SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
DAFANIB 70 mg film coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Active substance:
Dasatinib (anhydrous) ..... 70 mg

Excipients:
Lactose monohydrate (derived from cow's milk) ..... 89.25 mg

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Film-coated tablets
White to off-white, biconvex, round film-coated tablets

4. CLINICAL PARTICULARS
4.1. Therapeutic indications
DAFANIB is indicated for the treatment of adult patients with the following conditions:
- Newly diagnosed Philadelphia chromosome positive chronic myelogenous leukemia (CML) in the chronic phase.
- Philadelphia chromosome positive chronic, accelerated or blast phase chronic myelogenous leukemia with resistance or intolerance to prior therapy including imatinib.
- For the induction of remission in combination with multi-agent chemotherapy regimens in the treatment of adult patients with relapsed/refractory Philadelphia chromosome positive (Ph+) ALL (acute lymphoblastic leukemia).

DAFANIB is indicated for the treatment of pediatric patients with the following conditions:
- Newly diagnosed Ph+ CML in chronic phase (Ph+ CML-CP) or Ph+ CML-CP resistant or intolerant to prior therapy including imatinib.
- Newly diagnosed Ph^+ ALL in combination with chemotherapy.

4.2. Posology and method of administration
Treatment should be initiated by a doctor experienced in diagnosis and treatment of leukemia.

Posology/frequency and duration of administration:
Adult patients
The recommended starting dose of DAFANIB in chronic-phase CML is 100 mg administered orally once daily, either in the morning or evening. To achieve the recommended dosage, DAFANIB is available as 20 mg, 50 mg, 70 mg, and 100 mg film-coated tablets (see sections 4.4, 4.8, and 5.1). A Phase III dose optimization study in chronic-phase CML patients found a lower incidence of pleural effusion, congestive heart failure/cardiac dysfunction, and myelosuppression in patients treated with 100 mg dasatinib once daily, so the starting dose in this patient group is 100 mg once daily.

The tablets should be taken regularly in the morning or evening.

The starting dosage of DAFANIB for accelerated, myeloid, or lymphoid blast phase (advanced phase) CML or Ph+ ALL is 70 mg administered orally twice daily, one tablet in the morning and one tablet

in the evening (see sections 4.8 and 5.1).

The dose may be increased or decreased depending on the patient's response and tolerance.

Frequency and duration of administration:
In clinical studies conducted in adult patients with Ph+ chronic-phase CML, accelerated, myeloid, or lymphoid blast (advanced-phase) CML, or Ph+ ALL, and in pediatric patients with Ph+ chronic-phase CML, dasatinib treatment was continued until disease progression or intolerance. The impact of discontinuing treatment after achieving a cytogenetic or molecular response (such as complete cytogenetic response (CCyR), major molecular response (MMR), and MR4.5) on long-term disease outcome has not been studied.

In clinical studies, dasatinib treatment was administered continuously in pediatric patients with Ph+ ALL and was added to the main sequential chemotherapy blocks for a maximum of two years. In patients who subsequently underwent stem cell transplantation, dasatinib could be administered for an additional year after transplantation.

To achieve the recommended dose, DAFANIB is available as 20 mg, 50 mg, 70 mg, 80 mg, 100 mg, and 140 mg film-coated tablets. It is recommended that the dose be reduced or increased based on patient response and tolerability.

Method of administration:
Administered orally. To reduce the risk of skin exposure, tablets should not be crushed or cut; they should be swallowed whole. DAFANIB can be taken with or on an empty stomach. In chronic-phase CML, the daily dose should be taken regularly in the morning or evening. In advanced-phase CML, the daily dose should be taken twice daily, in the morning and evening. Film-coated tablets should not be dissolved, as exposure is lower in patients taking dissolved tablets compared to patients taking the tablets whole.

DAFANIB can be taken with or without food and should be taken regularly in the morning or evening.
DAFANIB should not be taken with grapefruit or grapefruit juice (see Section 4.5).

Dose escalation:
In clinical studies conducted in adult chronic-phase CML and Ph+ ALL patients, dose escalation to 140 mg once daily (chronic-phase CML) or 180 mg once daily (advanced-phase CML or Ph+ ALL) was permitted in patients who failed to respond hematologically or cytogenetically at the recommended starting dose.

According to current treatment guidelines, the dose escalations indicated in Table 1 below are recommended for pediatric Ph+ chronic-phase CML patients who failed to respond hematologically, cytogenetically, or molecularly at the recommended time and tolerated treatment.

Table 1: Dose escalation for pediatric patients with Ph+ CML-CP

	Dose (maximum dose per day)	
	Starting dose	**Escalation**
Tablets	40 mg	50 mg
	60 mg	70 mg
	70 mg	90 mg

	100 mg	120 mg

Dose escalation is not recommended for pediatric patients with Ph+ ALL, as DAFANIB is administered in combination with chemotherapy in these patients.

Dose adjustment for adverse reactions:

Myelosuppression:
In clinical studies, myelosuppression was managed by dose interruption, dose reduction, or discontinuation of study therapy. Platelet transfusion and red cell transfusion were used as appropriate. Hematopoietic growth factor has been used in patients with resistant myelosuppression.

Guidelines for dose modifications in adults are summarized in Table 2 and in pediatric patients with Ph+ CML-CP in Table 3. Guidelines for paediatric patients with Ph^+ ALL treated in combination with chemotherapy are in a separate paragraph following the tables.

Table 2: Dosage adjustments in neutropenia and thrombocytopenia in adults

Adults with chronic phase CML (initial dose 100 mg once daily)	ANC < 0.5 x 10^9 /L and/or platelets < 50 x 10^9 /L	**1.** Stop treatment until ANC ≥ 1.0 x 10^9/L and platelets ≥ 50 x 10^9/L. **2.** Resume treatment at the original initial dose. **3.** If platelets < 25 x 10^9/L and/or recurrence of ANC < 0.5 x 10^9/L for > 7 days, repeat step 1 and resume treatment at a reduced dose of 80 mg once daily for second episode. For third episode, further reduce dose to 50 mg once daily (for newly diagnosed patients) or discontinue (for patients resistant or intolerant to prior therapy including imatinib).
Adults with accelerated and blast phase CML and Ph+ ALL (initial dose 70 mg twice daily)	ANC < 0.5 x 10^9 /L and/or platelets < 10 x 10^9 /L	**1.** Check if cytopenia is related to leukemia (marrow aspirate or biopsy). **2.** If cytopenia is unrelated to leukemia, stop treatment until ANC ≥ 1.0 x 10^9/L and platelets ≥ 20 x 10^9 /L and resume at the original initial dose. **3.** If recurrence of cytopenia, repeat step 1 and resume treatment at a reduced dose of 50 mg twice daily (second episode) or 40 mg twice daily (third episode). **4.** If cytopenia is related to leukemia, consider dose escalation to 180 mg once daily.
ANC: absolute neutrophil count		

Table 3: Dose adjustments in neutropenia and thrombocytopenia in pediatric patients with Ph+ CML-CP

		Dose (maximum dose per day)		
		Original initial dose	**One-level dose reduction**	**Two-level dose reduction**
1. If cytopenia persists for more than 3 weeks, check if cytopenia is related to leukemia (marrow aspirate or biopsy). **2.** If cytopenia is unrelated to leukemia, stop treatment until ANC ≥ 1.0 x 10^9/L and platelets ≥ 75 x 10^9 /L and resume at the original initial dose or at a reduced dose.	**Tablets**	40 mg	20 mg	*
		60 mg	40 mg	20 mg
		70 mg	60 mg	50 mg

3. If cytopenia recurs, repeat bone marrow aspirate/biopsy and		100 mg	80 mg	70 mg
ANC: absolute neutrophil count *lower tablet dose not available				

For pediatric patients with Ph+ CML-CP, if Grade ≥3 neutropenia or thrombocytopenia recurs during complete hematologic response, DAFANIB should be interrupted, and may be subsequently resumed at a reduced dose. Temporary dose reductions for intermediate degrees of cytopenia and disease response should be implemented as needed.

For pediatric patients with Ph+ ALL, no dose modification is recommended in cases of hematologic Grade 1 to 4 toxicities. If neutropenia and/or thrombocytopenia result in delay of the next block of treatment by more than 14 days, DAFANIB should be interrupted and resumed at the same dose level once the next block of treatment is started. If neutropenia and/or thrombocytopenia persist and the next block of treatment is delayed another 7 days, a bone marrow assessment should be performed to assess cellularity and percentage of blasts. If marrow cellularity is <10%, treatment with DAFANIB should be interrupted until ANC >500/µL (0.5×10^9 /L), at which time treatment may be resumed at full dose. If marrow cellularity is >10%, resumption of treatment with DAFANIB may be considered.

Non-hematologic adverse reactions:
If a moderate, grade 2, non-hematologic adverse reaction develops with DAFANIB, treatment should be interrupted until the adverse reaction has resolved or returned to baseline. The same dose should be resumed if this is the first occurrence and the dose should be reduced if this is a recurrent adverse reaction. If a severe grade 3 or 4, non-hematologic adverse reaction develops with dasatinib, treatment must be withheld until the adverse reaction has resolved. Thereafter, treatment can be resumed as appropriate at a reduced dose depending on the initial severity of the adverse reaction. For patients with chronic phase CML who received 100 mg once daily, dose reduction to 80 mg once daily with further reduction from 80 mg once daily to 50 mg once daily, if needed, is recommended. For patients with advanced phase CML or Ph^+ ALL who received 140 mg once daily, dose reduction to 100 mg once daily with further reduction from 100 mg once daily to 50 mg once daily, if needed, is recommended.

In CML-CP pediatric patients with non-hematologic adverse reactions, the dose reduction recommendations for hematologic adverse reactions described above should be followed.
In Ph+ ALL pediatric patients with non-hematologic adverse reactions, if needed, one level of dose reduction should be followed, according to the dose reduction recommendations for hematologic adverse reactions that are described above.

Pleural effusion:
If a pleural effusion is diagnosed, dasatinib should be interrupted until patient is examined, asymptomatic or has returned to baseline. If the episode does not improve within approximately one week, a course of diuretics or corticosteroids or both concurrently should be considered (see sections 4.4 and 4.8). Following resolution of the first episode, reintroduction of dasatinib at the same dose level should be considered. Following resolution of a subsequent episode, dasatinib at one dose level reduction should be reintroduced. Following resolution of a severe (grade 3 or 4) episode, treatment can be resumed as appropriate at a reduced dose depending on initial severity of adverse reaction.

Dose reduction for concomitant use of strong CYP3A4 inhibitors
The concomitant use of strong CYP3A4 inhibitors and grapefruit juice with DAFANIB should be

avoided (see section 4.5). If possible, an alternative concomitant medication with no or minimal enzyme inhibition potential should be selected. If DAFANIB must be administered with a strong CYP3A4 inhibitor, consider a dose decrease to:

- 40 mg daily for patients taking DAFANIB 140 mg tablet daily.
- 20 mg daily for patients taking DAFANIB 100 mg tablet daily.
- 20 mg daily for patients taking DAFANIB 70 mg tablet daily.

For patients taking DAFANIB 60 mg or 40 mg daily, consider interrupting the dose of DAFANIB until the CYP3A4 inhibitor is discontinued. Allow a washout period of approximately 1 week after the inhibitor is stopped before reinitiating DAFANIB.

These reduced doses of DAFANIB are predicted to adjust the area under the curve (AUC) to the range observed without CYP3A4 inhibitors; however, clinical data are not available with these dose adjustments in patients receiving strong CYP3A4 inhibitors. If DAFANIB is not tolerated after dose reduction, either discontinue the strong CYP3A4 inhibitor or interrupt DAFANIB until the inhibitor is discontinued. Allow a washout period of approximately 1 week after the inhibitor is stopped before the DAFANIB dose is increased.

Additional information on special populations
Renal impairment:
No clinical studies were conducted with dasatinib in patients with decreased renal function (the study in patients with newly diagnosed chronic phase CML excluded patients with serum creatinine concentration > 3 times the upper limit of the normal range, and studies in patients with chronic phase CML with resistance or intolerance to prior imatinib therapy excluded patients with serum creatinine concentration > 1.5 times the upper limit of the normal range). Since the renal clearance of dasatinib and its metabolites is < 4%, a decrease in total body clearance is not expected in patients with renal insufficiency.

Hepatic impairment:
Patients with mild, moderate and severe hepatic impairment may receive the recommended initial dose. However, DAFANIB should be used with caution in patients with hepatic impairment (see sections 4.4 and 5.2).

Pediatric population (Ph+ CML-CP and Ph+ ALL):
Dosing for children and adolescents is based on body weight (see Table 1). Dasatinib is administered orally once daily in the form of DAFANIB film-coated tablets. The dose should be recalculated every 3 months based on changes in body weight, or more often if necessary. The tablet form is not recommended for patients weighing less than 10 kg. Dose increase or reduction is recommended based on individual patient response and tolerability. There is no experience with the use of DAFANIB in children under 1 year of age.

Initial recommended daily dose of DAFANIB tablets in pediatric patients is shown in Table 4.

Table 4: Dosage of DAFANIB tablets for pediatric patients with Ph+ CML-CP or Ph+ ALL

Body weight (kg)[a]	Daily dose (mg)
10 to less than 20 kg	40 mg
20 to less than 30 kg	60 mg
30 to less than 45 kg	70 mg
at least 45 kg	100 mg
[a] The tablet is not recommended for patients weighing less than 10 kg.	

It should be taken into consideration that the film-coated tablet form carries a risk of swallowing difficulties in younger age groups.

Geriatric population:
No clinically significant age-related pharmacokinetic differences have been observed in this patient population. No specific dose recommendation is necessary in elderly.

4.3. Contraindications
Contraindicated in case of allergy to dasatinib or other components of the drug (see section 6.1).

4.4. Special warnings and precautions for use

Clinically relevant interactions

Dasatinib is a substrate and an inhibitor of cytochrome P450 (CYP) 3A4. Therefore, there is a potential for interaction with other concomitantly administered medicinal products that are metabolized primarily by or modulate the activity of CYP3A4 (see section 4.5).

Concomitant use of dasatinib and medicinal products or substances that potently inhibit CYP3A4 (e.g. ketoconazole, itraconazole, erythromycin, clarithromycin, ritonavir, telithromycin, grapefruit juice) may increase the efficacy of dasatinib. Therefore, in patients receiving DAFANIB, co-administration of a potent CYP3A4 inhibitor is not recommended (see section 4.5).

Concomitant use of dasatinib and medicinal products that induce CYP3A4 (e.g. dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital or herbal preparations containing *Hypericum perforatum*, also known as St. John's Wort) may substantially reduce exposure to dasatinib, potentially increasing the risk of therapeutic failure. Therefore, in patients receiving DAFANIB, co-administration of alternative medicinal products with less potential for CYP3A4 induction should be selected (see section 4.5).

Concomitant use of dasatinib and a CYP3A4 substrate may increase exposure to the CYP3A4 substrate (see section 4.5). Therefore, concomitant administration of DAFANIB with CYP3A4 substrates with a narrow therapeutic index, such as astemizole, terfenadine, cisapride, pimozide, quinidine, bepridil or ergot alkaloids (ergotamine, dihydroergotamine), requires caution (see section 4.5).

The concomitant use of dasatinib and a histamine-2 (H_2) antagonist (e.g. famotidine), proton pump inhibitor (e.g. omeprazole), or aluminum hydroxide/magnesium hydroxide may reduce the exposure to dasatinib. Thus, H_2 antagonists and proton pump inhibitors are not recommended and aluminum hydroxide/magnesium hydroxide products should be administered up to 2 hours prior to, or 2 hours following the administration of dasatinib (see section 4.5).

Special populations
Based on the findings from a single-dose pharmacokinetic study, patients with mild, moderate or severe hepatic impairment may receive the recommended initial dose (see section 5.2). Due to the limitations of this clinical study, caution is recommended when administering dasatinib to patients with hepatic impairment.

Important adverse drug reactions
Myelosuppression

Treatment with dasatinib is associated with anemia, neutropenia and thrombocytopenia. Their occurrence is earlier and more frequent in patients with advanced phase CML or Ph+ ALL than in chronic phase CML. Complete blood counts should be performed weekly for the first two months, then monthly or more frequently if clinically indicated. In adult and pediatric patients with chronic phase CML, complete blood counts should be performed every 2 weeks for 12 weeks, then every 3 months thereafter or as clinically indicated.

Myelosuppression is generally reversible and usually managed by withholding dasatinib temporarily or by dose reduction. In pediatric patients with Ph+ ALL treated with dasatinib in combination with chemotherapy, CBCs should be performed prior to the start of each block of chemotherapy and as clinically indicated. During the consolidation blocks of chemotherapy, CBCs should be performed every 2 days until recovery (see sections 4.2 and 4.8).

Bleeding
In patients with chronic phase CML (n=548), 5 patients (1%) receiving dasatinib had grade 3 or 4 hemorrhage. In clinical studies in patients with advanced phase CML receiving the recommended dose of dasatinib (n=304), severe central nervous system (CNS) hemorrhage occurred in 1% of patients. One case was fatal and was associated with Common Toxicity Criteria (CTC) grade 4 thrombocytopenia. Grade 3 or 4 gastrointestinal hemorrhage occurred in 6% of patients with advanced phase CML and generally required treatment interruptions and transfusions. Other grade 3 or 4 hemorrhage occurred in 2% of patients with advanced phase CML. Most bleeding related adverse reactions in these patients were typically associated with grade 3 or 4 thrombocytopenia (see section 4.8). Additionally, *in vitro* and *in vivo* platelet assays suggest that dasatinib treatment reversibly affects platelet activation.

Caution should be exercised if patients are required to take medicinal products that inhibit platelet function or anticoagulants.

Fluid retention
Dasatinib is associated with fluid retention. In the Phase III clinical study in patients with newly diagnosed chronic phase CML, grade 3 or 4 fluid retention was reported in 13 patients (5%) in the dasatinib-treatment group and in 2 patients (1%) in the imatinib-treatment group after a minimum of 60 months follow-up (see section 4.8). In all dasatinib treated patients with chronic phase CML, severe fluid retention occurred in 32 patients (6%) receiving dasatinib at the recommended dose (n=548). In clinical studies in patients with advanced phase CML or Ph+ ALL receiving dasatinib at the recommended dose (n=304), grade 3 or 4 fluid retention was reported in 8% of patients, including grade 3 or 4 pleural and pericardial effusion reported in 7% and 1% of patients, respectively. In these patients grade 3 or 4 pulmonary edema and pulmonary hypertension were each reported in 1% of patients.

Patients who develop symptoms suggestive of pleural effusion such as dyspnea or dry cough should be evaluated by chest X-ray. Grade 3 or 4 pleural effusion may require thoracocentesis and oxygen therapy. Fluid retention adverse reactions were typically managed by supportive care measures that include diuretics and short courses of steroids. Patients aged 65 years and older are more likely than younger patients to experience pleural effusion, dyspnea, cough, pericardial effusion and congestive heart failure, and should be monitored closely. Cases of chylothorax have also been reported in patients presenting with pleural effusion (see section 4.8).

Pulmonary arterial hypertension (PAH)

PAH (pre-capillary pulmonary arterial hypertension confirmed by right heart catheterization) has been reported in association with dasatinib treatment (see section 4.8). In these cases, PAH was reported after initiation of dasatinib therapy, including after more than 1 year of treatment.

Patients should be evaluated for signs and symptoms of underlying cardiopulmonary disease prior to initiating dasatinib therapy. An echocardiography should be performed at treatment initiation in every patient presenting symptoms of cardiac disease and considered in patients with risk factors for cardiac or pulmonary disease. Patients who develop dyspnea and fatigue after initiation of therapy should be evaluated for common etiologies including pleural effusion, pulmonary edema, anemia, or lung infiltration. In accordance with recommendations for management of non-hematologic adverse reactions (see section 4.2) the dose of dasatinib should be reduced or therapy interrupted during this evaluation. If no explanation is found, or if there is no improvement with dose reduction or interruption, the diagnosis of PAH should be considered. The diagnostic approach should follow standard practice guidelines. If PAH is confirmed, dasatinib should be permanently discontinued. Follow up should be performed according to standard practice guidelines. Improvements in hemodynamic and clinical parameters have been observed in dasatinib-treated patients with PAH following cessation of dasatinib therapy.

QT Prolongation
In vitro data suggest that dasatinib has the potential to prolong cardiac ventricular repolarisation (QT interval) (see section 5.3). In 258 dasatinib-treated patients and 258 imatinib-treated patients with a minimum of 60 months follow-up in the Phase III study in newly diagnosed chronic phase CML, 1 patient (< 1%) in each group had QTc prolongation reported as an adverse reaction. The median changes in QTcF from baseline were 3 msec in dasatinib-treated patients compared to 8.2 msec in imatinib-treated patients. One patient (< 1%) in each group experienced a QTcF > 500 msec. In 865 patients with leukemia treated with dasatinib in Phase II clinical studies, the mean changes from baseline in QTc interval using Fridericia's method (QTcF) were 4 - 6 msec; the upper 95% confidence intervals for all mean changes from baseline were < 7 msec (see section 4.8).

Of the 2182 patients with resistance or intolerance to prior to imatinib therapy who received dasatinib in clinical studies, 15 (1%) had QTc prolongation reported as an adverse reaction.
Twenty-one of these patients (1%) experienced a QTcF > 500 msec.

DAFANIB should be given with caution to patients who have or may develop prolongation of QTc. These include patients with hypokalemia or hypomagnesemia, patients with congenital long QT syndrome, patients taking anti-arrhythmic medicinal products or other medicinal products, which lead to QT prolongation, and cumulative high dose anthracycline therapy. Hypokalemia or hypomagnesemia should be corrected prior to DAFANIB administration.

Cardiac adverse reactions
Dasatinib was studied in a randomized clinical study of 519 patients with newly diagnosed CML in chronic phase, which included patients with prior cardiac disease. The cardiac adverse reactions of congestive heart failure/cardiac dysfunction, pericardial effusion, arrhythmias, palpitations, QT prolongation and myocardial infarction (including fatal) were reported in patients taking dasatinib. Cardiac adverse reactions were more frequent in patients with risk factors or a history of cardiac disease. Patients with risk factors (e.g. hypertension, hyperlipidemia, diabetes) or a history of cardiac disease (e.g. prior percutaneous coronary intervention, documented coronary artery disease) should be monitored carefully for clinical signs or symptoms consistent with cardiac dysfunction such as chest pain, shortness of breath, and diaphoresis.

If these clinical signs or symptoms develop, physicians are advised to interrupt dasatinib administration and consider the need for alternative CML-specific treatment. After resolution, a functional assessment should be performed prior to resuming treatment with dasatinib. Dasatinib may be resumed at the original dose for mild/moderate adverse reactions (≤ grade 2) and resumed at a dose level reduction for severe adverse reactions (≥ grade 3) (see section 4.2). Patients continuing treatment should be monitored periodically.

Patients with uncontrolled or significant cardiovascular disease were excluded in clinical trials.

Thrombotic microangiopathy (TMA)
BCR-ABL tyrosine kinase inhibitors have been associated with thrombotic microangiopathy (TMA), including individual case reports for dasatinib (see section 4.8). If laboratory or clinical findings associated with TMA occur in a patient receiving DAFANIB, treatment with DAFANIB should be discontinued and thorough evaluation for TMA, including ADAMTS13 activity and anti-ADAMTS13-antibody determination, should be completed. If anti-ADAMTS13-antibody is elevated in conjunction with low ADAMTS13 activity, treatment with DAFANIB should not be resumed.

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 DAFANIB. 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 DAFANIB 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).

Effects on growth and development in pediatric patients
In pediatric trials of dasatinib in imatinib-resistant/intolerant Ph+ CML-CP pediatric patients and treatment-naive Ph+ CML-CP pediatric patients after at least 2 years of treatment, treatment-related adverse events associated with bone growth and development were reported in 6 (4.6%) patients, one of which was severe in intensity (Growth Retardation Grade 3). These 6 cases included cases of epiphyses delayed fusion, osteopenia, growth retardation, and gynecomastia (see section 5.1). These results are difficult to interpret in the context of chronic diseases such as CML, and require long-term follow-up.

In pediatric trials of dasatinib in combination with chemotherapy in newly diagnosed Ph+ ALL pediatric patients after a maximum of 2 years of treatment, treatment-related adverse events associated with bone growth and development were reported in 1 (0.6%) patient. This case was a Grade 1 osteopenia.

Growth retardation has been observed in pediatric patients treated with dasatinib in clinical trials (see section 4.8). Monitoring of bone growth and development in pediatric patients is recommended.

Lactose
This medicinal product contains 89.25 mg of lactose monohydrate in each tablet. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5. Interactions with other medicinal products and other forms of interaction

Active substances that may increase dasatinib plasma concentrations

In vitro studies indicate that dasatinib is a CYP3A4 substrate. Concomitant use of dasatinib and medicinal products or substances that potently inhibit CYP3A4 (e.g. ketoconazole, itraconazole, erythromycin, clarithromycin, ritonavir, telithromycin, grapefruit juice) may increase exposure to dasatinib. Therefore, in patients receiving DAFANIB, systemic administration of a potent CYP3A4 inhibitor is not recommended.

At clinically relevant concentrations, binding of dasatinib to plasma proteins is approximately 96% on the basis of *in vitro* experiments. No studies have been performed to evaluate dasatinib interaction with other protein-bound medicinal products. The potential for displacement and its clinical relevance are unknown.

Active substances that may decrease dasatinib plasma concentrations

When dasatinib was administered following 8 daily evening administrations of 600 mg rifampicin, a potent CYP3A4 inducer, the AUC of dasatinib was decreased by 82%. Other medicinal products that induce CYP3A4 activity (e.g. dexamethasone, phenytoin, carbamazepine, phenobarbital or herbal preparations containing *Hypericum perforatum*, also known as St. John´s Wort) may also increase metabolism and decrease dasatinib plasma concentrations. Therefore, concomitant use of potent CYP3A4 inducers with DAFANIB is not recommended. In patients in whom rifampicin or other CYP3A4 inducers are indicated, alternative medicinal products with less enzyme induction potential should be used. Concomitant use of dexamethasone, a weak CYP3A4 inducer, with dasatinib is allowed; dasatinib AUC is predicted to decrease approximately 25% with concomitant use of dexamethasone, which is not likely to be clinically meaningful.

Histamine-2 antagonists and proton pump inhibitors:

Long-term suppression of gastric acid secretion by H_2 antagonists or proton pump inhibitors (e.g. famotidine and omeprazole) is likely to reduce dasatinib exposure. In a single-dose study in healthy subjects, the administration of famotidine 10 hours prior to a single dose of dasatinib reduced dasatinib exposure by 61%. In a study of 14 healthy subjects, administration of a single 100-mg dose of dasatinib following a 4-day, 40-mg omeprazole dose at steady state reduced the AUC of dasatinib by 43% and the C_{max} of dasatinib by 42%. The use of antacids should be considered in place of H_2 antagonists or proton pump inhibitors in patients receiving dasatinib therapy (see section 4.4).

Antacids:

Non-clinical data demonstrate that the solubility of dasatinib is pH-dependent. In healthy subjects, the concomitant use of aluminum hydroxide/magnesium hydroxide antacids with dasatinib reduced the AUC of a single dose of dasatinib by 55% and the C_{max} by 58%. However, when antacids were administered 2 hours prior to a single dose of dasatinib, no relevant changes in dasatinib concentration or exposure were observed. Thus, antacids may be administered up to 2 hours prior to or 2 hours following dasatinib (see section 4.4).

Active substances that may have their plasma concentrations altered by DAFANIB:

Concomitant use of dasatinib and a CYP3A4 substrate may increase exposure to the CYP3A4 substrate. In a study in healthy subjects, a single 100 mg dose of dasatinib increased AUC and C_{max} exposure to simvastatin, a known CYP3A4 substrate, by 20 and 37% respectively. It cannot be excluded that the effect is larger after multiple doses of dasatinib. Therefore, CYP3A4 substrates known to have a narrow therapeutic index (e.g. astemizole, terfenadine, cisapride, pimozide,

quinidine, bepridil or ergot alkaloids [ergotamine, dihydroergotamine]) should be administered with caution in patients receiving DAFANIB (see section 4.4).

In vitro data indicate a potential risk of interaction with CYP2C8 substrates, such as glitazones.

Additional information on special populations
Pediatric patients:
Interaction studies have only been performed in adults.

4.6. Pregnancy and lactation
General recommendation:
Pregnancy category: D

Women of childbearing potential/Birth control (Contraception)
Both sexually active men and women of childbearing potential should use effective methods of contraception during treatment with DAFANIB.

Pregnancy
Based on human experience, dasatinib is suspected to cause congenital malformations including neural tube defects, and harmful pharmacological effects on the fetus when administered during pregnancy. Studies in animals have shown reproductive toxicity (see section 5.3). DAFANIB should not be used during pregnancy unless the clinical condition of the woman requires treatment with dasatinib. If DAFANIB is used during pregnancy, the patient must be informed of the potential risk to the fetus.
Dasatinib may cause fetal harm when administered to a pregnant woman. There have been postmarketing reports of spontaneous abortion, as well as fetal and infant anomalies, in women who received dasatinib during pregnancy.

Breast-feeding
There is insufficient/limited data on the excretion of dasatinib in human or animal breast milk. Therefore, it cannot be ignored that there is a risk for the breastfeeding child.

Breastfeeding should be stopped during treatment with DAFANIB.

Reproductive ability / Fertility
In animal studies, the fertility of male and female rats was not affected by treatment with dasatinib (see section 5.3). Physicians and other healthcare providers should counsel male patients of appropriate age about possible effects of DAFANIB on fertility, and this counseling may include consideration of semen deposition.

4.7. Effects on the ability to drive and use machines
DAFANIB has minor influence on the ability to drive and use machines. Patients should be advised that they may experience adverse reactions such as dizziness or blurred vision during treatment with dasatinib.

4.8. Undesirable effects

a. Summary of the safety profile

The data described below reflect the exposure to dasatinib as single-agent therapy at all doses tested in clinical studies (N=2900), including 324 adult patients with newly diagnosed chronic phase CML,

2,388 adult patients with imatinib-resistant or -intolerant chronic or advanced phase CML or Ph+ ALL, and 188 pediatric patients.

In the 2712 adult patients with either chronic phase CML, advanced phase CML or Ph+ ALL, the median duration of therapy was 19.2 months (range 0 to 93.2 months). In a randomized trial in patients with newly diagnosed chronic phase CML, the median duration of therapy was approximately 60 months. The median duration of therapy in 1,618 adult patients with chronic phase CML was 29 months (range 0 to 92.9 months). The median duration of therapy in 1,094 adult patients with advanced phase CML or Ph+ ALL was 6.2 months (range 0 to 93.2 months). Among 188 patients in pediatric studies, the median duration of therapy was 26.3 months (range 0 to 99.6 months). In the subset of 130 chronic phase CML dasatinib-treated pediatric patients, the median duration of therapy was 42.3 months (range 0.1 to 99.6 months).

The majority of dasatinib-treated patients experienced adverse reactions at some time. In the overall population of 2712 dasatinib-treated adult subjects, 520 (19%) experienced adverse reactions leading to treatment discontinuation.

The overall safety profile of dasatinib in the pediatric Ph+ CML-CP population was similar to that of the adult population, regardless of formulation, with the exception of no reported pericardial effusion, pleural effusion, pulmonary edema, or pulmonary hypertension in the pediatric population. Of the 130 dasatinib-treated pediatric subjects with CML-CP, 2 (1.5%) experienced adverse reactions leading to treatment discontinuation.

b. Summary of adverse reactions

The following adverse reactions, excluding laboratory abnormalities, were reported in patients treated with dasatinib used as single-agent therapy in clinical studies and post-marketing experience. These reactions are presented by system organ class and by frequency. Frequencies are defined as: 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); unknown (cannot be estimated from available post-marketing data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Infections and infestations

Very common:	Infection (bacterial, viral, fungal, non-specified)
Common:	Pneumonia (including bacterial, viral, and fungal), upper respiratory tract infection/inflammation, herpes virus infection (including cytomegalovirus - CMV), enterocolitis infection, sepsis (including uncommon cases with fatal outcomes)
Unknown:	Hepatitis B reactivation

Blood and lymphatic system disorders

Very common:	Myelosuppression (including anemia, neutropenia, thrombocytopenia)
Common:	Febrile neutropenia
Uncommon:	Lymphadenopathy, lymphopenia
Rare:	Aplasia pure red cell

Immune system disorders

Uncommon:	Hypersensitivity (including erythema nodosum)
Rare:	Anaphylactic shock

Endocrine disorders

Uncommon:	Hypothyroidism
Rare:	Hyperthyroidism, thyroiditis

Metabolism and nutrition disorders

Common:	Appetite disturbances[a], hyperuricemia
Uncommon:	Tumor lysis syndrome, dehydration, hypoalbuminemia, hypercholesterolemia
Rare:	Diabetes mellitus

Psychiatric disorders

Common:	Insomnia, depression
Uncommon:	Anxiety, confusional state, affect lability, libido decreased

Nervous system disorders

Very common:	Headache
Common:	Neuropathy (including peripheral neuropathy), dizziness, dysgeusia, somnolence
Uncommon:	CNS hemorrhage*[b], syncope, tremor, amnesia, balance disorder
Rare:	Cerebrovascular accident, transient ischemic attack, convulsion, optic neuritis, VIIth nerve paralysis, dementia, ataxia

Eye disorders

Common:	Visual disorder (including vision blurred and visual acuity reduced), dry eye
Uncommon:	Visual impairment, conjunctivitis, photophobia, lacrimation increased.

Ear and labyrinth disorders

Common:	Tinnitus
Uncommon:	Hearing loss, vertigo

Cardiac disorders

Common:	Congestive heart failure/cardiac dysfunction*[c], pericardial effusion*, arrhythmia (including tachycardia), palpitations
Uncommon:	Myocardial infarction (including fatal outcome)*, electrocardiogram QT prolongation, pericarditis, ventricular arrhythmia (including ventricular tachycardia), angina pectoris, cardiomegaly, electrocardiogram T wave abnormal, troponin increased
Rare:	Cor pulmanale, myocarditis, acute coronary syndrome, cardiac arrest, electrocardiogram PR prolongation, coronary artery disease, pleuropericarditis
Unknown:	Atrial fibrillation/atrial flutter

Vascular disorders

Very common:	Hemorrhage*[d]
Common:	Hypertension, flushing
Uncommon:	Hypotension, thrombophlebitis, thrombosis
Rare:	Deep vein thrombosis, embolism, livedo reticularis
Unknown:	Thrombotic microangiopathy

Respiratory, thoracic and mediastinal disorders

Very common:	Pleural effusion*, dyspnea
Common:	Pulmonary edema*, pulmonary hypertension*, lung infiltration, pneumonia, cough
Uncommon:	Pulmonary arterial hypertension, bronchospasm, asthma, chylothorax*
Rare:	Pulmonary embolism, acute respiratory distress syndrome
Unknown:	Interstitial lung disease

Gastrointestinal disorders

Very common:	Diarrhea, vomiting, nausea, abdominal pain.
Common:	Gastrointestinal bleeding*, colitis (including neutropenic colitis), gastritis, mucosal inflammation (including mucositis, stomatitis), dyspepsia, constipation, abdominal distension, oral soft tissue disorder
Uncommon:	Pancreatitis (including acute pancreatitis), upper gastrointestinal ulcer, esophagitis, ascites*, anal fissure, dysphagia, gastroesophageal reflux disease
Rare:	Protein-losing gastroenteropathy, ileus, anal fistula
Unknown:	Fatal gastrointestinal hemorrhage*

Hepatobiliary diseases

Uncommon:	Hepatitis, cholecystitis, cholestasis

Skin and subcutaneous tissue disorders

Very common:	Skin rash[e]
Common:	Alopecia, dermatitis (including eczema), pruritus, acne, dry skin, urticaria, hyperhidrosis
Uncommon:	Neutrophilic dermatosis, photosensitivity, pigmentation disorder, panniculitis, skin ulcer, bullous conditions, nail disorder, palmar-plantar erythrodysaesthesia syndrome, hair disorder
Rare:	Leukocytoclastic vasculitis, skin fibrosis
Unknown:	Stevens-Johnson Syndrome[f]

Musculoskeletal, connective tissue, and bone disorders

Very common:	Musculoskeletal pain[g]
Common:	Arthralgia, myalgia, muscle weakness, musculoskeletal stiffness, muscle spasm
Uncommon:	Rhabdomyolysis, osteonecrosis, tendonitis, muscle inflammation, arthritis
Rare:	Delayed epiphyses fusion[h], growth retardation[h]

Renal and urinary tract disorders

Uncommon:	Renal impairment (including renal failure), frequent urination, proteinuria
Unknown:	Nephrotic syndrome

Pregnancy, puerperium and perinatal conditions

Rare:	Abortion

Reproductive system and breast disorders

Uncommon:	Gynecomastia, menstrual disorder

General disorders and administration site conditions

Very common:	Peripheral edema[i], fatigue, pyrexia, face edema[j]

Common:	Asthenia, pain, chest pain, generalized edema*[k], chills
Uncommon:	Malaise, heat intolerance, other superficial edema[l]
Rare:	Gait disturbance

Investigations

Common:	Weight decreased, weight increased
Uncommon:	Blood creatine phosphokinase increased, gamma-glutamyltransferase increased

Injury, poisoning and procedural complications

Common:	Contusion (bruise)

[a] Includes decreased appetite, early satiety, increased appetite
[b] Includes central nervous system hemorrhage, cerebral hematoma, cerebral hemorrhage, extradural hematoma, intracranial hemorrhage, hemorrhagic stroke, subarachnoid hemorrhage, subdural hematoma, and subdural hemorrhage
[c] Includes increased brain natriuretic peptide, ventricular dysfunction, left ventricular dysfunction, right ventricular dysfunction, cardiac failure, acute cardiac failure, chronic cardiac failure, congestive cardiac failure, cardiomyopathy, congestive cardiomyopathy, diastolic dysfunction, decreased ejection fraction and ventricular failure, left ventricular failure, right ventricular failure, ventricular hypokinesia.
[d] Excludes gastrointestinal bleeding and CNS bleeding; these adverse reactions are reported under the gastrointestinal disorders system organ class and the nervous system disorders system organ class, respectively.
[e] Includes drug eruption, erythema, erythema multiforme, erythrosis, exfoliative rash, generalized erythema, fungal rash, generalized erythema, genital rash, heat rash, milia, miliary, pustular psoriasis, rash, erythematous rash, follicular rash, generalized rash, macular rash, maculo-papular rash, papular rash, pruritic rash, pustular rash, vesicular rash, skin exfoliation, toxic skin eruption, skin irritation, vesiculous urticaria and vasculitic rash.
[f] In the post-marketing setting, individual cases of Stevens-Johnson syndrome have been reported. It could not be determined whether these mucocutaneous adverse reactions were directly related to dasatinib or to concomitant medicinal product.
[g] Musculoskeletal pain reported during or after discontinuing treatment.
[h] Frequency reported as common in pediatric studies.
[i] Gravitational edema, localized edema, peripheral edema
[j] Includes conjunctival edema, mouth edema, eye edema, eye swelling, eyelid edema, face edema, lip edema, macular edema, orbital edema, periorbital edema, face swelling.
[k] Fluid overload, fluid retention, gastrointestinal edema, generalized edema, peripheral swelling, edema, edema due to cardiac disease, perinephric effusion, post-procedure edema, visceral edema.
[l] Genital swelling, incision site edema, genital edema, penile edema, penile swelling, scrotal edema, skin swelling, testicular swelling, vulvovaginal swelling.
* For additional details, see section "Description of selected adverse reactions".

Definitions of selected adverse reactions:

Myelosuppression

Treatment with dasatinib is associated with anemia, neutropenia and thrombocytopenia. Their occurrence is earlier and more frequent in patients with advanced phase CML or Ph+ ALL than in chronic phase CML (see section 4.4).

Bleeding

Drug-related bleeding reactions, ranging from petechia and epistaxis to grade 3 or 4 gastrointestinal hemorrhage and CNS bleeding, were reported in patients using dasatinib (see section 4.4).

Fluid retention
Miscellaneous adverse reactions such as pleural effusion, ascites, pulmonary edema and pericardial effusion with or without superficial edema may be collectively described as "fluid retention". In the newly diagnosed chronic phase CML study after a minimum of 60 months follow-up, dasatinib-related fluid retention adverse reactions included pleural effusion (28%), superficial edema (14%), pulmonary hypertension (5%), generalized edema (4%), and pericardial effusion (4%). Congestive heart failure/cardiac dysfunction and pulmonary edema were reported in < 2% of patients.

The cumulative rate of dasatinib-related pleural effusion (all grades) over time was 10% at 12 months, 14% at 24 months, 19% at 36 months, 24% at 48 months and 28% at 60 months. A total of 46 dasatinib-treated patients had recurrent pleural effusions. 17 patients had 2 separate adverse reactions, 6 had 3 adverse reactions, 18 had 4 to 8 adverse reactions and 5 had > 8 episodes of pleural effusions.

The median time to first dasatinib-related grade 1 or 2 pleural effusion was 114 weeks (range: 4 to 299 weeks). Less than 10% of patients with pleural effusion had severe (grade 3 or 4) dasatinib-related pleural effusions. The median time to first occurrence of grade ≥ 3 dasatinib-related pleural effusion was 175 weeks (range: 114 to 274 weeks). The median duration of dasatinib-related pleural effusion (all grades) was 283 days (~40 weeks).

Pleural effusion was usually reversible and managed by interrupting dasatinib treatment and using diuretics or other appropriate supportive care measures (see sections 4.2 and 4.4). Among dasatinib-treated patients with drug-related pleural effusion (n=73), 45 (62%) had dose interruptions and 30 (41%) had dose reductions. Additionally, 34 (47%) received diuretics, 23 (32%) received corticosteroids, and 20 (27%) received both corticosteroids and diuretics. Nine (12%) patients underwent therapeutic thoracentesis.

Six percent of dasatinib-treated patients stopped treatment due to drug-related pleural effusion.

Pleural effusion did not impair the ability of patients to obtain a response. Among the dasatinib-treated patients with pleural effusion, 96% achieved a cCCyR, 82% achieved a MMR, and 50% achieved a MR4.5 despite dose interruptions or dose adjustment.

See section 4.4 for further information on patients with chronic phase CML and advanced phase CML or Ph+ ALL.

Cases of chylothorax have been reported in patients presenting with pleural effusion. Some cases of chylothorax resolved upon dasatinib discontinuation, interruption, or dose reduction, but most cases also required additional treatment.

Pulmonary arterial hypertension (PAH)
PAH (pre-capillary pulmonary arterial hypertension confirmed by right heart catheterization) has been reported in association with dasatinib exposure. In these cases, PAH was reported after initiation of dasatinib therapy, including after more than one year of treatment. Patients with PAH reported during dasatinib treatment were often taking concomitant medicinal products or had co-morbidities in addition to the underlying malignancy. Improvements in hemodynamic and clinical parameters have been observed in patients with PAH following discontinuation of dasatinib.

QT Prolongation

In the Phase III study in patients with newly diagnosed chronic phase CML, one patient (< 1%) of the dasatinib-treated patients had a QTcF > 500 msec after a minimum of 12 months follow-up (see section 4.4). No additional patients were reported to have QTcF > 500 msec after a minimum of 60 months follow-up.

In 5 Phase II clinical studies in patients with resistance or intolerance to prior imatinib therapy, repeated baseline and on-treatment ECGs were obtained at pre-specified time points and read centrally for 865 patients receiving dasatinib 70 mg twice daily. QT interval was corrected for heart rate by Fridericia's method. At all post-dose time points on day 8, the mean changes from baseline in QTcF interval were 4 - 6 msec, with associated upper 95% confidence intervals < 7 msec. Of the 2,182 patients with resistance or intolerance to prior imatinib therapy who received dasatinib in clinical studies, 15 (1%) had QTc prolongation reported as an adverse reaction. Twenty-one patients (1%) experienced a QTcF > 500 msec (see section 4.4).

Cardiac adverse reactions
Patients with risk factors or a history of cardiac disease should be monitored carefully for signs or symptoms consistent with cardiac dysfunction and should be evaluated and treated appropriately (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).

In the Phase III dose-optimization study in patients with chronic phase CML with resistance or intolerance to prior imatinib therapy (median duration of treatment of 30 months), the incidence of pleural effusion and congestive heart failure/cardiac dysfunction was lower in patients treated with dasatinib 100 mg once daily than in those treated with dasatinib 70 mg twice daily. Myelosuppression was also reported less frequently in the 100 mg once daily treatment group (see Laboratory test abnormalities below). The median duration of therapy in the 100 mg once daily group was 37 months (range 1-91 months). Cumulative rates of selected adverse reactions that were reported in the 100 mg once daily recommended initial dose are shown in Table 5a.

Table 5a: Selected adverse reactions reported in a phase 3 dose optimization study (imatinib intolerant or resistant chronic phase CML)[a]

	Minimum of 2 years follow up		**Minimum of 5 years follow up**		**Minimum of 7 years follow up**	
	All grades	**Grade 3/4**	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**
Preferred term	Percent (%) of patients					
Diarrhea	27	2	28	2	28	2
Fluid retention	34	4	42	6	48	7
Superficial edema	18	0	21	0	22	0
Pleural effusion	18	2	24	4	28	5
Generalized edema	3	0	4	0	4	0
Pericardial effusion	2	1	2	1	3	1

Pulmonary hypertension	0	0	0	0	2	1
Hemorrhage	11	1	11	1	12	1
Gastrointestinal bleeding	2	1	2	1	2	1
[a] Phase 3 dose optimization study results reported in recommended initial dose of 100 mg once daily (n=165) population						

In the Phase III dose-optimization study in patients with advanced phase CML and Ph+ ALL, the median duration of treatment was 14 months for accelerated phase CML, 3 months for myeloid blast CML, 4 months for lymphoid blast CML and 3 months for Ph+ ALL. Selected adverse reactions that were reported in the recommended initial dose of 140 mg once daily are shown in Table 5b. A 70 mg twice daily regimen was also studied. The 140 mg once daily regimen showed a comparable efficacy profile to the 70 mg twice daily regimen but a more favorable safety profile.

Table 5b: Selected adverse reactions reported in phase III dose-optimization study: Advanced phase CML and Ph+ ALL[a]

	140 mg once daily n= 304	
	All grades	**Grade 3/4**
Preferred term	**Percent (%) of patients**	
Diarrhea	28	3
Fluid retention	33	7
Superficial edema	15	< 1
Pleural effusion	20	6
Generalized edema	2	0
Congestive heart failure/cardiac dysfunction[b]	1	0
Pericardial effusion	2	1
Pulmonary edema	1	1
Hemorrhage	23	8
Gastrointestinal bleeding	8	6
[a] Phase 3 dose optimization study results reported at the recommended initial dose of 140 mg once daily (n=304) population at 2 year final study follow up. [b] Includes ventricular dysfunction, cardiac failure, cardiac failure congestive, cardiomyopathy, congestive cardiomyopathy, diastolic dysfunction, ejection fraction decreased, and ventricular failure.		

In addition, there were two studies in a total of 161 pediatric patients with Ph+ ALL in which dasatinib was administered in combination with chemotherapy In the pivotal study, 106 pediatric patients received dasatinib in combination with chemotherapy on a continuous dosing regimen. In a supportive study, of 55 pediatric patients, 35 received dasatinib in combination with chemotherapy on a discontinuous dosing regimen (two weeks on treatment followed by one to two weeks off) and 20 received dasatinib in combination with chemotherapy on a continuous dosing regimen. Among the 126 Ph+ ALL pediatric patients treated with dasatinib on a continuous dosing regimen, the median duration of therapy was 23.6 months (range 1.4 to 33 months).

Of the 126 Ph+ ALL pediatric patients on a continuous dosing regimen, 2 (1.6%) experienced adverse reactions leading to treatment discontinuation. Adverse reactions reported in these two pediatric studies at a frequency of ≥ 10% in patients on a continuous dosing regimen are shown in Table 6. Of note, pleural effusion was reported in 7 (5.6%) patients in this group, and is therefore not included in the table.

Table 6: Adverse reactions reported in ≥10% of pediatric patients with Ph+ ALL treated with dasatinib on a continuous dosing regimen in combination with chemotherapy (N=126)[a]

	Percent (%) of patients	
Adverse reaction	**All grades**	***Grade 3/4***
Febrile neutropenia	27	26.2
Nausea	20.6	5.6
Vomiting	20.6	4.8
Abdominal pain	14.3	3.2
Diarrhea	12.7	4.8
Pyrexia	12.7	5.6
Headache	11.1	4.8
Decreased appetite	10.3	4.8
Tiredness	10.3	0

[a] In the pivotal study, among 106 total patients, 24 patients received the powder for oral suspension at least once, 8 of whom received the powder for oral suspension formulation exclusively.

Laboratory test abnormalities
Hematology
In the Phase III newly diagnosed chronic phase CML study, the following grade 3 or 4 laboratory abnormalities were reported after a minimum of 12 months follow-up in patients taking dasatinib: neutropenia (21%), thrombocytopenia (19%) and anemia (10%). After a minimum of 60 months follow-up, the cumulative rates of neutropenia, thrombocytopenia, and anemia were 29%, 22% and 13%, respectively.

In dasatinib-treated patients with newly diagnosed chronic phase CML who experienced grade 3 or 4 myelosuppression, recovery generally occurred following brief dose interruptions and/or reductions and permanent discontinuation of treatment occurred in 1.6% of patients after a minimum of 12 months follow-up. After a minimum of 60 months follow-up, the cumulative rate of permanent discontinuation due to grade 3 or 4 myelosuppression was 2.3%.

In patients with CML with resistance or intolerance to prior imatinib therapy, cytopenias (thrombocytopenia, neutropenia, and anemia) were a consistent finding. However, the occurrence of cytopenias was also clearly dependent on the stage of the disease. The frequency of grade 3 and 4 hematological abnormalities is presented in Table 7.

Table 7: CTC grades 3/4 hematological laboratory abnormalities in clinical studies in patients with resistance or intolerance to prior imatinib therapy[a]

	Chronic phase (n= 165)[b]	**Accelerated phase (n= 157)[c]**	**Myeloid blast phase (n= 74)[c]**	**Lymphoid blast phase and Ph+ ALL (n= 168)[c]**
Percent (%) of patients				
Hematology parameters				
Neutropenia	36	58	77	76
Thrombocytopenia	23	63	78	74
Anemia	13	47	74	44

[a] Phase 3 dose optimization study results reported at two-year study follow-up.
[b] CA180-034 study results in recommended initial dose of 100 mg once daily.
[c] CA180-035 study results in recommended initial dose of 140 mg once daily.

CTC grades: neutropenia (Grade 3 ≥ 0.5– < 1.0 × 109/l, Grade 4 < 0.5 × 109/l); thrombocytopenia (Grade 3 ≥ 25 – < 50 × 109/l, Grade 4 < 25 × 109/l); anemia (hemoglobin Grade 3 ≥ 65 – < 80 g/l, Grade 4 < 65 g/l).

Cumulative grade 3 or 4 cytopenias among patients treated with 100 mg once daily were similar at 2 and 5 years including: neutropenia (35% vs. 36%), thrombocytopenia (23% vs. 24%) and anemia (13% vs. 13%).

In patients who experienced grade 3 or 4 myelosuppression, recovery generally occurred following brief dose interruptions and/or reductions and permanent discontinuation of treatment occurred in 5% of patients. Most patients continued treatment without further evidence of myelosuppression.

Biochemistry
In the newly diagnosed chronic phase CML study, grade 3 or 4 hypophosphatemia was reported in 4% of dasatinib-treated patients, and grade 3 or 4 elevations of transaminases, creatinine, and bilirubin were reported in ≤ 1% of patients after a minimum of 12 months follow-up. After a minimum of 60 months follow-up, cumulative rate of grade 3 or 4 hypophosphatemia was 7%, grade 3 or 4 elevations of creatinine and bilirubin was 1% and grade 3 or 4 elevations of transaminases remained 1%. There were no discontinuations of dasatinib therapy due to these biochemical laboratory parameters.

2-year follow up
Grade 3 or 4 elevations of transaminases or bilirubin were reported in patients with chronic phase CML (resistant or intolerant to imatinib), but elevations were reported with an increased frequency of 1 to 7% of patients with advanced phase CML and Ph+ ALL. It was usually managed with dose reduction or interruption. In the Phase III dose-optimization study in chronic phase CML, grade 3 or 4 elevations of transaminases or bilirubin were reported in ≤ 1% of patients with similar low incidence in the four treatment groups. In the Phase III dose-optimization study in advanced phase CML and Ph+ALL, grade 3 or 4 elevations of transaminases or bilirubin were reported in 1% to 5% of patients across treatment groups.

Approximately 5% of the dasatinib-treated patients who had normal baseline levels experienced grade 3 or 4 transient hypocalcaemia at some time during the course of the study. In general, there was no association of decreased calcium with clinical symptoms. Patients developing grade 3 or 4 hypocalcaemia often had recovery with oral calcium supplementation. Grade 3 or 4 hypocalcemia, hypokalemia, and hypophosphatemia were reported in patients with all phases of CML but were reported with an increased frequency in patients with myeloid or lymphoid blast phase CML and Ph+ ALL. Grade 3 or 4 elevations in creatinine were reported in < 1% of patients with chronic phase CML and were reported with an increased frequency of 1 to 4% of patients with advanced phase CML.

Pediatric population
The safety profile of dasatinib administered as single-agent therapy in pediatric patients with Ph+ CML-CP was comparable to the safety profile in adults. The safety profile of dasatinib administered in combination with chemotherapy in pediatric patients with Ph+ ALL was consistent with the known safety profile of dasatinib in adults and the expected effects of chemotherapy, with the exception of a lower pleural effusion rate in pediatric patients as compared to adults.
In the pediatric CML studies, the rates of laboratory abnormalities were consistent with the known profile for laboratory parameters in adults.

In the pediatric ALL studies, the rates of laboratory abnormalities were consistent with the known profile for laboratory parameters in adults, within the context of an acute leukemia patient receiving

a background chemotherapy regimen.

Additional information on special populations:
While the safety profile of dasatinib in elderly was similar to that in the younger population, patients aged 65 years and older are more likely to experience the commonly reported adverse reactions such as fatigue, pleural effusion, dyspnea, cough, lower gastrointestinal hemorrhage, and appetite disturbance and more likely to experience less frequently reported adverse reactions such as abdominal distention, dizziness, pericardial effusion, congestive heart failure, and weight decrease and should be monitored closely (see section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9. Overdose and treatment
Experience with overdose of dasatinib in clinical studies is limited to isolated cases. The highest overdose of 280 mg per day for one week was reported in two patients and both developed a significant decrease in platelet counts. Since dasatinib is associated with grade 3 or 4 myelosuppression (see section 4.4), patients who ingest more than the recommended dose should be closely monitored for myelosuppression and given appropriate supportive treatment.

5. PHARMACOLOGICAL PROPERTIES
5.1. Pharmacodynamic properties
Pharmacotherapeutic group: Antineoplastic agents, Protein kinase inhibitors
ATC code: L01EA02

Pharmacodynamics
Dasatinib inhibits the activity of the BCR-ABL kinase and SRC family kinases along with a number of other selected oncogenic kinases including c-KIT, ephrin (EPH) receptor kinases, and PDGFβ receptor. Dasatinib is a potent, subnanomolar inhibitor of the BCR-ABL kinase with potency at concentration of 0.6-0.8 nM. It binds to both the inactive and active conformations of the BCR-ABL enzyme.

Mechanism of action
In vitro, dasatinib is active in leukemic cell lines representing variants of imatinib-sensitive and resistant disease. These non-clinical studies show that dasatinib can overcome imatinib resistance resulting from BCR-ABL overexpression, BCR-ABL kinase domain mutations, activation of alternate signaling pathways involving the SRC family kinases (LYN, HCK), and multidrug resistance gene overexpression. Additionally, dasatinib inhibits SRC family kinases at subnanomolar concentrations.

In vivo, in separate experiments using murine models of CML, dasatinib prevented the progression of chronic CML to blast phase and prolonged the survival of mice bearing patient-derived CML cell lines grown at various sites, including the central nervous system.

Clinical efficacy and safety
In the Phase I study, haematologic and cytogenetic responses were observed in all phases of CML and in Ph+ ALL in the first 84 patients treated and followed for up to 27 months. Responses were durable across all phases of CML and Ph+ ALL.

Four single-arm, uncontrolled, open-label Phase II clinical studies were conducted to determine the safety and efficacy of dasatinib in patients with CML in chronic, accelerated, or myeloid blast phase, who were either resistant or intolerant to imatinib. One randomized non-comparative study was conducted in chronic phase patients who failed initial treatment with 400 or 600 mg imatinib. The initial dose was 70 mg dasatinib twice daily. Dose modifications were allowed for improving activity or management of toxicity (see section 4.2).

Two randomized, open-label Phase III studies were conducted to evaluate the efficacy of dasatinib administered once daily compared with dasatinib administered twice daily. In addition, one open-label, randomized, comparative Phase III study was conducted in adult patients with newly diagnosed chronic phase CML.

The efficacy of dasatinib is based on hematological and cytogenetic response rates.

Durability of response and estimated survival rates provide additional evidence of dasatinib clinical benefit.

A total of 2712 patients were evaluated in clinical studies; of these 23% were ≥ 65 years of age and 5% were ≥ 75 years of age.

Chronic phase CML - Newly diagnosed
An international open-label, multicenter, randomized, comparative Phase III study was conducted in adult patients with newly diagnosed chronic phase CML. Patients were randomized to receive either dasatinib 100 mg once daily or imatinib 400 mg once daily. The primary endpoint was the rate of confirmed complete cytogenetic response (cCCyR) within 12 months. Secondary endpoints included time in cCCyR (measure of durability of response), time to cCCyR, major molecular response (MMR) rate, time to MMR, progression free survival (PFS) and overall survival (OS). Other relevant efficacy results included CCyR and complete molecular response (CMR) rates. The study is ongoing.

A total of 519 patients were randomized to a treatment group: 259 to dasatinib and 260 to imatinib. Baseline characteristics were well balanced between the two treatment groups with respect to age (median age was 46 years for the dasatinib group and 49 years for the imatinib group with 10% and 11% of patients 65 years of age or older, respectively), gender (women 44% and 37%, respectively), and race (Caucasian 51% and 55%; Asian 42% and 37%, respectively). At baseline, the distribution of Hasford Scores was similar in the dasatinib and imatinib treatment groups (low risk: 33% and 34%; intermediate risk 48% and 47%; high risk: 19% and 19%, respectively).

With a minimum of 12 months follow-up, 85% of patients randomized to the dasatinib group and 81% of patients randomized to the imatinib group were still receiving first-line treatment. Discontinuation within 12 months due to disease progression occurred in 3% of dasatinib-treated patients and 5% of imatinib-treated patients.

With a minimum of 60 months follow-up, 60% of patients randomized to the dasatinib group and 63% of patients randomized to the imatinib group were still receiving first-line treatment. Discontinuation within 60 months due to disease progression occurred in 11% of dasatinib-treated patients and 14% of imatinib-treated patients.

Efficacy results are presented in Table 8. A statistically significantly greater proportion of patients in the dasatinib group achieved a cCCyR compared with patients in the imatinib group within the first

12 months of treatment. Efficacy of dasatinib was consistently demonstrated across different subgroups, including age, gender, and baseline Hasford score.

Table 8: Efficacy results from a phase 3 study of newly diagnosed patients with chronic phase CML

	Dasatinib n= 259	Imatinib n= 260	p-value
Response rate (95% CI)			
Cytogenetic response within 12 months			
cCCyR[a]	76.8% (71.2-81.8)	66.2% (60.1–71.9)	p< 0.007*
CCyR[b]	85.3% (80.4-89.4)	73.5% (67.7-78.7)	—
within 24 months			
cCCyR[a]	80.3%	74.2%	—
CCyR[b]	87.3%	82.3%	—
within 36 months			
cCCyR[a]	82.6%	77.3%	—
CCyR[b]	88.0%	83.5%	—
within 48 months			
cCCyR[a]	82.6%	78.5%	—
CCyR[b]	87.6%	83.8%	—
within 60 months			
cCCyR[a]	83.0%	78.5%	—
CCyR[b]	88.0%	83.8%	—
Major molecular response[c]			
12 months	52.1% (45.9–58.3)	33.8% (28.1–39.9)	p< 0.00003*
24 months	64.5% (58.3-70.3)	50% (43.8-56.2)	—
36 months	69.1% (63.1-74.7)	56.2% (49.9-62.3)	—
48 months	75.7% (70.0-80.8)	62.7% (56.5-68.6)	—
60 months	76.4% (70.8-81.5)	64.2% (58.1-70.1)	p=0.0021
	Hazard ratio (HR) within 12 months (99.99% CI)		
Time-to cCCyR	1.55 (1.0 -2.3)		p< 0.0001*
Time-to MMR	2.01 (1.2 -3.4)		p< 0.0001*
Durability of cCCyR	0.7 (0.4 -1.4)		p< 0.035
	within 24 months (95% CI)		
Time-to cCCyR	1.49 (1.22 -1.82)		—
Time-to MMR	1.69 (1.34 -2.12)		—
Durability of cCCyR	0.77 (0.55 -1.10)		—
	within 36 months (95% CI)		
Time-to cCCyR	1.48 (1.22 -1.80)		—
Time-to MMR	1.59 (1.28 -1.99)		—
Durability of cCCyR	0.77 (0.53 -1.11)		—
	within 48 months (95% CI)		
Time-to cCCyR	1.45 (1.20 -1.77)		—
Time-to MMR	1.55 (1.26 -1.91)		—
Durability of cCCyR	0.81 (0.56 -1.17)		—
	within 60 months (95% CI)		
Time-to cCCyR	1.46 (1.20 -1.77)		p=0.0001

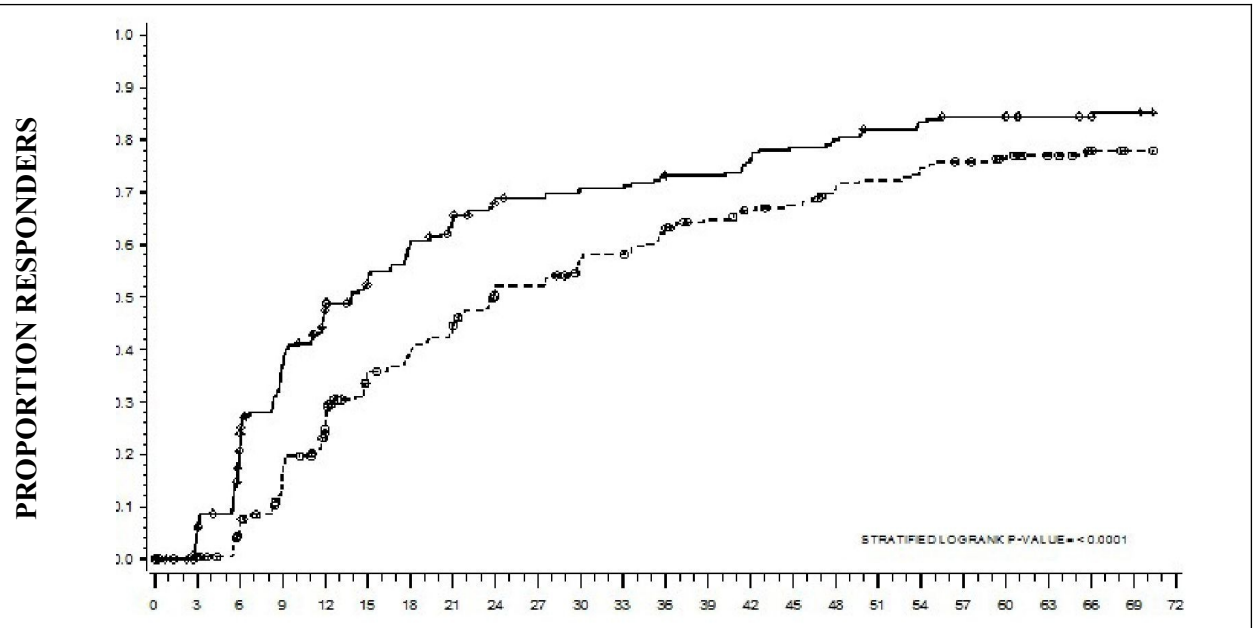
Time-to MMR	1.54 (1.25 -1.89)	p<0.0001
Durability of cCCyR	0.79 (0.55 -1.13)	p=0.1983

[a] Confirmed complete cytogenetic response (cCCyR) is defined as a response noted on two consecutive occasions (at least 28 days apart).
[b] Complete cytogenetic response (CCyR) is based on a single bone marrow cytogenetic evaluation.
[c] Major molecular response (at any time) was defined as BCR ABL ratios ≤ 0.1% by RQ PCR in peripheral blood samples standardized on the International scale. These are cumulative rates representing minimum follow up for the timeframe specified.
[*] Adjusted for Hasford Score and indicated statistical significance at a pre-defined nominal level of significance.
CI=confidence interval.

After 60 months of follow-up, median time to cCCyR was 3.1 months in the dasatinib group and 5.8 months in the imatinib group in patients with a confirmed CCyR. Median time to MMR after 60 months of follow-up was 9.3 months in the dasatinib group and 15.0 months in the imatinib group in patients with a MMR. These results are consistent with those seen at 12, 24 and 36 months.

The time to MMR is displayed graphically in Figure 1. The time to MMR was consistently shorter in dasatinib-treated patients compared with imatinib-treated patients.

Figure 1: Kaplan-Meier estimate of time to major molecular response (MMR)



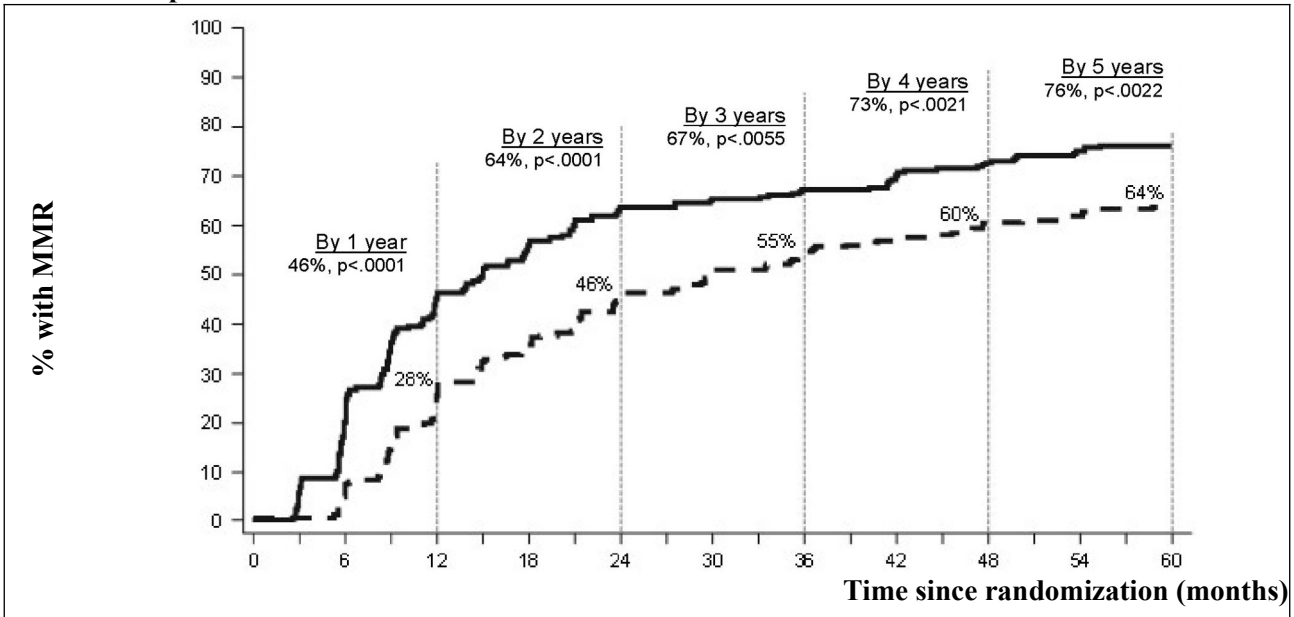
GROUP	# RESPONDERS / # RANDOMIZED	HAZARD RATIO (95% CI)
Dasatinib	198/259	
Imatinib	167/260	
Dasatinib over imatinib		1.54 (1.25 -1.89)

The rates of cCCyR in the dasatinib and imatinib treatment groups, respectively, within 3 months (54% and 30%), 6 months (70% and 56%), 9 months (75% and 63%), 24 months (80% and 74%), 36

months (83% and 77%), 48 months (83% and 79%) and 60 months (83% and 79%) were consistent with the primary endpoint. The rates of MMR in the dasatinib and imatinib treatment groups, respectively, within 3 months (8% and 0.4%), 6 months (27% and 8%), 9 months (39% and 18%), 12 months (46% and 28%), 24 months (64% and 46%), 36 months (67% and 55%), 48 months (73% and 60%) and 60 months (76% and 64%) were also consistent with the primary endpoint.

MMR rates by specific time point are displayed graphically in Figure 2. Rates of MMR were consistently higher in dasatinib-treated patients compared with imatinib-treated patients.

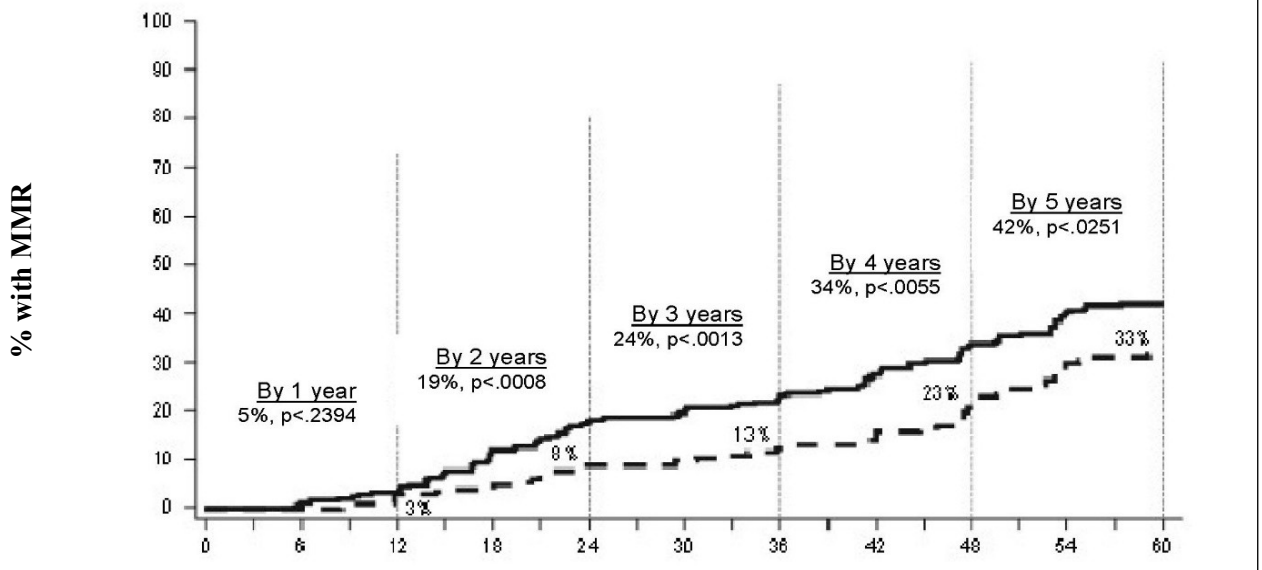
Figure 2: MMR rates over time - all randomized patients in a phase 3 study of newly diagnosed patients with chronic phase CML



	N
Dasatinib 100 mg once daily	259
Imatinib 400 mg once daily	260

The proportion of patients achieving BCR-ABL ratio of ≤0.01% (4-log reduction) at any time was higher in the dasatinib group compared to the imatinib group (54.1% versus 45%). The proportion of patients achieving BCR-ABL ratio of ≤0.0032% (4.5-log reduction) at any time was higher in the dasatinib group compared to the imatinib group (44% versus 34%).
MR4.5 rates over time are displayed graphically in Figure 3. Rates of MR4.5 over time were consistently higher in dasatinib-treated patients compared with imatinib-treated patients.

Figure 3: MR4.5 rates over time - all randomized patients in a phase 3 study of newly diagnosed patients with chronic phase CML



	N
Dasatinib 100 mg once daily	259
Imatinib 400 mg once daily	260

The rate of MMR at any time in each risk group determined by Hasford score was higher in the dasatinib group compared with the imatinib group (low risk: 90% and 69%; intermediate risk: 71% and 65%; high risk: 67% and 54%, respectively).

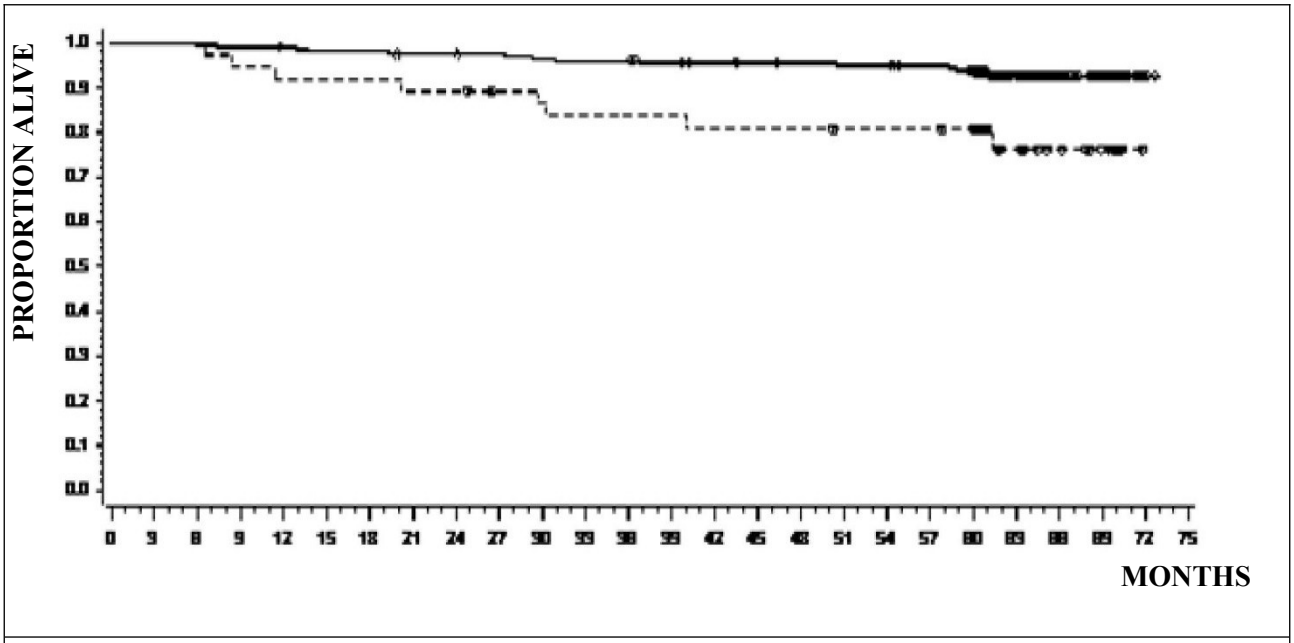
In an additional analysis, more dasatinib-treated patients (84%) achieved early molecular response (defined as BCR-ABL levels ≤ 10% at 3 months) compared with imatinib-treated patients (64%). Patients achieving early molecular response had a lower risk of transformation, higher rate of progression-free survival (PFS) and higher rate of overall survival (OS), as shown in Table 9.

Table 9: Dasatinib patients with BCR-ABL ≤ 10% and > 10% at 3 months

Dasatinib N=235	Patients with BCR-ABL ≤ 10% at 3 months	Patients with BCR-ABL > 10% at 3 months
Number of patients (%)	198 (84.3)	37 (15.7)
Transformation at 60 months, n/N (%)	6/198 (3.0)	5/37 (13.5)
Rate of PFS at 60 months (95% CI)	92.0% (89.6, 95.2)	73.8% (52.0, 86.8)
Rate of OS at 60 months (95% CI)	93.8% (89.3, 96.4)	80.6% (63.5, 90.2)

The OS rate by specific time point is displayed graphically in Figure 4. Rate of OS was consistently higher in dasatinib treated patients who achieved BCR-ABL level ≤ 10% at 3 months than those who did not.

Figure 4: Landmark plot for overall survival for dasatinib by BCR-ABL level (≤ 10% or > 10%) at 3 months in a phase 3 study of newly diagnosed patients with chronic phase CML



Patients at risk

<=10%	198	198	197	196	195	193	193	191	191	190	188	187	187	184	182	181	180	179	179	177	171	96	54	29	3	0
>10%	37	37	37	35	34	34	34	33	33	31	30	29	29	29	28	28	28	27	27	27	26	15	10	6	0	0

≤ 10% > 10% Censored Censored

GROUP	# DEATHS / # Land Patient	MEDIAN (95% CI)	HAZARD RATIO (95% CI)
≤ 10%	14/198	.(. - .)	
> 10%	8/37	.(. - .)	
			0.29 (0.12 - 0.69)

Disease progression was defined as increasing white blood cells despite appropriate therapeutic management, loss of CHR, partial CyR or CCyR, progression to accelerated phase or blast phase, or death. The estimated 60-month PFS rate was 88.9% (CI: 84% - 92.4%) for both the dasatinib and imatinib treatment groups. At 60 months, transformation to accelerated or blast phase occurred in fewer dasatinib-treated patients (n=8; 3%) compared with imatinib-treated patients (n=15; 5.8%). The estimated 60-month survival rates for dasatinib and imatinib-treated patients were 90.9% (CI: 86.6% - 93.8%) and 89.6% (CI: 85.2% - 92.8%), respectively. There was no difference in OS (HR 1.01, 95% CI: 0.58-1.73, p= 0.9800) and PFS (HR 1.00, 95% CI: 0.58-1.72, p = 0.9998) between dasatinib and imatinib.

In patients who report disease progression or discontinue dasatinib or imatinib therapy, BCR-ABL sequencing was performed on blood samples from patients where these are available. Similar rates of mutation were observed in both the treatment arms. The mutations detected among the dasatinib-treated patients were T315I, F317I/L and V299L. A different spectrum of mutation was not detected in the imatinib treatment arm. Dasatinib does not appear to be active against the T315I mutation, based on *in vitro* data.

Chronic phase CML - Resistance or intolerance to prior imatinib therapy
Two clinical studies were conducted in patients resistant or intolerant to imatinib; the primary efficacy endpoint in these studies was Major Cytogenetic Response (MCyR).

Study 1

An open-label, randomized, non-comparative multicenter study was conducted in patients who failed initial treatment with 400 or 600 mg imatinib. They were randomized (2:1) to either dasatinib (70 mg twice daily) or imatinib (400 mg twice daily). Crossover to the alternative treatment arm was allowed if patients showed evidence of disease progression or intolerance that could not be managed by dose modification. The primary endpoint was MCyR at 12 weeks. Results are available for 150 patients: 101 were randomized to dasatinib and 49 to imatinib (all imatinib-resistant). The median time from diagnosis to randomization was 64 months in the dasatinib group and 52 months in the imatinib group. All patients were extensively pretreated. Prior complete hematologic response (CHR) to imatinib was achieved in 93% of the overall patient population. A prior MCyR to imatinib was achieved in 28% and 29% of the patients in the dasatinib and imatinib arms, respectively.

Median duration of treatment was 23 months for dasatinib (with 44% of patients treated for > 24 months to date) and 3 months for imatinib (with 10% of patients treated for > 24 months to date).

Ninety-three percent of patients in the dasatinib arm and 82% of patients in the imatinib arm achieved a CHR prior to crossover.

At 3 months, a MCyR occurred more often in the dasatinib arm (36%) than in the imatinib arm (29%). Notably, 22% of patients reported a complete cytogenetic response (CCyR) in the dasatinib arm while only 8% achieved a CCyR in the imatinib arm. With longer treatment and follow-up (median of 24 months), MCyR was achieved in 53% of the dasatinib-treated patients (CCyR in 44%) and 33% of the imatinib-treated patients (CCyR in 18%) prior to crossover. Among patients who had received imatinib 400 mg prior to study entry, MCyR was achieved in 61% of patients in the dasatinib arm and 50% in the imatinib arm.

Based on the Kaplan-Meier estimates, the proportion of patients who maintained MCyR for 1 year was 92% (95% CI: [85%-100%]) for dasatinib (CCyR 97%, 95% CI: [92%-100%]) and 74% (95% CI: [49%-100%]) for imatinib (CCyR 100%). The proportion of patients who maintained MCyR for 18 months was 90% (95% CI: [82%-98%]) for dasatinib (CCyR 94%, 95% CI: [87%-100%]) and 74% (95% CI: [49%-100%]) for imatinib (CCyR 100%).

Based on the Kaplan-Meier estimates, the proportion of patients who had progression-free survival (PFS) for 1 year was 91% (95% CI: [85%-97%]) for dasatinib and 73% (95% CI: [54%-91%]) for imatinib. The proportion of patients who had PFS at 2 years was 86% (95% CI: [78%-93%]) for dasatinib and 65% (95% CI: [43%-87%]) for imatinib.

A total of 43% of the patients in the dasatinib arm, and 82% in the imatinib arm had treatment failure, defined as disease progression or cross-over to the other treatment (lack of response, intolerance of study medicinal product, etc.).

Major molecular response rate (defined as BCR-ABL/control transcripts ≤ 0.1% by RQ-PCR in peripheral blood samples) prior to crossover was 29% for dasatinib and 12% for imatinib.

Study 2
An open-label, single-arm, multicenter study was conducted in patients resistant or intolerant to imatinib (i.e. patients who experienced significant toxicity during treatment with imatinib that precluded further treatment).

A total of 387 patients received dasatinib 70 mg twice daily (288 resistant and 99 intolerant). The median time from diagnosis to start of treatment was 61 months. The majority of the patients (53%)

had received prior imatinib treatment for more than 3 years. Most resistant patients (72%) had received > 600 mg imatinib. In addition to imatinib, 35% of patients had received prior cytotoxic chemotherapy, 65% had received prior interferon, and 10% had received a prior stem cell transplant. Thirty-eight percent of patients had baseline mutations known to confer imatinib resistance. Median duration of treatment on dasatinib was 24 months with 51% of patients treated for > 24 months to date. Efficacy results are reported in Table 11. MCyR was achieved in 55% of imatinib-resistant patients and 82% of imatinib-intolerant patients.

With a minimum of 24 months follow-up, 21 of the 240 patients who had achieved a MCyR had progressed and the median duration of MCyR had not been reached.

Based on the Kaplan-Meier estimates, 95% (95% CI: [92%-98%]) of the patients maintained MCyR for 1 year and 88% (95% CI: [83%-93%]) maintained MCyR for 2 years. The proportion of patients who maintained CCyR for 1 year was 97% (95% CI: [94%-99%]) and for 2 years was 90% (95% CI: [86%-95%]). Forty-two percent of the imatinib-resistant patients with no prior MCyR to imatinib (n= 188) achieved a MCyR with dasatinib.

There were 45 different BCR-ABL mutations in 38% of patients enrolled in this study. Complete hematologic response or MCyR was achieved in patients harboring a variety of BCR-ABL mutations associated with imatinib resistance except T315I. The rates of MCyR at 2 years were similar whether patients had any baseline BCR-ABL mutation, P-loop mutation, or no mutation (63%, 61% and 62%, respectively).

Among imatinib-resistant patients, the estimated rate of PFS was 88% (95% CI: [84%-92%]) at 1 year and 75% (95% CI: [69%-81%]) at 2 years. Among imatinib-intolerant patients, the estimated rate of PFS was 98% (95% CI: [95%-100%]) at 1 year and 94% (95% CI: [88%-99%]) at 2 years.

The rate of major molecular response at 24 months was 45% (35% for imatinib-resistant patients and 74% for imatinib-intolerant patients).

Accelerated phase CML
An open-label, single-arm, multicenter study was conducted in patients intolerant or resistant to imatinib. A total of 174 patients received dasatinib 70 mg twice daily (161 resistant and 13 intolerant to imatinib). The median time from diagnosis to start of treatment was 82 months. Median duration of treatment on dasatinib was 14 months with 31% of patients treated for > 24 months to date. The rate of major molecular response (assessed in 41 patients with a CCyR) was 46% at 24 months. Further efficacy results are reported in Table 10.

Myeloid blast phase CML
An open-label, single-arm, multicenter study was conducted in patients intolerant or resistant to imatinib. A total of 109 patients received dasatinib 70 mg twice daily (99 resistant and 10 intolerant to imatinib). The median time from diagnosis to start of treatment was 48 months. Median duration of treatment on dasatinib was 3.5 months with 12% of patients treated for > 24 months to date. The rate of major molecular response (assessed in 19 patients with a CCyR) was 68% at 24 months. Further efficacy results are reported in Table 10.

Lymphoid blast phase CML and Ph+ ALL
An open-label, single-arm, multicenter study was conducted in patients with lymphoid blast phase CML or Ph+ ALL who were resistant or intolerant to prior imatinib therapy. A total of 48 patients with lymphoid blast CML received dasatinib 70 mg twice daily (42 resistant and 6 intolerant to

imatinib). The median time from diagnosis to start of treatment was 28 months. Median duration of treatment on dasatinib was 3 months with 2% of patients treated for > 24 months to date. The rate of major molecular response (all 22 treated patients with a CCyR) was 50% at 24 months. In addition, 46 patients with Ph+ ALL received dasatinib 70 mg twice daily (44 resistant and 2 intolerant to imatinib). The median time from diagnosis to start of treatment was 18 months. Median duration of treatment on dasatinib was 3 months with 7% of patients treated for > 24 months to date. The rate of major molecular response (all 25 treated patients with a CCyR) was 52% at 24 months. Further efficacy results are reported in Table 10. Of note, major hematologic responses (MaHR) were achieved quickly (most within 35 days of first dasatinib administration for patients with lymphoid blast CML, and within 55 days for patients with Ph+ ALL).

Table 10: Efficacy in phase II dasatinib single-arm clinical studies[a]

	Chronic (n= 387)	**Accelerated (n= 174)**	**Myeloid blast (n= 109)**	**Lymphoid blast (n= 48)**	**Ph+ ALL (n= 46)**
Hematological response rate[b] (%)					
MaHR (95% CI)	n/a	**64% (57-72)**	**33% (24-43)**	**35% (22-51)**	**41% (27-57)**
CHR (95% CI)	**91% (88-94)**	50% (42-58)	26% (18-35)	29% (17-44)	35% (21-50)
NEL (95% CI)	n/a	14% (10-21)	7% (3-14)	6% (1-17)	7% (1-18)
Duration of MaHR (%; Kaplan-Meier estimates)					
1 year	n/a	79% (71-87)	71% (55-87)	29% (3-56)	32% (8-56)
2 years	n/a	60% (50-70)	41% (21-60)	10% (0-28)	24% (2-47)
Cytogenetic response[c](%)					
MCyR (95% CI)	**62% (57-67)**	40% (33-48)	34% (25-44)	52% (37-67)	57% (41-71)
CCyR (95% CI)	54% (48-59)	33% (26-41)	27% (19-36)	46% (31-61)	54% (39-69)
Survival (%; Kaplan-Meier estimates)					
Progression-free					
1 year	91% (88-94)	64% (57-72)	35% (25-45)	14% (3-25)	21% (9-34)
2 years	80% (75-84)	46% (38-54)	20% (11-29)	5% (0-13)	12% (2-23)
Overall					
1 year	97% (95-99)	83% (77-89)	48% (38-59)	30% (14-47)	35% (20-51)
2 years	94% (91-97)	72% (64-79)	38% (27-50)	26% (10-42)	31% (16-47)

Data described in this table are from studies using a initial dose of 70 mg twice daily. See section 4.2 for the recommended initial dose.

[a] Numbers in bold font are the results of primary endpoints.

[B] Hematologic response criteria (all responses confirmed after 4 weeks): Major hematologic response (MaHR) = complete hematologic response (CHR) + no evidence of leukemia (NEL).

CHR (chronic CML): WBC ≤ institutional ULN, platelets < 450,000/mm^3, no blasts or promyelocytes in peripheral blood, < 5% myelocytes plus metamyelocytes in peripheral blood, basophils in peripheral

blood < 20%, and no extramedullary involvement.
CHR (advanced CML/Ph+ ALL): WBC ≤ institutional ULN, ANC ≥ 1,000/mm^3, platelets ≥ 100,000/mm^3, no blasts or promyelocytes in peripheral blood, bone marrow blasts ≤ 5%, < 5% myelocytes plus metamyelocytes in peripheral blood, basophils in peripheral blood < 20%, and no extramedullary involvement.
NEL: same criteria as for CHR but ANC ≥ 500/mm^3 and < 1,000/mm^3 or platelets ≥ 20,000/mm^3 and ≤ 100,000/mm^3.
[c] Cytogenetic response criteria: complete (0% Ph+ metaphases) or partial (0%–35%). MCyR (0%-35%) combines both complete and partial responses.
n/a = not applicable; CI = confidence interval; ULN = upper limit of normal range.

The outcome of patients with bone marrow transplantation after dasatinib treatment has not been fully evaluated.

Phase III clinical studies in patients with CML in chronic, accelerated, or myeloid blast phase, and Ph+ ALL who were resistant or intolerant to imatinib
Two randomized open-label studies were conducted to evaluate the efficacy of dasatinib administered once daily compared with dasatinib administered twice daily. Results described below are based on a minimum of 2 years and 7 years follow-up after initiation of dasatinib therapy.

Study 1
In the study in chronic phase CML, the primary endpoint was MCyR in imatinib-resistant patients. The main secondary endpoint was MCyR by total daily dose level in the imatinib-resistant patients. Other secondary endpoints included duration of MCyR, PFS, and overall survival. A total of 670 patients, of whom 497 were imatinib-resistant, were randomized to the dasatinib 100 mg once daily, 140 mg once daily, 50 mg twice daily, or 70 mg twice daily group. The median duration of treatment for all patients still on therapy with a minimum of 5 years of follow-up (n=205) was 59 months (range 28-66 months). Median duration of treatment for all patients at 7 years of follow-up was 29.8 months (range < 1-92.9 months).

Efficacy was achieved across all dasatinib treatment groups with the once daily schedule demonstrating comparable efficacy (non-inferiority) to the twice daily schedule on the primary efficacy endpoint (difference in MCyR 1.9%; 95% confidence interval [-6.8% - 10.6%]); however, the 100 mg once daily regimen demonstrated improved safety and tolerability. Efficacy results are presented in Tables 11 and 12.

Table 11: Efficacy of dasatinib in phase III dose-optimization study: imatinib resistant or intolerant chronic phase CML (2-year results)[a]

All patients	**n=167**
Imatinib-resistant patients	**n=124**
Hematological response rate[b] (%) (95% CI)	
CHR	**92% (86-95)**
Cytogenetic response[c] (%) (95% CI)	
MCyR	
All patients	**63% (56-71)**
Imatinib-resistant patients	**59% (50-68)**
CCyR	
All patients	**50% (42-58)**
Imatinib-resistant patients	**44% (35-53)**
Major molecular response in patients achieving CCyRd[d] (%) (95% CI)	

All patients	**69% (58-79)**
Imatinib-resistant patients	**72% (58-83)**

[a] Results reported in recommended initial dose of 100 mg once daily.
[B] Hematologic response criteria (all responses confirmed after 4 weeks): Complete hematological response (CHR) (chronic CML): WBC ≤ institutional ULN, platelets < 450,000/mm^3, no blasts or promyelocytes in peripheral blood, < 5% myelocytes plus metamyelocytes in peripheral blood, basophils in peripheral blood < 20%, and no extramedullary involvement.
[C] Cytogenetic response criteria: complete (0% Ph+ metaphases) or partial (0%–35%). MCyR (0%-35%) combines both complete and partial responses.
[d] Major molecular response criteria: Defined as BCR-ABL/control transcripts ≤0.1% by RQ-PCR in peripheral blood samples.
CI = confidence interval ULN = Upper Limit of Normal Interval.

Table 12: Long term efficacy of dasatinib in phase 3 dose optimization study: imatinib resistant or intolerant chronic phase CML patients[a]

	Minimum follow-up period			
	1 year	**2 years**	**5 years**	**7 years**
Major molecular response				
All patients	n/a	37% (57/154)	44% (71/160)	46% (73/160)
Imatinib-resistant patients	NA	35% (41/117)	42% (50/120)	43% (51/120)
Imatinib-intolerant patients	NA	43% (16/37)	53% (21/40)	55% (22/40)
Progression-free survival[b]				
All patients	90% (86, 95)	80% (73,87)	51% (41, 60)	42% (33, 51)
Imatinib-resistant patients	88% (82, 94)	77% (68, 85)	49% (39, 59)	39% (29, 49)
Imatinib-intolerant patients	97% (92, 100)	87% (76, 99)	56% (37, 76)	51% (32, 67)
Overall survival				
All patients	96% (93, 99)	91% (86, 96)	78% (72, 85)	65% (56, 72)
Imatinib-resistant patients	94% (90, 98)	89% (84, 95)	77% (69, 85)	63% (53, 71)
Imatinib-intolerant patients	100% (100, 100)	95% (88, 100)	82% (70, 94)	70% (52, 82)

[a] Results reported in recommended initial dose of 100 mg once daily.
[b] Progression was defined as increasing WBC count, loss of CHR or MCyR, ≥30% increase in Ph+ metaphases, confirmed AP/BP disease or death. PFS was analyzed on an intent-to-treat principle and patients were followed to events including subsequent therapy.

Based on the Kaplan-Meier estimates, the proportion of patients treated with dasatinib 100 mg once daily who maintained MCyR for 18 months was 93% (95% CI: [88%-98%]).

Efficacy was also assessed in patients who were intolerant to imatinib. In this population of patients who received 100 mg once daily, MCyR was achieved in 77% and CCyR in 67%.

Study 2
In the study in advanced phase CML and Ph+ ALL, the primary endpoint was MaHR. A total of 611 patients were randomized to either the dasatinib 140 mg once daily or 70 mg twice daily group. Median duration of treatment was approximately 6 months (range 0.03-31 months).

The once daily schedule demonstrated comparable efficacy (non-inferiority) to the twice daily schedule on the primary efficacy endpoint (difference in MaHR 0.8%; 95% confidence interval [-7.1% - 8.7%]). However, the 140 mg once daily regimen demonstrated improved safety and tolerability. Response rates are presented in Table 13.

Table 13: Efficacy of dasatinib in phase III dose-optimization study: advanced phase CML and Ph+ ALL (2-year results)[a]

	Accelerated (n=158)	**Myeloid blast (n= 75)**	**Lymphoid blast (n= 33)**	**Ph+ ALL (n= 40)**
MaHR[b]	66%	28%	42%	38%
(95% CI)	(59-74)	(18-40)	(26-61)	(23-54)
CHR[b]	47%	17%	21%	33%
(95% CI)	(40-56)	(10-28)	(9-39)	(19-49)
NEL[b]	19%	11%	21%	5%
(95% CI)	(13-26)	(5-20)	(9-39)	(1-17)
MCyR[c]	39%	28%	52%	70%
(95% CI)	(31-47)	(18-40)	(34-69)	(54-83)
CCyR	32%	17%	39%	50%
(95% CI)	(25-40)	(10-28)	(23-58)	(34-66)

[a] Results reported in recommended initial dose of 140 mg once daily (see section 4.2).
[B] Hematologic response criteria (all responses confirmed after 4 weeks): Major hematologic response (MaHR) = complete hematologic response (CHR) + no evidence of leukemia (NEL).
CHR: WBC ≤ institutional ULN, ANC ≥ 1,000/mm^3, platelets ≥ 100,000/mm^3, no blasts or promyelocytes in peripheral blood, bone marrow blasts ≤ 5%, < 5% myelocytes plus metamyelocytes in peripheral blood, basophils in peripheral blood < 20%, and no extramedullary involvement.
NEL: same criteria as for CHR but ANC ≥ 500/mm^3 and < 1,000/mm^3 or platelets ≥ 20,000/mm^3 and ≤ 100,000/mm^3.
[c] MCyR combines both complete (0% Ph+ metaphases) and partial (> 0%-35%) responses.
CI = confidence interval; ULN = upper limit of normal range.

In patients with accelerated phase CML treated with the 140 mg once daily regimen, the median duration of MaHR and the median overall survival was not reached and the median PFS was 25 months.

In patients with myeloid blast phase CML treated with the 140 mg once daily regimen, the median duration of MaHR was 8 months, the median PFS was 4 months, and the median overall survival was 8 months. In patients with lymphoid blast phase CML treated with the 140 mg once daily regimen, the median duration of MaHR was 5 months, the median PFS was 5 months, and the median overall survival was 11 months.

In patients with Ph+ ALL treated with 140 mg once daily regimen, median duration of MaHR was 5 months, median PFS was 4 months, and median overall survival was 7 months.

Pediatric population

Pediatric patients with CML
Among 130 patients with chronic phase CML (CML-CP) treated in two pediatric studies, a Phase I, open-label, nonrandomized dose-ranging trial and a Phase II, open-label, nonrandomized trial, 84 patients (exclusively from the Phase II trial) were newly diagnosed with CML-CP and 46 patients (17 from the Phase I trial and 29 from the Phase II trial) were resistant or intolerant to previous treatment with imatinib. Ninety-seven of the 130 pediatric patients with CML-CP were treated with dasatinib tablets 60 mg/m^2 once daily (maximum dose of 100 mg once daily for patients with high BSA). Patients were treated until disease progression or unacceptable toxicity.

Key efficacy endpoints were: complete cytogenetic response (CCyR), major cytogenetic response (MCyR) and major molecular response (MMR). Results are shown in Table 14.

Table 14: Efficacy of dasatinib in pediatric patients with CML-CP – Cumulative response over time by minimum follow-up period

	3 months	6 months	12 months	24 months
CCyR (95% CI)				
Newly diagnosed (N = 51)[a]	43.1% (29.3, 57.8)	66.7% (52.1, 79.2)	96.1% (86.5, 99.5)	96.1% (86.5, 99.5)
Prior imatinib (N = 46)[b]	45.7% (30.9, 61.0)	71.7% (56.5, 84.0)	78.3% (63.6, 89.1)	82.6% (68.6, 92.2)
MCyR (95% CI)				
Newly diagnosed (N = 51)[a]	60.8% (46.1, 74.2)	90.2% (78.6, 96.7)	98.0% (89.6, 100)	98.0% (89.6, 100)
Prior imatinib (N = 46)[b]	60.9% (45.4, 74.9)	82.6% (68.6, 92.2)	89.1% (76.4, 96.4)	89.1% (76.4, 96.4)
MMR (95% CI)				
Newly diagnosed (N = 51)[a]	7.8% (2.2, 18.9)	31.4% (19.1, 45.9)	56.9% (42.2, 70.7)	74.5% (60.4, 85.7)
Prior imatinib (N = 46)[b]	15.2% (6.3, 28.9)	26.1% (14.3, 41.1)	39.1% (25.1, 54.6)	52.2% (36.9, 67.1)

[a] Patients from Phase II pediatric study of newly diagnosed CML-CP receiving oral tablet formulation
[b] Patients from Phase I and Phase II pediatric studies of imatinib-resistant or intolerant CML-CP receiving oral tablet formulation

In the Phase I pediatric study, after a minimum of 7 years of follow-up among the 17 patients with imatinib-resistant or intolerant CML-CP, the median duration of PFS was 53.6 months and the rate of OS was 82.4%.

In the Phase II pediatric study, in patients receiving the tablet formulation, estimated 24-month PFS rate among the 51 patients with newly diagnosed CML-CP was 94.0% (82.6, 98.0), and 81.7% (61.4, 92.0) among the 29 patients with imatinib-resistant/intolerant CML-CP. After 24 months of follow-up, OS in newly diagnosed patients was 100%, and 96.6% in imatinib-resistant or intolerant patients.

In the Phase II pediatric study, 1 newly diagnosed patient and 2 imatinib-resistant or intolerant patients progressed to blast phase CML.

There were 33 newly diagnosed pediatric patients with CML-CP who received dasatinib powder for oral suspension at a dose of 72 mg/m^2. This dose represents 30% lower exposure compared to the recommended dose. In these patients, CCyR and MMR were CCyR: 87.9% [95% CI: (71.8-96.6)] and MMR: 45.5% [95% CI: (28.1-63.6)] at 12 months.

Among dasatinib-treated CML-CP pediatric patients previously exposed to imatinib, the mutations detected at the end of treatment were: T315A, E255K and F317L. However, E255K and F317L were also detected before treatment. There were no mutations detected in newly diagnosed CML-CP patients at the end of treatment.

Pediatric patients with ALL
The efficacy of dasatinib in combination with chemotherapy was evaluated in a pivotal study in pediatric patients over one year of age with newly diagnosed Ph+ ALL.

In this multicenter, historically-controlled Phase II study of dasatinib added to standard chemotherapy, 106 pediatric patients with newly diagnosed Ph+ ALL, of whom 104 patients had confirmed Ph+ ALL, received dasatinib at a daily dose of 60 mg/m^2 on a continuous dosing regimen for up to 24 months, in combination with chemotherapy. Eighty-two patients received dasatinib tablets exclusively and 24 patients received dasatinib powder for oral suspension at least once, 8 of whom received dasatinib powder for oral suspension exclusively. The backbone chemotherapy regimen was the same as used in the AIEOP-BFM ALL 2000 trial (chemotherapeutic standard multi-agent chemotherapy protocol). The primary efficacy endpoint was 3-year event-free survival (EFS), which was 65.5% (55.5, 73.7).

The minimal residual disease (MRD) negativity rate assessed by Ig/TCR rearrangement was 71.7% by the end of consolidation in all treated patients. When this rate was based on the 85 patients with evaluable Ig/TCR assessments, the estimate was 89.4%. The MRD negativity rates at the end of induction and consolidation as measured by flow cytometry were 66.0% and 84.0%, respectively.

5.2. Pharmacokinetic properties

General properties

Pharmacokinetics of dasatinib were evaluated in 229 adult healthy subjects and in 84 patients.

Absorption:
Dasatinib is rapidly absorbed in patients following oral administration, with peak concentrations between 0.5-3 hours. Following oral administration, the increase in the mean exposure (AUCτ) is approximately proportional to the dose increment across doses ranging from 25 mg to 120 mg twice daily. The overall mean terminal half-life of dasatinib is approximately 5-6 hours in patients.

Data from healthy subjects administered a single 100 mg dose of dasatinib 30 minutes following a high-fat meal indicated a 14% increase in the mean AUC of dasatinib.

A low-fat meal 30 minutes prior to dasatinib resulted in a 21% increase in the mean AUC of dasatinib. The observed food effects do not represent clinically relevant changes in exposure. Dasatinib exposure variability is higher under fasted conditions (47% CV) compared to light-fat meal (39% CV) and high-fat meal (32% CV) conditions.

Based on the patient population PK analysis, variability in dasatinib exposure was estimated to be mainly due to inter-occasion variability in bioavailability (44% CV) and, to a lesser extent, due to inter-individual variability in bioavailability and inter-individual variability in clearance (30% and 32% CV, respectively). The random inter-occasion variability in exposure is not expected to affect the cumulative exposure and efficacy or safety.

Distribution:
In patients, dasatinib has a large apparent volume of distribution (2,505 L), coefficient of variation (CV% 93%), suggesting that the medicinal product is extensively distributed in the extravascular space. At clinically relevant concentrations of dasatinib, binding to plasma proteins was approximately 96% on the basis of *in vitro* experiments.

Biotransformation:
Dasatinib is extensively metabolized in humans with multiple enzymes involved in the generation of the metabolites. In healthy subjects administered 100 mg of [^{14}C]-labelled dasatinib, unchanged dasatinib represented 29% of circulating radioactivity in plasma. Plasma concentration and measured *in vitro* activity indicate that metabolites of dasatinib are unlikely to play a major role in the observed pharmacology of the product. CYP3A4 is a major enzyme responsible for the metabolism of dasatinib.

Elimination:
The mean terminal half-life of dasatinib is 3 hours to 5 hours. The mean apparent oral clearance is 363.8 L/hr (CV% 81.3%).

Elimination is predominantly in the feces, mostly as metabolites. Following a single oral dose of [^{14}C]-labelled dasatinib, approximately 89% of the dose was eliminated within 10 days, with 4% and 85% of the radioactivity recovered in the urine and feces, respectively. Unchanged dasatinib accounted for 0.1% and 19% of the dose in urine and feces, respectively, with the remainder of the dose as metabolites.

Linearity/Nonlinearity:
Insufficient data available.

Patient characteristics
Renal impairment:
No clinical studies have been conducted with dasatinib in patients with reduced renal function (patients with serum creatinine concentrations >1.5 times the upper limit of the normal range were excluded from the studies). Because the renal clearance of dasatinib and its metabolites is <4%, a decrease in total body clearance is not expected in patients with renal impairment.
Dasatinib and its metabolites are minimally excreted via the kidney.

Hepatic impairment:
The effect of hepatic impairment on the single-dose pharmacokinetics of dasatinib was assessed in 8 moderately hepatic-impaired subjects who received a 50 mg dose and 5 severely hepatic-impaired

subjects who received a 20 mg dose compared to matched healthy subjects who received a 70 mg dose of dasatinib. The mean C_{max} and AUC of dasatinib adjusted for the 70 mg dose were decreased by 47% and 8%, respectively, in subjects with moderate hepatic impairment compared to subjects with normal hepatic function. In severely hepatic-impaired subjects, the mean C_{max} and AUC adjusted for the 70 mg dose were decreased by 43% and 28%, respectively, compared to subjects with normal hepatic function (see sections 4.2 and 4.4).

Pediatric population:
The pharmacokinetics of dasatinib have been evaluated in 104 pediatric patients with leukemia or solid tumors (72 who received the tablet formulation and 32 who received the powder for oral suspension).

In a pediatric pharmacokinetics study, dose-normalized dasatinib exposure (C_{avg}, C_{min} and C_{max}) appears similar between 16 patients with Ph+ ALL.

Pharmacokinetics of the tablet formulation of dasatinib were evaluated for 72 pediatric patients with relapsed or refractory leukemia or solid tumors at oral doses ranging from 60 to 120 mg/m^2 once daily and 50 to 110 mg/m^2 twice daily. Data was pooled across two studies and showed that dasatinib was rapidly absorbed. Mean T_{max} was observed between 0.5 and 6 hours and mean half-life ranged from 2 to 5 hours across all dose levels and age groups. Dasatinib PK showed dose proportionality with a dose-related increase in exposure observed in pediatric patients. There was no significant difference of dasatinib PK between children and adolescents. The geometric means of dose- normalized dasatinib C_{max}, $AUC_{(0-T)}$, and AUC (INF) appeared to be similar between children and adolescents at different dose levels. A PPK model-based simulation predicted that the body weight tiered dosing recommendation described for the tablet, in section 4.2, is expected to provide similar exposure to a tablet dose of 60 mg/m^2.

5.3. Preclinical safety data
The non-clinical safety profile of dasatinib was assessed in a battery of *in vitro* and *in vivo* studies in mice, rats, monkeys, and rabbits.

The primary toxicities occurred in the gastrointestinal, hematopoietic, and lymphoid systems. Gastrointestinal toxicity was dose-limiting in rats and monkeys, as the intestine was a consistent target organ. In rats, minimal to mild decreases in erythrocyte parameters were accompanied by bone marrow changes; similar changes occurred in monkeys at a lower incidence. Lymphoid toxicity in rats consisted of lymphoid depletion of the lymph nodes, spleen, and thymus, and decreased lymphoid organ weights. Changes in the gastrointestinal, hematopoietic and lymphoid systems were reversible following cessation of treatment.

Renal changes in monkeys treated for up to 9 months were limited to an increase in background kidney mineralization. Cutaneous hemorrhage was observed in an acute, single-dose oral study in monkeys but was not observed in repeat-dose studies in either monkeys or rats. In rats, dasatinib inhibited platelet aggregation *in vitro* and prolonged cuticle bleeding time *in vivo*, but did not invoke spontaneous hemorrhage.

Dasatinib activity *in vitro* in hERG and Purkinje fiber assays suggested a potential for prolongation of cardiac ventricular repolarization (QT interval). However, in an *in vivo* single-dose study in conscious telemetered monkeys, there were no changes in QT interval or ECG wave form.

Dasatinib was not mutagenic in *in vitro* bacterial cell assays (Ames test) and was not genotoxic in

an *in vivo* rat micronucleus study. Dasatinib was clastogenic *in vitro* to dividing Chinese Hamster Ovary (CHO) cells.

Dasatinib did not affect male or female fertility in a conventional rat fertility and early embryonic development study, but induced embryolethality at dose levels approximating human clinical exposures. In embryofetal development studies, dasatinib likewise induced embryolethality with associated decreases in litter size in rats, as well as fetal skeletal alterations in both rats and rabbits. These effects occurred at doses that did not produce maternal toxicity, indicating that dasatinib is a selective reproductive toxicant from implantation through the completion of organogenesis.

In mice, dasatinib induced immunosuppression, which was dose-related and effectively managed by dose reduction and/or changes in dosing schedule. Dasatinib had phototoxic potential in an *in vitro* neutral red uptake phototoxicity assay in mouse fibroblasts. Dasatinib was considered non-phototoxic *in vivo* after a single oral administration to female hairless mice at exposures up to 3-fold the human exposure following administration of the recommended therapeutic dose (based on AUC).

In a two-year carcinogenicity study, rats were administered oral doses of dasatinib at 0.3, 1, and 3 mg/kg/day. The highest dose resulted in a plasma exposure (AUC) level generally equivalent to the human exposure at the recommended range of initial doses from 100 mg to 140 mg daily. A statistically significant increase in the combined incidence of squamous cell carcinomas and papillomas in the uterus and cervix of high-dose females and of prostate adenoma in low-dose males was noted. The relevance of the findings from the rat carcinogenicity study for humans is not known.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Tablet core:
Lactose monohydrate (derived from cow milk)
Microcrystalline cellulose, PH 101
Croscarmellose sodium
Hydroxypropyl cellulose
Magnesium stearate

Film coating:
Opadry® White 03H280006
Hpmc 2910/Hypromellose
Titanium dioxide
Propylene glycol

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

24 months

6.4. Special precautions for storage

Store at room temperature below 30°C.

6.5. Nature and contents of the container
The primary packaging of the product is clear PVC/Aclar and aluminum foil blister. Blisters are packed in cardboard box. It is available in blisters of 60 film-coated tablets in a box with a package leaflet.

6.6. Special precautions for disposal and other handling
DAFANIB tablets consist of a core tablet, surrounded by a film-coating to prevent exposure of healthcare professionals to the active substance. However, if the tablets are crushed or broken, healthcare professionals should wear disposable chemotherapy gloves.

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

7. MARKETING AUTHORIZATION HOLDER
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