy.

Increases in blood glucose levels have been reported with nilotinib therapy (see section 4.4). Blood glucose levels should be assessed prior to initiating nilotinib therapy and monitored during treatment.

Paediatric population
Tasigna is not indicated for paediatric patients

Method of administration

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

For patients who are unable to swallow capsules, the content of each capsule may be dispersed in one teaspoon of apple sauce (puréed apple) and should be taken immediately. Not more than one teaspoon of apple sauce and no food other than apple sauce must be used (see sections 4.4 and 5.2).

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Myelosuppression

Treatment with nilotinib is associated with (National Cancer Institute Common Toxicity Criteria grade 3 and 4) thrombocytopenia, neutropenia and anaemia. Occurrence is more frequent in patients with imatinib-resistant or intolerant CML, in particular in patients with accelerated-phase CML. Complete blood counts should be performed every two weeks for the first 2 months and then monthly thereafter, or as clinically indicated. Myelosuppression was generally reversible and usually managed by withholding Tasigna temporarily or dose reduction (see section 4.2).

QT prolongation

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

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

In the Phase II study in imatinib-resistant and intolerant CML patients in chronic and accelerated phase receiving 400 mg nilotinib twice daily, the change from baseline in mean time-averaged QTcF interval at steady state was 5 and 8 msec, respectively. QTcF of >500 msec was observed in <1% of these patients. No episodes of torsade de pointes were observed in clinical studies.

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

Significant prolongation of the QT interval may occur when nilotinib is inappropriately taken with strong CYP3A4 inhibitors and/or medicinal products with a known potential to prolong the QT interval, and/or food (see section 4.5). The presence of hypokalaemia and hypomagnesaemia may further enhance this effect. Prolongation of the QT interval may expose patients to the risk of fatal outcome.

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 nilotinib therapy and as clinically indicated. Hypokalaemia or hypomagnesaemia must be corrected prior to Tasigna administration and potassium and magnesium blood levels should be monitored periodically during therapy, particularly in patients at risk for these electrolyte abnormalities.

Sudden death

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

Fluid retention and oedema

Severe forms of drug-related fluid retention such as pleural effusion, pulmonary oedema, and pericardial effusion were uncommonly (0.1 to 1%) observed in a Phase III study of newly diagnosed

CML patients. Similar events were observed in post-marketing reports. Unexpected, rapid weight gain should be carefully investigated. If signs of severe fluid retention appear during treatment with nilotinib, the aetiology should be evaluated and patients treated accordingly (see section 4.2 for instructions on managing non-haematological toxicities).

Cardiovascular events

Cardiovascular events were reported in a randomised Phase III study in newly diagnosed CML patients and observed in post-marketing reports. In this clinical study with a median on-therapy time of 60.5 months, Grade 3-4 cardiovascular events included peripheral arterial occlusive disease (1.4% and 1.1% at 300 mg and 400 mg nilotinib twice daily, respectively), ischaemic heart disease (2.2% and 6.1% at 300 mg and 400 mg nilotinib twice daily, respectively) and ischaemic cerebrovascular events (1.1% and 2.2% at 300 mg and 400 mg nilotinib twice daily, respectively). Patients should be advised to seek immediate medical attention if they experience acute signs or symptoms of cardiovascular events. The cardiovascular status of patients should be evaluated and cardiovascular risk factors monitored and actively managed during nilotinib therapy according to standard guidelines. Appropriate therapy should be prescribed to manage cardiovascular risk factors (see section 4.2 for instructions on managing non-haematological toxicities).

Hepatitis B reactivation

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

Patients should be tested for HBV infection before initiating treatment with nilotinib. Experts in liver disease and in the treatment of hepatitis B should be consulted before treatment is initiated in patients with positive hepatitis B serology (including those with active disease) and for patients who test positive for HBV infection during treatment. Carriers of HBV who require treatment with nilotinib should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy (see section 4.8).

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

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

Monitoring of patients who have discontinued therapy
Frequent monitoring of BCR-ABL transcript levels in patients eligible for treatment discontinuation must be performed with a quantitative diagnostic test validated to measure molecular response levels with a sensitivity of at least MR4.5 (BCR-ABL/ABL ≤0.0032% IS). BCR-ABL transcript levels must be assessed prior to and during treatment discontinuation (see sections 4.2 and 5.1).

Loss of major molecular response (MMR=BCR-ABL/ABL ≤0.1%IS) in CML patients who received nilotinib as first-or second-line therapy, or confirmed loss of MR4 (two consecutive measures separated by at least 4 weeks showing loss of MR4 (MR4=BCR-ABL/ABL ≤0.01%IS)) in CML patients who received nilotinib as second-line therapy will trigger treatment re-initiation within 4 weeks of when loss of remission is known to have occurred. Molecular relapse can occur during the treatment-free phase, and long-term outcome data are not yet available. It is therefore crucial to perform frequent monitoring of BCR-ABL transcript levels and complete blood count with differential in order to detect possible loss of remission (see section 4.2). For patients who fail to achieve MMR after three months of treatment re-initiation, BCR-ABL kinase domain mutation testing should be performed.

Laboratory tests and monitoring

Blood lipids
In a Phase III study in newly diagnosed CML patients, 1.1% of the patients treated with 400 mg nilotinib twice daily showed a Grade 3-4 elevation in total cholesterol; no Grade 3-4 elevations were however observed in the 300 mg twice daily dose group (see section 4.8). It is recommended that the lipid profiles be determined before initiating treatment with nilotinib, assessed at month 3 and 6 after initiating therapy and at least yearly during chronic therapy (see section 4.2). If a HMG-CoA reductase inhibitor (a lipid-lowering agent) is required, please refer to section 4.5 before initiating treatment since certain HMG-CoA reductase inhibitors are also metabolised by the CYP3A4 pathway.

Blood glucose
In a Phase III study in newly diagnosed CML patients, 6.9% and 7.2% of the patients treated with 400 mg nilotinib and 300 mg nilotinib twice daily, respectively, showed a Grade 3-4 elevation in blood glucose. It is recommended that the glucose levels be assessed before initiating treatment with Tasigna and monitored during treatment, as clinically indicated (see section 4.2). If test results warrant therapy, physicians should follow their local standards of practice and treatment guidelines.

Interactions with other medicinal products

The administration of Tasigna with agents that are strong CYP3A4 inhibitors (including, but not limited to, ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin, ritonavir) should be avoided. Should treatment with any of these agents be required, it is recommended that nilotinib therapy be interrupted if possible (see section 4.5). If transient interruption of treatment is not possible, close monitoring of the individual for prolongation of the QT interval is indicated (see sections 4.2, 4.5 and 5.2).

Concomitant use of nilotinib with medicinal products that are potent inducers of CYP3A4 (e.g., phenytoin, rifampicin, carbamazepine, phenobarbital and St. John's Wort) is likely to reduce exposure to nilotinib to a clinically relevant extent. Therefore, in patients receiving nilotinib, co-administration of alternative therapeutic agents with less potential for CYP3A4 induction should be selected (see section 4.5).

Food effect

The bioavailability of nilotinib is increased by food. Tasigna must not be taken in conjunction with food (see sections 4.2 and 4.5) and should be taken 2 hours after a meal. No food should be consumed for at least one hour after the dose is taken. Grapefruit juice and other foods that are known to inhibit CYP3A4 should be avoided. For patients who are unable to swallow capsules, the content of each capsule may be dispersed in one teaspoon of apple sauce and should be taken immediately. Not more than one teaspoon of apple sauce and no food other than apple sauce must be used (see section 5.2).

Hepatic impairment

Hepatic impairment has a modest effect on the pharmacokinetics of nilotinib. Single dose administration of 200 mg of nilotinib resulted in increases in AUC of 35%, 35% and 19% in subjects with mild, moderate and severe hepatic impairment, respectively, compared to a control group of subjects with normal hepatic function. The predicted steady-state C_{max} of nilotinib showed an increase of 29%, 18% and 22%, respectively. Clinical studies have excluded patients with alanine transaminase (ALT) and/or aspartate transaminase (AST) >2.5 (or >5, if related to disease) times the upper limit of the normal range and/or total bilirubin >1.5 times the upper limit of the normal range. Metabolism of nilotinib is mainly hepatic. Patients with hepatic impairment might therefore have increased exposure to nilotinib and should be treated with caution (see section 4.2).

Serum lipase

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

Total gastrectomy

The bioavailability of nilotinib might be reduced in patients with total gastrectomy (see section 5.2). More frequent follow-up of these patients should be considered.

Tumour lysis syndrome

Due to possible occurrence of tumour lysis syndrome (TLS) correction of clinically significant dehydration and treatment of high uric acid levels are recommended prior to initiating nilotinib therapy (see section 4.8).

Lactose

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

4.5 Interaction with other medicinal products and other forms of interaction

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

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

Substances that may increase nilotinib serum concentrations

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

The exposure to nilotinib in healthy subjects was increased 3-fold when co-administered with the strong CYP3A4 inhibitor ketoconazole. Concomitant treatment with strong CYP3A4 inhibitors, including ketoconazole, itraconazole, voriconazole, ritonavir, clarithromycin, and telithromycin, should therefore be avoided (see section 4.4). Increased exposure to nilotinib might also be expected with moderate CYP3A4 inhibitors. Alternative concomitant medicinal products with no or minimal CYP3A4 inhibition should be considered.

Substances that may decrease nilotinib serum concentrations

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

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

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

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

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

Substances that may have their systemic concentration altered by nilotinib

In vitro, nilotinib is a relatively strong inhibitor of CYP3A4, CYP2C8, CYP2C9, CYP2D6 and UGT1A1, with Ki value being lowest for CYP2C9 (Ki=0.13 microM).

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

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

The combination of nilotinib with those statins that are mainly eliminated by CYP3A4, may increase the potential for statin-induced myopathy, including rhabdomyolysis.

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

Nilotinib should be used with caution in patients who have or may develop prolongation of the QT interval, including those patients taking anti-arrhythmic medicinal products such as amiodarone, disopyramide, procainamide, quinidine and sotalol or other medicinal products that may lead to QT prolongation such as chloroquine, halofantrine, clarithromycin, haloperidol, methadone and moxifloxacin (see section 4.4).

Food interactions

The absorption and bioavailability of nilotinib are increased if it is taken with food, resulting in a higher serum concentration (see sections 4.2, 4.4 and 5.2). Grapefruit juice and other foods that are known to inhibit CYP3A4 should be avoided.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception

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

Pregnancy

There are no or limited amount of data from the use of nilotinib in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Tasigna should not be used during pregnancy unless the clinical condition of the woman requires treatment with nilotinib. If it is used during pregnancy, the patient must be informed of the potential risk to the foetus.

If a woman who is being treated with nilotinib is considering pregnancy, treatment discontinuation may be considered based on the eligibility criteria for discontinuing treatment as described in sections 4.2 and 4.4. There is a limited amount of data on pregnancies in patients while attempting treatment-free remission (TFR). If pregnancy is planned during the TFR phase, the patient must be informed of a potential need to re-initiate nilotinib treatment during pregnancy (see sections 4.2 and 4.4).

Breast-feeding

It is unknown whether nilotinib is excreted in human milk. Available toxicological data in animals have shown excretion of nilotinib in milk (see section 5.3). Since a risk to the newborns/infants cannot be excluded, women should not breast-feed during Tasigna treatment and for 2 weeks after the last dose.

Fertility

Animal studies did not show an effect on fertility in male and female rats (see section 5.3).

4.7 Effects on ability to drive and use machines

Tasigna has no or negligible influence on the ability to drive and use machines. However, it is recommended that patients experiencing dizziness, fatigue, visual impairment or other undesirable effects with a potential impact on the ability to drive or use machines safely should refrain from these activities as long as the undesirable effects persist (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The safety profile is based on pooled data from 3,422 patients treated with Tasigna in 13 clinical studies in the approved indications: adults patients with newly diagnosed Philadelphia chromosome positive chronic myelogenous leukaemia (CML) in the chronic phase (5 clinical studies with 2,414 patients), adult patients with chronic phase and accelerated phase Philadelphia chromosome positive CML with resistance or intolerance to prior therapy including imatinib (6 clinical studies with 939 patients). These pooled data represents 9,039.34 patient-years of exposure.

The safety profile of nilotinib is consistent across indications.

The most common adverse reactions (incidence ≥15%) from the pooled safety data were: rash (26.4%), upper respiratory tract infection (including pharyngitis, nasopharyngitis, rhinitis) (24.8%) headache (21.9%), hyperbilirubinaemia (including blood bilirubin increased) (18.6%), arthralgia (15.8%), fatigue (15.4%), nausea (16.8%), pruritus (16.7%) and thrombocytopenia (16.4%).

Tabulated list of adverse reactions

Adverse reactions from clinical studies and post-marketing reports (Table 2) are listed by MedDRA system organ class and frequency category. Frequency categories are defined using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

Table 2 Adverse drug reactions

Infections and infestations	
Very common	upper respiratory tract infection (including pharyngitis, nasopharyngitis, rhinitis)
Common:	Folliculitis, bronchitis, candidiasis (including oral candidiasis) pneumonia, gastroenteritis , Urinary tract infection,
Uncommon:	, Herpes virus infection, candidiasis (candida infection) anal abscess, furuncle, sepsis, subcutaneous abscess, tinea pedis
Rare	hepatitis B reactivation
Neoplasms benign, malignant and unspecified (including cysts and polyps)	
Uncommon:	Skin papilloma
Rare:	Oral papilloma, paraproteinaemia
Blood and lymphatic system disorders	
Very common:	Anaemia, thrombocytopenia,
Common:	Leukopenia, leukocytosis, neutropenia, thrombocythaemia
Uncommon:	Eosinophilia, febrile neutropenia, lymphopenia, pancytopenia,
Immune system disorders	
Uncommon:	Hypersensitivity
Endocrine disorders	
Common:	Hypothyroidism
Uncommon:	Hyperthyroidism,
Rare:	Hyperparathyroidism secondary, thyroiditis
Metabolism and nutrition disorders	
Common:	Electrolyte imbalance (including hypomagnesaemia, hyperkalaemia, hypokalaemia, hyponatraemia, hypocalcaemia, hypercalcaemia, hyperphosphataemia), diabetes mellitus, hyperglycaemia, hypercholesterolaemia, hyperlipidaemia, hypertriglyceridaemia decreased appetite, hypophosphataemia (including blood phosphorus decreased), gout, Hyperuricaemia,
Uncommon:	Dehydration, increased appetite, dyslipidaemia, hypoglycaemia
Rare:	appetite disorder, tumour lysis syndrome
Psychiatric disorders	
Common:	Depression, insomnia, anxiety
Uncommon	Amnesia, confusional state, disorientation
Rare:	dysphoria

Nervous system disorders	
Very common:	Headache
Common:	Dizziness, hypoaesthesia, paraesthesia, migraine
Uncommon:	Cerebrovascular accident , intracranial/cerebral haemorrhage, ischaemic stroke, transient ischaemic attack, cerebral infarction, , loss of consciousness (including syncope), tremor, disturbance in attention, hyperaesthesia, dysaesthesia, lethargy, peripheral neuropathy, restless legs syndrome, facial paralysis
Rare:	, Brain oedema, optic neuritis, basilar artery stenosis
Eye disorders	
Common:	Conjunctivitis, dry eye (including xerophthalmia), eye irritation, hyperaemia (scleral, conjunctival, ocular), vision blurred
Uncommon:	Visual impairment, conjunctival haemorrhage, visual acuity reduced, eyelid oedema, blepharitis, photopsia, conjunctivitis allergic, diplopia, eye haemorrhage, eye pain, eye pruritus, eye swelling, ocular surface disease, periorbital oedema, photophobia
Rare:	Papilloedema, chorioretinopathy,
Ear and labyrinth disorders	
Common:	Vertigo, ear pain, tinnitus
Uncommon:	Hearing impaired (hypoacusis)
Cardiac disorders	
Common:	Angina pectoris, arrhythmia (including atroventricular block, cardiac flutter, extrasystoles, tachycardia, atrial fibrillation, ventricular extrasystoles, bradycardia), palpitations, electrocardiogram QT prolonged, coronary artery disease
Uncommon:	Myocardial infarction, cardiac failure, cardiac murmur, pericardial effusion, diastolic dysfunction, left bundle branch block, pericarditis,
Rare:	Cyanosis, ejection fraction decreased
Not known:	Ventricular dysfunction,
Vascular disorders	
Common:	Hypertension, flushing, peripheral arterial occlusive disease
Uncommon:	Hypertensive crisis, intermittent claudication, peripheral artery stenosis, haematoma, arteriosclerosis, hypotension, thrombosis
Rare:	Shock haemorrhagic, arterial stenosis limb
Respiratory, thoracic and mediastinal disorders	
Very common:	Cough
Common:	Dyspnoea, dyspnoea exertional, epistaxis, oropharyngeal pain
Uncommon:	Pulmonary oedema, pleural effusion, interstitial lung disease, pleuritic pain, pleurisy, throat irritation, dysphonia, Pulmonary hypertension, wheezing
Rare:	Pharyngolaryngeal pain
Gastrointestinal disorders	
Very common	Nausea, upper abdominal pain, constipation, diarrhoea, vomiting
Common:	Pancreatitis, abdominal discomfort, abdominal distension, flatulence, abdominal pain, dyspepsia, gastritis, gastroesophageal reflux, haemorrhoids, stomatitis
Uncommon:	Gastrointestinal haemorrhage, melaena, mouth ulceration, oesophageal pain, dry mouth, sensitivity of teeth (hyperaesthesia teeth), dysgeusia, enterocolitis, gastric ulcer, gingivitis, hiatus hernia, rectal haemorrhage
Rare:	Gastrointestinal ulcer perforation, retroperitoneal haemorrhage, haematemesis, oesophagitis ulcerative, subileus.

Hepatobiliary disorders	
Very common:	Hyperbilirubinaemia (including blood bilirubin increased)
Common:	Hepatic function abnormal
Uncommon:	Hepatotoxicity, toxic hepatitis, jaundice, cholestasis, hepatomegaly
Skin and subcutaneous tissue disorders	
Very common:	Rash, pruritus, alopecia
Common:	Night sweats, eczema, urticaria, erythema, hyperhidrosis, contusion, acne, dermatitis (including allergic, exfoliative and acneiform), dry skin
Uncommon:	Exfoliative rash, drug eruption, skin pain, ecchymosis, swelling face, blister, dermal cysts, erythema nodosum, hyperkeratosis, petechiae, photosensitivity, psoriasis, skin discolouration, skin exfoliation, skin hyperpigmentation, skin hypertrophy, skin ulcer,
Rare:	Erythema multiforme, palmar-plantar erythrodysaesthesia syndrome, sebaceous hyperplasia, skin atrophy,
Musculoskeletal and connective tissue disorders	
Very common:	Myalgia, arthralgia, back pain, pain in extremity
Common:	Musculoskeletal chest pain, musculoskeletal pain, neck pain, muscular weakness, muscle spasms, bone pain
Uncommon:	Musculoskeletal stiffness, joint swelling, arthritis, flank pain,
Renal and urinary disorders	
Common:	Pollakiuria, dysuria
Uncommon:	Micturition urgency, nocturia, chromaturia, haematuria, renal failure, urinary incontinence
Reproductive system and breast disorders	
Common	Erectile dysfunction, menorrhagia
Uncommon:	Breast pain, gynaecomastia, nipple swelling
Rare:	Breast induration,
General disorders and administration site conditions	
Very common	Fatigue, pyrexia
Common:	Chest pain (including non-cardiac chest pain), pain, , chest discomfort, malaise, asthenia and oedema peripheral, chills, influenza-like illness
Uncommon:	Face oedema, gravitational oedema, feeling body temperature change (including feeling hot, feeling cold), localised oedema
Rare:	Sudden death
Investigations	
Very common:	Alanine aminotransferase increased, lipase increased,
Common:	Haemoglobin decreased, blood amylase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, gamma-glutamyltransferase increased, blood creatinine phosphokinase increased, weight decreased, weight increased, elevated creatinine, total cholesterol increased
Uncommon:	Blood lactate dehydrogenase increased, blood urea increased, blood bilirubin unconjugated increased, blood parathyroid hormone increased, blood triglycerides increased, globulins decreased, lipoprotein cholesterol (including low density and high density) increased, troponin increased
Rare	Blood glucose decreased, blood insulin decreased, blood insulin increased, insulin C-peptide decreased

Description of selected adverse reactions

Sudden death
Uncommon cases (0.1 to 1%) of sudden deaths have been reported in Tasigna clinical studies and/or compassionate use programs in patients with imatinib-resistant or intolerant CML in chronic phase or

accelerated phase with a past medical history of cardiac disease or significant cardiac risk factors (see section 4.4).

Hepatitis B reactivation
Hepatitis B reactivation has been reported in association with BCR-ABL TKIs. Some cases resulted in acute hepatic failure or fulminant hepatitis leading to liver transplantation or a fatal outcome (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il

4.9 Overdose

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, BCR-ABL tyrosine kinase inhibitors, ATC code: L01EA03
Mechanism of action

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

Pharmacodynamic effects

Nilotinib has little or no effect against the majority of other protein kinases examined, including Src, except for the PDGF, KIT and Ephrin receptor kinases, which it inhibits at concentrations within the range achieved following oral administration at therapeutic doses recommended for the treatment of CML (see Table 3).

Table 3 Kinase profile of nilotinib (phosphorylation IC_{50} nM)

BCR-ABL	PDGFR	KIT
20	69	210

Clinical efficacy

Clinical studies in newly diagnosed CML in chronic phase
An open-label, multicentre, randomised Phase III study was conducted to determine the efficacy of nilotinib versus imatinib in 846 adult patients with cytogenetically confirmed newly diagnosed Philadelphia chromosome positive CML in the chronic phase. Patients were within six months of diagnosis and were previously untreated, with the exception of hydroxyurea and/or anagrelide. Patients were randomised 1:1:1 to receive either nilotinib 300 mg twice daily (n=282), nilotinib 400 mg twice daily (n=281) or imatinib 400 mg once daily (n=283). Randomisation was stratified by Sokal risk score at the time of diagnosis.

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

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

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

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

The MMR rate at 12, 24, 36, 48, 60 and 72 months is presented in Table 4.

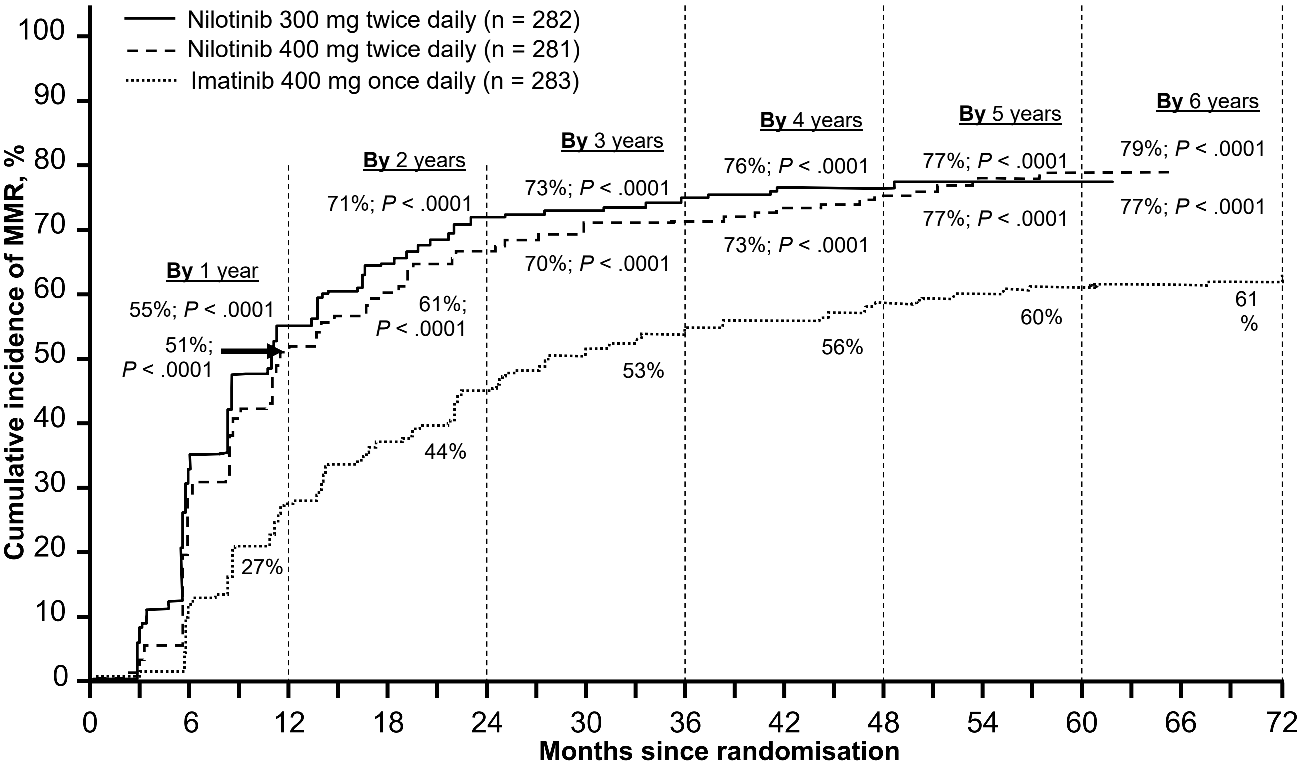
Table 4 MMR rate

	Nilotinib 300 mg twice daily n=282 (%)	Nilotinib 400 mg twice daily n=281 (%)	Imatinib 400 mg once daily n=283 (%)
MMRat 12 months			
Response (95% CI)	44.3[1] (38.4; 50.3)	42.7[1] (36.8; 48.7)	22.3 (17.6; 27.6)
MMR at 24 months			
Response (95% CI)	61.7[1] (55.8; 67.4)	59.1[1] (53.1; 64.9)	37.5 (31.8; 43.4)
MMR at 36 months[2]			
Response (95% CI)	58.5[1] (52.5; 64.3)	57.3[1] (51.3; 63.2)	38.5 (32.8; 44.5)
MMR at 48 months[3]			
Response (95% CI)	59.9[1] (54.0; 65.7)	55.2 (49.1; 61.1)	43.8 (38.0; 49.8)
MMR at 60 months[4]			
Response (95% CI)	62.8 (56.8; 68.4)	61.2 (55.2; 66.9)	49.1 (43.2; 55.1)
MMR at 72 months[5]			
Response (95% CI)	52.5 (46.5; 58.4)	57.7 (51.6; 63.5)	41.7 (35.9; 47.7)

[1] Cochran-Mantel-Haenszel (CMH) test p-value for response rate (vs. imatinib 400 mg) <0.0001
[2] Only patients who were in MMR at a specific time point are included as responders for that time point. A total of 199 (35.2%) of all patients were not evaluable for MMR at 36 months (87 in the nilotinib 300 mg twice daily group and 112 in the imatinib group) due to missing/unevaluable PCR assessments (n=17), atypical transcripts at baseline (n=7), or discontinuation prior to the 36-month time point (n=175).
[3] Only patients who were in MMR at a specific time point are included as responders for that time point. A total of 305 (36.1%) of all patients were not evaluable for MMR at 48 months (98 in the nilotinib 300 mg 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 twice daily group, 93 in the nilotinib 400 mg twice daily group and 130 in the imatinib group) due to missing/unevaluable PCR assessments (n=9), atypical transcripts at baseline (n=8) or discontinuation prior to the 60-month time point (n=305).
[5] Only patients who were in MMR at a specific time point are included as responders for that time point. A total of 395 (46.7%) of all patients were not evaluable for MMR at 72 months (130 in the nilotinib 300 mg twice daily group, 110 in the nilotinib 400 mg twice daily group and 155 in the imatinib group) due to missing/unevaluable PCR assessments (n=25), atypical transcripts at baseline (n=8) or discontinuation prior to the 72-month time point (n=362).

MMR rates by different time points (including patients who achieved MMR at or before those time points as responders) are presented in the cumulative incidence of MMR (see 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 ≤10% at 3 months of treatment compared to 67% (176/264) of patients on imatinib 400 mg once daily. Patients with BCR-ABL levels ≤10% at 3 months of treatment show a greater overall survival at 72 months compared to those who did not achieve this molecular response level (94.5% vs. 77.1% respectively [p=0.0005]).

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

The proportion of patients who had a molecular response of ≤0.01% and ≤0.0032% by IS at different time points are presented in Table 5 and the proportion of patients who had a molecular response of ≤0.01% and ≤0.0032% by IS by different time points are presented in Figures 2 and 3. Molecular responses of ≤0.01% and ≤0.0032% by IS correspond to a ≥4 log reduction and ≥4.5 log reduction, respectively, of BCR-ABL transcripts from a standardised baseline.

Table 5 Proportions of patients who had molecular response of ≤0.01% (4 log reduction) and ≤0.0032% (4.5 log reduction)

	Nilotinib 300 mg twice daily n=282 (%)		Nilotinib 400 mg twice daily n=281 (%)		Imatinib 400 mg once daily n=283 (%)	
	≤0.01%	**≤0.0032%**	**≤0.01%**	**≤ 0.0032%**	**≤0.01%**	**≤0.0032%**
At 12 months	11.7	4.3	8.5	4.6	3.9	0.4
At 24 months	24.5	12.4	22.1	7.8	10.2	2.8
At 36 months	29.4	13.8	23.8	12.1	14.1	8.1
At 48 months	33.0	16.3	29.9	17.1	19.8	10.2
At 60 months	47.9	32.3	43.4	29.5	31.1	19.8
At 72 months	44.3	31.2	45.2	28.8	27.2	18.0

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

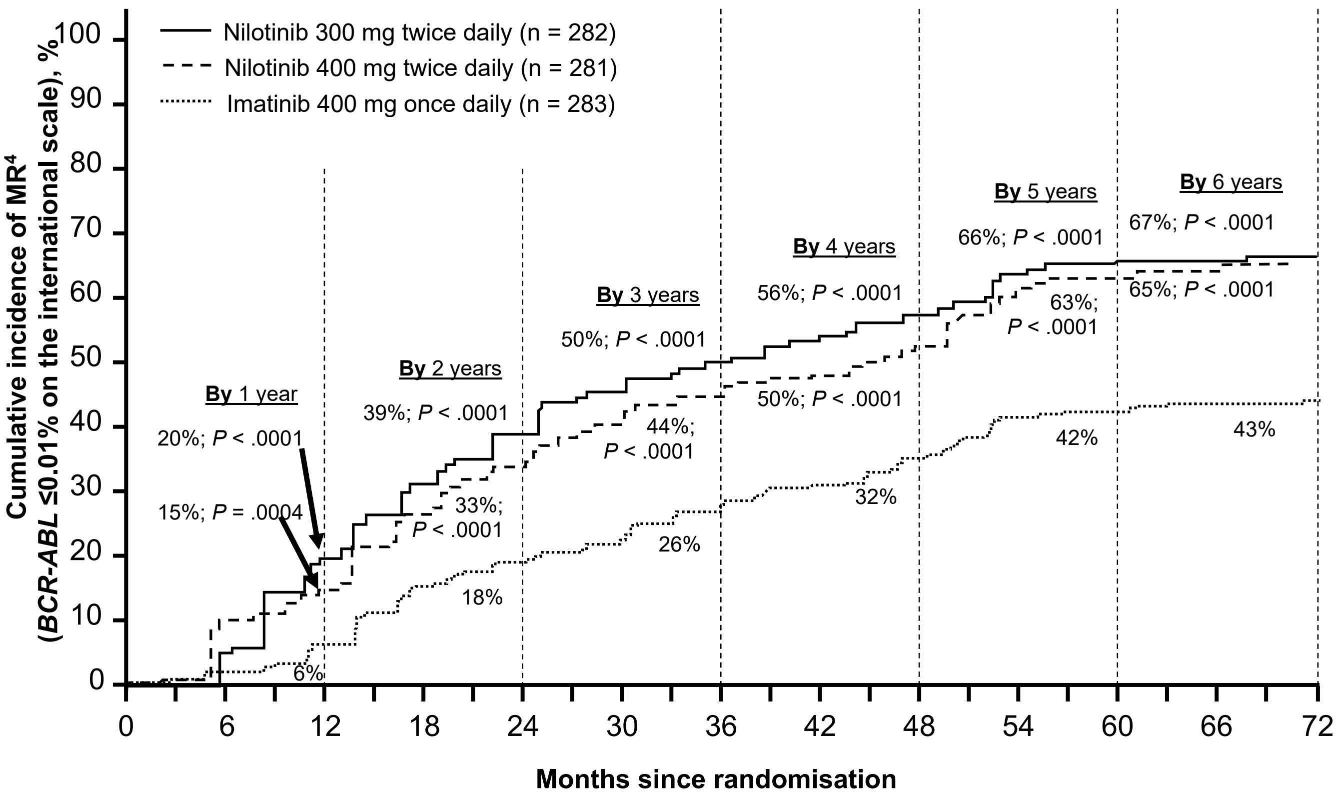
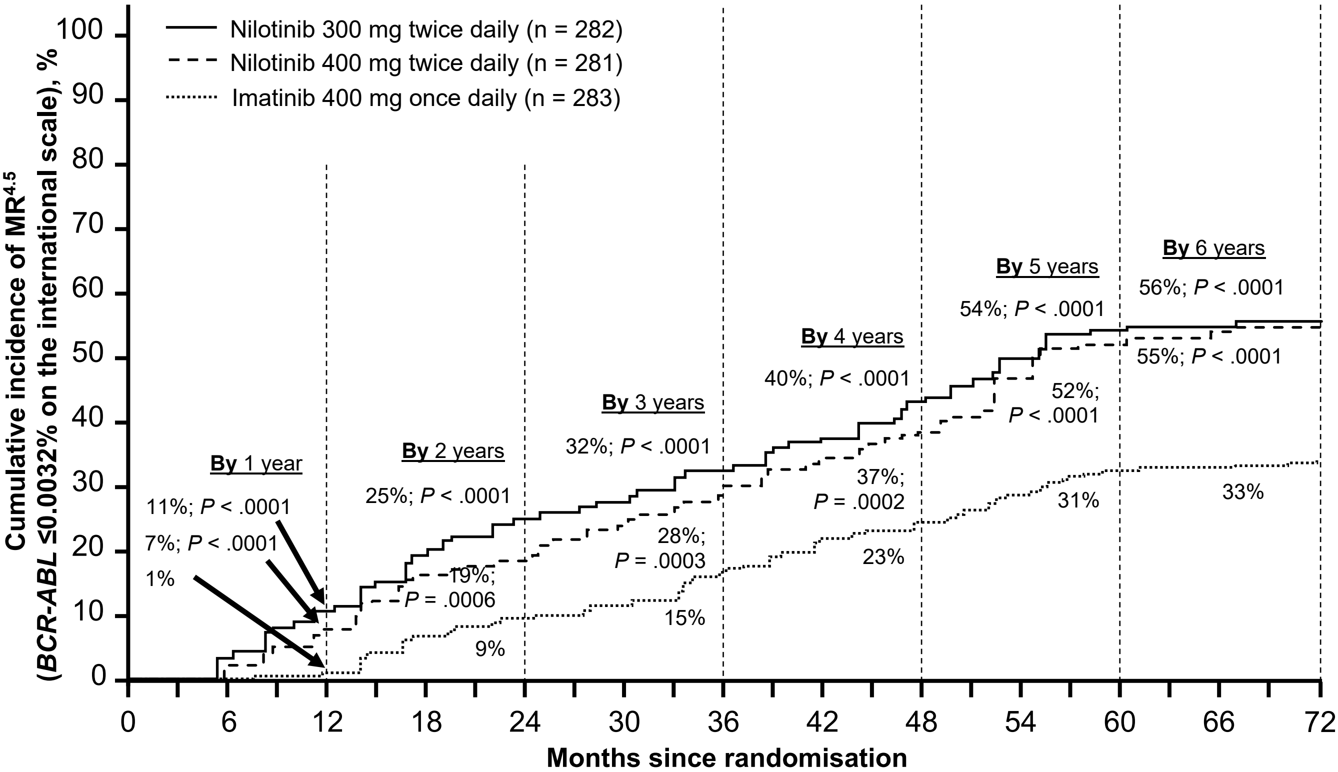


Figure 3 Cumulative incidence of molecular response of ≤0.0032% (4.5 log reduction)



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

Complete cytogenetic response (CCyR) was defined as 0% Ph+ metaphases in the bone marrow based on a minimum of 20 metaphases evaluated. Best CCyR rate by 12 months (including patients who achieved CCyR at or before the 12 month time point as responders) was statistically higher for both nilotinib 300 mg and 400 mg twice daily compared to imatinib 400 mg once daily, see Table 6.

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

Table 6 Best CCyR rate

	Nilotinib 300 mg twice daily n=282 (%)	Nilotinib 400 mg twice daily n=281 (%)	Imatinib 400 mg once daily n=283 (%)
By 12 months			
Response (95% CI)	80.1 (75.0; 84.6)	77.9 (72.6; 82.6)	65.0 (59.2; 70.6)
No response	19.9	22.1	35.0
CMH test p-value for response rate (versus imatinib 400 mg once daily)	<0.0001	0.0005	
By 24 months			
Response (95% CI)	86.9 (82.4; 90.6)	84.7 (79.9; 88.7)	77.0 (71.7; 81.8)
No response	13.1	15.3	23.0
CMH test p-value for response rate (versus imatinib 400 mg once daily)	0.0018	0.0160	

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

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

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

A total of 55 patients died during treatment or during the follow-up after discontinuation of treatment (21 in the nilotinib 300 mg twice daily group, 11 in the nilotinib 400 mg twice daily group and 23 in the imatinib 400 mg once daily group). Twenty-six (26) of these 55 deaths were related to CML (6 in the nilotinib 300 mg twice daily group, 4 in the nilotinib 400 mg twice daily group and 16 in the imatinib 400 mg once daily group). The estimated rates of patients alive at 72 months were 91.6%, 95.8% and 91.4%, respectively (HR=0.8934 and stratified log-rank p=0.7085 between nilotinib 300 mg twice daily and imatinib, HR=0.4632 and stratified log-rank p=0.0314 between nilotinib 400 mg twice daily and imatinib). Considering only CML-related deaths as events, the estimated rates of overall survival at 72 months were 97.7%, 98.5% and 93.9%, respectively (HR=0.3694 and stratified log-rank p=0.0302 between nilotinib 300 mg twice daily and imatinib, HR=0.2433 and stratified log-rank p=0.0061 between nilotinib 400 mg twice daily and imatinib).

Clinical studies in imatinib-resistant or intolerant CML in chronic phase and accelerated phase
An open-label, uncontrolled, multicentre Phase II study was conducted to determine the efficacy of

nilotinib in adult patients with imatinib resistant or intolerant CML with separate treatment arms for chronic and accelerated phase disease. Efficacy was based on 321 CP patients and 137 AP patients enrolled. Median duration of treatment was 561 days for CP patients and 264 days for AP patients (see Table 7). Tasigna was administered on a continuous basis (twice daily 2 hours after a meal and with no food for at least one hour after administration) unless there was evidence of inadequate response or disease progression. The dose was 400 mg twice daily and dose escalation to 600 mg twice daily was allowed.

Table 7 Duration of exposure with nilotinib

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

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

Overall, 73% of patients were imatinib-resistant, while 27% were imatinib-intolerant. The majority of patients had a long history of CML that included extensive prior treatment with other antineoplastic agents, including imatinib, hydroxyurea, interferon, and some had even failed organ transplant (Table 8). The median highest prior imatinib dose had been 600 mg/day. The highest prior imatinib dose was ≥600 mg/day in 74% of all patients, with 40% of patients receiving imatinib doses ≥800 mg/day.

Table 8 CML disease history characteristics

	Chronic phase (n=321)	Accelerated phase (n=137)*
Median time since diagnosis in months (range)	58 (5–275)	71 (2–298)
Imatinib Resistant Intolerant without MCyR	 226 (70%) 95 (30%)	 109 (80%) 27 (20%)
Median time of imatinib treatment in days (25^{th}-75^{th} percentiles)	975 (519-1,488)	857 (424-1,497)
Prior hydroxyurea	83%	91%
Prior interferon	58%	50%
Prior bone marrow transplant	7%	8%

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

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

Chronic phase
The MCyR rate in 321 CP patients was 51%. Most responders achieved their MCyR rapidly within 3 months (median 2.8 months) of starting nilotinib treatment and these were sustained. The median

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

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

The rates of response for the two treatment arms are reported in Table 9.

Table 9 Response in CML

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

NEL = no evidence of leukaemia/marrow response
[1] 114 CP patients had a CHR at baseline and were therefore not assessable for complete haematological response
* Missing information on imatinib-resistant/intolerant status for one patient.

Efficacy data in patients with CML-BC are not yet available. Separate treatment arms were also included in the Phase II study to investigate 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. Of these patients 30/36 (83%) were treatment resistant not intolerant. In 22 CP patients evaluated for efficacy nilotinib induced a 32% MCyR rate and a 50% CHR rate. In 11 AP patients, evaluated for efficacy, treatment induced a 36% overall HR rate.

After imatinib failure, 24 different BCR-ABL mutations were noted in 42% of chronic phase and 54% of accelerated phase CML patients who were evaluated for mutations. Tasigna demonstrated efficacy in patients harboring a variety of BCR-ABL mutations associated with imatinib resistance, except T315I.

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

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

- the 4 last quarterly assessments (taken every 12 weeks) were at least MR4.0 (BCR-ABL/ABL ≤0.01% IS), and maintained for one year
- the last assessment being MR4.5 (BCR-ABL/ABL ≤0.0032% IS)
- no more than two assessments falling between MR4.0 and MR4.5 (0.0032% IS < BCR-ABL/ABL ≤0.01% IS).

The primary endpoint was the percentage of patients in MMR at 48 weeks after starting the TFR phase (considering any patient who required re-initiation of treatment as non-responder).

Table 10 Treatment-free remission after nilotinib first-line treatment

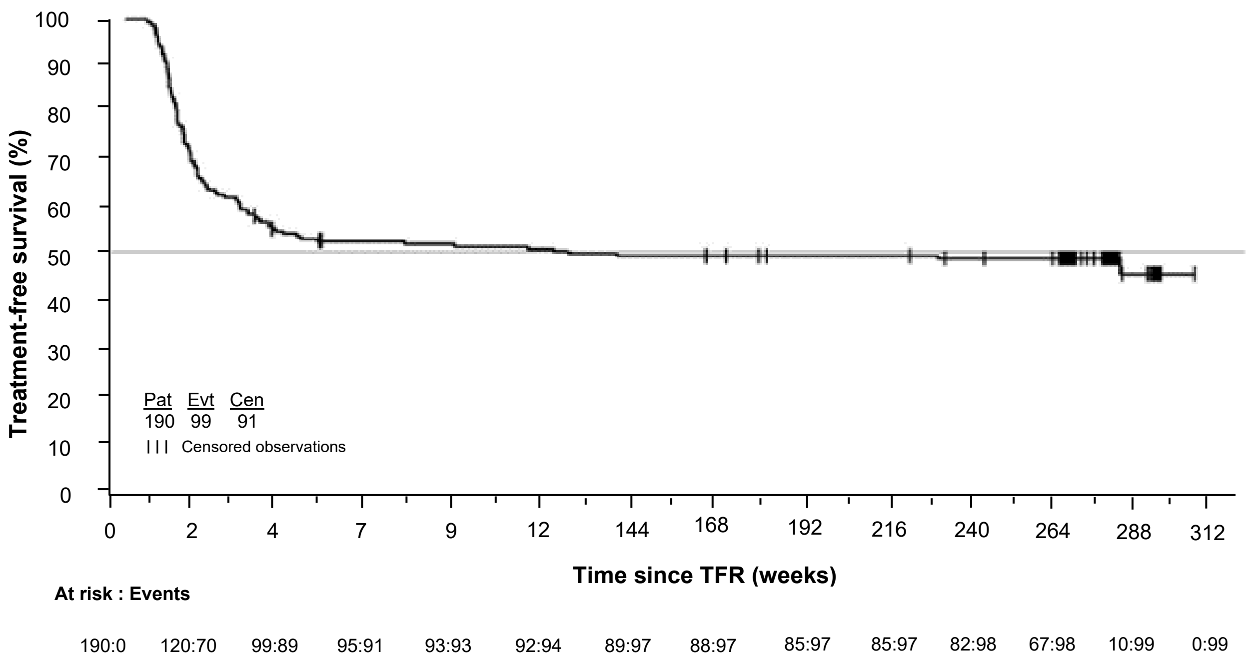
Patients entered TFR phase	190	
weeks after starting TFR phase	48 weeks	264 weeks
patients remaining in MMR or better	98 (51.6%, [95% CI: 44.2, 58.9])	79[2] (41.6%, 95% CI: 34.5, 48.9)
Patients discontinued TFR phase	93 [1]	109
due to loss of MMR	88 (46.3%)	94 (49.5%)
due to other reasons	5	15
Patients restarted treatment after loss of MMR	86	91
regaining MMR	85 (98.8%)	90 (98.9%)
regaining MR4.5	76 (88.4%)	84 (92,3%)

[1] One patient did not lose MMR by week 48 but discontinued TFR phase.
[2] For 2 patients, PCR assessment was not available at week 264 therefore their response was not considered for the week 264 data cut-off analysis.

The time by which 50% of all retreated patients regained MMR and MR4.5 was 7 and 12.9 weeks, respectively. The cumulative rate of MMR regained at 24 weeks after treatment re-initiation was 97.8% (89/91 patients) and MR4.5 regained at 48 weeks was 91.2% (83/91 patients).

The Kaplan-Meier estimate of median treatment-free survival (TFS) was 120.1 weeks (95% CI: 36.9, not estimable [NE]) (Figure 4); 91 of 190 patients (47.9%) did not have a TFS event.

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



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

In an open-label, single-arm study, 163 adult patients with Ph+ CML in chronic phase taking tyrosine kinase inhibitors (TKIs) for ≥3 years (imatinib as initial TKI therapy for more than 4 weeks without documented MR4.5 on imatinib at the time of switch to nilotinib, then switched to nilotinib for at least two years), and who achieved MR4.5 on nilotinib treatment as measured with the MolecularMD MRDx BCR-ABL test were enrolled to continue nilotinib treatment for additional 52 weeks (nilotinib consolidation phase). 126 of 163 patients (77.3%) entered the TFR phase after achieving a sustained deep molecular response during the consolidation phase, defined by the following criterion:

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

The primary endpoint was the proportion of patients without confirmed loss of MR4.0 or loss of MMR within 48 weeks following treatment discontinuation.

Table 11 Treatment-free remission after nilotinib treatment following prior imatinib therapy

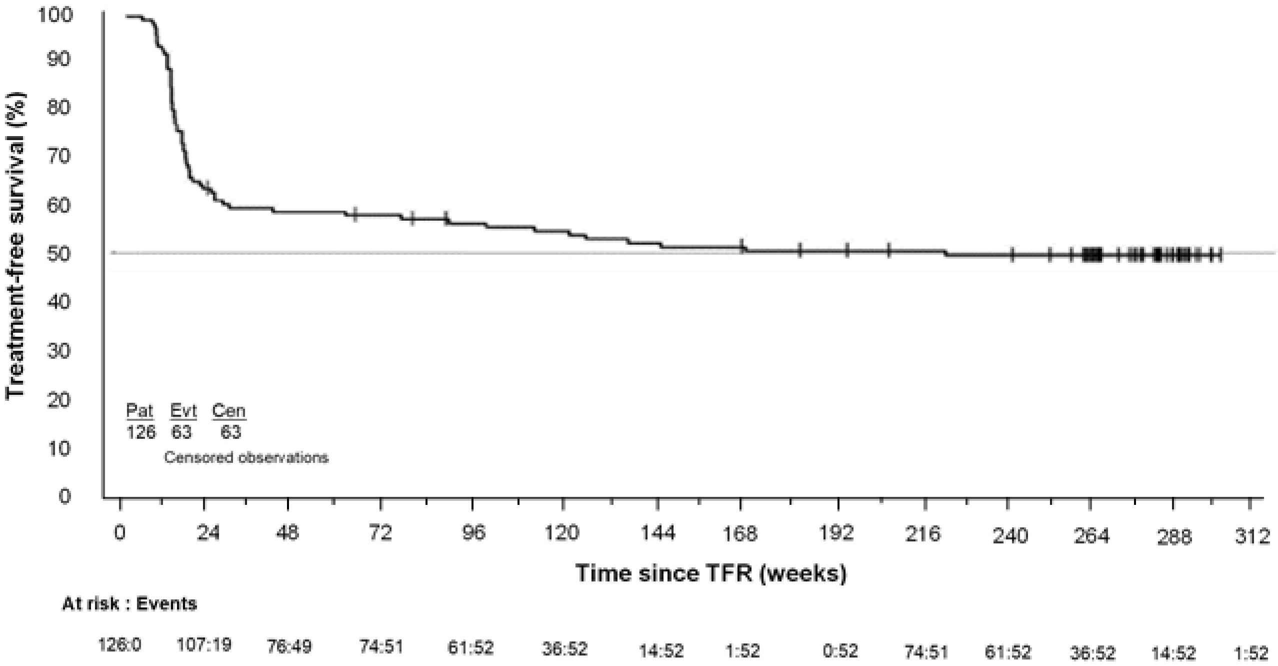
Patients entered TFR phase	126	
weeks after starting TFR phase	48 weeks	264 weeks
patients remaining in MMR, no confirmed loss of MR4.0, and no re-initiation of nilotinib	73 (57.9%, [95% CI: 48.8, 66.7])	54 (42.9% [54/126, 95% CI: 34.1, 52.0])
Patients discontinued TFR Phase	53	74 [1]
due to confirmed loss of MR4.0 or loss of MMR	53 (42.1%)	61 (82.4%)
due to other reasons	0	13
Patients restarted treatment after loss of MMR or confirmed loss of MR4.0	51	59
regaining MR4.0	48 (94.1%)	56 (94.9%)
regaining MR4.5	47 (92.2%)	54 (91.5%)

[1] two patients had MMR (PCR assessment) at 264 weeks but were discontinued later and had no further PCR assessment.

The Kaplan-Meier estimated median time on nilotinib to regain MR4.0 and MR4.5 was 11.1 weeks (95% CI:8.1, 12.1) and 13.1 weeks (95% CI:12.0, 15.9), respectively. The cumulative rate of MR4 and MR4.5 regained by 48 weeks after treatment re-initiation was 94.9% (56/59 patients) and 91.5% (54/59 patients), respectively.

The median TFS Kaplan-Meier estimate is 224 weeks (95% CI: 39.9, NE) (Figure 5); 63 of 126 patients (50.0%) did not have a TFS event.

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



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5.2 Pharmacokinetic properties

Absorption

Peak concentrations of nilotinib are reached 3 hours after oral administration. Nilotinib absorption following oral administration was approximately 30%. The absolute bioavailability of nilotinib has not been determined. As compared to an oral drink solution (pH of 1.2 to 1.3), relative bioavailability of nilotinib capsule is approximately 50%. In healthy volunteers, C_{max} and area under the serum concentration-time curve (AUC) of nilotinib are increased by 112% and 82%, respectively, compared to fasting conditions when 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 sections 4.2, 4.4 and 4.5).

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

Distribution

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

Biotransformation

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

Elimination

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

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

Linearity/non-linearity

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

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

Bioavailability/bioequivalence studies

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

5.3 Preclinical safety data

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

Safety pharmacology studies

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

Repeated-dose toxicity studies

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

Genotoxicity studies

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

Carcinogenicity studies

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

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

Reproductive toxicity and fertility studies

Nilotinib did not induce teratogenicity, but did show embryo- and foetotoxicity at doses that also showed maternal toxicity. Increased post-implantation loss was observed in both the fertility study, which involved treatment of both males and females, and the embryotoxicity study, which involved treatment of females. Embryo-lethality and foetal effects (mainly decreased foetal weights, premature fusion of the facial bones (fused maxilla/zygomatic) visceral and skeletal variations) in rats and increased resorption of foetuses and skeletal variations in rabbits were present in the embryotoxicity studies. In a pre- and postnatal development study in rats, maternal exposure to nilotinib caused reduced pup body weight with associated changes in physical development parameters as well as reduced mating and fertility indices in the offspring. Exposure to nilotinib in females at No-Observed-Adverse-Effect-Levels was generally less or equal to that in humans at 800 mg/day.

No effects on sperm count/motility or on fertility were noted in male and female rats up to the highest tested dose, approximately 5 times the recommended dosage for humans.

Juvenile animal studies

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

Phototoxicity studies

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tasigna 150mg capsules
Capsule content: lactose monohydrate, crospovidone, poloxamer 188, silica colloidal anhydrous, magnesium stearate.

Capsule shell: gelatin, titanium dioxide (E171), iron oxide red, (E172), iron oxide yellow (E172).
Printing ink, black: Shellac, iron oxide black, N-butyl alcohol, purified water, propylene glycol, dehydrated ethanol, isopropyl alcohol, ammonium hydroxide.

Tasigna 200mg capsules
Capsule content: Lactose monohydrate, crospovidone, poloxamer 188, silica colloidal anhydrous, magnesium stearate

Capsule shell: gelatin, titanium dioxide (E171), iron oxide yellow (E172)
Printing ink, red:
Printing ink a: Shellac, dehydrated alcohol, isopropyl alcohol, butyl alcohol, propylene glycol, strong ammonia solution, iron oxide red (E172), potassium hydroxide, purified water.
Printing ink b: Shellac, iron oxide red (E172), iron oxide black (E172), n-butyl alcohol, purified water, titanium dioxide (E171), propylene glycol, industrial methylated spirit, isopropyl alcohol.
The printing ink used is ‘Printing ink a’ or alternatively ‘Printing ink b’.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Do not store above 30°C.

Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

PVC/PVDC/Alu blisters.

Tasigna 150mg is available in the following pack sizes:
- Multipacks containing 112 (4 packs of 28) capsules

Tasigna 200mg is available in the following pack sizes:
- Multipacks containing 120 (3 packs of 40) capsules

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. REGISTRATION HOLDER AND IMPORTER AND IT'S ADDRESS

Novartis Israel Ltd.
P.O.B. 7126, Tel Aviv

8. REGISTRATION NUMBERS

Tasigna 150 mg : 145 84 33271
Tasigna 200 mg : 138 17 31681

Revised in September 2022 according to MOH guidelines.