14 September 2017
EMA/54558/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Tasigna

International non-proprietary name: nilotinib

Procedure No. EMEA/H/C/000798/X/0088/G

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AE	Adverse event
AESI	Adverse event of special interest
ALL	Acute lymphoid leukemia
ALAG	Absorption lag time
ALT	Alanine aminotransferase
AP	Accelerated phase
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
BC	Blast crisis
BCR-ABL	Fusion gene from breakpoint cluster region and Abelson genes
Bid	Twice daily
BSA	Body surface area
CCyR	Complete cytogenetic response
CHR	Complete hematologic response
CI	Confidence interval
CML	Chronic myeloid leukemia
CP	Chronic phase
CPP	Critical process parameters
CTCAE	Common Terminology Criteria for Adverse Events
CVE	Cardiovascular event
DILI	Drug-induced liver injury
ECG	Electrocardiogram
EFS	Event free survival
GI	Gastrointestinal
GCP	Good clinical practice
GMP	Good manufacturing practice
HLA	Human leucocyte antigen
HSCT	Hematopoietic stem cell transplant
IFN	Interferon
IFNα	Interferon alpha
IPC	In-process control
MCyR	Major cytogenetic response
MedDRA	Medical Dictionary for Regulatory Activities
MMR	Major molecular response
MTD	Maximum tolerated dose
OS	Overall survival
PCyR	Partial cytogenetic response
PD	Pharmacodynamics
Ph	Philadelphia chromosome
PK	Pharmacokinetics
SAE	Serious adverse event
SOP	Standard operating procedure

TKI	Tyrosine kinase inhibitor
ULN	Upper limit of normal
WBC	White blood cell

1. Background information on the procedure

1.1. Submission of the dossier

Novartis Europharm Ltd submitted on 2 November 2016 a group of variation(s) consisting of an extension of the marketing authorisation and the following variation(s):

Variation(s) requested		Type
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Extension of Indication to include treatment of paediatric patients with newly diagnosed Philadelphia chromosome-positive chronic myelogenous leukaemia in chronic phase (Ph+ CML-CP), or with Ph+ CML-CP resistant or intolerant to prior therapy including imatinib, based on results from two clinical studies in paediatric patients conducted in accordance with the approved Tasigna Paediatric Investigation Plan (PIP); the Phase I PK study CAMN107A2120 and the Phase II safety and efficacy study CAMN107A2203. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated and the package leaflet has been updated accordingly. In addition, the MAH took the opportunity to implement minor editorial changes and to align the annexes with the latest QRD template. An updated RMP version 18.0 was provided as part of the application.

Extension of the marketing authorisation to add a new strength of 50mg hard capsules; the MAH proposed to merge the SmPCs for the 50 mg and 200 mg strengths

The legal basis for this application refers to:

Article 7.2 of Commission Regulation (EC) No 1234/2008 – Group of variations

Tasigna was designated as an orphan medicinal product EU/3/06/375 on 21/11/2007in the following condition: treatment of Philadelphia chromosome positive chronic myelogenous leukaemia (CML).

The new indication, which is the subject of this application, falls within the above mentioned orphan designation.

Information on Paediatric requirements

The application included an EMA Decision(s) P/0297/2015 on the agreement of a paediatric investigation plan (PIP) and on the granting of a product-specific waiver in the paediatric population less than 1 year of age.

At the time of submission of the application, the PIP P/0297/2015 was completed.

The PDCO issued an opinion on compliance for the PIP P/0297/2015.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

Scientific Advice / Protocol Assistance

The MAH received Scientific Advice from the CHMP on 21 April 2005 and 17 November 2005 and Protocol Assistance from the CHMP on 24 July 2008.

The Scientific Advice and Protocol Assistance pertained to non-clinical and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Sinan B. Sarac Co-Rapporteur: Harald Enzmann

CHMP Peer reviewer(s): N/A

- The application was received by the EMA on 2 November 2016.
- The procedure started on 24 November 2016.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 13 February 2017. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 28 February 2017. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 24 February 2017.
- During the meeting on 23 March 2017, the CHMP agreed on the consolidated List of Questions to be sent to the MAH.
- The MAH submitted the responses to the CHMP consolidated List of Questions on 17 May 2017.
- The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on 03 July 2017.
- During the meeting on 20 July 2017, the CHMP agreed on the consolidated List of Outstanding Issues to be sent to the MAH.
- The MAH submitted the responses to the CHMP consolidated List of Outstanding Issues on 14 August 2017.
- The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on 30 August 2017.
- During the meeting on 14 September 2017, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for an extension of the marketing authorisation for Tasigna and an extension of indication.
- The CHMP adopted a report on similarity of Tasigna with Sprycel (dasatinib), Bosulif (bosutinib) &

Iclusig (ponatinib) on 14 September 2017.

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Tasigna is indicated for the treatment of:

- paediatric patients with newly diagnosed Philadelphia chromosome positive chronic myelogenous leukaemia (CML) in the chronic phase,
- paediatric patients with Philadelphia chromosome positive CML in chronic phase with resistance or intolerance to prior therapy including imatinib.

2.1.2. Epidemiology and risk factors

CML in childhood is rare, accounting for less than 3% of all paediatric leukaemias. The incidence increases with age, being exceptionally rare in infancy at 0.7/million/year at ages 1 to 14 years and rising to 1.2/million/year in adolescents (Suttorp and Millot 2010).

2.1.3. Biologic features, aetiology and pathogenesis

Chronic myelogenous leukaemia is a myeloproliferative disorder characterized by clonal expansion of hematopoietic stem cells expressing the BCR-ABL gene. The initial, chronic phase (CP) of CML is characterized by overproduction of immature myeloid cells and mature granulocytes in the spleen, bone marrow, and peripheral blood. If untreated, the disease progresses to an accelerated phase (AP), marked by the presence of primitive blast cells in the bone marrow and peripheral blood, followed by a terminal blast-crisis (BC) phase. Patients with persistent molecular disease are also at risk for progression. Inhibition of the BCR –ABL TK is an effective treatment modality for Ph+ CML.

Similarly to adults, the pathology in CML in children is driven by the BCR -ABL fusion protein, a product of the Philadelphia (Ph) chromosome, which is formed by a translocation between the long arms of chromosomes 9 and 22. As in adults, the disease is characterized by progression through defined stages, starting with the relatively long-lasting chronic phase (CP), then accelerated phase (AP), and finally blast crisis (BC) (Melo and Barnes 2007).

Though the disease aetiology shows no difference between adults and children, some differences are observed with respect to a different breakpoint distribution pattern in the BCR gene and a higher proportion of breakpoints within Alu repeat regions in children compared with adults with CML-CP. This could be the reason for a more aggressive clinical presentation of the disease (markedly raised leukocyte count and higher rate of splenomegaly) in children (Tanizawa 2016).

However, similar to adults, not all paediatric patients respond to or tolerate imatinib treatment, and resistance to imatinib during treatment may develop, usually through the emergence of point mutations in BCR-ABL; other mechanisms of resistance include genomic amplification of BCR-ABL and modulation of drug transporters (Melo and Chuah 2007).

2.1.4. Clinical presentation, diagnosis and stage / prognosis

Common signs and symptoms of CML CP, when present, result from anaemia and splenomegaly. These include fatigue, weight loss, malaise and left upper quadrant fullness or pain. Rare manifestations include bleeding (associated with a low platelet count and/or platelet dysfunction), thrombosis (associated with thrombocytosis and/or marked leukocytosis), gouty arthritis (from elevated uric acid levels), retinal haemorrhages and upper gastrointestinal ulceration (from elevated histamine levels due to basophilia). Leukostatic symptoms (priapism, dyspnoea, drowsiness, loss of coordination, confusion) due to leukaemic cells sludging in the blood vessels are uncommon in CP despite white blood cell (WBC) count often exceeding 100 ×109/L. Splenomegaly is the most consistent physical sign detected in 40%–50% of cases. Headaches, bone pain, arthralgias, pain from splenic infarction and fever are more frequent with CML transformation.

2.1.5. Management

Prior to the availability of imatinib, IFN-α was the treatment of choice for adult and paediatric patients not eligible for hematopoietic stem cell transplant (HSCT), with patients who achieved complete cytogenetic response on IFN surviving more than a decade.

However, only a small proportion (5–10%) of patients responds to IFN. Therefore, until 2000, although the morbidity and mortality attributable to HSCT were appreciable, it was state of the art to offer HSCT to younger patients who had suitable HLA-matched donors. The risk factors and outcomes of HSCT in children are considered comparable to those in young adult patients (Suttorp 2008).

The availability of imatinib (first approved for the use in children in 2001) resulted in a dramatic reduction in the frequency of HSCT in paediatric CML patients, and it has now become the standard first-line treatment in paediatric patients. Imatinib is approved in paediatric patients with newly diagnosed Ph+ CML for whom bone marrow transplantation is not considered as the first line of treatment, and in paediatric patients with Ph+ CML in CP after failure of interferon-alpha therapy, or in AP or BC. Imatinib has reduced the yearly risk of progression from CP to advanced stages to less than 1% per year. In a study conducted in 51 paediatric patients with de novo CML-CP, the CCyR rate was 64.7%, and the MMR rate was 27.3% (Champagne et al 2011). Similar results were reported by Millot et al (2011) in a study conducted in 44 paediatric patients with newly diagnosed CML-CP, with CCyR and MMR rates of 61% and 31%, respectively, at 12 months.

However, imatinib and second generation TKIs seems not curing the disease and in the majority of patients leukemic cells will persist; furthermore not all patients respond to, or tolerate imatinib as first line treatment. Some patients who initially respond to imatinib subsequently relapse, usually due to the emergence of mutations in BCR-ABL that confer resistance to imatinib, or due to overexpression of the BCR-ABL protein.

An unmet medical need exists for alternative, more effective treatment options in paediatric patients with CML. Considering that imatinib is currently the only approved BCR-ABL-targeted TKI in paediatric patients with CML-CP, other therapeutic alternatives particularly in children in whom resistance or intolerance to imatinib develops, is needed.

About the product

Nilotinib is a potent inhibitor of the ABL tyrosine kinase activity of the BCR-ABL oncoprotein both in cell lines and in primary Philadelphia-chromosome positive leukaemia cells. The substance binds with high

affinity to the ATP-binding site in such a manner that it is a potent inhibitor of wild-type BCR-ABL and maintains activity against 32/33 imatinib-resistant mutant forms of BCR-ABL. As a consequence of this biochemical activity, nilotinib selectively inhibits the proliferation and induces apoptosis in cell lines and in primary Philadelphia-chromosome positive leukaemia cells from CML patients. In murine models of CML, as a single agent nilotinib reduces tumour burden and prolongs survival following oral administration (SmPC, section 5.1).

Dosing in paediatric patients is individualised and is based on body surface area (mg/m^2). The recommended dose of Tasigna is 230 mg/m^2 twice daily, rounded to the nearest 50 mg dose (to a maximum single dose of 400 mg). Different strengths of Tasigna hard capsules can be combined to attain the desired dose (SmPC, section 4.2).

Type of Application and aspects on development

The applicant requested the approval for the following indication:

Tasigna is indicated for the treatment of:

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

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

The CHMP adopted this indication without changes.

For dosing of paediatric patients with small body weight and children who cannot swallow the available 150 mg or 200 mg capsule, a smaller 50 mg capsule with the same qualitative composition as the authorised 150 mg and 200 mg strengths was developed. The request for marketing authorisation for the new 50 mg capsule strength is also part of this application.

The application for extending the indication to include the treatment of paediatric patients with Ph+ CML-CP is based on data from two clinical studies in paediatric patients which were conducted in accordance with the approved Tasigna PIP:

- Study CAMN107A2120 was a Phase I, open-label, multi-center study evaluating the pharmacokinetics (PK), safety, and preliminary efficacy of nilotinib at a dose of 230 mg/m2 twice daily in paediatric patients with Ph+ CML resistant or intolerant to imatinib or dasatinib (n=11) or refractory/relapsed Ph+ acute lymphoid leukemia (ALL; n=4). The study was completed as planned, after all patients had completed at least 12 treatment cycles of 28 days or discontinued early from the study.

- Study CAMN107A2203 is a Phase II, open-label, multi-center study evaluating the efficacy and safety of nilotinib 230 mg/m2 twice daily conducted in 58 pediatric patients with Ph+ CML (33 patients were resistant or intolerant to imatinib or dasatinib, and 25 patients were newly diagnosed). At the time of the data cut-off of the primary analysis (01-Jun-2016), all patients had completed at least 12 cycles of 28 days of treatment, or discontinued early. The study is ongoing, and will continue for a total of 66 cycles.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as hard capsules containing 50 mg of nilotinib hydrochloride monohydrate as active substance.

Other ingredients of the hard capsule content are lactose monohydrate, crospovidone, poloxamer, silica colloidal anhydrous and magnesium stearate. The hard capsule shell is composed of gelatin, titanium dioxide (E171), red iron oxide (E172) and yellow iron oxide (E172); and the printing ink is composed of shellac, propylene glycol, ammonium hydroxide and black iron oxide (E172)

The product is available in PVC/PVDC/Alu blisters as described in section 6.5 of the SmPC.

2.2.2. Active Substance

The active substance used for the proposed Tasigna 50 mg hard capsules is the same as that for the already approved Tasigna 150 mg and 200 mg hard capsules. The information on the active substance is described in the quality dossier which was previously reviewed and approved as part of the Tasigna 150 mg and 200 mg strength marketing authorisation applications. No new information is provided with this application.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The finished product is presented as a hard gelatine capsule with immediate release dosage form for oral administration. It is a hard capsule size 4 with red opaque cap with black radial imprint “NVR” above “ABL” and light yellow opaque body, containing white to yellowish powder.

The objective of the pharmaceutical development was to develop an immediate release solid dosage form for oral administration containing 50 mg of nilotinib hydrochloride monohydrate to extend the current indication to include the treatment of paediatric patients.

The pharmaceutical development of this new strength is supported by the data generated by the drug product development of the 200 mg and 150 mg hard capsules, which are currently the approved dosage strengths of nilotinib. The composition of the capsule fill is qualitatively identical for all dosage strengths. They differ only in the amount of capsule fill filled in the capsule shell, the capsule colour, size and imprint.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. Compatibility between the drug substance and excipients has been demonstrated. The same manufacturing process of wet granulation was chosen for the new strength.

Particle sizes are not critical for the dissolution. The development of the dissolution method is adequately described and the discriminatory properties have been satisfactorily demonstrated. The dissolution method for routine testing is identical to the already marketed 150 mg and 200 mg hard capsules and the dissolution profiles across the dosage strengths are similar.

The primary packaging for Tasigna is PVC/ PVDC (duplex) blister packs, consisting of a PVC/ PVDC film backed with a heat sealable lacquered aluminium foil. The PVDC film is in contact with the drug product. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product. The primary packaging material complies with EU-Regulations No.10/2011 and No.1935/2004/EC.

Manufacture of the product and process controls

The manufacturing process of Tasigna 50 mg hard capsules is considered as a standard process which comprises the following main steps: mixing, wet-granulation, drying, blending, capsule filling and primary packaging.

The manufacturing process has been described in sufficient detail. It is the same used for the manufacture of the 150 mg and 200 mg capsules already approved. A common blend is used for the manufacture of all strengths.

The manufacturing process for the common blend, later encapsulated into 50 mg, 150 mg and 200 mg hard capsules, has previously been validated during the manufacture of the initially registered strengths 150 mg and 200 mg.

The critical steps in the manufacturing process of Tasigna 50 mg hard capsules are controlled by the in-process controls (IPCs) during the manufacturing process, which have been presented and are adequately justified. The control strategy ensures that the manufacturing process consistently delivers a product that meets the defined criteria for all release specifications.

A bulk holding time for capsules prior to primary packaging has been established, supported with provided stability data.

It is considered that the manufacturing process of 50 mg capsules is sufficiently robust to provide assurance that hard capsules of consistent quality, complying with the designated specification, are produced.

Product specification

The specification of Tasigna 50 mg hard capsules for batch release and shelf-life includes the following tests: appearance (visual examination), identification (UV and HPLC), mean mass of capsules content (weight), dissolution (UV), impurities (HPLC), microbial limit tests (Ph. Eur.), uniformity of dosage units (Ph. Eur.) and assay (HPLC).

Adequate specifications for control of the finished product at release and during shelf-life have been established. The analytical methods used have been adequately described and validated. Satisfactory information regarding the reference standards used in the routine analysis of finished product has been presented.

The batch analysis data from a verification commercial scale batch of Tasigna 50 mg hard capsules has been provided. In addition, batch analysis from three pre-validation batches and a clinical batch manufactured from the full common blend has also been provided. The results complied with the proposed specifications, providing evidence that the quality of the finished product is properly controlled by the analytical methods and the set specifications.

Stability of the product

Stability data of three pre-validation production scale batches (larger than the proposed commercial scale batches) manufactured from the full common blend of finished product stored under long term conditions for 36 months at 25ºC / 60% RH, for up to 36 months at intermediate conditions 30ºC / 75% RH and for up to 6 months under accelerated conditions at 40ºC / 75% RH, according to the ICH guidelines, were provided. The batches of Tasigna 50 mg hard capsules are representative of those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, mean mass of capsule content, dissolution, assay, degradation products and microbial purity. The methods used were the same as for release testing and are stability indicating. No changes in appearance, mean mass, or microbial testing were seen during storage at any of the storage conditions. A tendency for an increase in one degradation product was observed during storage. The increase is most pronounced at high temperature and humidity, but the results remains within specification and below the proposed limit. All results are within the specifications at long term storage conditions (25°C / 60% RH and 30°C / 75% RH).

At accelerated storage conditions (40°C / 75% RH), an out of specification (OOS) result was observed for one of the tested parameters. Satisfactory investigation and explanation have been provided and proposed shelf-life and storage conditions reflect the findings of the stability.

Stability testing has additionally been performed for up to 6 months at -20°C / ambient RH, up to 36 months at 5°C / ambient RH and up to 3 months at 50°C / ambient RH. All batches met the specification criteria and the data show that the stability of the capsules is not impacted by freezing.

A photostability study was carried out on one pre-validation scale batch in accordance with the ICH Q1B guideline. There was no significant difference in the results obtained for the directly exposed unpacked sample and the control. Therefore, it can be concluded that the finished product is not sensitive to light.

Based on the provided stability data, the proposed shelf life of 36 months with the storage condition “do not store above 30°C” and “store in the original package in order to protect from moisture” as stated in the SmPC (section 6.3 and 6.4) is acceptable.

Adventitious agents

The lactose monohydrate and the gelatin in capsule shell are of animal origin. For lactose, a declaration of compliance with EMA Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products, EMA/410/01 rev. 3, is provided.

Information on the country of origin of source materials, the nature of animal tissue used in manufacture and the manufacturing process is provided for gelatine in the EDQM certificates of suitability for the suppliers currently used.

No other materials of human or animal origin are used in the manufacture of Tasigna 50 mg hard capsule.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important

product quality characteristics, and these in turn lead to the conclusion that from a quality perspective the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Discussion on chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

N/A

2.3. Non-clinical aspects

No new non clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.3.1. Ecotoxicity / environmental risk assessment

No ERA studies were submitted (see discussion on non-clinical aspects).

2.3.2. Discussion and Conclusion on non-clinical aspects

The justification provided by the MAH for not performing environmental risk assessment studies was considered acceptable. The addition of the paediatric population to the currently approved indications is not expected to significantly increase the use of nilotinib on the EU market. CML in childhood is rare, accounting for less than 10% of all cases of CML and less than 3% of all paediatric leukemias. The incidence increases with age, being exceptionally rare in infancy at 0.7/million/year at ages 1 to 14 years and rising to 1.2/million/year in adolescents (Suttorp M, Millot F 2010).

The most recent ERA (May 2016) as well as the SmPC already include a statement that any unused product should be disposed according to local regulations, and not be disposed of via domestic sewage. The inclusion of the paediatric indication would not warrant any additional cautionary statements; hence the absence of a stand-alone ERA for this procedure is acceptable.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

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

- Tabular overview of clinical studies

Table 1 Overview of the studies and their status

Study	Study design	No. of patients included in the analyses	FPFV/LPLV; Status
[A2203]	Phase II, open-label multi-center study evaluating efficacy and safety of nilotinib 230 mg/m2 in pediatric patients with newly diagnosed Ph+ CML-CP, or imatinib/dasatinib-resistant/intolerant Ph+ CML-CP or -AP	Total: 58 patients resistant/intolerant CML-CP: 33 newly diagnosed CML-CP: 25	20-Aug-2013/ 01-Jun-2016 Ongoing; All patients had completed 12 x 28- day cycles or discontinued
[A2120]	Phase I open-label multi-center study evaluating PK, PD, safety, and preliminary efficacy of nilotinib 230 mg/m2 in pediatric patients with newly diagnosed Ph+ CML- CP, imatinib/dasatinib-resistant/intolerant Ph+ CML-CP or -AP, or refractory/relapsed Ph+ ALL	Total: 15 patients resistant/intolerant CML-CP: 11 relapsed/refractory ALL: 4	14-Apr-2011/ 01-Jul-2015 Completed
CML = chronic myeloid leukemia; CP = chronic phase; AP = accelerated phase; Ph+ = Philadelphia chromosome positive; ALL = acute lymphoblastic leukemia; PK = pharmacokinetic; PD = pharmacodynamics; FPFV=first patient first visit; LPLV=last patient last visit			

2.4.2. Pharmacokinetics

Table 2 summarizes the clinical studies submitted with a pharmacokinetic component.

Table 2 Overview of studies used for clinical pharmacology evaluation

Study Code/Study status with data cut-off date	Study design	Patient population/No. of patients enrolled	Dose strength of Capsule used	Treatment Duration Medication dose/dosage regimen	PK Sampling
A2120/ completed with last patient last visit on 01-Jul-2015	Phase I, open-label multicenter study evaluating PK, PD, and safety/tolerability of nilotinib in pediatric patients	**Total, N=15** • Newly diagnosed Ph+ CML-CP (n=0), or • Ph+ CML-CP resistant/intolerant to imatinib and/or dasatinib (n=11) or • Ph+ CML-AP resistant/intolerant to imatinib and/or dasatinib (n=0), or • Relapsed/ refractory Ph+ ALL(n=4) • Group 1: ages 1 year to < 10 years, n=8 • Group 2, ages ≥ 10 years to < 18 years, n=7	50 mg 150 mg 200 mg	Patients were administered nilotinib 230 mg/m^2 bid, orally, rounded to the nearest 50 mg (max single dose 400 mg) for 28 days (1 cycle) for up to 12 cycles prior to protocol amendment 3 and up to 24 cycles post Amendment 3.	Following a single oral dose on Day 1: at pre- dose (0 hour), 1, 2, 3, 5, 8, 12 and 24 hours post-dose. Pre-dose/trough samples were also collected on Days 8, 15, 22, and 28.

A2203/ ongoing, data cut-off of 01-Jun-2016	A Phase II, open-label multicenter study evaluating efficacy, safety, and PK of nilotinib in pediatric patients	**Total, N=59** • Ph+ CML-CP patients resistant or intolerant to either imatinib or dasatinib, n = 34 • Ph+ CML-AP patients resistant or intolerant to either imatinib or dasatinib[b], n = 0 • Newly diagnosed Ph+ CML-CP patients in chronic phase, n =25	50 mg 150 mg 200 mg	Patients were administered nilotinib 230 mg/m^2 bid All patients to be treated for 28 days (1 cycle) for up to 66 cycles. The current report presents the results of the primary analyses with a cut-off date of 01-Jun-2016, at which time all patients had either completed 12 cycles of treatment or discontinued study treatment early	Pre-dose (0 hour) on Cycle 1 Day 1 Following three consecutive days without dose interruption or dose modification of nilotinib administration: • pre-dose (0 hour) Cycle 1 Day 8, 15, 22 and 28 • pre-dose (0 hour) Cycle 3, 6, 9, 12 Day 28 Two additional PK samples were collected on Cycle 1 Day 1 and Day 8: 1 sample between 1-5 hours and 1 sample between 6-12 hours post-dose.

Pharmacokinetics

Data from patients with Ph+ CML-CP in studies A2203 and A2120 were pooled and the following populations were used for various analyses:

- Pooled patients with Ph+ CML-CP or ALL in both A2120 and A2203 (for dose-exposure analyses)
- Pooled patients with Ph+ CML-CP in both A2120 and A2203 (for dose-exposure analyses)
- Pooled patients with Ph+ CML-CP resistant/intolerant to either imatinib/dasatinib in both A2120 and A2203 (for dose-exposure and exposure-response analyses), and
- Newly diagnosed Ph+ CML-CP patients, from only A2203 for dose-exposure and exposure-response analyses, as A2120 did not enroll newly diagnosed CML-CP patients.

The following analyses were performed:

- Dose-Exposure – Inter/Intra-patient variability, ethnic sensitivity among Caucasians, Asians and others, as well as dose-exposure relationship after a single dose and multiple doses of 230 mg/m^2. These data are presented for the pooled PK population of studies, the pooled Ph+ CML-CP PK population and the pooled imatinib/dasatinib resistant/intolerant PK population.
- Exposure-Efficacy – Trough concentrations vs. BCR-ABL/ABL% ratio over time, time averaged trough concentration vs. probability of major molecular response (MMR) at multiple time points.
- Exposure-Safety – Concentration vs. ECG parameter prolongation, last observed trough concentration prior to onset vs. probability of adverse events of special interest (AESI) and time of AESI, last observed trough concentration prior to onset of event vs. probability of hepatic abnormality, time to ALT elevations vs. last observed trough concentration prior to elevation, normalized ALT elevations over time vs. time-averaged trough concentration until assessment of elevation. All exposure-response analyses were performed separately for the resistant/intolerant patients and for the newly diagnosed patients. Indications were not pooled.

Population PK analyses

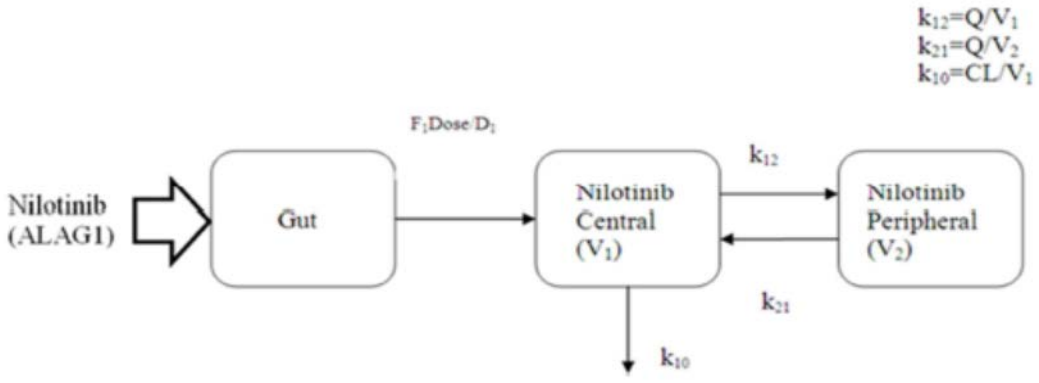
In addition, a population PK analysis was performed to characterize the PK of nilotinib and the effects of potential covariates, such as demographic and clinical factors, through the use of nonlinear mixed effects models. This report also summarized model-based population and individual predictions of PK exposure in pediatrics based on a dose of 230 mg/m^2 twice daily compared to that of adults based on 400 mg twice daily.

The population PK analysis used the following data:

- pediatric patients in Phase I [Study CAMN107A2120] (N=14 with evaluable PK) pediatric patients in Phase II [Study CAMN107A2203] (N=58 with evaluable PK)
- adult patients in [Study CAMN107A2101] with at least one PK profile for a 400 mg twice daily regimen (N=17)
- adult patients in [Study CAMN107A2303] with at least one PK profile for a 400 mg twice daily regimen (N=18)

The inclusion of patients from the adult trials with at least one PK profile for a 400 mg twice daily dose was to provide a reference population at a comparable dose to that of pediatric patients in the analysis population and to not overwhelm the pediatric data with data from over 1000 adults with sparse data at various doses.

This analysis adopted a two-compartment model, with an absorption lag time (ALAG1, h) followed by a zero-order absorption of duration (D1, h), and with elimination described by a first-order process. The covariates assessed included body size, age, liver function tests, indication, ethnicity, and gender. Covariates were incorporated into the model by forward selection ($p<0.01$) and backward elimination ($p\geqslant 0.01$). The following Figure 1 provides an overview:



ALAG1 refers to absorption lag time, F_1 refers to the relative bioavailability, and D_1 refers to the zero-order input duration. CL is the clearance, V_1 is the volume of distribution of central compartment, V_2 is the volume of the peripheral compartment, and Q is the inter-compartmental clearance. k_{12} and k_{21} refer to the transfer rate constant between the central and peripheral compartments, and k_{10} refer to the elimination rate constant from central compartment.

Figure 1: Structural model for the PK of nilotinib

Typical model-based population predictions of steady-state apparent clearance (CL/F1, L/h), BSA-normalized clearance (L/h/m^2), and three exposure measures – AUC (h × ng/mL), Ctrough (ng/mL), and Cmax (ng/mL) – were estimated at the median values of covariates within each age group 2 to < 12 years, 12 to <18 years, and ⩾ 18 years. Furthermore, 90% asymptotic confidence intervals on the ratios of AUC for each age group of children compared to adult AUC were computed based on the normal distribution of log transformed parameters. Model-based individual predictions of clearances and exposure measures were also summarized by age categories. Both typical population predictions and individual predictions were based on 400 mg twice daily dose for adults and based on 230 mg/m^2 twice daily dose rounded to the nearest multiple of 50 mg not to exceed 400 mg for children.
PK parameters have been log-transformed to guarantee positive and asymmetric confidence intervals when untransformed. PK parameters have been reported with summary statistics.

The serum-concentrations of nilotinib were measured by validated liquid chromatography tandem mass spectrometry (LC-MS/MS) assay. LLOQ/ ULOQ was 2.50 ng/mL and 5000 ng/mL, respectively.

Absorption

N/A

Distribution

N/A

Elimination

N/A

Dose proportionality and time dependencies

Dose proportionality

Dose-Exposure Relationship after single dose

Nilotinib concentration after single dose was summarized for each designated post-dose time window by CML cohort, for the pooled CML population, and for the total population (CML and ALL). It was also summarized by age group (2 to <12 years, 12 to <18 years, pooled).

In general, the observed concentrations of nilotinib at 1-5 h and 6-12 h post-single dose were comparable across the cohorts, within the respective age groups and time windows. During the 6-12h window, older patients generally had a higher exposure compared to younger patients, and older newly diagnosed patients had higher exposures compared to the other disease cohorts (Figure 2). The geometric-mean (geo-V%) values of the nilotinib concentrations at 6-12 h post dose were as follows:

Age group: 2 to <12 years

- Newly diagnosed patients: 235 ng/mL (182%)
- Resistant/intolerant patients: 230 ng/mL (62.1%)
- Paediatric patients (Ph+ CML-CP or ALL): 234 ng/mL (65.6%)

Age group: 12 to <18 years

- Newly diagnosed patients: 675 ng/mL (64.9%)
- Resistant/intolerant patients: 361 ng/mL (70.0%)
- Paediatric patients (Ph+ CML-CP or ALL): 413 ng/mL (74.7%)

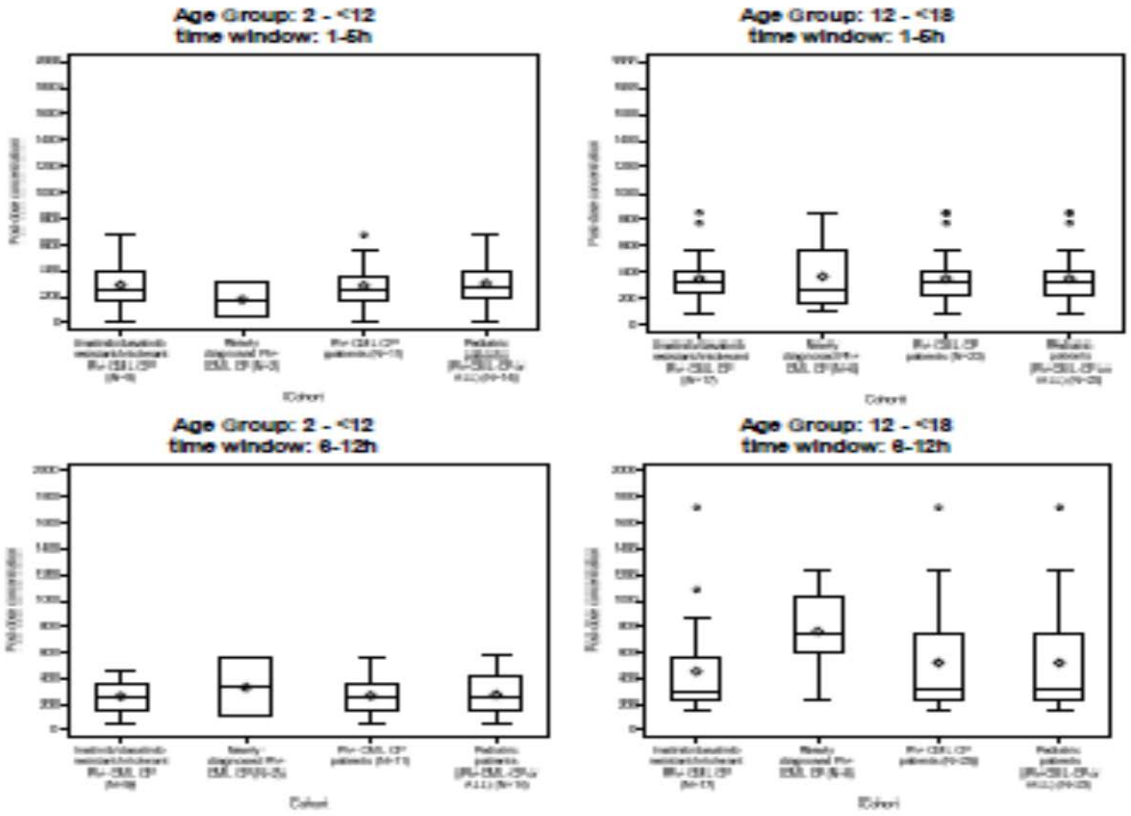


Figure 2 Boxplot of post dose concentrations, by cohort and age group (PAS)

Dose-Exposure Relationship after multiple doses

Exposure data after multiple doses was summarized by CML cohort, for the pooled CML population, and for the total population (CML and ALL). It was also summarized by age group (2 to <12 years, 12 to <18 years, pooled). Pre-dose (trough) concentrations were summarized by time point with the accumulation ratio from one observation to the next also presented.

Trough concentrations were similar across the cohorts within the respective age groups. However, 12-<18 years age group had slightly higher concentrations compared to the 2-<12 years age group. Following multiple oral doses of nilotinib, steady state concentrations were generally achieved as early as Cycle 1 Day 8 across the disease cohorts and age groups. However, in the 2-<12 years age group, an apparent increasing trend in concentration was observed over time. At the end of the Cycle 1, the trough concentrations were at similar levels for both the 2-<12 and 12-<18 years groups. In the 12-<18 years age group, the trough concentrations of nilotinib remained stable after Cycle 1 Day 8 up to Cycle 12 Day 28 (Figure 3). This notion was corroborated by the population PK analysis. The

geometric-mean (geo-CV%) ratio of accumulation from C1D8 to D15 and from C9D28 to C12D28 across age groups and disease cohorts were as follows:

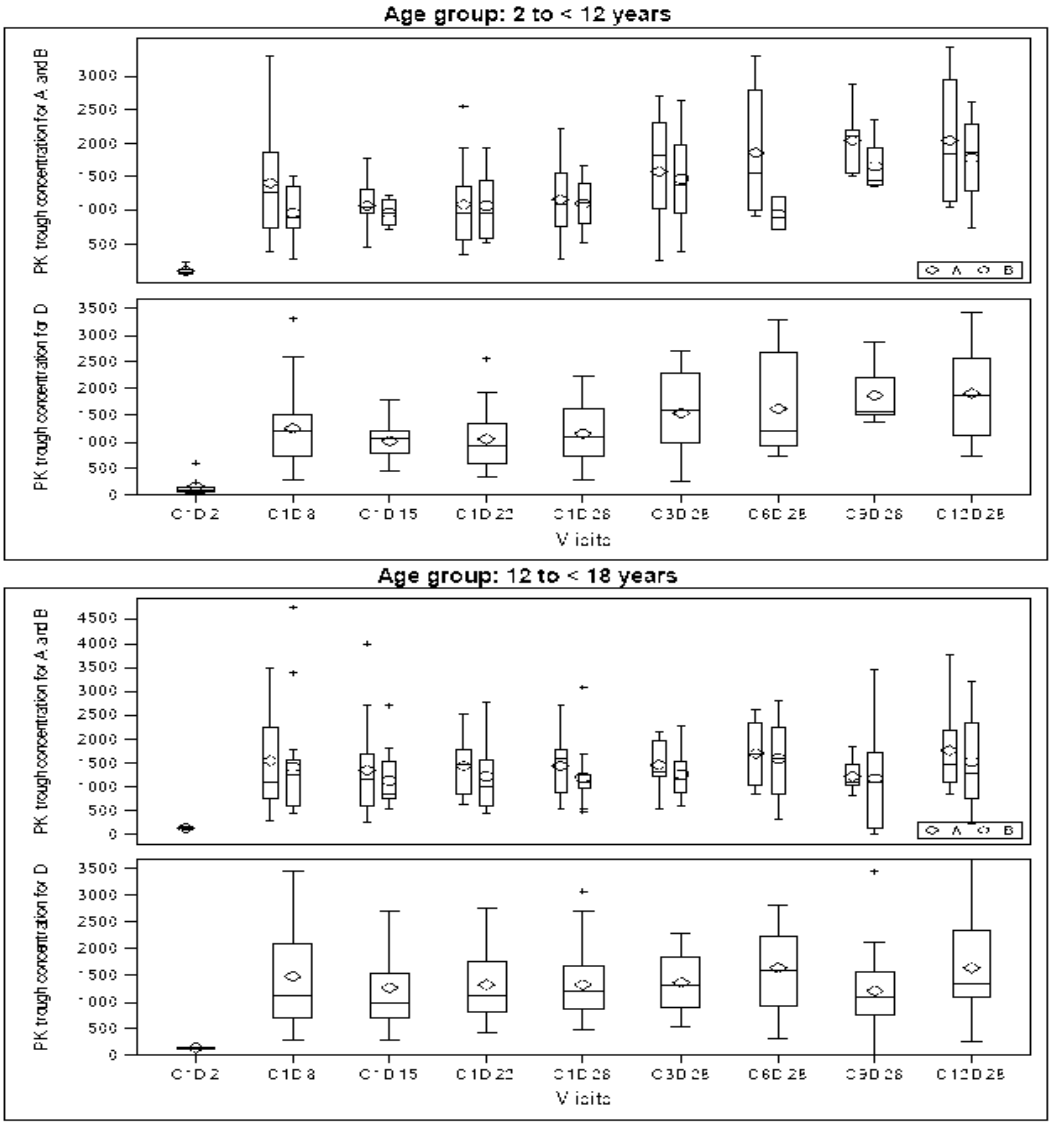
Age group: 2 to <12 years

- Newly diagnosed patients: 1.17 (71.2%) and 1.00 (57.5%), respectively
- Resistant/intolerant patients: 0.902 (74.7%) and 1.13 (54.8%), respectively
- Paediatric patients (Ph+ CML-CP or ALL): 0.977 (66.2%) and 1.06 (52.0%), respectively

Age group: 12 to <18 years

- Newly diagnosed patients: 1.12 (57.3%) and 0.98 (46.4%), respectively
- Resistant/intolerant patients: 1.09 (101.7%) and 1.12 (32.3%), respectively
- Paediatric patients (Ph+ CML-CP or ALL): 1.10 (83.0%) and 1.05 (39.1%), respectively

Note: After Cycle 1 Day 28, no additional PK data was available for the ALL patients from A2120 study. Hence, after Cycle 1 Day 28, concentrations were identical for pooled paediatric patients and pooled CML patients. There were no ALL patients in 12-<18 years age group.



A=Imatinib/dasatinib resistant/intolerant Ph+ CML CP patients, B=Newly diagnosed Ph+ CML CP patients, D=Pediatric patients (Ph+CML-CP or ALL)

Figure 3 Boxplot of trough concentrations over time, by cohort and age group (PAS)

- **Time dependency**

N/A

Special populations

Analyses were summarized by disease cohort and CML pool and overall paediatric pool. The overall paediatric pool contain four ALL patients whose PK are understood to be comparable to CML patients. Therefore, analyses are presented by disease cohort and overall paediatric pool only, unless there is a difference between the CML pool and the overall paediatric pool.

- *Ethnic origin*

A linear mixed effects model compared the trough concentrations of Caucasian to Asian patients. There were insufficient numbers of other ethnicities to compare further (Table 3).

Table 3 Summary of statistical analysis of effect of ethnicity on trough concentrations for plasma nilotinib by cohort (SD PAS)

					Comparison 90% CI		
Population	**Race**	**n***	**Adjusted/Geo-Mean**	**Comparison**	**Geo-Mean Ratio**	**Lower**	**Upper**
Newly diagnosed Ph+ CML-CP	Caucasian	17	3.46	Asian:Caucasian BSA adjusted	0.906	0.675	1.22
	Asian	7	3.14				
Imatinib/ dasatinib resistant/ intolerant Ph+ CML-CP	Caucasian	20	3.73				
Paediatric	Asian	15	5.11	Asian:Caucasian BSA adjusted	1.37	1.07	1,76
	Caucasian	39	3.66				
	Asian	23	4.26	Asian:Caucasian BSA adjusted	1.16	0.968	1.4

Model is a linear fixed effect model with race as fixed effect.
n* = number of subjects with non-missing values.
The analysis was conducted on log transformed PK parameters. Then the results are back transformed to get adjusted geo-mean, GM ratio, and 90% CI.

- *Gender*

The effect of gender was investigated by comparing dose-adjusted trough concentrations of nilotinib between male and female patients using a linear mixed effects model. The analysis was performed using dose-adjusted exposure (adjusted to 1 mg) such that any differences between genders were not subject to differences in doses across patients of different ages. For newly diagnosed patients, race and BSA both had a significant effect on exposure and were therefore kept in the model. Model based comparisons between genders were therefore conducted adjusted for race and BSA.

Table 4 Summary of statistical analysis of effect of gender on trough concentrations for plasma nilotinib by cohort (SD PAS)

					Comparison 90% CI		
Population	**Gender**	**n***	**Adjusted/ Geo-Mean**	**Comparison**	**Geo-Mean Ratio**	**Lower**	**Upper**
Newly diagnosed Ph+ CML-CP	Male	13	3.09	Female:Male BSA and race adjusted	1.16	0.88	1.52
	Female	11	3.57				
Imatinib/ dasatinib resistant/ intolerant Ph+ CML-CP	Male	25	3.95		0.933	0.725	1.2
	Female	15	3.69				
Pediatric	Male	39	3.63		1.02	0.852	1.22
	Female	28	3.69				

- *Children*

Study CAMN107A2120

Study CAMN107A2120 was a multi-centre, open-label study to characterize the PK of nilotinib administered at a dose of 230 mg/m^2 bid to paediatric patients (N=15) with

- Newly diagnosed CP-Ph+ CML (none recruited), or
- CP or AP-Ph+ CML resistant/intolerant to imatinib and/or dasatinib, (no AP patient recruited) or
- Relapsed/refractory Ph+ ALL

Patients were enrolled into two strata of two age groups:

- Group 1: 8 patients ages 1 year to < 10 years, and
- Group 2: 7 patients ages ≥ 10 years to < 18 years.

Safety, tolerability, and activity (hematologic, cytogenetic, and molecular response) were to be assessed through EOS. Adverse events (AEs) were graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. The design of the study is consistent with the historic trial design utilized for cytotoxic chemotherapeutic agents in paediatric populations, beginning paediatric dose escalation at 70% to 80% of the adult MTD (600 mg bid).

The primary objective of the study was to characterize the PK of nilotinib in paediatric patients with newly diagnosed CP-Ph+ CML, or CP or AP-Ph+ CML resistant/intolerant to imatinib and/or dasatinib, or refractory/relapsed Ph+ ALL to standard therapy.

The study had the following secondary objectives:

- To assess the safety and tolerability of nilotinib.
- To assess the pharmacodynamics of nilotinib by its activity (hematologic, cytogenetic, and molecular responses).
- To assess mutations in BCR-ABL at baseline and at the end of treatment.

Patients were administered nilotinib 230 mg/m^2 bid, orally, rounded to the nearest 50 mg (max single dose 400 mg) for 28 days (1 cycle) for up to 12 cycles prior to protocol amendment 3 and up to 24 cycles post amendment 3. For patients having difficulty swallowing capsules, the capsule was opened and the contents administered with one teaspoon of apple sauce. Results from study [CAMN107A2127] showed that apple sauce did not have an impact on the PK of nilotinib.

Both single- and multiple-dose PK of nilotinib were evaluated in paediatric patients, and compared against adult reference data from Study A2101, where patients received 400 mg bid [CAMN107A2101].

Nilotinib shows moderate to high inter-patient variability in PK values (32% to 64% in AUC and 34% to 72% in Cmax) in adult patients [CAMN107A2101-Phase IA]. Based on the observed variability as well as the safety profiles of nilotinib in adult patients, a two-fold difference in AUC or CL/F between adults and paediatrics was considered to be clinically meaningful, therefore, this difference was considered when comparing paediatric patients in A2120 to adult patients in A2101.

Evaluable pharmacokinetic data was available from 14 paediatric patients in study CAMN107A2120.

The PK of nilotinib following the single dose were comparable between Group 1 (1 year to <10 years) and Group 2 (≥ 10 years to < 18 years), given the observed variability and low sample size. No marked difference was observed between Group 1 and 2 with regard to the steady-state PK exposure and clearance of nilotinib. The coefficient of variance (CV%) for the geometric means was also similar in both groups (30% or higher) (Table 5 and Table 6).

Table 5 Summary of nilotinib non-compartmental PK parameters for Cycle 1 Day 1 by age group (PAS)

Age Group	Statistics	Cmax (ng/mL)	Tmax (h)	AUClast (ng*h/mL)	AUC0-12h (ng*h/mL)
Group 1: Age 1 year to < 10 years	N[a]	7	7	7	7
	Geo-mean	405	Median: 2.00	4160.99	2795.78
	CV% geomean	42.5	[Min; Max]: [1.02; 7.08]	38.5	35.7
Group 2: Age ≥ 10 years to < 18 years	N[a]	7	7	7	7
	Geo-mean	403	Median: 2.00	5707.36	3393.21
	CV% geomean	35.2	[Min; Max]: [2.00;7.88]	51.2	30.4
All pediatric patients	N[a]	14	14	14	14
	Geo-mean	404	Median: 2.53	4873.21	3080
	CV% geomean	37.2	[Min; Max]: [1.02; 7.88]	46.8	33.5

AUC = area under the curve; Geo-mean = geometric mean; CV% Geo-mean = sqrt ((exp (variance for log transformed data)-1))*100; Last = 24 hrs; PAS = PK analysis set; PK = pharmacokinetic; Tmax = time to reach maximum serum concentration a = number of patients with corresponding PK parameter available.Source: [Study A2120-Table 14.2-1.1]

Table 6 Summary of nilotinib steady-state PK parameters estimated from non-compartmental analysis by age group (PAS)

Age Group	Statistics	AUCss (ng*h/mL)	CL/F (BSA adjusted) (L/h/m^2)	Cmin (ng/mL)
Group 1: Age 1 to < 10 years	na	7	7	7
	Geo-mean	15129.18	15.4	805
	CV% geo-mean	38.0	38.7	33.7
Group 2: Age ≥10 to <18 years	na	7	7	7

	Geo-mean	14383.08	15.9	1072.85
	CV% geo-mean	33.6	37.0	20.5
All pediatric patients	na	14	14	14
	Geo-mean	14751.41	15.6	929
	CV% geo-mean	34.5	36.3	30.9

AUC = area under the curve; AUCss = AUCtau for bid dose at steady state; CL/F = apparent a number of patients with corresponding PK parameter available All pediatric patients:1 year to < 18 years Source: [Study A2120-Table 14.2-1.2]systemic clearance; Cmin = lowest trough concentration observed as the average value of the evaluable Ctrough from C1D8, C1D15, C1D22 and C1D28; Geo-mean = geometric mean; CV% Geo-mean = sqrt ((exp (variance for log transformed data)-1))*100; PAS = PK analysis set; PK = pharmacokinetic.

Steady-state PK parameters (AUCtau and CL/F) were calculated from an approximation based on AUC0-12 on Cycle 1 Day 1, multiplied by the trough concentration accumulation ratio after multiple bid doses. The steady-state PK exposure and clearance of nilotinib in the pediatric patients administered 230 mg/m^2 bid were similar (within 2-fold) to those observed in adult patients administered 400 mg bid (Table 7).

Table 7 Summary of geometric-mean ratio of steady-state PK parameters estimated from non-compartmental analysis in pediatric population compared to adult population with 90% CI by age group (PAS)

					Age Group Comparison		
						90% CI	
PK Parameter (unit)	**Age group**	**N[a]**	**Adjusted Geo- mean**	**Comparison**	**Geo-mean Ratio**	**Lower**	**Upper**
AUCss (ng*h/mL)	**Adult**	**17**	**17102.86**				
	Group 1: Age 1 year to < 10 years	7	15129.18	Group 1 / Adult	0.885	0.683	1.145
	Group 2: Age ≥ 10 years to < 18 years	7	14383.08	Group 2 / Adult	0.841	0.650	1.089
	All pediatric	14	14751.41	All pediatric / Adult	0.863	0.701	1.061
CL/F (BSAadjusted)(L/h/m2)	**Adult**	**17**	**12.0**				
	Group 1: Age 1 year to < 10 years	7	15.4	Group 1 / Adult	1.28	0.971	1.68
	Group 2: Age ≥ 10 years to < 18 years	7	15.9	Group 2 / Adult	1.32	1.01	1.74
	All pediatric	14	15.6	pediatric / Adult	1.30	1.04	1.62

ANOVA = analysis of variance; AUCss = AUCtau for bid dose at steady state; BSA = body surface area; CI = confidence interval; CL/F = apparent systemic clearance; Geo-mean = geometric mean; PK = pharmacokinetic All pediatric patients: 1 year to <18 years Adult: patients from [Study A2101] whose PK data are used as reference. ANOVA model of the log-transformed PK parameters. Included in the model was age group as main effect. Results were back transformed to get adjusted geometric mean, geometric mean ratio and 90% CI. a number of patients with evaluable PK data.

Study CAMN107A2203

Study CAMN107A2203 was a multi-center, open-label, non-controlled Phase II study to assess efficacy, safety of 230 mg/m^2 twice daily nilotinib in pediatric patients (1 to <18 years old). Three patient cohorts were planned based on the disease classification:

- Ph+ CML-CP patients resistant or intolerant to either imatinib or dasatinib, n=34
- Ph+ CML-AP patients resistant or intolerant to either imatinib or dasatinib, n=0
- Newly diagnosed Ph+ CML patients in chronic phase, n=25

All patients are planned to be treated for 66 cycles.

Overall, 30 patients in the resistant/intolerant cohort and 25 patients in the newly diagnosed cohort had evaluable PK data. In both the cohorts, steady state concentration was achieved approximately on C1D8. The geometric-mean (CV%) trough concentration of nilotinib were as follows:

- Resistant/intolerant cohort: 1407.89 ng/mL (41.67%)
- Newly diagnosed cohort: 1274.30 ng/mL (46.21%).

The inter-patient variability was similar across the cohorts and was moderate for both the cohorts. Similar trend was observed for intra-patient variability across the cohorts (Table 8).

Table 8 Analysis of inter- and intra-patient variability in nilotinib trough concentration by cohort (PAS)

Parameter unit)	n	Intra-patient variance	Intra-patient CV%	Inter-patient variance Inter-patient CV%
Cohort: Imatinib/dasatinib resistant/intolerant Ph+ CML-CP				
Cmin* (ng/m L)	29	0.18	43.94	0.15
Cohort: Newly diagnosed Ph+ CML-CP				
Cmin* (ng/m L)	24	0.25	53.67	0.12
The intra-patient and inter-patient variations were estimated using linear mixed effects model with logtransformed trough concentration and visit as a fixed effect, and patient as a random effect. * Cmin is the nilotinib trough concentration n: number of patients used in the model analysis. CV% = sqrt (exp (estimate)-1)*100, where 'estimate' is the inter/intra-patient variance estimated from model.				

BCR-ABL/ABL ratio (%) at 12 cycles vs. average PK trough concentration:

There was no observed association between the nilotinib trough concentration and the BCRABL/ ABL% ratio at 12 cycles, across the cohorts (Figure 4).

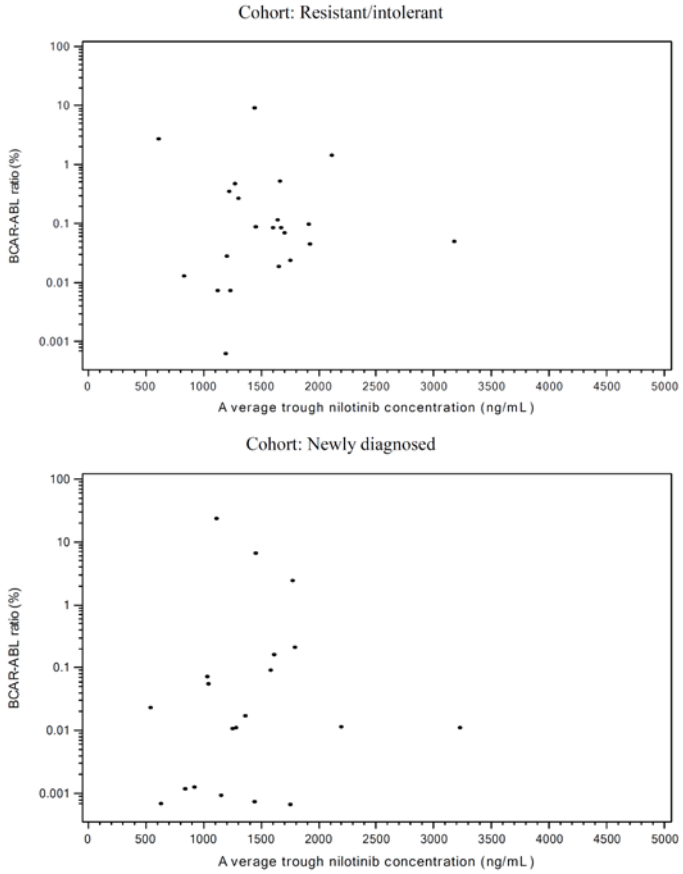


Figure 4 Average trough nilotinib concentration vs. BCR-ABL/ABL ratio (%) at cycle 12 by cohort (PAS)

Population PK results

The population PK analysis evaluated the impact of covariates such as body surface area, body weight, age, gender, indication, ethnicity, ALT, AST and total bilirubin on the PK. The final population PK model incorporated effects of BSA on volumes and clearances and total bilirubin on clearance.

Typical population predictions of BSA-normalized clearances at median values of covariates in the 2 to < 12 years, 12 to < 18 years, and ≥ 18 years age groups were 16.0, 13.5, and 13.0 L/h/m^2, respectively (Table 9). The changes in exposure as measured by steady-state AUC in pediatric patients following 230 mg/m^2 bid dosing compared to that in adult patients following 400 mg bid dosing were -6.1% (90% CI: -19% to 9%) in patients 2 to <12 years of age and -0.8% (90% CI: -5% to 3%) in patients 12 to <18 years of age.

Table 9 Typical steady-state apparent clearance and AUC at median values of covariates in the three age groups based on final nilotinib population PK model

					Final nilotinib model (N=107)		
Ages (y)	**Median age at baseline (y)**	**Median BSA at baseline (m^2)**	**Dose[a] (mg)**	**Total bilirubin normalized**	**CL/F (L/h)**	**CL/F (L/h/m^2)**	**AUC[c] (h x ng/mL)**
2 to <12	10.1	0.98	250	0.75	15.7	16.0	15923
12 to<18	15.3	1.54	350	0.86	20.8	13.5	16817
≥18	52	1.82	400	0.80	23.6	13.0	16956

a mg dose is 400 bid for ages ≥ 18 year and 230 × BSA bid rounded to nearest 50 mg not to exceed 400 mg for ages 2 to less than 18 year.
b Total bilirubin normalized (BIL) = (value-LLN)/(ULN-LLN), where LLN and ULN are the lower and upper limits for normal. Values

presented in the table are median values one or more weeks after first dose.
c AUC = 1000 x Dose/(CL/F)
d Typical apparent clearance CL/F (L/h) = 24.4 × (BSA/1.73)0.678 × exp(-0.221(BIL-0.5))

A population pharmacokinetic analysis has been conducted including data from adults receiving 400 mg twice daily (n=35) and paediatric patients receiving 230 mg/m^2 twice daily (n=72). The paediatric dose was expected to be equivalent to the adult dose with respect of resulting exposure (AUC). The structural PK model used for nilotinib in adult patients was adopted in this analysis. It was a two-compartment model, with an absorption lag time followed by a zero –order duration of absorption, and with elimination described by a first-order process. Body surface area was correlated with apparent clearances and volumes. Normalized total bilirubin was correlated with apparent clearance, which was similar to previous results in adults. The effects of body surface area played the major role for accounting for differences in pharmacokinetics between paediatrics (ages 2 to <18 y) and adults, and thus mg/m^2 dosing was considered appropriate in paediatrics.

PopPK and PBPK model

Both the population pharmacokinetics (PopPK) and the physiologically-based pharmacokinetic (PBPK) model were developed and qualified to predict the nilotinib exposure in the paediatric population. The mechanism-based paediatric PBPK model combines and links physiological parameters and nilotinib drug-specific parameters in a physiologically realistic model (Johnson et al. 2011). The nilotinib PBPK model was initially constructed and verified using observed adult data. The pediatric population with integrated age-dependent CYP enzyme ontogeny profiles (Upreti 2016) was then used within the Simcyp paediatric module (Johnson et al. 2006; Johnson et al. 2011) to develop the paediatric nilotinib PBPK model. This pediatric PBPK model has been verified using the observed data in pediatric patients from 6 to 12 years of age. At age 2, CYP3A4 reaches full maturity and hence nilotinib clearance (CL) is determined by the hepatic flow rate and the liver size rather than CYP3A4 activity (Johnson, Rostami-Hodjegan, & Tucker, 2006)

PK parameters computed with each of the methods are presented in Table 10. Figure 5 and Figure 6 show the population PK simulations and the simulations from the PBPK model in the pediatric population from 2 to <6 years of age, respectively.

Table 10 Summary statistics predicted PK parameters for the age groups 2 to <6 years old

Age group 2 to <6 years				
Dosing	**PK Parameters at steady-state**	**Observation**	**PopPK Simulations (5th– 95th percentile)**	**PBPK Simulations mean (5th– 95th percentile)**
Simulations			Simulation of 500 trials of 100 pediatric patients with BSA corresponding to a 2 to <6 yrs of age	20 trials × 20 patients simulation in Simcyp v.16 pediatric module to a 2 to <6 yrs of age
Single Dose	Cmax (ng/mL) (n= 1 patient)	259	749.30 (394 – 1513)	744 (169 – 3379)
	AUC_{0-12h} (ng.hr/mL)	2896	3364.77 (1644 – 6974)	7304 (1613 – 33451)

Age group 2 to <6 years				
Dosing	**PK Parameters at steady-state**	**Observation**	**PopPK Simulations (5th– 95th percentile)**	**PBPK Simulations mean (5th– 95th percentile)**
	(n= 1 patient)			
Multiple Dose	$Cmax_{ss}$ (ng/mL) (n= 2 patients)	NA	2271.50 (1303 – 4022)	1620 (328 – 7559)
	$Cmin_{ss}$ (ng/mL) (n= 2 patients)	Mean (CV%) 1110 (107)	873.27 (275 – 2072)	1067 (195 – 5772)
	$AUC_{0\text{-}12h,ss}$ (ng.hr/mL) (n = 2 patients)	NA	12912.05 (7013 – 23387)	17032 (3353 – 84032)

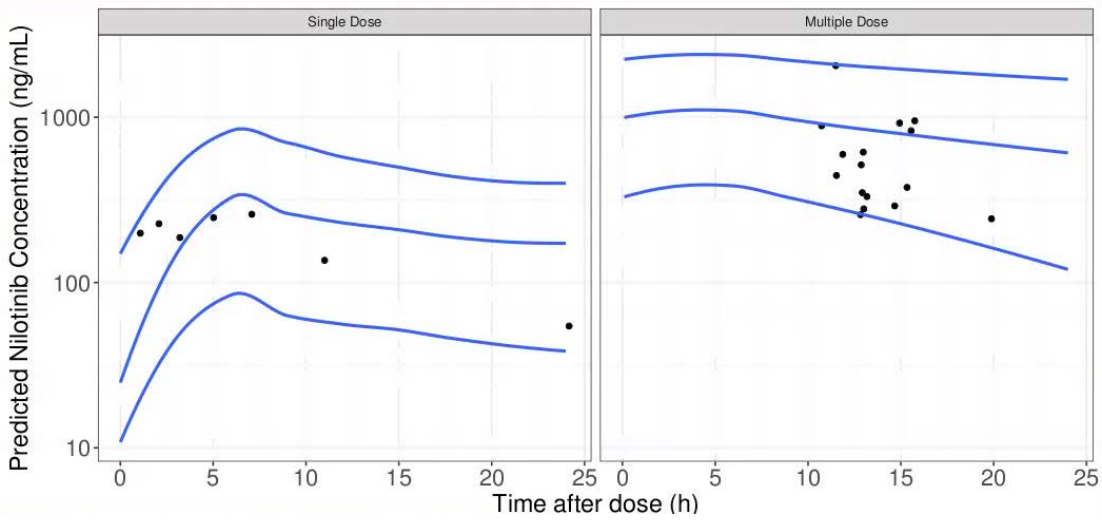


Figure 5 Simulation for final population PK model stratified by 1st dose (left column) and by multiple dose (right column), for pediatric patients below 6 years of age

Dots are the actual observations. Solid lines are the 95th, 50th, and 5th percentiles predicted by the model. Observed and predicted concentrations below the lower limit of quantification (LLOQ) were plotted at LLOQ=2.5 ng/mL.

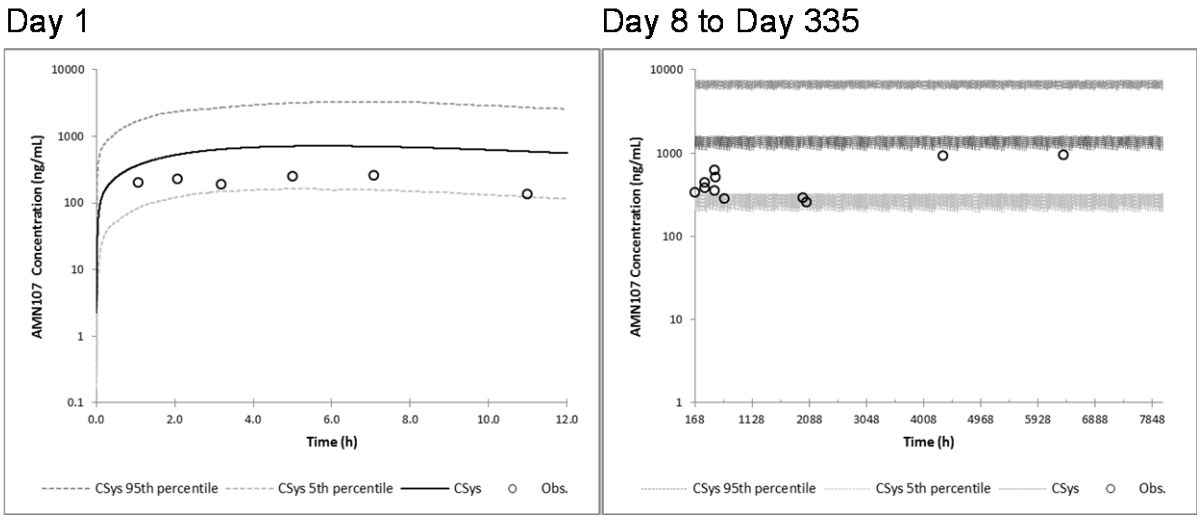


Figure 6 Predicted versus observed AMN107 plasma concentration profiles in 2 to <6 years old pediatric patients after 230 mg/m^2 AMN107 BID dosing

The solid line represents the mean simulated plasma concentrations of 10 trials of 10 subjects in each trial and the dotted lines above and below represents the upper 95th and lower 5th percentiles of the simulated plasma concentrations. The circle symbols represent the observed individual plasma concentrations in CSR-CAMN107A2120 and CAMN107A2203.

Pharmacokinetic interaction studies

No drug-drug interactions studies in paediatric patients have been submitted.

Pharmacokinetics using human biomaterials

N/A

2.4.3. Pharmacodynamics

Data from A2120 and A2203 were pooled for dose-exposure and exposure-response (efficacy and safety) assessments. All exposure-response analyses were performed separately for the resistant/intolerant patients and for the newly diagnosed patients. Indications were not pooled.

A summary of various exposure response analyses performed is provided in Table 11.

Table 11 Summary of exposure-response relationships - CML

Endpoint	Section	Any clinically relevant exposure response relationship?	Parameters	Nature of the relationship
Exposure Efficacy				
MMR	3.4.1	No	P(MMR) at 6 or 12 months vs. time-averaged trough concentration	Higher Ctrough were not associated with higher probability of MMR at 6 or 12 months
Molecular response	3.4.2	No	BCR-ABL/ABL % ratio over time vs. trough concentration	Increasing Ctrough was not associated with lower BCR-ABL/ABL% ratio
Exposure Safety				
AESIs	3.5.1	No	P(AESI) vs. last observed trough concentration prior to AE onset	Similar odds of AESIs with increasing concentration of nilotinib
			Risk of AESI over time vs. concentration quartiles	No difference in risk of AESI over time with higher exposure levels
Liver toxicity >3xULN in ALT or AST >2xULN of Total bilirubin	3.5.2	No	P(Hepatic Abnormalities) vs. last observed trough concentration prior to event onset	Similar odds of hepatic abnormalities with increasing/decreasing concentration of nilotinib.
			Risk of hepatic abnormality over time vs. concentration quartiles	No difference in risk of hepatic abnormality over time with higher exposure levels.
Combination of both (>3xULN of AST/ALT and >2xULN Total Bilirubin		*This analysis was not performed as there were <10% of patients with this event*).		
ECG change from baseline (QTcF, QTcB, PR, QRS, HR)	3.5.3	Yes – For QTcF, QTcB	ECG change from baseline vs. concentration	QTc change from baseline was associated with increasing concentration of nilotinib. QTc prolongation was expected with increasing concentration.
		No - for PR, QRS, and HR.		PR/QRS prolongation was not associated with exposure. HR increase/decrease was not associated with exposure.

The QTc prolongation potential and cardiac safety of nilotinib exposure in paediatrics was investigated with a linear mixed effects model for the change from baseline in QTcF, QTcB, and other ECG parameters (PR, HR, and QRS).

Given the sparse sampling in paediatric patients, PopPK predictions of Cmax (estimated at Tmax=4.6h) were utilized to enhance the database and provide more robust assessments of ECG prolongation.

Nilotinib concentrations (trough concentrations on C1D8, D15, D22, D28, C3D28, C6D28, C9D28, C12D28, post-dose concentrations on C1D1 and D8) were associated with QTcF prolongation. An increase in trough concentration corresponded to an increase in change from baseline in QTcF interval.

At the expected steady state exposure for 230 mg/m^2 bid (C1D15), the estimated mean change in QTcF from baseline was 4.63 msec (SE: 2.13; 95% CI: 0.1698, 9.1) in newly diagnosed cohort, and 4.15 msec (SE: 1.19; 95% CI: 1.75, 6.56) in the resistant/intolerant cohort.

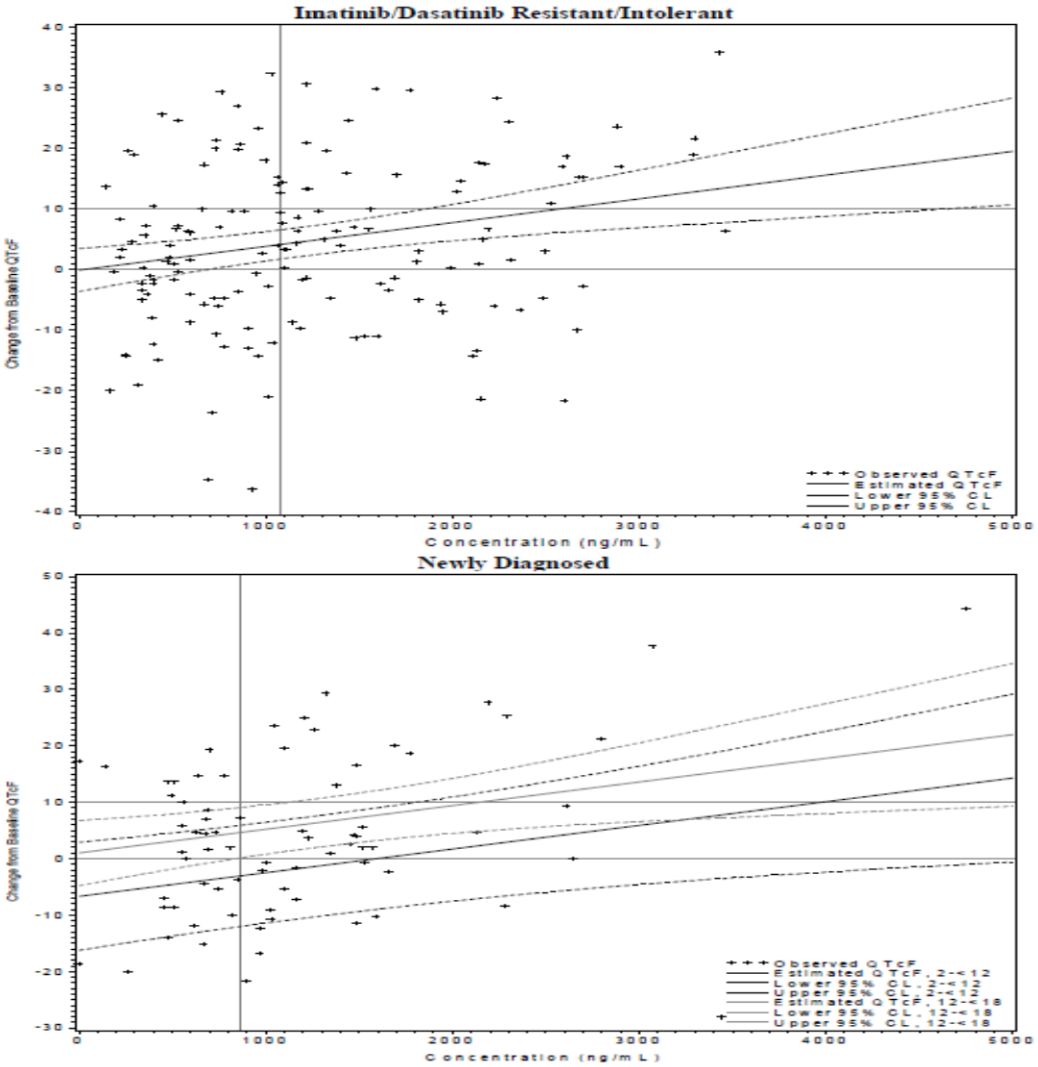


Figure 7 QTcF change from baseline vs. plasma concentration by cohort (PKSAF)

2.4.4. Discussion on clinical pharmacology

The pharmacokinetics of nilotinib in children have been investigated in two paediatric studies: a phase 1 study (A2120) in 11 children with resistant/intolerant Ph+ CML-CP and four children with relapsed/refractory Ph+ ALL and a phase 2 study (A2203) in 34 children with resistant/intolerant Ph+ CML-CP and 25 children with newly diagnosed Ph+CML-CP. Population PK analysis was performed with data from the paediatric trials and data from a study in adult patients. The presented methodology is in accordance with state-of-the-art procedures for PoP-PK analysis. The model development has been adequately documented and the final model is well validated. Goodness of fit plots and visual predictive checks (with 95% prediction intervals) support the final model.

Overall, the number of paediatric patients with evaluable PK data is acceptable. However, no data are available in children < 2 years of age and data in children < 5 years of age are limited. However, it is acknowledged that generation of more “real data” in children below the age of 6 is not feasible, due to the rarity of the disease and the competitive enrolment in other studies. The model used to simulate and predict PK in children below the age of 6 is adequate. Both the popPK model and a PBPK model consistently predict exposure in children below the age of 6 and have also compared the predicted PK results to the limited available observed data. This supports the suitability of the current PopPK model. The model indicated that BSA based-dosing also is suitable in children below the age of 6. It is acknowledged that generation of additional PK data in children below the age of 6 is infeasible. The PopPK model suggests BSA based dosing in also children below the age of 6 which is acceptable.

However, although, most children had a high enough nilotinib exposure (>500 ng/ml), it is uncertain whether this will be the case for all children. To ensure that all children have a high enough nilotinib exposure, it is recommended to monitor the children for nilotinib concentrations. The CHMP recommended that the MAH will collect efficacy and exposure data in patients < 6 years and that based on this information the popPK model is updated in order to alleviate the current uncertainties related to this model.

In both the paediatric studies, patients were administered 230 mg/m^2 bid. The dose was expected to be comparable to the adult dose of 400 mg bid normalized to the typical BSA (= 1.73 m^2). The paediatric dose was rounded to the nearest multiple of 50 mg (lowest tablet content of nilotinib) and should not exceed 400 mg bid.

Results from both the individual studies and the population PK analysis indicated that the pharmacokinetics of nilotinib is comparable in paediatric and adult patients. The PK of nilotinib follows a two-compartment model with an absorption lag-time followed by zero-order absorption and first-order elimination. The typical clearance was slightly higher in the youngest age group, but the impact on AUCss seems small. While exposure is slightly lower in the younger age groups due to higher clearance, the clinical importance seems to be small. Comparable predicted Ctrough/Cmin values for the 230 mg/m^2 dose across age groups are reassuring.

Following both single and multiple doses, exposure was slightly higher in the older children compared to the youngest age group. Data are limited in the age group 2 to <6 years, but exposure and variability appears to be comparable. Data are limited in the youngest age group, but overall, the model approach is acceptable and the 230 mg/m^2 dose supported in CML patients from 2 to 18 years of age. Of the covariates evaluated in the population PK analysis BSA and total bilirubin was incorporated in the final model. BSA was the most important of the covariates, and this supports the BSA-based dosing in paediatric patients.

The paediatric dose of 230 mg/m^2 led to exposure comparable to that of adult patients after both multiple and single dose. There was no apparent differences in exposure across disease cohorts and within the age groups (2 to <10 and 12 - <18). The slightly higher clearance in the youngest age group is expected to have minimal impact on exposure. Generally, exposure in paediatric patients was comparable to exposure in the adults.

An exposure-efficacy response relationship for nilotinib has been demonstrated in adult patients and could also be expected in a paediatric patient population.

All exposure-response analyses were performed separately for each cohort, resistant/intolerant patients and newly diagnosed paediatric patients. The exposure-efficacy relation was investigated with trough concentrations vs. BCR-ABL/ABL% ratio over time and time-averaged trough concentration vs. probability of major molecular response (MMR) at multiple time points. The analysis did not reveal any

exposure-efficacy response relationship in paediatric patients. However since the exposure range was narrow as all paediatric patients were treated with a dose of 230 mg/m^2 and the number of paediatric patients subgroups is limited, this could explain why no significant exposure-efficacy relationship could be found.

The population PK analysis indicated that clearance was higher in the youngest age group, and exposure in the youngest age group was also slightly lower than the exposure in the oldest age group. Theoretically the lower exposure in the youngest could lead to diminished efficacy. However, data on exposure in the very young (< 5 years of age) are very limited. However, there is evidence to support that the observed lower exposure in the youngest patients could have a negative effect on efficacy. Steady-state exposure was generally comparable across age groups. Also, no clear exposure-efficacy relationship was found within the range of observed exposures. No relationship between trough concentration and the probability of MMR has been established for either resistant/intolerant patients or newly diagnosed patients. A similar pattern of no relationship was found between trough concentrations and BCR-ABL% for both disease cohorts.

No significant correlation between Ctrough and AESIs, AESIs grade 3-4 or hepatic abnormalities including bilirubin elevation was identified. This was consistent between cohorts. Recalculated AUCss predictions with patient characteristics and actual dose, not planned dose as requested, showed a 10 % difference in AUCss, which is as expected, since the dose intensity is smaller than the planned dose. Exposure-response analysis with the recalculated AUCss confirm a strong relationship between AUCss and probability of bilirubin elevation.

In line with what has been shown in adult patients, Ctrough concentration was associated with QTcF prolongation. As in adult patients, paediatric patients treated with nilotinib are at risk of QT prolongation and ECG should be monitored with ECG as described in the SmPC. No other correlations between exposure and other relevant ECG parameters, including heart rate was observed.

2.4.5. Conclusions on clinical pharmacology

The chosen paediatric dose of 230 mg/m^2 bid is supported. The two clinical studies in paediatric patients and the population PK analysis provide sufficient data to support that the pharmacokinetics including exposure in paediatric patients from the age of 5 are comparable to what has been established in adult patients dosed 400 mg bid.

In conclusion, the new pharmacokinetics and pharmacodynamics data submitted support the new indication.

2.5. Clinical efficacy

2.5.1. Dose response studies

Study A2120

The dose selection in paediatric patients was determined based on the results of Study A2101, which was conducted in adult patients with imatinib-resistant Ph+ CML, relapsed or refractory Ph+ ALL, or other haematological malignancies, and Study A2303, which compared two doses of nilotinib (300 mg bid and 400 mg bid) with imatinib in adult patients with newly diagnosed Ph+ CML-CP. The recommended dosage of nilotinib in adult patients was established to be 300 mg bid for newly diagnosed CML-CP patients, and 400 mg bid for resistant or intolerant CML-CP and CML-AP patients.

The PK, safety, and activity of nilotinib in paediatric patients was first evaluated in Study A2120 conducted in paediatric patients with Ph+ disease (CML and acute lymphoblastic leukemia; ALL), where patients were administered nilotinib at a dose of 230 mg/m^2 bid, rounded to the nearest 50 mg dose, with a maximum single dose of 400 mg (see clinical pharmacology section). The dose of 230 mg/m^2 bid in children was selected to provide similar exposure as the dose of 400 mg bid in adults, considering that CML in children may be more aggressive than in adults (Tanizawa 2016), and in view of the dose of 400 mg bid being the dose for resistant or intolerant adult CML patients. The results confirmed 230 mg/m^2 bid as the recommended dose in paediatric patients with Ph+ CML/ALL. This dose was subsequently evaluated and confirmed in Study A2203.

The 230 mg/m^2 dose was considered adequate for the Ph+ CML-CP and -AP paediatric patients resistant or intolerant to either imatinib or dasatinib as it was equivalent to the adult dose of 400 mg, indicated for this population. The 230 mg/m^2 dose was also selected for newly diagnosed paediatric patients for the following reasons:

- Overlapping PK results from the 300 mg and 400 mg bid dose and acceptable safety profile at the 400 mg dose level (CAMN107A2303).
- Interim analysis data from study CAMN107A2120 in a group of paediatric patients showed a safety profile at the 230 mg/m^2 dose consistent with that observed in adults while providing adequate PK exposure coverage of both the 300 mg and 400 mg bid adult doses.
- A slightly higher dose than the 300 mg bid dose was considered as paediatric leukemia in some instances progresses more rapidly than in adults (Andolina 2012). The dose was adjusted to the body surface area and thereby, the chances of overexposure were reduced.

2.5.2. Main study

Study A2203

Methods

Study A2203 was a multi-center, open label, non-controlled Phase II study to evaluate the efficacy and safety of oral nilotinib in paediatric patients with newly diagnosed Ph+ chronic myelogenous leukemia in chronic phase (CP) or with Ph+ CML in CP or accelerated phase (AP) resistant or intolerant to either imatinib or dasatinib.

Study Participants

Inclusion criteria

1. Written informed consent obtained prior to any Screening procedures. However, if requested tests were performed as part of clinical practice within the window required per protocol, this data was used provided all parameters required per protocol were verified.

2. Male or female patients 1 to <18 years of age at study entry.

3. Patients with newly diagnosed Ph+ CML-CP or Ph+ CML-CP or CML-AP resistant or intolerant to either imatinib or dasatinib

a. Newly diagnosed Ph+ CML-CP:

- Patients with CML-CP within 6 months of diagnosis.
- Diagnosis of CML in CP with cytogenetic confirmation of Ph chromosome with (9;22) translocations. Standard conventional cytogenetic analysis was to be done on bone marrow. FISH could not be used.

b. Ph+ CML-CP:

- <15% blasts in peripheral blood and bone marrow.
- <30% blasts plus promyelocytes in peripheral blood and bone marrow.
- <20% basophils in the peripheral blood.
- ⩾ 100×109/L platelets.
- No evidence of extramedullary leukemic involvement, with the exception of hepatosplenomegaly.

c. Ph+ CML-AP:

- ⩾ 15% blasts in the peripheral blood or bone marrow aspirate, but < 30% blasts in both the peripheral blood and bone marrow aspirate.
- ⩾ 30% blasts plus promyelocytes in peripheral blood or bone marrow aspirate
- ⩾ 20% basophils in the peripheral blood.
- Thrombocytopenia (<100×109/L) unrelated to therapy.

d. Imatinib or dasatinib resistant Ph+ CML:

- Increasing white blood cells (WBC) or platelet count while on imatinib or dasatinib therapy indicative of a haematological relapse or primary resistance to imatinib or dasatinib.
- Cytogenetic or molecular response consistent with suboptimal response, warning, or failure according to criteria adapted from ELN criteria (ELN 2009 and ELN 2013).
- Appearance of accelerated phase or blast crisis while on imatinib or dasatinib therapy.
- Reappearance of Ph+ bone marrow clones after an initial complete cytogenetic response to imatinib or dasatinib.
- A greater than 30% increase in Ph+ cells in bone marrow or peripheral blood while on imatinib or dasatinib therapy.
- Loss of molecular response on imatinib or dasatinib therapy.

e. Imatinib or dasatinib intolerance Ph+ CML (at any dose or duration) was defined as the development of any adverse event (AE) requiring discontinuation of imatinib or dasatinib.

4. Performance status: Karnofsky ⩾ 50% for patients >10 years of age, and Lansky ⩾ 50 for patients ⩽ 10 years of age.

5. Patients must have had adequate renal, hepatic and pancreatic function defined as:

- Creatinine clearance or a serum creatinine based on age/gender.
- Total bilirubin (sum of conjugated+unconjugated) ⩽ 1.5×upper limit of normal (ULN) for age.
- Serum lipase ⩽ 1.5×ULN.

- Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ⩽ 2.5×ULN for age.

6. Patients had potassium, magnesium, phosphorus and total calcium values ⩾ lower limit of normal or corrected to within normal limits with supplements prior to the first dose of study medication.

Exclusion criteria

1. Patients actively receiving therapy with strong CYP3A4 inhibitors or inducers and the treatment could not be either discontinued or switched to a different medication at least 14 days prior to starting study drug.

2. Patients who were receiving treatment with any medications that had a known risk or possible risk to prolong the QT interval and the treatment could not be either discontinued or switched to a different medication prior to starting study drug.

3. Acute or chronic liver, pancreatic or severe renal disease considered unrelated to CML.

4. History of pancreatitis within 12 months prior to starting study drug or past medical history of chronic pancreatitis.

5. Impaired cardiac function including any one of the following:

- Inability to determine the QT interval on electrocardiogram (ECG).
- Complete left bundle branch block.
- Use of a ventricular-paced pacemaker.
- Congenital long QT syndrome or a known family history of long QT syndrome.
- Clinically significant resting brachycardia (<50 beats per minute).
- QTcF >450 ms on Baseline ECG. If QTcF >450 ms and electrolytes were not within normal ranges, electrolytes were to be corrected and then the patient re-screened for QTcF.
- Shortening fraction of <27% by echocardiogram (ECHO), or ejection fraction of <50% by multigated acquisition (MUGA) scan.
- Other clinically significant heart disease.

6. Patients with documented T315I mutation in BCR-ABL.

7. Previous treatment with more than one TKI for imatinib or dasatinib resistant/intolerant Ph+ CML patients. Previous treatment with any TKI for newly diagnosed Ph+ CML patients was not permitted unless the patient had received imatinib for less than 2 weeks prior to the first dose of study drug and discontinued at least 5 days prior to the first dose of nilotinib.

8. Patients who received myelosuppressive chemotherapy within 3 weeks, imatinib within 5 days, or dasatinib within 3 days prior to the first dose of study drug.

9. Patients who did not recover from all acute toxicities from all prior myelosuppressive chemotherapy prior to starting study drug.

10. Patients receiving hydroxyurea greater than 21 days for the treatment of Ph+ CML either prior to initiation of nilotinib or with maximum duration planned to exceed one week post initiation of nilotinib.

11. Patients who received hematopoietic growth factors within 7 days prior to starting study drug.

12. Patients who received pegfilgrastim within 14 days prior to starting study drug.

13. In case of stem cell transplant or rescue without total body irradiation: Evidence of either active graft vs. host disease or less than 3 months since stem cell transplant.

14. In case of radiation therapy: less than 2 weeks if local palliative, less than 3 months after total body irradiation, or craniospinal radiation therapy or if at least 50% radiation of pelvis; less than 6 weeks after other substantial bone marrow radiation.

15. Patients with known Hepatitis B, Hepatitis C, or HIV infection.

16. Severe and/or uncontrolled concurrent medical disease that in the opinion of the investigator could cause unacceptable safety risks or compromise compliance with the protocol.

Treatments

Nilotinib was administered orally at 230 mg/m^2 bid, rounded to the nearest 50 mg dose (to a maximum single dose of 400 mg) for 28 days (one cycle) and for a total of up to 66 cycles (or discontinued early).

Patients could receive hydroxyurea for 21 days or less for the treatment of CML but should discontinue treatment within one week after initiation of nilotinib. Patients were informed of a possible drug interaction with acetaminophen and asked to restrict the use of over-the-counter and prescription medicines containing acetaminophen. Patients on anticonvulsants were required to have regular monitoring of plasma concentration of these agents. Anti-diarrheal therapy was permitted at the Investigator's discretion.

Patients who were at high risk for developing tumor lysis syndrome were allowed to receive allopurinol. The colony-stimulating growth factors (G-CSF and GM-CSF) such as sargramostim, filgrastim, and pegfilgrastim were permitted to treat recurrent grade 3 neutropenia. Antiemetic medication could be used as clinically indicated. Antiemetic medication that prolongs the QT-time such as domperidone was to be avoided. Coumarin derivatives (warfarin) were permitted as needed.

CYP3A4 substrates: Nilotinib is a moderate CYP3A4 inhibitor in vivo. Drugs known to be sensitive substrates of CYP3A4 and drugs with narrow therapeutic indices were permitted with caution.

Antacid drugs: Nilotinib has a pH-dependent solubility; therefore, in order not to impact nilotinib PK, H2 blocker (famotidine) was required to be administered approximately 10 hours before or approximately 2 hours after the nilotinib dose; antacid (e.g. hydroxide/magnesium hydroxide/simethicone) was required to be administered approximately 2 hours before or approximately 2 hours after the nilotinib dose.

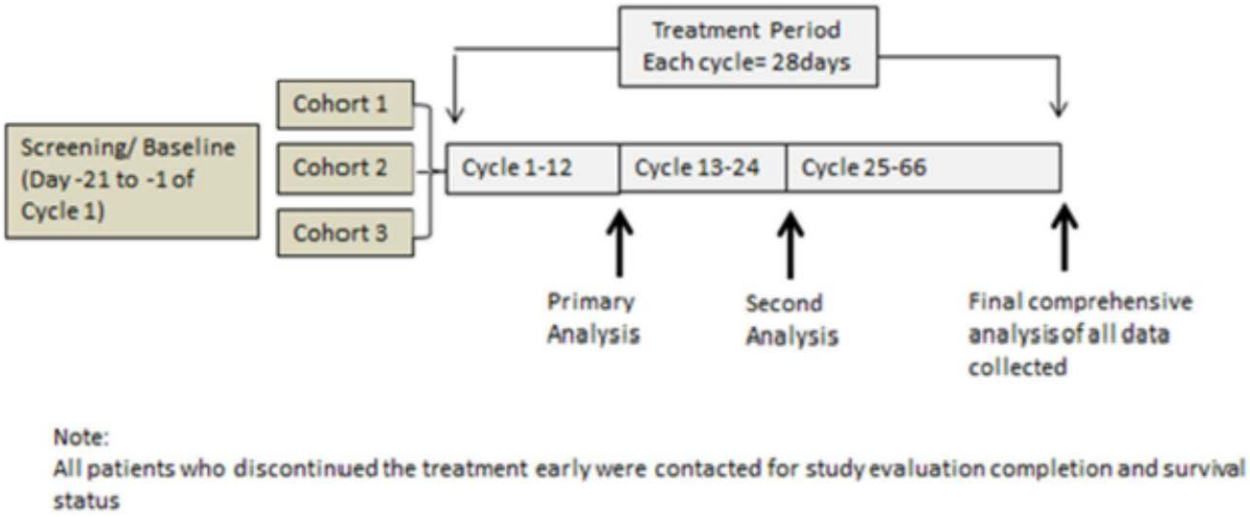


Figure 8 Study design and planned analysis - Study A2203

Objectives

Primary objectives

- To assess the efficacy of nilotinib in paediatric patients with Ph+ CML-CP resistant or intolerant to either imatinib or dasatinib.
- To assess the efficacy of nilotinib in paediatric patients with Ph+ CML-AP resistant or intolerant to either imatinib or dasatinib.
- To assess the efficacy of nilotinib in paediatric patients with newly diagnosed Ph+ CMLCP.

Secondary objectives

- To further characterize the efficacy and the PK profile of nilotinib in paediatric patients with Ph+ CML.
- To further characterize the safety and tolerability of nilotinib in paediatric patients with Ph+ CML.
- To assess the long term effect on growth, development and maturation of nilotinib treatment in paediatric patients with Ph+ CML.
- To identify emerging signs of resistance to nilotinib.
- To describe the acceptability of the study drug formulation.

Exploratory objectives

To assess the long term effect of nilotinib on bone metabolism.

Outcomes / endpoints

Primary endpoint:

The primary endpoint for cohorts 1 and 3 was major molecular response (MMR) defined as Fusion gene from breakpoint cluster region and Abelson genes (BCR-ABL)/ABL % ⩽ 0.1% by International scale (IS) as measured by RQ-PCR (Real-Time Quantitative-Polymerase Chain Reaction), confirmed by duplicate analysis of the same sample.

Table 12 List of primary efficacy endpoints - Study A2203

Cohort 1- Ph+ CML-CP patients resistant or intolerant to either imatinib or dasatinib	Cohort 3- Newly diagnosed Ph+ CML-CP patients
Rate of MMR at 6 cycles. A patient was counted as having MMR at 6 cycles if the patient met the MMR criteria at the Cycle 6 Visit.	Rate of MMR by 12 cycles. A patient was counted as having MMR by 12 cycles if the patient met the MMR criteria at least once at any time between first study drug intake and Cycle 12 visit included.
	Rate of CCyR at 12 cycles. A patient was counted as CCyR at 12 cycles if the patient met the CCyR criteria at the Cycle 12 Visit.
CCyR: Complete cytogenetic response; MMR: Major molecular response	

Secondary endpoints:

The list of secondary efficacy endpoints for study A2203 is displayed in Table 13.

Table 13 List of secondary efficacy endpoints - Study A2203

Both for newly diagnosed patients and resistant or intolerant patients cohorts	Additional endpoints only valid for newly diagnosed patients cohort
Molecular response	
- Rate of MMR by cohort at and by all time-points with data available - Time to MMR - Duration of MMR - BCR-ABL transcripts levels determined with standard protocols in peripheral blood at and by all time-points with data available	
Cytogenetic Response	
- Rate of each cytogenetic response category (complete, partial, major, minor, minimal and no response) at and by all time-points with data available	- Rate of CCyR at and by all time-points with data available and not already analyzed as part of the primary endpoint analysis - Time to CCyR - Duration of CCyR - Rate of MCyR at and by all time-points with data available - Time to MCyR - Duration of MCyR
Hematologic response	
	- Rate of CHR by all-time points with data available - Time to CHR - Duration of CHR
Long term outcomes	
- Time to disease progression on treatment; overall survival and event free survival	
CCyR: Complete cytogenetic response; CHR: Complete hematological response; MCyR: Major cytogenetic response; MMR: Major molecular response	

Sample size

There was no formal power-based calculation done for this single-arm trial. A minimum of 50 patients (including a minimum of 15 newly diagnosed Ph+CML-CP patients and 15 Ph+CML-CP patients

resistant or intolerant to either imatinib or dasatinib) were selected principally on the basis of operational and feasibility criteria, and in accordance with the minimal numbers required by the Health Authorities.

Randomisation

This was a single-arm study.

Blinding (masking)

The study was open-label.

Statistical methods

The data from all centres within each patient cohort was pooled for analysis. Because no patients were enrolled in cohort 2 (Ph+ CML-AP patients resistant or intolerant to imatinib or dasatinib), analyses were only performed for cohorts 1 and 3.

The primary efficacy endpoints were analysed descriptively for each cohort using the FAS, without hypothesis testing. Response rates were provided with 95% confidence intervals (CIs) using Clopper-Pearson's method by cohort. The secondary endpoints were also analysed descriptively using the FAS. The number and percentage of patients for each response category was provided at and by all scheduled time-points with available data. The cumulative response rates (i.e. by a time-point) as well as response rates at scheduled time-points were provided with 95% CIs using the Pearson-Clopper method. The cumulative incidence of response was graphically displayed by an increasing step-function. BCR-ABL transcript levels were summarized as BCR-ABL transcript ratio (BCR-ABL/ABL) (%) by cohort by and at all time-points with available data. Summary statistics for time to first MMR, first CCyR, first MCyR and first CHR among patients who achieved MMR, CCyR, MCyR, CHR, respectively, were provided for responders only. Time to first response was also estimated and graphically displayed using the Kaplan Meier (K-M) method.

Results

Participant flow

Table 14 Patient disposition by cohort (enrolled patients set) - Study A2203

Disposition Reason	Imatinib/dasatinib resistant/intolerant N=34 n (%)	Newly Diagnosed N=25 n (%)
Patients enrolled		
Untreated	1 (2.9)	0
Treated	33 (97.1)	25 (100)
Patients treated		
Treatment ongoing[1]	25 (73.5)	19 (76.0)
End of treatment	8 (23.5)	6 (24.0)
Primary reason for end of treatment		
Adverse event(s)	5 (14.7)	4 (16.0)
Subject withdrew consent	0	1 (4.0)
Administrative problems	1 (2.9)	1 (4.0)
Disease progression	1 (2.9)	0
Protocol deviation	1 (2.9)	0

[1]Patients ongoing at the time of the cut-off 01-Jun-2016

"Administrative problems" are one case of "lack of efficacy" for newly diagnosed patients and one case of "new cancer therapy" for imatinib/dasatinib resistant/intolerant patients (the CRF does not have separate reasons for discontinuation for such cases, the information was thus voluntarily stored under the category "administrative problem")

Recruitment

Study A2203 was conducted in 36 centres across 13 countries (USA: 10, Japan: 5, France: 4; Italy: 4; Turkey: 1, Thailand: 3, UK: 2; Spain: 1, Republic of Korea: 2, Malaysia: 1, Hungary: 1, Netherlands: 1, Russia: 1).

The first patient was enrolled on 20 August 2013 and the study was closed to enrolment on 6 July 2015, prior to the analysis cut-off date (1 June 2016 defined as the date by which all patients have completed 12 cycles of 28 days or discontinued study treatment early). Currently, the study is ongoing.

Conduct of the study

Protocol amendments

The study protocol was amended four times.

1) Amendment 1 (15-Sep-2014): Main changes were: Following PDCO recommendation for the assessment of potential long-term safety and efficacy issues the study duration was extended from 24 to 66 cycles

• The primary efficacy endpoint was revised as recommended by the FDA. For Cohort 1, the "Rate of MCyR by 12 months" was revised to "Rate of MCyR at 6 cycles" and for Cohort 3, the "Rate of MCyR by 12 months" was revised to "Rate of CCyR at 12 cycles". To add EFS as a new secondary endpoint, two sensitivity analyses for disease progression, collection of additional bio specimens from patients participating on the clinical trial for future research studies (Children's Oncology Group's sites

only), pre- and post-dose ECG measurements throughout the study in order to provide additional safety information in regards to nilotinib's effect on QT prolongation.

2) Amendment 2 (4-May-2015): The main purpose of this amendment was to adjust the minimum total sample size, as well as the minimum sample size of the newly diagnosed Ph+ CML-CP (cohort 3), to reflect the agreements with the US FDA and the EMA PDCO and the updated feasibility assessment in view of the very low incidence of Ph+ CML in the paediatric population and the actual trial accrual rates, and to enable timely availability of information in this population. The original study enrollment target of 65 total patients of which at least 50 would be Ph+CML newly diagnosed was reduced to at least 50 patients in total with at least 15 newly diagnosed Ph+ CML-CP patients.

3) Amendment 3 (8-Feb-2016): The primary endpoint for cohort 1 was revised to enable an assessment of the impact of therapy in patients with Ph+ CML-CP resistant or intolerant to either imatinib or dasatinib. The rationale for this change was that as part of routine study monitoring, it was observed that a significant number of patients enrolling in this cohort were already in MCyR or CCyR at baseline. This finding was also consistent with findings from a recently published study (Zwaan 2013). The protocol was additionally amended, to remove the binary endpoints related to CHR, MCyR and CCyR which were no longer appropriate measures to evaluate the therapeutic effect of nilotinib in this patient population. The determination of BCR-ABL molecular response was also clarified.

4) Amendment 4 (18-Apr-2016): The primary purpose for the amendment was to include hepatitis B virus testing as one of the study procedures and to identify study patients who might be at risk of hepatitis B virus reactivation. No other changes in study conduct occurred.

Changes in planned analysis

The original statistical analysis plan (RAP Module 3 Detailed statistical methodology) (22- Nov-2013) was based on protocol version 3. Amendment 1 (30-Mar-2016) was created before the database lock for primary analysis (19-Jul-2016) mainly to reflect the changes in protocol amendments 1, 2 and 3.

A RAP Module 3 Amendment 2 (13-Jul-2016) was created before the database lock for primary analysis (19-Jul-2016). This RAP amendment 2 included the following main modifications:

- The growth data analyses were updated to use the references provided by the WHO. This change also impacted the vital signs analyses.
- It was clarified that any dose decrease in 'mg' due to a change in body surface area was not to be considered as a dose decrease unless it affected the dose in 'mg/m2'.

Protocol deviations

There was no protocol deviation leading to exclusion from the PPS.

Baseline data

The demographic characteristics and baseline disease characteristics are displayed in Table 15 and Table 16.

Table 15 Demographic characteristics by cohort (FAS) - Study A2203

		Imatinib/dasatinib resistant/intolerant N=33	Newly Diagnosed N=25
Age (years)	N	33	25
	Mean (SD)	12.4 (3.61)	13.2 (2.11)
	Median (Min-Max)	13.0 (2-17)	13.0 (10-16)
Age category – n (%)	1 to <12 years	12 (36.4)	6 (24.0)
	12 to <18 years	21 (63.6)	19 (76.0)
Gender – n (%)	Female	12 (36.4)	12 (48.0)
	Male	21 (63.6)	13 (52.0)
Race – n (%)	Caucasian	12 (36.4)	18 (72.0)
	Black	3 (9.1)	0
	Asian	16 (48.5)	7 (28.0)
	Native American	1 (3.0)	0
	Other	1 (3.0)	0
Ethnicity – n (%)	Hispanic/Latino	6 (18.2)	4 (16.0)
	Japanese	7 (21.2)	1 (4.0)
	Mixed ethnicity	2 (6.1)	1 (4.0)
	Other	16 (48.5)	16 (64.0)
	Missing	2 (6.1)	3 (12.0)
Weight (kg)	N	33	25
	Mean (SD)	42.92 (17.882)	50.72 (13.089)
	Median (Min-Max)	42.70 (10.8-76.0)	51.30 (28.3-83.3)
Height (cm)	N	33	25
	Mean (SD)	148.16 (23.178)	159.99 (12.868)
	Median (Min-Max)	155.20 (80.0-178.0)	162.00 (135.3-185.0)
BSA (m^2)	N	33	25
	Mean (SD)	1.315 (0.3738)	1.495 (0.2403)
	Median (Min-Max)	1.370 (0.49-1.92)	1.540 (1.06-2.01)
BMI (kg/m^2)	N	33	25
	Mean (SD)	18.55 (4.120)	19.60 (3.546)
	Median (Min-Max)	18.09 (12.6-32.2)	19.27 (13.6-27.5)
Female child bearing potential -n (%)	Able to bear children	5 (15.2)	9 (36.0)
	Pre-menarche	7 (21.2)	3 (12.0)

BMI=body mass index; BSA=body surface area
Source: Table 14.1-3.1

Demographic characteristics using the PPS (Table 14.1-3.2) and PAS (Table 14.1-3.3) were similar to those using the FAS.

Table 16 Disease characteristics by cohort (FAS) - Study A2203

		Imatinib/dasatinib resistant/intolerant N=33	Newly diagnosed N=25
Time since first diagnosis of CML (days)	n	33	25
	Mean (SD)	1146.5 (1144.96)	15.2 (10.17)
	Median (Min-Max)	658.0 (189-4131)	14.0 (1-51)
Time since first diagnosis of CML (days) – n (%)	<30	0	24 (96.0)
	≥ 30-<90	0	1 (4.0)
	≥ 90-<180	0	0
	≥ 180	33 (100.0)	0
Patients imatinib/dasatinib intolerant– n (%)	Imatinib	6 (18.2)	NA
	Dasatinib	0	
Time since imatinib/dasatinib intolerant (days)	n	6	NA
	Mean (SD)	145.2 (251.50)	
	Median (Min-Max)	54.0 (1-652)	
Time since imatinib/dasatinib intolerant (days) – n (%)	<30	2 (6.1)	NA
	≥ 30-<90	2 (6.1)	
	≥ 90-<180	1 (3.0)	
	≥ 180	1 (3.0)	
Patients imatinib/dasatinib resistant– n (%)	Imatinib	28 (84.8)	NA
	Dasatinib	2 (6.1)	
Time since imatinib/dasatinib resistance (days)	n	30	NA
	Mean (SD)	123.1 (162.42)	
	Median (Min-Max)	65.0 (5-653)	
Time since imatinib/dasatinib resistance(days) – n (%)	<30	6 (18.2)	NA
	≥ 30-<90	16 (48.5)	
	≥ 90-<180	3 (9.1)	
	≥ 180	5 (15.2)	

The bone marrow analysis at baseline is displayed in Table 17.

Table 17 Bone marrow analysis at baseline (FAS) – Study A2203

	Imatinib/dasatinib resistant/intolerant N=33	Newly Diagnosed N=25
Blasts (%) in BM		
n (%)	31 (93.9)	24 (96.0)
Median	0	2.00
25-75th percentiles	0.00-1.80	1.00-3.50
Minimum - Maximum	0.0-7.0	0.0-11.0
<15% - n (%)	31 (93.9)	24 (96.0)
Promyelocytes (%) in BM		
n (%)	31 (93.9)	24 (96.0)
Median	1.00	4.50
25-75th percentiles	0.00-4.00	2.50-8.50
Minimum - Maximum	0.0-20.0	0.0-12.8
Blasts + promyelocytes (%) in BM		
n (%)	31 (93.9)	24 (96.0)
Median	2.40	7.50
25-75th percentiles	0.00-5.20	4.50-11.50
Minimum - Maximum	0.0-20.0	0.6-15.2
Any other chromosomal abnormalities in Ph+ metaphases? - n (%)		
Yes	2 (6.1)	3 (12.0)
No	28 (84.8)	22 (88.0)
Missing	3 (9.1)	0
Any chromosomal abnormalities in Ph- metaphases? - n (%)		
Yes	2 (6.1)	0
No	28 (84.8)	25 (100)
Missing	3 (9.1)	0
Percentage Ph+ metaphase category - n (%)		
>95% (None)	4 (12.1)	21 (84.0)
>65% - 95% (Minimal cytogenetic response)	1 (3.0)	3 (12.0)
>35% - 65% (Minor cytogenetic response)	1 (3.0)	0
>0% - 35% (Partial cytogenetic response)	7 (21.2)	1 (4.0)
0% (Complete cytogenetic response)	14 (42.4)	0
Missing	6 (18.2%)	0

The molecular status at baseline is discpayed in Table 18.

Table 18 Molecular status at Baseline (FAS) - Study A2203

	Imatinib/dasatinib resistant/intolerant N=33	Newly Diagnosed N=25
BCR-ABL ratio categories at Baseline – n (%)		
≤ 0.0032%	1 (3.0)	0
>0.0032% - ≤ 0.01%	1 (3.0)	0
>0.01% - ≤ 0.1%	5 (15.2)	0
>0.1% - ≤ 1%	10 (30.3)	0
>1%< - ≤ 10%	9 (27.3)	0
>10%	5 (15.2)	25 (100)
Atypical transcripts at Baseline	1 (3.0)	0
Missing	1 (3.0)	0

Numbers analysed

The numbers analysed are displayed in Table 19.

Table 19 Analysis sets - Study A2203

Analysis population	Imatinib/dasatinib resistant/intolerant N=34 n (%)	Newly Diagnosed N=25 n (%)
Enrolled patients Set	34 (100)	25 (100)
Age 1 to <12	12 (35.3)	6 (24.0)
Age 12 to <18	22 (64.7)	19 (76.0)
Full Analysis Set (FAS)	33 (97.1)	25 (100)
Age 1 to <12	12 (35.3)	6 (24.0)
Age 12 to <18	21 (61.8)	19 (76.0)
Safety Set (SAF)	33 (97.1)	25 (100)
Age 1 to <12	12 (35.3)	6 (24.0)
Age 12 to <18	21 (61.8)	19 (76.0)
Per Protocol Set (PPS)	32 (94.1)	25 (100)
Age 1 to <12	11 (32.4)	6 (24.0)
Age 12 to <18	21 (61.8)	19 (76.0)
Pharmacokinetic Analysis Set (PAS)	32 (94.1)	25 (100)
Age 1 to <12	12 (35.3)	6 (24.0)
Age 12 to <18	20 (58.8)	19 (76.0)

Outcomes and estimation

- **Analysis of efficacy in imatinib / dasatinib resistant / intolerant CML-CP patients**

Primary endpoint: Major molecular response

The results of the major molecular response at 6 cycles are displayed in Table 20.

Table 20 Major molecular response at 6 cycles in Ph+ CML CP patients who were resistant or intolerant to imatinib or dasatinib (FAS)

	Imatinib/dasatinib resistant/intolerant N=33
MMR status at 6 cycles	
Response – n (%)	13 (39.4)[a]
95% CI for response (%)	(22.9, 57.9)
No response - n (%)	20 (60.6)

[a] 6 of those 13 patients were in MMR already at Baseline.

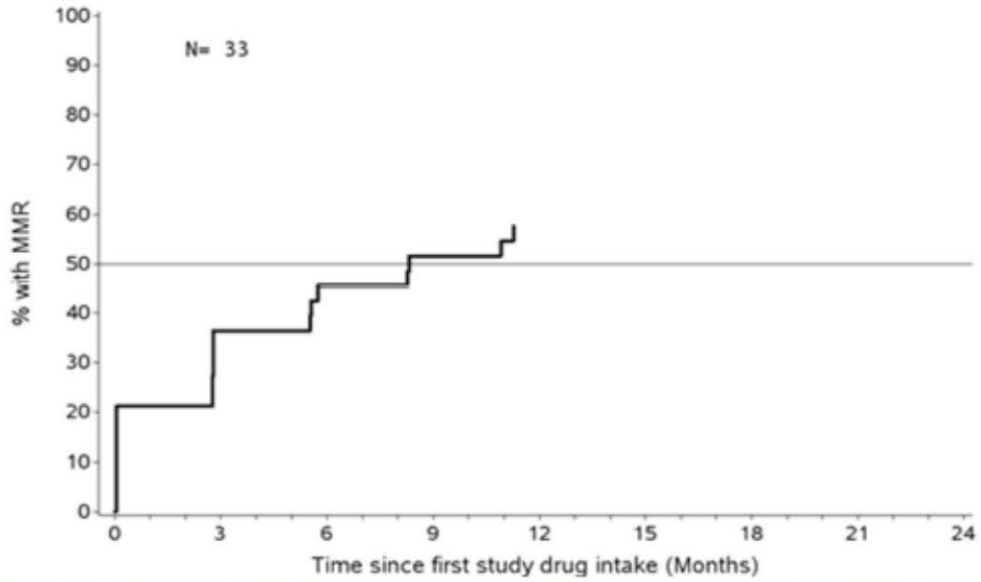
Age subgroup analyses (1 to <12 years, ≥ 12 to <18 years) were conducted for the primary efficacy endpoints. The MMR rates at 6 cycles for the age category of 1 to <12 years was 50% (95% CI: 21.1, 78.9) and for the age category of ≥ 12 to <18 years was 33.3% (95% CI: 14.6, 57.0).

Secondary endpoint: Major molecular response by time point

The results of the secondary endpoint major molecular response by time point are displayed in Table 21 and Figure 9.

Table 21 Major molecular response by time point in Ph+ CML-CP patients resistant or intolerant to imatinib or dasatinib (FAS) - Study A2203

MMR status		Imatinib/dasatinib resistant/intolerant N=33
Overall	Response - n (%)	19 (57.6)
	95% CI for response (%)	(39.2, 74.5)
	No response - n (%)	14 (42.4)
By cycle 6	Response - n (%)	15 (45.5)
	95% CI for response (%)	(28.1, 63.6)
	No response - n (%)	18 (54.5)
By cycle 12	Response - n (%)	19 (57.6)
	95% CI for response (%)	(39.2, 74.5)
	No response - n (%)	14 (42.4)



Note: Seven patients were already MMR at baseline, reason for which the cumulative curve starts at 21% on Day 1.

Figure 9 Cumulative incidence of major molecular response in Ph+ CML-CP patients resistant or intolerant to imatinib or dasatinib (FAS) - Study A2203

Secondary endpoint: Time to first major molecular response

Time to first MMR in the imatinib/dasatinib resistant/intolerant patients is presented for the responders in Table 22. K-M analyses are presented in Table 23 and Figure 10.

Table 22 Summary of time to first major molecular response (MMR) among imatinib or dasatinib resistant or intolerant CML-CP patients who achieved MMR (FAS) Study A2203

	Imatinib/dasatinib N=33
Time to MMR (months)	
n	19
Mean (SD)	3.67 (3.806)
Median [95% CI]	2.79 (0, 5.7)
25-75th percentiles	0.03-5.75
Minimum – maximum	0.0-11.3

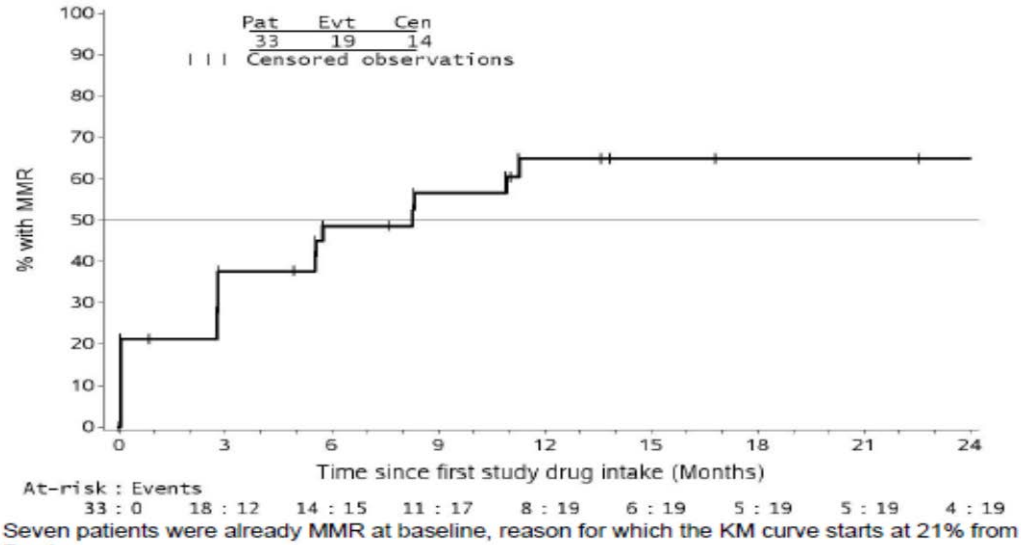
Time to first response is summarized only among responders.

95% distribution-free confidence interval provided for the median time to MMR.
Seven patients were already MMR at baseline, reason for which the minimum time to MMR is equal to 0

Table 23 Kaplan-Meier estimates of time to first MMR in Ph+ CML-CP patients resistant or intolerant to imatinib or dasatinib (FAS) Study A2203

Category	Imatinib/dasatinib resistant/intolerant N=33
Number of events - n (%)	19 (57.6)
Number censored - n (%)	14 (42.4)
Percentiles (95% CI)	
25th	2.8 (0.0, 5.5)
50th	8.3 (2.8, NE)
75th	NE (10.9, NE)
Kaplan-Meier estimate (95% CI)	
3 months	37.6 (23.3, 56.8)
6 months	48.6 (32.6, 67.5)
9 months	56.5 (39.6, 74.8)
12 months	64.9 (47.3, 81.9)
15 months	64.9 (47.3, 81.9)
18 months	64.9 (47.3, 81.9)
21 months	64.9 (47.3, 81.9)
24 months	64.9 (47.3, 81.9)

NE: Not estimable



Seven patients were already MMR at baseline, reason for which the KM curve starts at 21% from Day1

Figure 10 Kaplan-Meier plot of time to first MMR in Ph+ CML-CP patients resistant or intolerant to imatinib or dasatinib (FAS) - Study A2203

Secondary endpoint: Duration of MMR

There was no patient with confirmed loss of MMR by the time of data cut-off date (1 June 2016), out of the 19 patients who were in MMR on treatment. The KM estimate of median duration of first MMR was not assessable.

Updated data (cut-off date 1 December 2016) representing additional 6 months of data showed that there were no additional patients gaining MMR.

An exploratory analyses was conducted by the applicant using different baseline characteristics including age, gender, race, resistance vs. no resistance to prior TKI, priori TKI (imatinib vs. dasatinib vs. both), level of molecular/cytogenetic/hematological response (MMR vs. CCyR but not MMR vs. CHR but not CCyR vs. no CHR/missing response) at baseline before switch to nilotinib. The results are displayed in Table 24.

Table 24 Best MMR according to baseline demographic and disease characteristics - Study A2203

Baseline factor		Imatinib/dasatinib resistant/intolerant Ph+ CML CP (N=44) n/N (%) [95% CI]	Newly diagnosed Ph+ CML CP (N=25) n/N (%) [95% CI]
Age	2 to 12 years	8/18 (44.4) [21.5, 69.2]	4/6 (66.7) [22.3,95.7]
	12 to 18 years	13/26 (50.0) [29.9, 70.1]	13/19 (68.4) [43.4, 87.4]
Gender	Male	13/27 (48.1) [28.7, 68.1]	10/13 (76.9) [46.2, 95.0]
	Female	8/17 (47.1) [23.0,72.2]	7/12 (58.3) [27.7, 84.8]
Race	Caucasian	7/21 (33.3) [14.6, 57.0]	11/18 (61.1) [35.7, 82.7]
	Asian	11/17 (64.7) [38.3, 85.8]	6/7 (85.7) [42.1, 99.6]
Prior TKI meds (from PTM panel)	Imatinib	21/37 (56.8) [39.5, 72.9]	NA
	Dasatinib	0/2 (0.0)	NA

Baseline factor		Imatinib/dasatinib resistant/intolerant Ph+ CML CP (N=44) n/N (%) [95% CI]	Newly diagnosed Ph+ CML CP (N=25) n/N (%) [95% CI]
		[0, 84.2]	
	Imatinib and Dasatinib	0/5 (0.0) [0, 52.2]	NA
Resistance status to any previous TKIs	Resistant	20/39 (51.3) [34.8, 67.6]	NA
	Not resistant	1/5 (20.0) [0.5, 71.6]	NA
Level of response at baseline	MMR	8/8 (100) [63.1, 100]	NA
	CCyR but not MMR	5/11 (45.5) [16.7, 76.6]	NA
	CHR but not CCyR	6/18 (33.3) [13.3, 59.0]	NA
	No CHR/missing	2/7 (28.6) [3.7, 71.0]	NA

Secondary endpoint: Cytogenetic response by category

By 12 cycles as well as by the data cut-off date (1 June 2016), the cytogenetic response was MCyR (CCyR+PCyR) in 28 (84.8%) patients (Table 25).

Table 25 cytogenetic response categories in imatinib / dasatinib resistant / intolerant CML-CP patients (FAS) Study A2203

Cytogenetic response categories		Imatinib/dasatinib resistant/intolerant N=33
Overall - n (%)	Major cytogenetic response	28 (84.8)
	Complete	27 (81.8)
	Partial	1 (3.0)
	Minimal	1 (3.0)
	None	1 (3.0)
	Missing	3 (9.1)
	Ongoing	3 (9.1)
By cycle 6 - n (%)	Major cytogenetic response	25 (75.8)
	Complete	24 (72.7)
	Partial	1 (3.0)
	Minimal	1 (3.0)
	Missing	7 (21.2)
	Ongoing	7 (21.2)
By cycle 12 - n (%)	Major cytogenetic response	28 (84.8)
	Complete	27 (81.8)
	Partial	1 (3.0)
	Minimal	1 (3.0)
	None	1 (3.0)
	Missing	3 (9.1)
	Ongoing	3 (9.1)

Based on the 1 December 2016, cut-off date, the patient who had a minimal cytogenetic response discontinued the study to undergo bone marrow transplantation, and the 3 patients with missing cytogenetic data discontinued treatment.

Secondary endpoint: Time to disease progression

By the data cut-off date, one imatinib resistant (A2203-3020-00005) progressed to AP/BC after 10.1 months on treatment. The patient discontinued the study treatment and was being followed-up for survival at the time of data cut-off. The median time to disease progression was not reached. The K-M estimated rate of progressions at 12-months was 3.7% (95% CI: 0.5, 23.5) (data not shown).

Secondary endpoints: EFS and OS

By the data cut-off date, one patient had an event and no death was reported in the study. The EFS and OS data are not mature yet.

- **Analysis of efficacy in newly diagnosed CML-CP patients**

Primary endpoint: Major molecular response rate by 12 cycles

Table 26 Major molecular response rate by 12 cycles in newly diagnosed Ph+ CML-CP patients (FAS) - Study A2203

	Newly diagnosed N=25
MMR status by cycle 12	
Response - n (%)	16 (64.0)
95% CI for response (%)	(42.5, 82.0)
No response - n (%)	9 (36.0)

Primary endpoint: Complete cytogenetic response rate by 12 cycles

Table 27 Complete cytogenetic response rate by 12 cycles in newly diagnosed Ph+ CML-CP patients (FAS) - Study A2203

	Newly diagnosed N=25
CCyR at 12 cycles	
Response - n (%)	16 (64.0)
95% CI for response (%)	(42.5, 82.0)
No response - n (%)	9 (36.0)

Subgroup analysis for the primary endpoints

The subgroup analyses by the age group category for the MMR rate (1 to <12 years: 66.7%, 95% CI: 22.3, 95.7; ⩾12 to <18 years: 63.2%, 95% CI: 38.4, 83.7) by 12 cycles as well as CCyR rate for the age group categories 1 to <12 years: 66.7% (95% CI: 22.3, 95.7); ⩾12 to <18 years: 63.2% (95%CI: 38.4, 83.7) at 12 cycles were consistent across subgroups.

At 12 cycles 16/25 (64%) patients had reached MMR and CCyR. Looking at efficacy based on age, there seem to be no major difference between age-groups 1-12 and 12-18. However, all patients in cohort 3 are or above ten years.

Secondary endpoint: MMR by time point

Time to first MMR in the imatinib/dasatinib resistant/intolerant patients is presented for the responders in Table 28. K-M analyses are presented in Figure 11.

Table 28 Major molecular response in newly diagnosed Ph+ CML-CP patients (FAS)

MMR status		Newly diagnosed N=25
Overall	Response - n (%)	17 (68.0)
	95% CI for response (%)	(46.5, 85.1)
	No response - n (%)	8 (32.0)
By cycle 6	Response - n (%)	13 (52.0)
	95% CI for response (%)	(31.3, 72.2)
	No response - n (%)	12 (48.0)
By cycle 12	Response - n (%)	16 (64.0)
	95% CI for response (%)	(42.5, 82.0)
	No response - n (%)	9 (36.0)

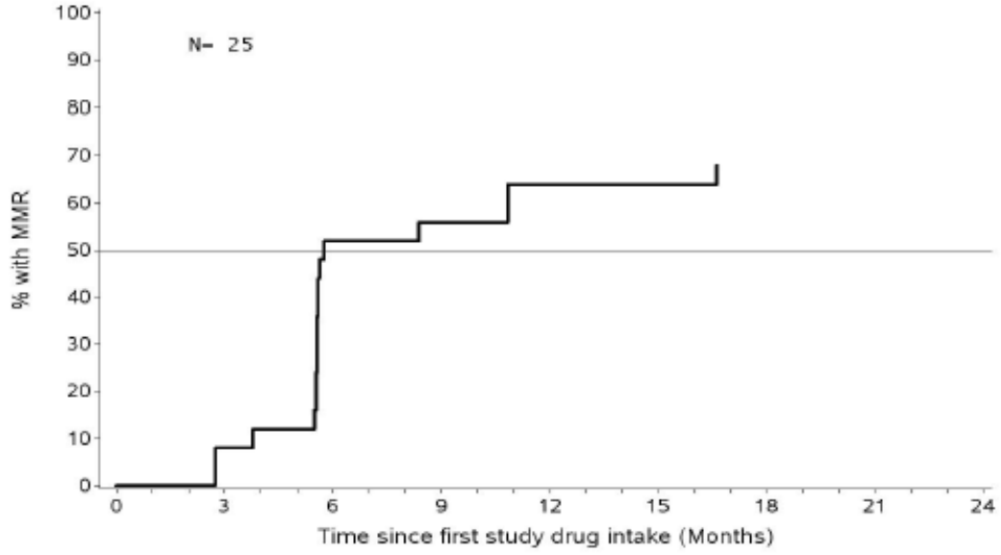


Figure 11 Cumulative incidence of MMR in newly diagnosed Ph+ CML-CP patients (FAS) - Study A2203

Secondary endpoint: BCR-ABL transcript levels

Fifteen (60.0%) newly diagnosed patients were in MMR (BCR-ABL ratios ⩽ 0.1) at 12 cycles (data not shown).

Secondary endpoint: Time to major molecular response

The time to first MMR analysis in the newly diagnosed patients is presented for responders in Table 29. The K-M analysis is presented in Table 30.

Table 29 summary of time to first major molecular response (MMR) among newly diagnosed Ph+ CML-CP patients who achieved MMR (FAS) - Study A2203

	Newly diagnosed N=25
Time to MMR (months)	
N	17
Mean (SD)	6.57 (3.430)
Median (95% CI)	5.55 (5.5, 5.7)
25-75th percentiles	5.52-5.75
Minimum – maximum	2.7-16.6

Time to first response is summarized only among responders.
95% distribution-free confidence interval provided for the median time to MMR.

Table 30 Kaplan-Meier estimates of time to first major molecular response in newly diagnosed Ph+ CML-CP patients FAS - Study A2203

Category	Newly diagnosed N=25
Number of events - n (%)	17 (68.0)
Number censored - n (%)	8 (32.0)
Percentiles (95% CI)	
25th	5.5 (2.7, 5.6)
50th	5.6 (5.6, 10.8)
75th	16.6 (5.7, NE)
Kaplan-Meier estimate (95% CI)	
3 months	8.3 (2.2,29.4)
6 months	57.2 (38.2,77.7)
9 months	62.0 (42.7,81.4)
12 months	72.9 (53.0,89.5)
15 months	72.9 (53.0,89.5)
18 months	86.4 (60.0,98.7)
21 months	86.4 (60.0,98.7)
24 months	86.4 (60.0,98.7)

NE: Not estimable

K-M analysis for time to first MMR is displayed in Figure 12.

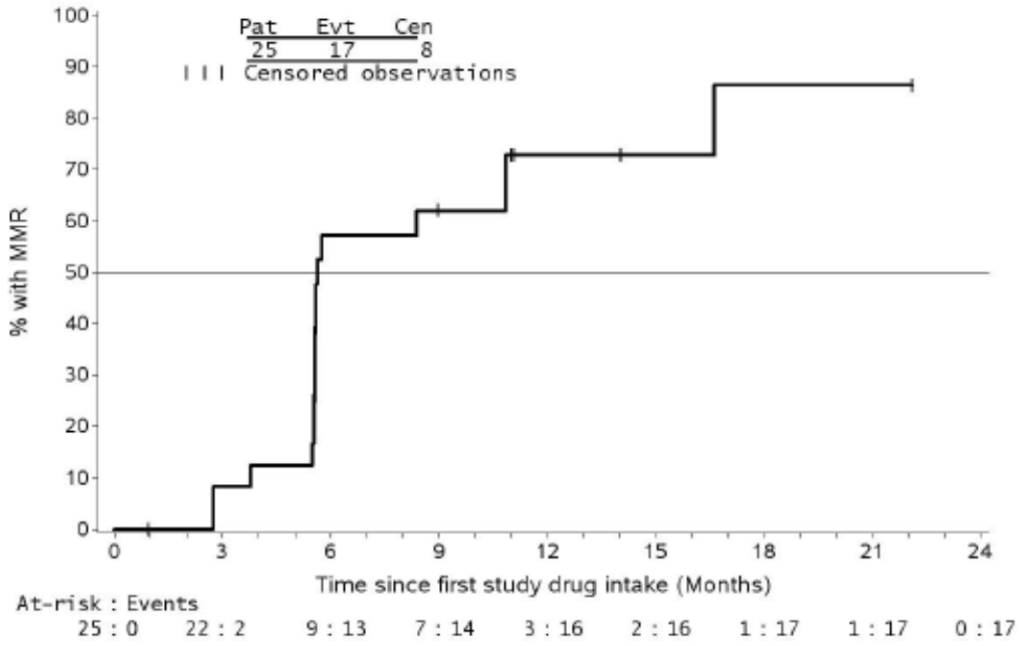


Figure 12 Kaplan-Meier estimates of time to first major molecular response in newly diagnosed Ph+ CML-CP patients (FAS) - Study A2203

Secondary endpoint: Duration of MMR

Of the 17 patients who achieved MMR on treatment, one patient (A2203-2070-00003) had confirmed loss of MMR. The patient was still on treatment at the time of data cut-off. Consequently, the median duration of first MMR in the newly diagnosed patients was not assessable and the K-M estimated rate

of patients in MMR for a duration of at least 12 months was 92.9% (95% CI: 59.1, 99.0) (data not shown).

Secondary endpoint: Complete cytogenetic response rate by time point

By the data cut-off, the CCyR rate was 84% (Table 31).

Table 31 Complete cytogenetic response rate in newly diagnosed Ph+ CML-CP patients (FAS) - Study A2203

CCyR status		Newly diagnosed N=25
Overall	Response - n (%)	21 (84.0)
	95% CI for response (%)	(63.9, 95.5)
	No response - n (%)	4 (16.0)
By cycle 6	Response - n (%)	21 (84.0)
	95% CI for response (%)	(63.9, 95.5)
	No response - n (%)	4 (16.0)
By cycle 12	Response - n (%)	21 (84.0)
	95% CI for response (%)	(63.9, 95.5)
	No response - n (%)	4 (16.0)

Secondary endpoint: Time to first complete cytogenetic response

Time to first CCyR analysis in the newly diagnosed patients is presented for responders in Table 32. The K-M analysis is presented in Table 33 and Figure 13.

Table 32 Summary of time to first complete cytogenetic response (CCyR) among newly diagnosed CML-CP patients who achieved CCyR (FAS) - Study A2203

	Newly diagnosed N=25
Time to CCyR (months)	
n	21
Mean (SD)	5.40 (0.607)
Median [95% CI]	5.55 (5.5, 5.6)
25-75th percentiles	5.49-5.59
Minimum – maximum	2.8-5.8

Time to first response is summarized only among responders.
95% distribution-free confidence interval provided for the median time to CCyR.

Table 33 Kaplan-Meier estimates of time of first complete cytogenetic response in newly diagnosed Ph+ CML-CP patients (FAS) - Study A2203

Category	Newly diagnosed N=25
Number of events - n (%)	21 (84.0)
Number censored - n (%)	4 (16.0)
Percentiles (95% CI)	
25th	5.5 (2.8, 5.6)
50th	5.6 (5.5, 5.6)
75th	5.6 (5.6, NE)
Kaplan-Meier estimate (95% CI)	
3 months	4.2 (0.6,26.1)
6 months	90.6 (74.4,98.4)
9 months	90.6 (74.4,98.4)

NE: Not estimable

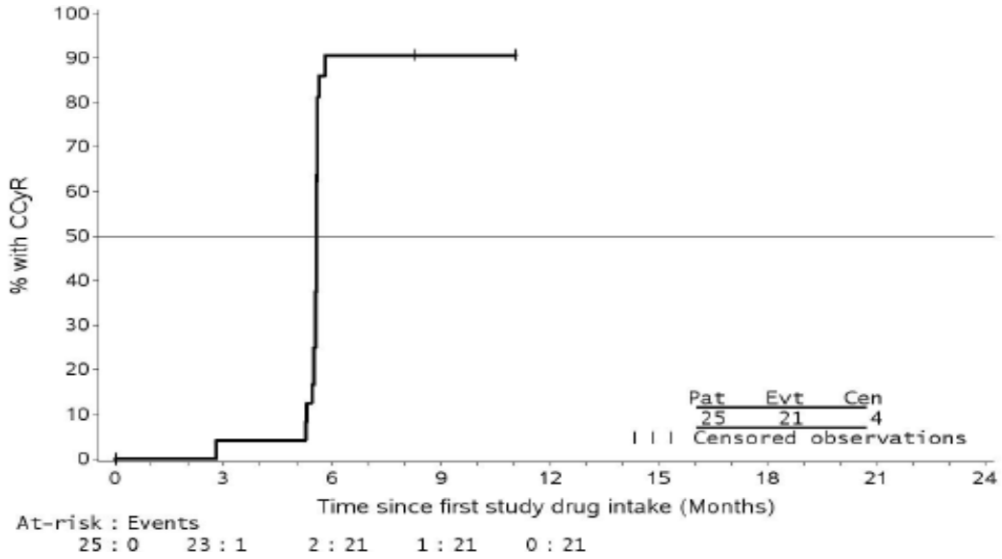


Figure 13 Kaplan-Meier estimates of time to first complete cytogenetic response in newly diagnosed Ph+ CML-CP patients (FAS) - Study A2203

Secondary endpoint: Duration of complete cytogenetic response

Of the 21 patients who achieved CCyR on treatment, one patient (A2203-2070-00003) had confirmed loss of CCyR. The patient was still on treatment at the time of data cut-off. Consequently, the median duration of first CCyR in the newly diagnosed patients was not estimable and the K-M estimated rate of patients in CCyR for duration of at least 6 months was 94.1% (95% CI: 65.0, 99.1) (data not shown).

Other endpoints

- Major cytogenetic response rate by time point

By the data cut-off, the MCyR rate was 88%. The MCyR rates by 6 and 12 cycles were the same as overall MCyR rate.

- Time to first major cytogenetic response

The median time to first MCyR was 5.55 months (95%CI: 5.5, 5.6) in 22 patients who achieved MCyR. The K-M estimated rate of achieving MCyR was 91.7% (95% CI: 76.7, 98.6) at 6 months.

- Complete haematological response by time point

By the data cut-off, the CHR rate in the newly diagnosed patients was 92.0%. By 6 and 12 cycles the CHR rates were 84% and 92%, respectively.

- Time to first complete haematological response

The median time to first CHR in the newly diagnosed patients was 1 month (95% CI: 1.0, 2.8). The K-M estimated rate of achieving CHR was 95.6% (95% CI: 81.6, 99.7) at 12 months

- Duration of complete haematological response

Of the 22 patients who achieved MCyR on treatment, one patient, who also had documented loss of CCyR) had confirmed loss of MCyR and the patient was still on treatment at the time of data cut-off. Consequently, the median duration of first MCyR was not estimable. The K-M estimate for the rate of patients in MCyR for duration of at least 12 months was 94.1% (95% CI: 65.0, 99.1).

- Time to disease progression

By the data cut-off, one newly diagnosed patient temporarily matched the technical definition for progression to AP/BC, one month after the start of nilotinib, due to increased basophil cell count. The treatment had been temporarily interrupted for 13 days during the first 28 days cycle due to prolonged QT. The patient remained in the study, went back to CP one month after the progression and was in CHR and CCyR by 6 cycles of nilotinib treatment.

- Event free survival

By the data cut-off, two patients had an event: one patient had confirmed loss of MCyR; another patient was meeting the technical definition of disease progression . The estimated rate of EFS was 90% (95%CI: 64.6, 97.5) at 12 months.

- Overall survival

By the data cut-off, no death was reported in the study.

Ancillary analyses

Table 34 shows best MMR by each time point by cohorts (resistant/intolerant & newly diagnosed).

Table 34 Best MMR by each time point by cohort (FAS) - Study A2203

	Imatinib/dasatinib resistant/intolerant Ph+ CML-CP N=33		Newly diagnosed Ph+ CML-CP N=25	
	n (%)	95% CI	n (%)	95% CI
Best MMR status - overall				
Major molecular response (MMR)	19 (57.6)	(39.2, 74.5)	17 (68.0)	(46.5, 85.1)
No major molecular response	14 (42.4)		8 (32.0)	
Best MMR status by cycle 1				
Major molecular response (MMR)	7 (21.2)	(9.0, 38.9)	0	(0 , 13.7)
No major molecular response	26 (78.8)		25 (100)	
Best MMR status by cycle 3				
Major molecular response (MMR)	12 (36.4)	(20.4, 54.9)	3 (12.0)	(2.5, 31.2)
No major molecular response	21 (63.6)		22 (88.0)	
Best MMR status by cycle 6				
Major molecular response (MMR)	15 (45.5)	(28.1, 63.6)	13 (52.0)	(31.3, 72.2)
No major molecular response	18 (54.5)		12 (48.0)	
Best MMR status by cycle 9				
Major molecular response (MMR)	17 (51.5)	(33.5, 69.2)	14 (56.0)	(34.9, 75.6)
No major molecular response	16 (48.5)		11 (44.0)	
Best MMR status by cycle 12				
Major molecular response (MMR)	19 (57.6)	(39.2, 74.5)	16 (64.0)	(42.5, 82.0)
No major molecular response	14 (42.4)		9 (36.0)	

Best MMR status by cycle 15				
Major molecular response (MMR)	19 (57.6)	(39.2, 74.5)	16 (64.0)	(42.5, 82.0)
No major molecular response	14 (42.4)		9 (36.0)	
Best MMR status by cycle 18				
Major molecular response (MMR)	19 (57.6)	(39.2, 74.5)	17 (68.0)	(46.5, 85.1)
No major molecular response	14 (42.4)		8 (32.0)	
Best MMR status by cycle 21				
Major molecular response (MMR)	19 (57.6)	(39.2, 74.5)	17 (68.0)	(46.5, 85.1)
No major molecular response	14 (42.4)		8 (32.0)	
Best MMR status by cycle 24				
Major molecular response (MMR)	19 (57.6)	(39.2, 74.5)	17 (68.0)	(46.5, 85.1)
No major molecular response	14 (42.4)		8 (32.0)	
Best MMR status by cycle 30				
Major molecular response (MMR)	19 (57.6)	(39.2, 74.5)	17 (68.0)	(46.5, 85.1)
No major molecular response	14 (42.4)		8 (32.0)	

Table 35 shows the best cytogenetic response by each time point by cohorts (resistant/intolerant & newly diagnosed).

Table 35 Best cytogenetic response by each time point by cohort (FAS) - Study A2203

	Imatinib/dasatinib resistant/intolerant Ph+ CML-CP N=33 n (%)	Newly diagnosed Ph+ CML-CP N=25 n (%)
Best cytogenetic response categories - overall		
Major cytogenetic response (MCyR)	28 (84.8)	22 (88.0)
Complete cytogenetic response (CCyR)	27 (81.8)	21 (84.0)
Partial cytogenetic response (PCyR)	1 (3.0)	1 (4.0)
Minimal cytogenetic response	1 (3.0)	0
No cytogenetic response	1 (3.0)	2 (8.0)
Missing	3 (9.1)	1 (4.0)
Ongoing	3 (9.1)	1 (4.0)
Best cytogenetic response categories by cycle 6		
Major cytogenetic response (MCyR)	25 (75.8)	22 (88.0)
Complete cytogenetic response (CCyR)	24 (72.7)	21 (84.0)
Partial cytogenetic response (PCyR)	1 (3.0)	1 (4.0)
Minimal cytogenetic response	1 (3.0)	0
No cytogenetic response	0	2 (8.0)
Missing	7 (21.2)	1 (4.0)
Ongoing	7 (21.2)	1 (4.0)
Best cytogenetic response categories by cycle 12		
Major cytogenetic response (MCyR)	28 (84.8)	22 (88.0)
Complete cytogenetic response (CCyR)	27 (81.8)	21 (84.0)
Partial cytogenetic response (PCyR)	1 (3.0)	1 (4.0)
Minimal cytogenetic response	1 (3.0)	0
No cytogenetic response	1 (3.0)	2 (8.0)
Missing	3 (9.1)	1 (4.0)
Ongoing	3 (9.1)	1 (4.0)
Best cytogenetic response categories by cycle 18		
Major cytogenetic response (MCyR)	28 (84.8)	22 (88.0)
Complete cytogenetic response (CCyR)	27 (81.8)	21 (84.0)
Partial cytogenetic response (PCyR)	1 (3.0)	1 (4.0)
Minimal cytogenetic response	1 (3.0)	0
No cytogenetic response	1 (3.0)	2 (8.0)
Missing	3 (9.1)	1 (4.0)
Ongoing	3 (9.1)	1 (4.0)

Best cytogenetic response categories by cycle 24		
Major cytogenetic response (MCyR)	28 (84.8)	22 (88.0)
Complete cytogenetic response (CCyR)	27 (81.8)	21 (84.0)
Partial cytogenetic response (PCyR)	1 (3.0)	1 (4.0)
Minimal cytogenetic response	1 (3.0)	0
No cytogenetic response	1 (3.0)	2 (8.0)
Missing	3 (9.1)	1 (4.0)
Ongoing	3 (9.1)	1 (4.0)
Best cytogenetic response categories by cycle 36		
Major cytogenetic response (MCyR)	28 (84.8)	22 (88.0)
Complete cytogenetic response (CCyR)	27 (81.8)	21 (84.0)
Partial cytogenetic response (PCyR)	1 (3.0)	1 (4.0)
Minimal cytogenetic response	1 (3.0)	0
No cytogenetic response	1 (3.0)	2 (8.0)
Missing	3 (9.1)	1 (4.0)
Ongoing	3 (9.1)	1 (4.0)

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 36 Summary of efficacy for trial A2203

Title: A multi-center, open label, non-controlled Phase II study to evaluate the efficacy and safety of oral nilotinib in paediatric patients with newly diagnosed Ph+ chronic myelogenous leukemia (CML) in chronic phase (CP) or with Ph+ CML in CP or accelerated phase (AP) resistant or intolerant to either imatinib or dasatinib.			
Study identifier	CAMN107A2203		
Design	Multi-center, open label, non-controlled Phase II study		
	Duration:	First patient enrolled: 20-Aug-2013 Last patients last Visit: Not applicable (study ongoing; cut-off date 01-Jun-2016 is defined as the date by which all patients have completed 12 cycles of 28 days or discontinued study treatment early)	
Hypothesis	Exploratory		
Treatments groups	Cohort 1		Ph+ CML-CP patients resistant or intolerant to either imatinib or dasatinib, N = 34
	Cohort 2		Ph+ CML-AP patients resistant or intolerant to either imatinib or dasatinib, N = 0
	Cohort 3		Newly diagnosed Ph+ CML-CP patients in chronic phase, N = 25
Endpoints and definitions	Primary endpoint	Cohort 1: MMR rate at 6 cycles	Cohort 3: MMR by 12 cycles and CCyR rate at 12 cycles

	Secondary endpoints	MMR, MCyR and CCyR rate by time-point. Time to first MMR, MCyR and CCyR Duration of MMR, CCyR and MCyR HR rate Time to CHR Duration of CHR EFS OS	MMR = Major molecular response MCyR = Major cytogenetic response CCyR = Complete cytogenetic response CHR = Complete Haematological response EFS = Event-Free Survival OS = Overall survival
Database lock	NA		
Results and Analysis			
Analysis description	Primary Analysis		
Analysis population and time point description	Intent to treat		

Descriptive statistics and estimate variability	Treatment group	Cohort 1	Cohort 3	
	Number of subject	N = 33	N = 25	
	MMR	13 (39.4%)	16 (64%)	
	95%CI	22.9, 57.9	42.5, 82.0	
	Time to first MMR (median in months)	2.79	5.55	
	95%CI	0, 5.7	5.5, 5.7	
	Duration of MMR (median in months)	NE	NE	

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

Data from patients with Ph+ CML in studies A2203 and A2120 were pooled and the pooled efficacy database comprised two sets of patients, drawn from the full analysis set (FAS) of the respective studies:

- Ph+ CML-CP resistant/intolerant to imatinib/dasatinib (N=44, including 33 patients from study A2203 and 11 patients from Study A2120), and
- Newly diagnosed Ph+ CML-CP (N=25, all from Study A2203)

The following efficacy endpoints were analysed:

- Rate of MMR at and by all-time points
- Time to MMR
- Duration of MMR
- BCR-ABL/ABL ratio (% International scale, IS) categories at and by all-time points.

When calculating molecular response, only results based on blood PCR testing according to classical criteria for MMR were considered for the pooled analyses.

Table 37 Overview of efficacy endpoints in Study A2203 and A2120

Study No.	Efficacy endpoint
A2203	**Primary efficacy end points**
	Resistant/intolerant CML-CP: Rate of MMR at 6 cycles.
	Newly diagnosed CML-CP: Rate of MMR by 12 cycles and CCyR at 12 cycles.
	Secondary efficacy end points
	Both resistant/intolerant and newly diagnosed CML-CP: Rate of MMR at and by all time-points with data available and not already included in primary endpoint analysis; time to MMR; duration of MMR; BCR-ABL transcripts levels.[1]
	Resistant/intolerant CML-CP: Rate of each cytogenetic response category (complete, partial, major, minor, minimal and no response) at and by all time-points with data available.
	Newly diagnosed CML-CP: Rate of CCyR at and by all time-points with data available and not already included in the primary endpoint analysis; time to CCyR; duration of CCyR; rate of MCyR at and by all time-points with data available; time to MCyR; duration of MCyR; rate of CHR by all time-points with data available; time to CHR; duration of CHR.
	Long-term outcomes: Time to disease progression on treatment; overall survival and event free survival
A2120[2]	Molecular, cytogenetic and hematological response rates, and time to responses, time to progression to AP/BC in CML patients.

AP/BC: Accelerated phase/Blast crisis; CCyR: Complete cytogenetic response; MCyR: Major cytogenetic response; MMR: Major molecular response; CHR: Complete hematologic response

[1] Complete description of timepoints for efficacy evaluation is provided in [Study A2203-Appendix 16.1.1-Table 3-1.]

[2] In Study A2120, the primary objective was to assess PK of nilotinib.

Efficacy results

Major molecular response

Table 38 Major molecular response rate at time points (Pooled set)

MMR at key time points	Imatinib/dasatinib resistant/intolerant Ph+ CML-CP N=44	Newly diagnosed Ph+ CML-CP N=25
MMR at Cycle 3		
Response – n (%)	14 (31.8)	3 (12.0)
95% CI for response (%)	(18.6, 47.6)	(2.5, 31.2)
No response – n (%)	30 (68.2)	22 (88.0)
MMR at Cycle 6		
Response – n (%)	15 (34.1)	13 (52.0)
95% CI for response (%)	(20.5, 49.9)	(31.3, 72.2)
No response – n (%)	29 (65.9)	12 (48.0)
MMR at Cycle 12		
Response – n (%)	18 (40.9)	15 (60.0)
95% CI for response (%)	(26.3, 56.8)	(38.7, 78.9)
No response – n (%)	26 (59.1)	10 (40.0)

MMR at key time points: Only patients with the endpoint occurring or sustained at the specific time point were considered as responders. Patients not achieving MMR, patients with missing PCR evaluations or patients with atypical transcripts at baseline were considered as non-responders.

Table 39 Best major molecular response by time points (Pooled set)

	Imatinib/dasatinib resistant/intolerant Ph+ CML-CP N=44	Newly diagnosed Ph+ CML-CP N=25
Best MMR status overall		
Response – n (%)	21 (47.7)	17 (68.0)
95% CI for response rate (%)	(32.5, 63.3)	(46.5, 85.1)
No response – n (%)	23 (52.3)	8 (32.0)
Best MMR by Cycle 6		
Response – n (%)	17 (38.6)	13 (52.0)
95% CI for response rate (%)	(24.4, 54.5)	(31.3, 72.2)
No response – n (%)	27 (61.4)	12 (48.0)
Best MMR by Cycle 12		
Response – n (%)	21 (47.7)	16 (64.0)
95% CI for response rate (%)	(32.5, 63.3)	(42.5, 82.0)
No response – n (%)	23 (52.3)	9 (36.0)

Best MMR status: patients who had achieved a response anytime on or before the specified time point were considered responders. Overall refers to best MMR up to data cut-off date.

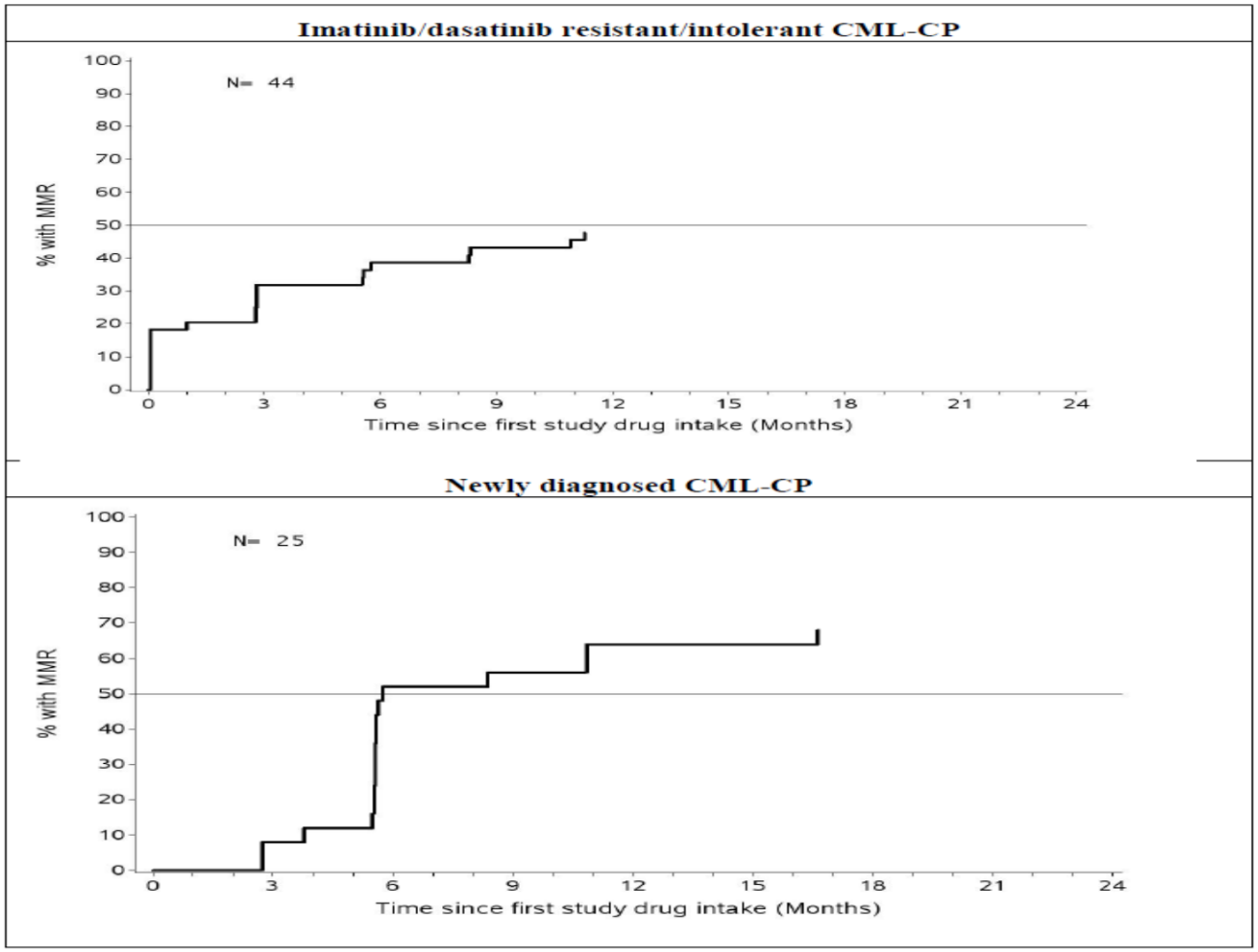


Figure 14 Cumulative incidence of MMR (Pooled set)

Time to first MMR

Table 40 Summary of time to first MMR among patients who achieved MMR (Pooled set)

	Imatinib/dasatinib resistant/intolerant Ph+ CML-CP N=44	Newly diagnosed Ph+ CML-CP N=25
Time to MMR (months)		
n	21	17
Mean (SD)	3.37 (3.737)	6.57 (3.430)
Median [95% CI]	2.76 (0.03, 5.55)	5.55 (5.52, 5.75)
25-75th percentiles	0.03 - 5.55	5.52 - 5.75
Minimum – maximum	0.0 - 11.3	2.7 - 16.6

Time to first response is summarized only among responders.

95% distribution-free confidence interval provided for the median time to MMR.

Table 41 Kaplan-Meier estimates of time to first MMR (Pooled set)

Category	Imatinib/dasatinib resistant/intolerant Ph+ CML-CP N=44	Newly diagnosed Ph+ CML-CP N=25
Number of events – n (%)	21 (47.7)	17 (68.0)
Number censored – n (%)	23 (52.3)	8 (32.0)
Percentiles (95% CI)		
25th percentile	2.8 (0, 5.6)	5.5 (2.7, 5.6)
Median	10.9 (5.5, NE)	5.6 (5.6, 10.8)
75th percentile	NE (NE,NE)	16.6 (5.7, NE)
Kaplan-Meier estimate (95% CI)		
3 months	33.5 (21.3, 50.0)	8.3 (2.2, 29.4)
6 months	41.9 (28.3, 58.8)	57.2 (38.2, 77.7)
9 months	48.0 (33.6, 64.9)	62.0 (42.7, 81.4)
12 months	55.9 (40.1, 73.0)	72.9 (53.0, 89.5)
15 months	55.9 (40.1, 73.0)	72.9 (53.0, 89.5)
18 months	55.9 (40.1, 73.0)	86.4 (60.0, 98.7)
21 months	55.9 (40.1, 73.0)	86.4 (60.0, 98.7)
24 months	55.9 (40.1, 73.0)	86.4 (60.0, 98.7)

NE: Not estimable.

Duration of MMR

None of the 21 resistant/intolerant patients, who were in MMR on treatment, had confirmed loss of MMR. Consequently, the median duration of first MMR was not reached in the resistant/intolerant patients (data not shown).

Disease progression and OS

No patient died or experienced disease progression in study A2120. No patient died in study A2203; however, two patients matched the technical definition of disease progression.

Clinical studies in special populations

N/A

Supportive study

Study A2120 is a PK/PD study that also included efficacy endpoints. These efficacy data have been pooled and assessed above (see section ‘‘Analysis performed across trials’’).

2.5.3. Discussion on clinical efficacy

The Applicant has provided two clinical studies, studies A2203 and A2120, where study A2203, a phase II study, is considered the pivotal study, while study A2120 (a phase I PK/PD study) is considered a supportive in terms of efficacy and safety.

Design and conduct of clinical studies

Study A2203 was agreed with the PDCO and fulfils the PIP as required. Cohort 1 included patients with CML-CP resistant or intolerant to imatinib or dasatinib, cohort 2 planned to include patients with CML-AP resistant or intolerant to imatinib or dasatinib, while cohort 3 included patients with newly-diagnosed CML-CP in chronic phase. In total 58 patients were treated with nilotinib, however, no patients were enrolled in cohort 2 because the number of planned patients per cohort was not based on a formal sample size calculation, but on feasibility considerations given that CML is a rare disease, and in accordance with patient enrollment and regulatory agreements . This is overall acceptable due to the very rare incidence of CML in the paediatric population and seems to reflect probably the limitation of feasibility of clinical studies in this population.

The inclusion/exclusion criteria clearly defined patients with newly diagnosed Ph+ CML-CP or Ph+ CML-CP or CML-AP resistant or intolerant to imatinib or dasatinib.

The objectives of this study were clearly defined and in accordance with the PIP. The primary objectives were to assess the efficacy of nilotinib in paediatric patients with Ph+ CML-CP resistant or intolerant to either imatinib or dasatinib, to assess the efficacy of nilotinib in paediatric patients with Ph+ CML-AP resistant or intolerant to either imatinib or dasatinib, and to assess the efficacy of nilotinib in paediatric patients with newly diagnosed Ph+ CMLCP. The secondary objectives were to further characterize efficacy, safety and PK/PD. The primary endpoints for the different cohorts were clearly defined. Rate of MMR is a clinically relevant and valid endpoint in these patient populations. Several supporting secondary endpoints, such as time to MMR, duration of MMR, BCR-ABL transcript levels, OS, etc., were also defined. These aim to further characterize and support the findings of the primary endpoint. The primary and secondary endpoints were in line with the objectives of the study and are as such endorsed.

With regard to conduct of the study, several amendments were installed during the study, however, none are considered critical. There were no protocol deviations. Median age was 13 years in both cohorts, ranging from 2 to 17 years in cohort 1 and 10-16 in cohort 3. The majority (63.6%) of the patients in cohort 1 were between 12-18 years, while all patients were above 10 in cohort 3. Most of the patients were Caucasian or Asian. Concerning baseline characteristics, median age was 13 years in both cohorts, ranging from 2 to 17 years in cohort 1 and 10-16 in cohort 3. As expected all patients in the Cohort 3 have a BCR-ABL ratio >10%, thus, none were in MMR at baseline. In comparison, 7

patients were in MMR in cohort 1 at baseline. Six (18.2%) patients were imatinib/dasatinib intolerant; however, they were all intolerant to imatinib.

Efficacy data and additional analyses

Imatinib/dasatinib resistant

Approximately 40% of the patients in cohort 1 were in MMR at 6 cycles, however, it should be noted that 6 out of 13 patients were already in MMR at baseline. Nonetheless, the results are encouraging, since treatment with nilotinib keeps these 6 patients in MMR and further patients are brought into MMR. As seen later, MMR by time point shows that 57.6% of the patients are in MMR by cycle 12. Although 14 patients did not obtain MMR, reflecting the resistant/refractory patient population, the observed results are nevertheless considered clinically highly relevant. Median time to first MMR is 2.79 months and by 12 months and onwards the MMR rate is 64.9%. Once a patient gained MMR they continued to stay in MMR by the time of data cut-off date. These clinically relevant findings support the primary endpoint.

Not all patients obtained MMR, however, by cycle twelve 84.8% (28 patients) of the patients had obtained MCyR, and of these, 27 had a complete MCyR. Only one patient did not have a cytogenetic response.

Newly diagnosed

At 12 cycles 16/25 (64%) patients had reached MMR and CCyR. Looking at efficacy based on age, there seem to be no major difference between age-groups 1-12 and 12-18. However, all patients in cohort 3 are or above ten years. Although, the results are considered clinically relevant, there are no data for children below 10 year, and furthermore the PK/PD models only included resistant/refractory patients. Satisfactory support has been provided and the SmPC reflects the limited data.

With regard to MMR by time point, 68% of the patients had gained MMR by cycle 12, while 68% had gained MMR by data cut-off. Thus, it seems as deep and prolonged responses are achieved in newly diagnosed patients treated with nilotinib.

The CCyR rate was 84% by the time of data cut-off. Median time to first complete cytogenetic response was 5.55 months. The KM estimated rate of CCyR was 90.6% by 6 months. Only 1/21 had a loss of CCyR at the time of data cut-off.

The above results are clinically relevant and in line with the observed effects of imatinib in newly diagnosed patients, where CHR rate of 78% after eight weeks of treatment and a CCyR rate of 65% were observed. Thus, the results available indicate efficacy also in newly diagnosed patients. However due to the limited observational period in trial A2203 the long-term efficacy will be provided post authorisation (see Annex II condition).

Overall, the analyses of the pooled dataset of studies A2203 and A2120 show consistent results with the findings in study A2203.

2.5.4. Conclusions on the clinical efficacy

Overall, clinically relevant and meaningful results have been shown in resistant/refractory and newly diagnosed paediatric patients with Ph+ CML. However, due to the limited observational period in trial A2203 the CHMP requested the applicant to provide the final results of the study.

The CHMP considers the following measures necessary to address issues related to efficacy:

The applicant should submit the final results of study CAMN107A2203, a phase II in paediatric patients with Ph+ CML CP resistant or intolerant to either imatinib or dasatinib and in newly diagnosed patients (see Annex II and RMP).

2.6. Clinical safety

The safety review is based on the pooled data from 73 paediatric patients treated with nilotinib 230 mg/m^2 bid in the two clinical studies A2203 and A2120. The pooled safety set included paediatric patients who received at least one dose of nilotinib in Study A2120 or Study A2203. Both studies (A2120 and A2203) contributed to the pooled safety data for patients with Ph+ CML-CP resistant/intolerant to either imatinib/dasatinib; however, only study A2203 enrolled newly diagnosed Ph+ CML-CP patients. Study A2120 also had enrolled four patients with refractory/relapsed Ph+ ALL, which are included in the pooled dataset (hereafter referred to as pooled patient population).

- Resistant/intolerant CML (44 patients)
- Newly diagnosed CML (25 patients)
- All CML (69 patients)
- All patients (CML and ALL) (73 patients)

Safety and tolerability were assessed by monitoring the frequency, duration, and severity of adverse events (AEs) and serious AEs (SAEs), and by evaluation of the laboratory data (haematology and clinical chemistry), as well as measurement of vital signs, description of physical examinations and assessment of 12-lead electrocardiograms (ECG). Growth data consisting of height, height velocity, weight, and weight velocity were also analysed. AEs and laboratory tests were assessed according to the Common Terminology Criteria for Adverse Events (CTCAE). Different versions of CTCAE had been used for AE and laboratory value grading in the individual studies (v3.0 for Study A2120 and v4.03 for Study A2203). In the pooled dataset, laboratory values were re-classified by programming into Common Toxicology Criteria (CTC) grades according to the CTCAE version 4.03 for both trials, while CTC grading for AEs had to remain the one of the original stud y (as per the Investigator's assessment). AEs in the pooled dataset were coded/re-coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 19.0 available at the time of the database lock of Study A2203.

In addition to the pooled data, the following safety assessments performed only in Study A2203 are also presented:

- Tanner staging for sexual maturation
- Thyroid function (serum free thyroxine [FT4] and thyroid stimulating hormone [TSH])
- Effect of nilotinib on bone metabolism, growth and maturation by –
- Bone age analyses (assessed by hand and wrist X-ray at baseline and annually)
- Dual-energy X-ray absorptiometry (DEXA) scan: lumbar spine z-score (also called standard deviation score [SDS]) and whole body less head z-score (assessed at baseline and annually)
- Bone biomarkers: Serum C-Telopeptide (CTX), serum N-Telopeptide, and serum bone specific alkaline phosphatase (ALP) (assessed at baseline and annually)

Patient exposure

Table 42 Extent of exposure (Safety set)

	Imatinib/dasatinib resistant/intolerant Ph+ CML-CP	Newly diagnosed Ph+ CML-CP	All patients Ph+ CML-CP	All patients Ph+ CML-CP and ALL
	N = 44	N = 25	N = 69	N = 73
	n (%)	n (%)	n (%)	n (%)
Time on treatment (months)				
n	44	25	69	73
Mean (SD)	14.94 (8.068)	15.20 (6.531)	15.04 (7.498)	14.75 (7.622)
Median	12.45	14.55	13.80	13.63
25-75th percentiles	10.46-22.03	11.04-19.42	10.87-19.61	10.84-19.61
Min – Max	0.7-30.9	1.4-27.6	0.7-30.9	0.7-30.9
Time on treatment (categories), n (%)				
≥ 3 months	42 (95.5)	24 (96.0)	66 (95.7)	69 (94.5)
≥ 6 months	38 (86.4)	23 (92.0)	61 (88.4)	63 (86.3)
≥ 9 months	36 (81.8)	21 (84.0)	57 (82.6)	59 (80.8)
≥ 12 months	22 (50.0)	15 (60.0)	37 (53.6)	38 (52.1)
≥ 18 months	14 (31.8)	9 (36.0)	23 (33.3)	24 (32.9)
≥ 24 months	8 (18.2)	2 (8.0)	10 (14.5)	10 (13.7)
Patient-months	657.5	379.9	1037.4	1076.4

Source: [SCS Appendix 1-Table 1.2-1.1]
Time on treatment = (Last dose date - start date of study drug + 1) / 30.4375
Patient-months are derived by taking the number of patients multiplied by the mean time on treatment (months)

The median actual dose intensity (25-75th percentiles) was 438.9 mg/m^2/day representing a median relative dose intensity of 95.4% compared to the planned dose of 230 mg/m^2 bid. The median actual dose intensity (25-75th percentiles) was 384.5 mg/m^2/day representing a median relative dose intensity was 83.6% compared to the planned dose of 230 mg/m^2 bid (Table 43).

Table 43 Dose intensity by cohort (Safety Set)

	Imatinib/dasatinib resistant/intolerant N=33	Newly diagnosed N=25
Actual dose intensity (mg/m²/day)		
n	33	25
Mean (SD)	398.3 (94.09)	366.8 (92.13)
Median (Min-Max)	438.9 (195-517)	384.5 (149-469)
25-75th percentiles	376.8-460.2	281.3-444.4
Relative dose intensity (%) n (%)		
<70	8 (24.2)	7 (28.0)
70 – 90	4 (12.1)	7 (28.0)
>90	21 (63.6)	11 (44.0)
n	33	25
Mean (SD)	86.6 (20.45)	79.7 (20.03)
Median (Min-Max)	95.4 (42-112)	83.6 (32-102)
25-75th percentiles	81.9-100.0	61.2-96.6

Actual dose intensity = (Total dose/time on treatment)×100.
Relative dose intensity = (Actual dose intensity/planned total daily dose) ×100.

Adverse events

Common AEs

Table 44 Adverse events by primary System Organ Class (Safety set)

	Imatinib/dasatinib resistant/intolerant Ph+ CML-CP		Newly diagnosed Ph+ CML-CP		All patients Ph+ CML-CP		All patients Ph+ CML-CP and ALL	
	N=44		N=25		N=69		N=73	
	All grades	Grade 3-4	All grades	Grade 3-4	All grades	Grade 3-4	All grades	Grade 3-4
System organ class	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Total	**44 (100)**	**19 (43.2)**	**25 (100)**	**16 (64.0)**	**69 (100)**	**35 (50.7)**	**73 (100)**	**37 (50.7)**
Skin and subcutaneous tissue disorders	32 (72.7)	5 (11.4)	20 (80.0)	2 (8.0)	52 (75.4)	7 (10.1)	54 (74.0)	7 (9.6)
Infections and infestations	29 (65.9)	1 (2.3)	19 (76.0)	0	48 (69.6)	1 (1.4)	52 (71.2)	1 (1.4)
Gastrointestinal disorders	25 (56.8)	0	19 (76.0)	1 (4.0)	44 (63.8)	1 (1.4)	47 (64.4)	2 (2.7)
Investigations	25 (56.8)	9 (20.5)	17 (68.0)	9 (36.0)	42 (60.9)	18 (26.1)	44 (60.3)	19 (26.0)
Nervous system disorders	23 (52.3)	1 (2.3)	16 (64.0)	0	39 (56.5)	1 (1.4)	41 (56.2)	1 (1.4)
General disorders and administration site conditions	20 (45.5)	0	14 (56.0)	0	34 (49.3)	0	36 (49.3)	0
Musculoskeletal and connective tissue disorders	18 (40.9)	0	13 (52.0)	0	31 (44.9)	0	32 (43.8)	0
Respiratory, thoracic and mediastinal disorders	14 (31.8)	0	10 (40.0)	0	24 (34.8)	0	27 (37.0)	0
Metabolism and nutrition disorders	9 (20.5)	1 (2.3)	8 (32.0)	2 (8.0)	17 (24.6)	3 (4.3)	17 (23.3)	3 (4.1)
Hepatobiliary disorders	9 (20.5)	2 (4.5)	7 (28.0)	4 (16.0)	16 (23.2)	6 (8.7)	17 (23.3)	6 (8.2)
Blood and lymphatic system disorders	8 (18.2)	6 (13.6)	6 (24.0)	2 (8.0)	14 (20.3)	8 (11.6)	15 (20.5)	8 (11.0)
Injury, poisoning and procedural complications	10 (22.7)	1 (2.3)	3 (12.0)	0	13 (18.8)	1 (1.4)	13 (17.8)	1 (1.4)
Reproductive system and breast disorders	5 (11.4)	1 (2.3)	5 (20.0)	0	10 (14.5)	1 (1.4)	10 (13.7)	1 (1.4)
Eye disorders	2 (4.5)	0	7 (28.0)	0	9 (13.0)	0	9 (12.3)	0
Cardiac disorders	2 (4.5)	0	4 (16.0)	0	6 (8.7)	0	6 (8.2)	0
Vascular disorders	2 (4.5)	0	3 (12.0)	0	5 (7.2)	0	5 (6.8)	0
Ear and labyrinth disorders	3 (6.8)	0	1 (4.0)	0	4 (5.8)	0	4 (5.5)	0
Endocrine disorders	1 (2.3)	0	2 (8.0)	0	3 (4.3)	0	3 (4.1)	0
Immune system disorders	3 (6.8)	0	0	0	3 (4.3)	0	3 (4.1)	0
Psychiatric disorders	1 (2.3)	0	2 (8.0)	0	3 (4.3)	0	3 (4.1)	0
Congenital, familial and genetic disorders	1 (2.3)	0	1 (4.0)	0	2 (2.9)	0	2 (2.7)	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)	2 (4.5)	0	0	0	2 (2.9)	0	2 (2.7)	0
Renal and urinary disorders	2 (4.5)	0	0	0	2 (2.9)	0	3 (4.1)	0

- Primary system organ class is sorted in descending frequency, as reported in the All patients Ph+ CML-CP group.
- A patient with multiple adverse events within a primary system organ class is counted only once in the total row.
- MedDRA version: 19.0

Table 45 Adverse events by preferred term (at least 10% in any group) (Safety set)

Preferred term	Imatinib/dasatinib resistant/intolerant Ph+ CML-CP		Newly diagnosed Ph+ CML-CP		All patients Ph+ CML-CP		All patients Ph+ CML-CP and ALL	
	N=44		N=25		N=69		N=73	
	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)
Total	**44 (100)**	**19 (43.2)**	**25 (100)**	**16 (64.0)**	**69 (100)**	**35 (50.7)**	**73 (100)**	**37 (50.7)**
Headache	17 (38.6)	1 (2.3)	14 (56.0)	0	31 (44.9)	1 (1.4)	33 (45.2)	1 (1.4)
Rash	11 (25.0)	2 (4.5)	11 (44.0)	1 (4.0)	22 (31.9)	3 (4.3)	22 (30.1)	3 (4.1)
Blood bilirubin increased	14 (31.8)	3 (6.8)	7 (28.0)	0	21 (30.4)	3 (4.3)	23 (31.5)	3 (4.1)
Alanine aminotransferase increased	11 (25.0)	3 (6.8)	9 (36.0)	3 (12.0)	20 (29.0)	6 (8.7)	21 (28.8)	6 (8.2)
Pyrexia	12 (27.3)	0	7 (28.0)	0	19 (27.5)	0	21 (28.8)	0
Nausea	10 (22.7)	0	7 (28.0)	0	17 (24.6)	0	17 (23.3)	0
Upper respiratory tract infection	11 (25.0)	1 (2.3)	6 (24.0)	0	17 (24.6)	1 (1.4)	17 (23.3)	1 (1.4)
Aspartate aminotransferase increased	9 (20.5)	1 (2.3)	7 (28.0)	0	16 (23.2)	1 (1.4)	17 (23.3)	1 (1.4)
Hyperbilirubinaemia	8 (18.2)	1 (2.3)	7 (28.0)	4 (16.0)	15 (21.7)	5 (7.2)	16 (21.9)	5 (6.8)
Vomiting	8 (18.2)	0	7 (28.0)	1 (4.0)	15 (21.7)	1 (1.4)	17 (23.3)	1 (1.4)
Pain in extremity	9 (20.5)	0	4 (16.0)	0	13 (18.8)	0	14 (19.2)	0
Abdominal pain	5 (11.4)	0	7 (28.0)	0	12 (17.4)	0	12 (16.4)	0
Nasopharyngitis	7 (15.9)	0	5 (20.0)	0	12 (17.4)	0	14 (19.2)	0
Arthralgia	7 (15.9)	0	4 (16.0)	0	11 (15.9)	0	11 (15.1)	0
Diarrhoea	6 (13.6)	0	4 (16.0)	0	10 (14.5)	0	12 (16.4)	0
Cough	4 (9.1)	0	4 (16.0)	0	8 (11.6)	0	10 (13.7)	0
Rash maculo-papular	5 (11.4)	2 (4.5)	3 (12.0)	1 (4.0)	8 (11.6)	3 (4.3)	9 (12.3)	3 (4.1)
Electrocardiogram QT prolonged	5 (11.4)	0	2 (8.0)	0	7 (10.1)	0	7 (9.6)	0
Fatigue	1 (2.3)	0	6 (24.0)	0	7 (10.1)	0	8 (11.0)	0
Oropharyngeal pain	6 (13.6)	0	1 (4.0)	0	7 (10.1)	0	7 (9.6)	0
Rhinitis	6 (13.6)	0	1 (4.0)	0	7 (10.1)	0	8 (11.0)	0
Acne	2 (4.5)	0	4 (16.0)	0	6 (8.7)	0	6 (8.2)	0
Chest pain	2 (4.5)	0	4 (16.0)	0	6 (8.7)	0	6 (8.2)	0
Erythema	3 (6.8)	0	3 (12.0)	0	6 (8.7)	0	6 (8.2)	0
Gastroenteritis	2 (4.5)	1 (2.3)	4 (16.0)	0	6 (8.7)	1 (1.4)	6 (8.2)	1 (1.4)
Platelet count decreased	1 (2.3)	0	5 (20.0)	2 (8.0)	6 (8.7)	2 (2.9)	6 (8.2)	2 (2.7)
Abdominal pain upper	2 (4.5)	0	3 (12.0)	0	5 (7.2)	0	6 (8.2)	0
Dry skin	5 (11.4)	0	0	0	5 (7.2)	0	5 (6.8)	0
Myalgia	1 (2.3)	0	4 (16.0)	0	5 (7.2)	0	5 (6.8)	0
Thrombocytopenia	2 (4.5)	0	3 (12.0)	1 (4.0)	5 (7.2)	1 (1.4)	5 (6.8)	1 (1.4)
Dizziness	1 (2.3)	0	3 (12.0)	0	4 (5.8)	0	4 (5.5)	0
Dysmenorrhoea	1 (2.3)	1 (2.3)	3 (12.0)	0	4 (5.8)	1 (1.4)	4 (5.5)	1 (1.4)
Dyspnoea	1 (2.3)	0	3 (12.0)	0	4 (5.8)	0	4 (5.5)	0
Neutrophil count decreased	1 (2.3)	1 (2.3)	3 (12.0)	3 (12.0)	4 (5.8)	4 (5.8)	4 (5.5)	4 (5.5)
Ocular hyperaemia	1 (2.3)	0	3 (12.0)	0	4 (5.8)	0	4 (5.5)	0
Weight decreased	1 (2.3)	0	3 (12.0)	0	4 (5.8)	0	5 (6.8)	0
Pruritus	0	0	3 (12.0)	0	3 (4.3)	0	3 (4.1)	0

- Preferred terms are sorted in descending frequency, as reported in the All patients Ph+ CML-CP group.
- A patient with multiple occurrences of an AE under one group is counted only once in the AE category for that group.
- MedDRA version: 19.0

Table 46 Adverse events suspected to be study drug related by preferred term (>10% in any cohort) (Safety Set)

Preferred term	Imatinib/dasatinib resistant/intolerant N=33 n (%)	Newly diagnosed N=25 n (%)	All patients N=58 n (%)
-Patients with at least one AE	28 (84.8)	22 (88.0)	50 (86.2)
Blood bilirubin increased	11 (33.3)	7 (28.0)	18 (31.0)
Alanine aminotransferase increased	8 (24.2)	9 (36.0)	17 (29.3)
Headache	8 (24.2)	8 (32.0)	16 (27.6)
Aspartate aminotransferase increased	7 (21.2)	7 (28.0)	14 (24.1)
Hyperbilirubinaemia	5 (15.2)	7 (28.0)	12 (20.7)
Rash	6 (18.2)	6 (24.0)	12 (20.7)
Nausea	4 (12.1)	5 (20.0)	9 (15.5)
Rash maculo-papular	5 (15.2)	3 (12.0)	8 (13.8)
Vomiting	2 (6.1)	5 (20.0)	7 (12.1)
Alopecia	4 (12.1)	2 (8.0)	6 (10.3)
Fatigue	0	5 (20.0)	5 (8.6)
Neutrophil count decreased	1 (3.0)	3 (12.0)	4 (6.9)
Pain in extremity	4 (12.1)	0	4 (6.9)
Abdominal pain	0	3 (12.0)	3 (5.2)
Chest pain	0	3 (12.0)	3 (5.2)
Platelet count decreased	0	3 (12.0)	3 (5.2)
Thrombocytopenia	0	3 (12.0)	3 (5.2)

AEs by preferred terms are presented in descending order of frequency in All patients group.

Adverse Events of Special Interest

Table 47 Adverse events of special interest (safety set)

	Imatinib/Dasatinib Resistant/intolerant CML-CP		Newly diagnosed PH+ CML-CP		All patients PH+ CML-CP		All patients PH+CMLCP and ALL	
	N=44		N=25		N=69		N=73	
	All grades	Grade 3-4	All grades	Grade 3-4	All grades	Grade 3-4	All grades	Grade 3-4
	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)
All Cardiovascular events	0	0	1 (4.0)	0	1 (1.4)	0	1 (1.4)	0
Ischemic cerebrovascular	0	0	0	0	0	0	0	0
Ischemic heart disease	0	0	1 (4.0)a	0	1 (1.4)	0	1 (1.4)a	0
Others	0	0	0	0	0	0	0	0
Peripheral artery occlusive disease	0	0	0	0	0	0	0	0
Blood cholesterol increased	3 (6.8)	0	1 (4.0)	1 (4.0)	4 (5.8)	1 (1.4)	4 (5.5)	1 (1.4)

Blood glucose increased	2 (4.5)	0	0	0	2 (2.9)	0	2 (2.7)	0
Cardiac failure	0	0	0	0	0	0	0	0
Fluid retention	2 (4.5)	0	3 (12.0)	1 (4.0)	5 (7.2)	1 (1.4)	5 (6.8)	1 (1.4)
Oedema and Other Fluid Retentions	2 (4.5)	0	3 (12.0)	1 (4.0)	5 (7.2)	1 (1.4)	5 (6.8)	1 (1.4)
Severe	0	0	0	0	0	0	0	0
Hepatic Transaminase an Bilirubin	**23 (52.3)**	**7 (15.9)**	**14 (56.0)**	**6 (24.0)**	**37 (53.6)**	**13 (18.8)**	**39 (53.4)**	**13 (17.8)**
Hepatotoxicity/Drug induced Liver injury	1 (2.3)	1 (2.3)	0	0	1 (1.4)	1 (1.4)	1 (1.4)	1 (1.4)
Myelosuppression (Thrombocytopenia	3 (6.8)	0	8 (32.0)	3 (12.0)	11 (15.9)	3 (4.3)	11 (15.1)	3 (4.1)
Pancreatitis	0	0	0	0	0	0	0	0
QT prolongation	6 (13.6)b	0	3 (12.0)	0	9 (13.0)	0	9 (12.3)	0
Rash	20 (45.5)	5 (11.4)	14 (56.0)	2 (8.0)	34 (49.3)	7 (10.1)	36 (49.3)	7 (9.6)
Renal Events	0	0	0	0	0	0	1 (1.4)	0
Significant Bleeding	0	0	0	0	0	0	0	0
CNS hemorrhage	0	0	0	0	0	0	0	0
GI hemorrhage	0	0	0	0	0	0	0	0

QT prolongation and sudden death

No cases of torsade de pointes, or sudden death, were reported in Study A2203 or Study A2120.

AESIs in the category QT prolongation (i.e., ECG QT prolonged, syncope) were reported in 13.0% of CML patients, with similar incidences in the resistant/intolerant (13.6%) and newly diagnosed (12.0%) populations. The events were SAEs in two patients (2.9%); in both patients the SAEs resolved following interruption of study drug, and the patients continued in the study. None of the events led to discontinuation of study drug.

Based on evaluation of ECGs, none of the patients had QTcF value >500 ms, or an increase in QTcF >60 ms from baseline. QTcF value >480 ms was observed in 4.4% of CML patients. The patient with syncope who was reported in this AESI category had normal QTcF documented on the day of syncope.

Cardiac and arterial vascular occlusive events

AESIs in the category CVE were reported in a single patient. This was a case of angina pectoris reported in a newly diagnosed CML patient who was reported as having angina pectoris on one occasion after 2 hours of sport with rapid recovery after stopping his effort. Consultation with a cardiologist revealed no cardiac problems, normal ECG and echocardiography results, and a normal stress test that excluded cardiac pathology according to the cardiologist.

No other cardiac or vascular occlusive events were reported, and no cases of cardiac failure were observed.

Fluid retention

AESIs in the category fluid retention (i.e. weight increased, eye swelling, and lip swelling) were reported in 7.2% of CML patients. These AEs were all grade 1-2, except for one patient with a grade 3 AE of weight increase.

None of the fluid retention events were SAEs, or led to discontinuation of study drug.

Growth

At the time of data cut-off, the information collected on growth was considered to be of an insufficient duration to draw any conclusions. The standard deviation scores (SDS) for height, height velocity, body mass index, and weight velocity were comparable both prior to and after start of nilotinib treatment in both resistant/intolerant and newly diagnosed patient populations. At Cycle 24, the height velocity SDS appears to be lower than at Cycle 18, however the number of observations at Cycle 24 is small. These patients had essentially SDS score within the normal range at baseline and without any clear evidence of a negative pattern over time with the limitations of short follow up. The proportion of patients in resistant/intolerant and in newly diagnosed with SDS values <5th percentile or >95th percentile on height, height velocity, body mass index, and weight velocity did not increase significantly after the start of nilotinib.

Bone biochemical markers

The SDS for bone biochemical biomarkers (serum C-telopeptide and bone specific alkaline phosphatase) was comparable both prior to and after start of nilotinib treatment in both patient populations. The proportions of resistant/intolerant patients and newly diagnosed patients with serum C-telopeptide and bone specific alkaline phosphatase SDS values <3rd percentile or >97th percentile did not change significantly over the 12 cycles of nilotinib treatment.

Sexual maturation

The scope of conclusion regarding the indication of delayed puberty or a trend for puberty on nilotinib treatment was limited in this study considering the limited sample size and short duration of follow up at the time of the data cut-off. By the time of data cut-off, among patients at risk when starting nilotinib treatment, no patients (irrespective of gender) had delayed puberty.

Overall, among patients in Tanner stage 1 at Baseline, Tanner stage 2 was attained in three out of eight male patient for genitalia, two out of five female patients for breast development and three out of nine female and two out of nine male patients for pubic hair. All patients who had not yet attained Tanner stage 2 at the time of the data cut-off date for genital development (male), breast development (female), or pubic hair (irrespective of gender) were <13 years of age at Baseline.

Three out of nine pre-menarchial female patients at baseline experienced menarche by the data cut-off. The median age for attaining menarche was 14.8 years. Puberty data including menarche status was not reported for one pre-menarchial patient. All the premenarchial female patients at baseline who did not experience menarche by the data cut-off were 10 years of age or less at baseline.

Serious adverse event/deaths/other significant events

Deaths

No patient died during any of the two studies, while on treatment or after study drug discontinuation.

Serious Adverse Events

Table 48 Serious adverse events by preferred term (Safety set)

Preferred term	Imatinib/Dasatinib Resistant/intolerant CML-CP	Newly diagnosed PH+ CML-CP	All patients PH+ CML-CP	All patients PH+CMLCP and ALL
	N=44	N=25	N=69	N=73
	n(%)	n(%)	n(%)	n(%)
Total	**8 (18.2)**	**2 (8.0)**	**10 (14.5)**	**13**
Gastroenteritis	2 (4.5)	0	2	2 (2.7)
Neutropenia	2 (4.5)	0	2	2 (2.7)
Pyrexia	2 (4.5)	0	2	3 (4.1)
Abdominal pain	0	1 (4.0)	1	1 (1.4)
Dehydration	1 (2.3)	0	1	1 (1.4)
Diarrhoea	0	1 (4.0)	1	1 (1.4)
Electrocardiogram QT prolonged	0	1 (4.0)	1 (1.4)	1 (1.4)
Growth hormone	1 (2.3)	0	1	1 (1.4)
Headache	0	1 (4.0)	1	1 (1.4)
Hyperaemia	1 (2.3)	0	1	1 (1.4)
Hyperbilirubinaemia	0	1 (4.0)	1	1 (1.4)
Leukocytosis	1 (2.3)	0	1	1 (1.4)
Muscle strain	1 (2.3)	0	1	1 (1.4)
Peripheral swelling	1 (2.3)	0	1	1 (1.4)
Rash	0	1 (4.0)	1	1 (1.4)
Syncope	0	1 (4.0)	1	1 (1.4)
Tonsillitis	1 (2.3)	0	1	1 (1.4)
Weight decreased	0	1 (4.0)	1	1 (1.4)
Appendix disorder	0	0	0	1 (1.4)
Influenza like illness	0	0	0	1 (1.4)
Renal failure	0	0	0	1 (1.4)

Laboratory findings

Haematology

Table 49 Newly occurring or worsening haematological abnormalities based on CTC grade (safety set)

	Imatinib/Dasatinib Resistant/intole		Newly diagnosed PH+ CML-CP		All patients PH+ CML-CP		All patients PH+CMLCP and ALL	
	N=44		N=25		N=69		N=73	
	All grade	Grade	All grade	Grade 3-	All grade	Grade 3-	All grade	Grade 3
	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)
Any abnormal Value	36 (81.8)	8 (18.2)	25 (100.0)	9 (36.0)	61 (88.4)	17 (24.6)	62 (84.9)	17 (23.3
Absolute Lymphocytes – Hyper	7 (15.9)	1 (2.3)	4 (16.0)	0	11 (15.9)	1 (1.4)	11 (15.1)	1 (1.4)
Absolute Lymphocytes – Hypo	13 (29.5)	1 (2.3)	9 (36.0)	1 (4.0)	22 (31.9)	2 (2.9)	23 (31.5)	2 (2.7)
Absolute Neutrophil (Seg. + Bands)	16 (36.4)	5 (11.4)	12 (48.0)	7 (28.0)	28 (40.6)	12 (17.4)	28 (38.4)	12 (16.4
Haemoglobin – Hypo	13 (29.5)	1 (2.3)	8 (32.0)	1 (4.0)	21 (30.4)	2 (2.9)	22 (30.1)	2 (2.7)
Platelet count (direct)	8 (18.2)	0	22 (88.0)	3 (12.0)	30 (43.5)	3 (4.3)	30 (41.1)	3 (4.1)
WBC (total)- Hyper	1 (2.3)	1 (2.3)	0	0	1 (1.4)	1 (1.4)	1 (1.4)	1 (1.4)
WBC (total) – Hypo	20 (45.5)	0	17 (68.0)	1 (4.0)	37 (53.6)	1 (1.4)	37 (50.7)	1 (1.4)

Clinical chemistry

Table 50 Newly occurring or worsening clinical chemistry abnormalities based on CTC grade (safety set)

	Imatinib/Dasatinib Resistant/intolerant CML-CP		Newly diagnosed PH+ CML-CP		All patients PH+ CML-CP		All patients PH+CMLCP and ALL	
	N=44		N=25		N=69		N=73	
	All grades	Grade 3-4	All grades	Grade 3-	All grades	Grade 3-	All grades	Grade 3-4
	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)
Any abnormal value	44 (100.0)	14 (31.8)	25 (100.0)	8 (32.0)	69 (100.0)	22 (31.9)	73 (100.0)	23 (31.5)
Albumin	6 (13.6)	0	2 (8.0)	0	8 (11.6)	0	8 (11.0)	0
Alkaline phosphatase	5 (11.4)	0	7 (28.0)	0	12 (17.4)	0	13 (17.8)	0
Amylase	3 (6.8)	2 (4.5)	5 (20.0)	1 (4.0)	8 (11.6)	3 (4.3)	8 (11.0)	3 (4.1)
Corrected calcium – Hyper	6 (13.6)	0	3 (12.0)	0	9 (13.0)	0	10 (13.7)	0
Corrected calcium – Hypo	3 (6.8)	0	6 (24.0)	0	9 (13.0)	0	9 (12.3)	0
Creatinine	4 (9.1)	0	2 (8.0)	0	6 (8.7)	0	7 (9.6)	0
Glucose - Hyper	**19 (43.2)**	**0**	**12 (48.0)**	**0**	**31 (44.9)**	**0**	**31 (42.5)**	**0**
Glucose - Hypo	4 (9.1)	0	4 (16.0)	0	8 (11.6)	0	9 (12.3)	0

Lipase	8 (18.2)	3 (6.8)	3 (12.0)	2 (8.0)	11 (15.9)	5 (7.2)	11 (15.1)	5 (6.8)
Magnesium - Hyper	13 (29.5)	2 (4.5)	4 (16.0)	0	17 (24.6)	2 (2.9)	19 (26.0)	3 (4.1)
Magnesium - Hypo	2 (4.5)	0	1 (4.0)	0	3 (4.3)	0	3 (4.1)	0
Phosphate	13 (29.5)	1 (2.3)	7 (28.0)	0	20 (29.0)	1 (1.4)	22 (30.1)	1 (1.4)
Potassium - Hyper	8 (18.2)	0	2 (8.0)	0	10 (14.5)	0	10 (13.7)	0
Potassium - Hypo	10 (22.7)	1 (2.3)	5 (20.0)	0	15 (21.7)	1 (1.4)	15 (20.5)	1 (1.4)
SGOT (AST)	**28 (63.6)**	**1 (2.3)**	**17 (68.0)**	**0**	**45 (65.2)**	**1 (1.4)**	**46 (63.0)**	**1 (1.4)**
SGPT (ALT)	**35 (79.5)**	**3 (6.8)**	**23 (92.0)**	**3 (12.0)**	**58 (84.1)**	**6 (8.7)**	**60 (82.2)**	**6 (8.2)**
Sodium - Hyper	1 (2.3)	0	1 (4.0)	0	2 (2.9)	0	2 (2.7)	0
Sodium - Hypo	9 (20.5)	0	6 (24.0)	0	15 (21.7)	0	16 (21.9)	0
Total bilirubin	**35 (79.5)**	**5 (11.4)**	**19 (76.0)**	**4 (16.0)**	**54 (78.3)**	**9 (13.0)**	**57 (78.1)**	**9 (12.3)**
Total cholesterol	14 (31.8)	0	12 (48.0)	1 (4.0)	26 (37.7)	1 (1.4)	27 (37.0)	1 (1.4)
Triglyceride	15 (34.1)	1 (2.3)	7 (28.0)	0	22 (31.9)	1 (1.4)	22 (30.1)	1 (1.4)

Liver function tests

Table 51 Summary of hepatic laboratory abnormalities (safety set)

	Imatinib/Dasatinib Resistant/intolerant CML-CP	**Newly diagnosed PH+ CML-CP**	**All patients PH+ CML-CP**
	N=44	**N=25**	**N=69**
	n (%)	**n(%)**	**n(%)**
Worst post-baseline values regardless of baseline status			
ALT >3x ULN	12 (27.3)	7 (28.0)	19 (27.5)
ALT >5x ULN	3 (6.8)	3 (12.0)	6 (8.7)
ALT >8x ULN	2 (4.5)	2 (8.0)	4 (5.8)
ALT >10x ULN	0	2 (8.0)	2 (2.9)
ALT >20x ULN	0	0	0
AST >3x ULN	6 (13.6)	3 (12.0)	9 (13.0)
AST >5x ULN	1 (2.3)	0	1 (1.4)
AST >8x ULN	0	0	0
AST >10x ULN	0	0	0
AST >20x ULN	0	0	0
ALT or AST >3x ULN	12 (27.3)	7 (28.0)	19 (27.5)
ALT or AST >5x ULN	3 (6.8)	3 (12.0)	6 (8.7)
ALT or AST >8x ULN	2 (4.5)	2 (8.0)	4 (5.8)
ALT or AST >10x ULN	0	2 (8.0)	2 (2.9)
ALT or AST >20x ULN	0	0	0
Total bilirubin (TBIL) >2x ULN	17 (38.6)	12 (48.0)	29 (42.0)
TBIL >3x ULN	5 (11.4)	4 (16.0)	9 (13.0)
Combined and concurrent values post-baseline			
ALT or AST >3x ULN & TBIL >2x ULN	**4 (9.1)**	**2(8.0)**	**6 (8.7)**
ALT or AST >3x ULN & TBIL >2x ULN &	**1 (2.3)**	**0**	**1 (1.4)**
ALT or AST >3x ULN & TBIL >2x ULN &	**3 (6.8)**	**2 (8.0)**	**5 (7.2)**

Five patients met the biochemical criteria for Hy's law (i.e., concurrent ALT or AST >3xULN, bilirubin >2xULN, and ALP ≤ 2xULN), based on laboratory results. For one of the 5 patients who met the biochemical criteria for Hy's law, confounding factors were present (ongoing hemolysis) that may provide an alternative explanation to the hepatic laboratory abnormalities.

For the remaining 4 patients, chronic elevation of bilirubin and transaminases was present throughout the course of nilotinib therapy, and the technical definition of Hy's Law was met in 1 blood sample for 3 patients, and in 2 blood samples for 1 patient. There were no obvious confounding factors. For one of the 4 patients DILI was reported as an AE.

Pancreatitis and elevated serum lipase

No AESIs of pancreatitis were reported. Elevations in lipase values were reported in 15.9% of CML patients, with 7.2% of patients having a grade 3-4 elevation based on laboratory results. A grade 4 elevation was seen in a single patient; this patient had a concurrent AE of DILI.

Electrolyte abnormalities

The use of nilotinib has been associated with hypophosphatemia, hypokalemia, hyperkalemia, hypocalcemia, and hyponatremia in adult patients. In the pediatric CML patients, the majority of newly occurring electrolyte abnormalities were grade 1-2. Grade 3-4 electrolyte abnormalities were seen in a small proportion of patients (decreased phosphate 1.4%, increased magnesium 2.9%, and decreased potassium 1.4%).

Bone biochemical markers

The SDS for bone biochemical biomarkers (CTX and bone specific ALP) was comparable prior to and after the first 12 cycles of nilotinib treatment in both patient populations. The proportion of patients in both patient populations with SDS values <3rd percentile or >97th percentile for CTX and bone specific ALP did not change significantly over time during the first 12 cycles of nilotinib.

<u>Special laboratory evaluations</u>

Thyroid function test (Study A2203 only)

Imatinib/dasatinib resistant/intolerant CML-CP

At baseline, 93.9% of 33 patients had a normal FT4 and 90.9% of patients had a normal TSH. One patient with a normal baseline TSH had a high TSH post-baseline and none had a low TSH. One patient with a normal baseline FT4 developed a low FT4 and one patient with a high FT4 at baseline had a normal post-baseline value.

Newly diagnosed CML-CP

At Baseline, 92.0% of 25 patients had normal TSH and 88.0% of patients had normal FT4. Two patients with a normal TSH at baseline developed a high TSH and two patients with a high TSH at Baseline had a normal TSH post baseline. One patient with a normal Baseline FT4 developed a high FT4 and one patient with a high FT4 at Baseline had a normal post baseline value.

Safety in special populations

Intrinsic factors

Age

In patients with Ph+ CML-CP, a total of 24 patients were aged 2 to <12 years and 45 patients were aged 12 to <18 years. The median time on nilotinib treatment in the age group of 2 to <12 years was 11.10 months (range: 2.4 to 26.0 months) and 14.55 months (range: 0.7 to 30.9 months) in the age group of 12 to <18 years. The median relative dose intensity of nilotinib in the age groups of 2 to <12 years and 12 to <18 years was 98.9% (57.0 to 112.0%) and 91.5% (32.0 to 105.0%), respectively.

Gender

In patients with Ph+ CML-CP, a total of 40 patients were males and 29 patients were females. The median time on nilotinib treatment in males was 13.82 months (range: 3.7 to 30.9 months) and 13.63 months (range: 0.7 to 27.6 months) in females. The median relative dose intensity of nilotinib in males was 93.7% (44.0 to 112.0%) and 95.4% (32.0 to 106.0%) in females.

Race

In patients with Ph+ CML-CP, a total of 39 patients were Caucasian and 24 patients were Asian. The median time on nilotinib treatment in Caucasians was 11.30 months (range: 1.4 to 30.9 months) and 19.32 months (range: 0.7 to 27.7 months) in Asians. The median relative dose intensity of nilotinib in Caucasians was 94.7% (32.0 to 112.0%) and 95.1% (42.0 to 106.0%) in Asians.

Vitals and ECG

In patients with Ph+ CML-CP, no clinically relevant difference was observed in the overall frequency of post-baseline vital sign parameters/weight abnormalities across the subgroups.

Table 52 Vital signs / weight abnormalities (safety set)

		Imatinib/dasatinib resistant/intolerant Ph+ CML-CP		Newly diagnosed Ph+ CML-CP		All patients Ph+ CML-CP		All patients Ph+ CML-CP and ALL	
Notable abnormality		N	n (%)	N	n (%)	N	n (%)	N	n (%)
Systolic BP	Low	39	1 (2.6)	23	1 (4.3)	62	2 (3.2)	65	2 (3.1)
	High	39	3 (7.7)	23	2 (8.7)	62	5 (8.1)	65	7 (10.8)
Diastolic BP	Low	39	1 (2.6)	23	0 (0.0)	62	1 (1.6)	65	1 (1.5)
	High	39	1 (2.6)	23	2 (8.7)	62	3 (4.8)	65	3 (4.6)
Pulse rate	Low	43	11 (25.6)	25	10 (40.0)	68	21 (30.9)	72	21 (29.2)
	High	43	4 (9.3)	25	6 (24.0)	68	10 (14.7)	72	12 (16.7)
Weight	Low	44	8 (18.2)	25	4 (16.0)	69	12 (17.4)	73	14 (19.2)
	High	44	6 (13.6)	25	5 (20.0)	69	11 (15.9)	73	11 (15.1)

Electrocardiogram

1. By age and gender, no clinically relevant difference was observed in the frequency of notable QTcF interval changes at post-baseline across the subgroups.

2. By race, the frequency of QTcF increase of >30 ms was higher in Caucasians (28.9% vs. 16.7% in Asians), although no relevant difference was observed in the incidence of new QTcF >450 ms between the subgroups.

Table 53 Patients with notable ECG intervals (Safety set)

	Imatinib/dasatinib resistant/intolerant Ph+ CML-CP N=44		Newly diagnosed Ph+ CML-CP N=25		All patients Ph+ CML-CP N=69		All patients Ph+ CML-CP and All N=73	
Category	Total	n (%)	Total	n (%)	Total	n (%)	Total	n (%)
QTcF (ms)								
New >450	43	3 (7.0)	24	1 (4.2)	67	4 (6.0)	71	4 (5.6)
New >480	44	2 (4.5)	24	1 (4.2)	68	3 (4.4)	72	3 (4.2)
New >500	44	0	24	0	68	0	72	0
Increase >30	44	10 (22.7)	24	7 (29.2)	68	17 (25.0)	72	18 (25.0)
Increase >60	44	0	24	0	68	0	72	0

Safety related to drug-drug interactions and other interactions

N/A

Discontinuation due to adverse events

Table 54 Patient disposition (Safety set)

	Imatinib/dasatinib resistant/intolerant Ph+ CML-CP	Newly diagnosed Ph+ CML-CP	All patients Ph+ CML-CP	All patients Ph+ CML-CP and ALL
	N = 44	N = 25	N = 69	N = 73
	n (%)	n (%)	n (%)	n (%)
Completed[1]	5 (11.4)	0	5 (7.2)	7 (9.6)
Treatment ongoing[2]	25 (56.8)	19 (76.0)	44 (63.8)	44 (60.3)
Discontinued treatment	14 (31.8)	6 (24.0)	20 (29.0)	22 (30.1)
Primary reason for end of treatment				
Adverse event(s)	5 (11.4)	4 (16.0)	9 (13.0)	10 (13.7)
Subject withdrew consent	0	1 (4.0)	1 (1.4)	1 (1.4)
Administrative problems	1 (2.3)	1 (4.0)	2 (2.9)[3]	2 (2.7)
New cancer therapy	5 (11.4)	0	5 (7.2)	6 (8.2)
Disease progression	2 (4.5)	0	2 (2.9)	2 (2.7)
Protocol deviation	1 (2.3)	0	1 (1.4)	1 (1.4)

[1] Completed is only applicable for study A2120

[2] Patients in study A2203 who were ongoing at the time of the cut-off 01-JUN-2016

[3] "Administrative problems" are 1 case of "lack of efficacy" for newly diagnosed patients and 1 case of "new cancer therapy" for imatinib/dasatinib resistant/intolerant patients in Study A2203 (the CRF of this trial does not have separate reasons for discontinuation for such cases, the information was thus voluntarily stored under the category "administrative problem" in the CRF)

Table 55 Adverse events leading to discontinuation, by preferred term (Safety set)

	Imatinib / Dasatinib Resistant / intolerant CML-CP	Newly diagnosed PH+ CML-CP	All patients PH+ CML-CP	All patients PH+CMLCP and ALL
	N=44	N=25	N=69	N=73
	n(%)	n(%)	n(%)	n(%)
Total	5 (11.4)	4 (16.0)	9 (13.0)	10 (13.7)
Blood bilirubin increased	**2 (4.5)**	**0**	**2 (2.9)**	**3 (4.1)**
Hyperbilirubinaemia	**1 (2.3)**	**1 (4.0)**	**2 (2.9)**	**2 (2.7)**
Rash	**1 (2.3)**	**1 (4.0)**	**2 (2.9)**	**2 (2.7)**
Alanine aminotransferase	0	1 (4.0)	1 (1.4)	1 (1.4)
Anaemia	1 (2.3)	0	1 (1.4)	1 (1.4)
Aspartate aminotransferase	0	1 (4.0)	1 (1.4)	1 (1.4)

increased				
Decreased appetite	1 (2.3)	0	1 (1.4)	1 (1.4)
Headache	1 (2.3)	0	1 (1.4)	1 (1.4)
Keratosis pilaris	1 (2.3)	0	1 (1.4)	1 (1.4)
Malaise	1 (2.3)	0	1 (1.4)	1 (1.4)
Nausea	1 (2.3)	0	1 (1.4)	1 (1.4)
Pain in extremity	1 (2.3)	0	1 (1.4)	1 (1.4)
Platelet count decreased	0	1 (4.0)	1 (1.4)	1 (1.4)
Rash maculo-papular	0	1 (4.0)	1 (1.4)	1 (1.4)
Blood creatinine increased	0	0	0	1 (1.4)
Blood urea increased	0	0	0	1 (1.4)
Blood uric acid increased	0	0	0	1 (1.4)

- Preferred terms are sorted in descending frequency, as reported in the All patients Ph+ CML-CP group.
- A patient with multiple occurrences of an AE under one group is counted only once in the AE category for that

Table 56 Adverse events leading to dose interruption or adjustment, by preferred term (Safety set)

	Imatinib/Dasatinib Resistant/intolerant CML-CP	**Newly diagnosed PH+ CML-CP**	**All patients PH+ CML-CP**	**All patients PH+CMLCP and ALL**
	N=44	**N=25**	**N=69**	**N=73**
Preferred term	**n(%)**	**n(%)**	**n(%)**	**n(%)**
Total	24 (54.5)	17 (68.0)	41 (59.4)	43 (58.9)
Blood bilirubin increased	**7 (15.9)**	**4 (16.0)**	**11 (15.9)**	**11 (15.1)**
Hyperbilirubinaemia	**3 (6.8)**	**7 (28.0)**	**10 (14.5)**	**10 (13.7)**
Alanine aminotransferase	3 (6.8)	4 (16.0)	7 (10.1)	8 (11.0)
Rash	4 (9.1)	2 (8.0)	6 (8.7)	6 (8.2)
Neutropenia	3 (6.8)	2 (8.0)	5 (7.2)	5 (6.8)
Aspartate aminotransferase	1 (2.3)	3 (12.0)	4 (5.8)	4 (5.5)
Electrocardiogram QT	2 (4.5)	2 (8.0)	4 (5.8)	4 (5.5)
Neutrophil count decreased	1 (2.3)	2 (8.0)	3 (4.3)	3 (4.1)
Rash maculo-papular	2 (4.5)	1 (4.0)	3 (4.3)	3 (4.1)
Lipase increased	1 (2.3)	1 (4.0)	2 (2.9)	2 (2.7)
Platelet count decreased	0	2 (8.0)	2 (2.9)	2 (2.7)
Thrombocytopenia	1 (2.3)	1 (4.0)	2 (2.9)	2 (2.7)
Vomiting	0	2 (8.0)	2 (2.9)	2 (2.7)
Amylase increased	1 (2.3)	0	1 (1.4)	1 (1.4)
Anaemia	1 (2.3)	0	1 (1.4)	1 (1.4)
Bilirubin conjugated	0	1 (4.0)	1 (1.4)	1 (1.4)
Blood cholesterol increased	0	1 (4.0)	1 (1.4)	1 (1.4)
Chest pain	1 (2.3)	0	1 (1.4)	1 (1.4)
Drug-induced liver injury	1 (2.3)	0	1 (1.4)	1 (1.4)
Gynaecomastia	0	1 (4.0)	1 (1.4)	1 (1.4)
Hand-foot-and-mouth	1 (2.3)	0	1 (1.4)	1 (1.4)
Hyperamylasaemia	0	1 (4.0)	1 (1.4)	1 (1.4)
Hypoalbuminaemia	1 (2.3)	0	1 (1.4)	1 (1.4)
Keratosis pilaris	1 (2.3)	0	1 (1.4)	1 (1.4)
Nausea	1 (2.3)	0	1 (1.4)	1 (1.4)
Rash generalised	1 (2.3)	0	1 (1.4)	1 (1.4)

Preferred term	Imatinib/Dasatinib Resistant/intolerant CML-CP	Newly diagnosed PH+ CML-CP	All patients PH+ CML-CP	All patients PH+CMLCP and ALL
	N=44	N=25	N=69	N=73
	n(%)	n(%)	n(%)	n(%)
Syncope	0	1 (4.0)	1 (1.4)	1 (1.4)
Tonsillitis	1 (2.3)	0	1 (1.4)	1 (1.4)
Weight decreased	0	1 (4.0)	1 (1.4)	1 (1.4)
Appendix disorder	0	0	0	1 (1.4)
Nasopharyngitis	0	0	0	1 (1.4)

- Preferred terms are sorted in descending frequency, as reported in the All patients Ph+ CML-CP group.
- A patient with multiple occurrences of an AE under one group is counted only once in the AE category for that group. MedDRA version: 19.0

Among 22 (30.1%) patients who discontinued treatment, the most frequent primary reasons for treatment discontinuation were AEs (10 [13.7%] patients) and new cancer therapy (6 [8.2%] patients).

In the pooled patient population (all Ph+ CML-CP), the most frequent AEs leading to study drug discontinuation (⩾ two patients) were blood bilirubin increased, hyperbilirubinaemia, and rash (two patients, each). Blood bilirubin increased (reported in two patients) leading to study drug discontinuation was reported in one patient. Similar adverse events were also responsible for dose reductions and interruptions.

Nine patients in the Ph+ CML population discontinued treatment during the trials. Reasons for discontinuation were liver enzyme increase, rash, and GI related events.

Post marketing experience

The results of the literature review did not reveal any important articles. There were no new or significant safety findings related to Tasigna published in the peer-reviewed scientific or made available as unpublished manuscripts during the reporting interval.

No new relevant safety data of significant impact were received from post-marketing surveillance during the recent PSUR reporting period.

2.6.1. Discussion on clinical safety

The Applicant has pooled safety data from studies A2203 and A2120 which is endorsed. Furthermore, safety assessments on growth, development and maturation are also provided. Mean and median time on treatment is 14.94 and 12.45 months respectively in cohort 1, while 15.20 and 14.55 months respectively in cohort 3. The general exposure is relatively short as indicated by a mean and median time on treatment of 14.94 and 12.45 months respectively in cohort 1 and 15.20 and 14.55 months respectively in cohort 3. However, as the number of patients treated for more than 18 months is about 40% long-term experience in children can be seen as sufficient taking the available experience in adults into account.

All patients experienced AEs, and the majority of these AEs were suspected to be related to nilotinib by the investigators. However, only few AEs led to discontinuation, while a considerable large number of AEs were managed by dose adjustments. The majority of AEs were clinically manageable, but requiring

additional therapy. There was no Grade 5 AE, while the number of Grade 3-4 AEs was 43.2% and 64% in cohort 1 and 3 respectively.

The most common AEs were related to skin/subcutaneous tissue disorders, infections, GI disorders, investigations, nervous system, respiratory and musculoskeletal disorders. More specifically, the most common AEs were headache, rash, liver enzyme increase, pyrexia, nausea, upper respiratory infection, vomiting, and pain. Overall, the most commonly observed AEs in the paediatric population are similar to the observed safety profile of nilotinib in the adult population.

With regard to AESI, they were clinically manageable. A part of the paediatric population (5/77) had chronic elevation of bilirubin and transaminases which met the biochemical criteria for Hy's law (technical definition met in one blood sample for 4 patients and in 2 separate blood samples for 1 patient). For one of the patients confounding factors were present, and the 4 remaining patients were effectively managed with close monitoring, and dose modification or interruptions.

Considering growth and sexual maturation, the duration of the follow-up is considered limited, due to the relative short follow-up. Impact of nilotinib on growth and sexual maturation cannot be assessed at present and updated information will be needed during these procedures as well as during the next years. As only 2 children below the age of 5 are included it seems rather unlikely that full clarification of this issue can be expected from the ongoing clinical trial. However, due to the rareness of the disease in the paediatric population the difficulties in elaborating this information are acknowledged. In total 10 patients (8 (18.2%) patients in cohort 1 and 2(8.0%) patients in cohort 3) experienced SAEs. The SAE are mostly related to GI. There were no new safety findings in these paediatric studies. All SAEs resolved, except for one patient. This patient developed growth hormone deficiency during the study, however, there are uncertainties related to this event. Slower growth was documented in this patient prior to treatment with nilotinib. Thus, this SAE cannot with certainty be related to nilotinib.

With regard to laboratory findings, as expected the majority of the patients experienced haematological abnormalities. Most common AEs were thrombocytopenia, neutropenia and anaemia. Nilotinib is known for its myelosuppressive effects. This clearly reflected in the SmPC and these AEs are clinically manageable, and only few patients had to discontinue treatment.

In paediatric patients, the frequency, type and severity of adverse reactions observed have been generally consistent with those observed in adults, with the exception of the laboratory abnormalities hyperbilirubinaemia (Grade 3/4: 13.0%) and transaminase elevation (AST Grade 3/4: 1.4%, ALT Grade 3/4: 8.7%) which were reported at a higher frequency than in adult patients. Bilirubin and hepatic transaminase levels should be monitored during treatment (SmPC, section 4.8).

Laboratory abnormalities of mild to moderate transient elevations of aminotransferases and total bilirubin have been observed in children at a higher frequency than in adults, indicating a higher risk of hepatotoxicity in the paediatric population. Liver function (bilirubin and hepatic transaminases levels) should be monitored monthly or as clinically indicated. Elevations of bilirubin and hepatic transaminases should be managed by withholding nilotinib temporarily, dose reduction and/or discontinuation of nilotinib. The long-term effects of prolonged treatment with nilotinib in children and adolescents are unknown (SmPC, sections 4.2 and 4.4).

No clinically significant ECG abnormalities were reported; there were no patients with QTcF prolongation >500 mg, or >60 ms prolonged from baseline. No cases of torsade de pointes were reported.

Subgroup analyses for demographic factors (age group, gender, and race) did not reveal any consistent differences in safety findings; however, due to the low number of patients in these subgroups, the results must be interpreted with caution.

Currently, there is limited information regarding the side effects of nilotinib in paediatric patients treated for duration longer than 18 months. Although data on growth and development was collected in Study A2203, the duration of follow-up at the time of the 18-month data cut-off is too short to allow any definite conclusions to be drawn. The final report of study A2203 will be submitted post authorisation.

2.6.2. Conclusions on the clinical safety

Safety results in paediatric patients treated with nilotinib were in general consistent with the known safety profile of nilotinib in adults with the exception of a more pronounced hepatotoxicity which was observed in the paediatric population.

The CHMP considers the following measures necessary to address issues related to safety:

- The final report of study A2203 will be submitted post authorisation (see Annex II and RMP).

2.6.3. PSUR cycle

The PSUR cycle remains unchanged.

2.7. Risk Management Plan

Safety concerns

Table 57 Summary of safety concerns

Important identified risks	QT prolongation Myelosuppression Cardiovascular events Significant bleeding Severe infections Hepatotoxicity Pancreatitis, lipase and amylase elevations Fluid retention Blood glucose increased Blood cholesterol increased Use in patients with hepatic impairment Interaction with strong CYP3A4 inhibitors Interaction with strong CYP3A4 inducers Interactions with sensitive CYP3A4 substrates Interaction with Food
Important potential risks	Sudden death Cardiac failure Reproductive toxicity/pregnancy Skin malignancy Interaction with P-gp inhibitors Interaction with drugs eliminated by CYP2C8, CYP2C9, CYP2D6 or substrates of UGT1A1, and P-gp and OCT1 transporters Interactions with drugs that may prolong the

	QT interval
Missing information	Long term follow-up in pediatric patients Pediatric patients below 2 years of age Use in patients with renal impairment Patients with uncontrolled or significant cardiac disease Risk of resistance (in TFR)

Pharmacovigilance Plan

Table 58 Ongoing and planned studies in the PhV development plan

Study / activity Type, title and category (1-3)	**Objectives**	**Safety concerns addressed**	**Status** (planned, started)	**Date for submission of interim or final Reports** (planned or actual)
Questionnaire for study CAMN107A2001 Details about the methodology to evaluate the use of educational material as a risk minimization activity Category 3	To assess the effectiveness of educational material for physicians and patients	QT prolongation, pancreatitis, lipase and amylase elevations, hepatic transaminase and bilirubin elevations, cardiac failure, use in patients with hepatic impairment , Strong CYP3A4 inhibitors and inducers, patients with uncontrolled or significant cardiac disease, Drugs that may prolong the QT interval, interaction with food	Ongoing	Interim CSR submitted: 18-Dec-2015
Collect and provide data on late relapses on a yearly basis from the ongoing studies ENESTfreedom (CAMN107I2201) and ENESTop (CAMN107A2408) Category 3	Collect and provide data on late relapses on a yearly basis from the ongoing studies ENESTfreedom (CAMN107I2201) and ENESTop (CAMN107A2408)	Risk of resistance (in TFR)	Ongoing	Planned Q1 2021

Study / activity Type, title and category (1-3)	**Objectives**	**Safety concerns addressed**	**Status** (planned, started)	**Date for submission of interim or final Reports** (planned or actual)
Collect data on gene signature in patients who relapse on TFR compared to patients who relapse on treatment and provide data on a yearly basis Category 3	Collect data on gene signature in patients who relapse on TFR compared to patients who relapse on treatment and provide data on a yearly basis	Risk of resistance (in TFR)	Ongoing	Planned Q1 2021

*Category 1 are imposed activities considered key to the benefit risk of the product.

Category 2 are specific obligations

Category 3 are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

The PRAC, having considered the updated data submitted, was of the opinion that the proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

The PRAC also considered that the studies in the post-authorisation development plan remain sufficient to monitor the effectiveness of the risk minimisation measures

Risk minimisation measures

Table 59 Summary table of Risk Minimisation Measures

Safety concern	**Routine risk minimization measures**	**Additional risk minimization measures**
Important identified risks		
QT prolongation	This item is appropriately communicated through current labeling. SmPC Sections 4.4, 4.8 and 5.3	Educational material
Myelosuppression	This item is appropriately communicated through current labeling. SmPC Sections 4.2, 4.4 and 4.8	None
Cardiovascular events	This item is appropriately communicated through current labeling. SmPC Sections 4.4	Educational material
Significant bleeding	This item is appropriately communicated through current labeling. SmPC Section 4.8	None
Severe infections	This item is appropriately communicated through current labeling.	None

Safety concern	Routine risk minimization measures	Additional risk minimization measures
	SmPC Sections 4.8	
Hepatotoxicity	This item is appropriately communicated through current labeling. SmPC Sections 4.2, 4.8 and 5.3	Educational material
Pancreatitis, lipase and amylase elevations	This item is appropriately communicated through current labeling. SmPC Sections 4.2, 4.4 and 4.8	Educational material
Fluid retention	This item is appropriately communicated through current labeling. SmPC Section 4.4, 4.8	Educational material
Blood glucose increased	SmPC Sections 4.2, 4.4 and 4.8	Educational material
Blood cholesterol increased	SmPC Sections 4.2, 4.4 and 4.8	Educational material
Use in patients with hepatic impairment	This item is appropriately communicated through current labeling. SmPC Sections 4.2 and 4.4	Educational material
Interaction with strong CYP3A4 inhibitors	This item is appropriately communicated through current labeling. SmPC Sections 4.4 and 4.5	Educational material
Interaction with strong CYP3A4 inducers	This item is appropriately communicated through current labeling. SmPC Sections 4.4 and 4.5	Educational material
Interactions with sensitive CYP3A4 substrates	This item is appropriately communicated through current labeling. SmPC Section 4.5	Educational material
Interaction with food	This item is appropriately communicated through current labeling. SmPC Sections 4.2, 4.4, 4.5 and 5.2	Educational material
Important potential risks		
Sudden death	This item is appropriately communicated through current labeling. SmPC Sections 4.4, 4.8	None
Cardiac failure	This item is appropriately communicated through current labeling. SmPC Section 4.8	Educational material

Safety concern	Routine risk minimization measures	Additional risk minimization measures
Reproductive toxicity/ pregnancy	This item is appropriately communicated through current labeling. SmPC Sections 4.6, 4.8 and 5.3	Educational material
Skin malignancy	This item is appropriately communicated through current labeling. SmPC Section 5.3	None
Interaction with P-gp inhibitors	This item is appropriately communicated through current labeling. SmPC section 4.5	None
Interactions with drugs eliminated by CYP2C8, CYP2C9, CYP2D6, or substrates of UGT1A1 and P-gp and OCT1 transporters	This item is appropriately communicated through current labeling. SmPC section 4.5	None
Interaction with drugs that may prolong the QT interval	This item is appropriately communicated through current labeling. SmPC Section 4.4 and 4.5	Educational material
Missing information		
Long term follow-up in pediatric patients	This item is appropriately communicated through current labeling. SmPC Section 4.2	None
Pediatric patients below 2 years of age	SmPC Section 4.2	None
Use in patients with renal impairment	This item is appropriately communicated through current labeling. SmPC Sections 4.2 and 4.8	None
Patients with uncontrolled or significant cardiac disease	This item is appropriately communicated through current labeling. SmPC Sections 4.2, 4.4 and 4.8	Educational material
Risk of resistance (in TFR)	This item is appropriately communicated through current labeling. SmPC Section 4.2, and 4.4	None

The PRAC, having considered the updated data submitted, was of the opinion that the proposed risk minimisation measures remains sufficient to minimise the risks of the product in the proposed indications; use of nilotinib in the treatment of the paediatric population.

MAH's Summary of the RMP

The summary of the RMP does not require revision following the conclusion of the procedure.

Conclusion

The CHMP and PRAC considered that the risk management plan version 20.0 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.9. Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

Furthermore, the MAH introduced 50 mg strength with subsequent changes to the Product Information.

In addition the Marketing authorisation holder (MAH) took the opportunity to include some editorial changes and to bring the product information in line with the latest QRD template version 10.

2.9.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

With this application, a separate Package Leaflet for Tasigna 50 mg hard capsules is introduced which is based on the approved Package Leaflet for Tasigna 200 mg hard capsules. No significant changes are introduced in the currently approved text of the Tasigna Package Leaflets. In particular, the key information in the Tasigna Package Leaflets remains unchanged and the changes to the Package Leaflets are limited.

3. Benefit-Risk Balance

3.1. Therapeutic Context

This application refers to the paediatric use in the indications of newly diagnosed Philadelphia chromosome positive chronic myelogenous leukaemia (CML) in the chronic phase and in Philadelphia chromosome positive CML in chronic phase with resistance or intolerance to prior therapy including imatinib.

3.1.1. Disease or condition

3.1.2. Available therapies and unmet medical need

Prior to the availability of imatinib, IFN-α was the treatment of choice for adult and paediatric patients not eligible for hematopoietic stem cell transplant (HSCT), with patients who achieved complete cytogenetic response on IFN surviving more than a decade. However, only a small proportion (5–10%) of patients responds to IFN. Imatinib (first approved for the use in children in 2001) has now become the standard first-line treatment in paediatric patients.

Imatinib has reduced the yearly risk of progression from CP to advanced stages to less than 1% per year. In a study conducted in 51 paediatric patients with de novo CML-CP, the CCyR rate was 64.7%, and the MMR rate was 27.3% (Champagne et al 2011). Similar results were reported in a study conducted in 44 paediatric patients with newly diagnosed CML-CP, with CCyR and MMR rates of 61% and 31%, respectively, at 12 months.

However, imatinib and second generation TKIs seem not curing the disease and in the majority of patients leukemic cells will persist; furthermore not all patients respond to, or tolerate imatinib as first line treatment. Some patients who initially respond to imatinib subsequently relapse, usually due to the emergence of mutations in BCR-ABL that confer resistance to imatinib, or due to overexpression of the BCR-ABL protein.

An unmet medical need exists for alternative, more effective treatment options in paediatric patients with CML. Considering that imatinib is currently the only approved BCR-ABL-targeted TKI in paediatric patients with CML-CP, other therapeutic alternatives particularly in children in whom resistance or intolerance to imatinib develops, is needed.

3.1.3. Main clinical studies

The pivotal study CAMN107A2203 was a Phase II, open-label, multi-center study evaluating the efficacy and safety of nilotinib 230 mg/m^2 bid conducted in 58 paediatric patients with Ph+ CML (33 were resistant or intolerant to imatinib or dasatinib (Cohort 1), and 25 were newly diagnosed (cohort 3)).

Additionally, study CAMN107A2120 was a Phase I, open-label, multi-center study that evaluated the pharmacokinetics (PK), safety, and preliminary efficacy of nilotinib 230 mg/m^2 bid in paediatric patients with Ph+ CML resistant or intolerant to imatinib or dasatinib (N=11) or refractory/relapsed Ph+ acute lymphoid leukemia (ALL; N=4).

3.2. Favourable effects

Imatinib/dasatinib resistant

Approximately 40% of the patients in cohort 1 were in MMR at 6 cycles, however, it should be noted that 6 out of 13 patients were already in MMR at baseline. Median time to first MMR is 2.79 months and by 12 months and onwards the MMR rate is 64.9%. Once a patient gained MMR they continued to stay in MMR by the time of data cut-off date.

Not all patient obtained MMR, however, by cycle twelve 84.8% (28 patients) of the patients had obtained MCyR, and of these, 27 had a complete MCyR. Only one patient did not have a cytogenetic response.

Newly diagnosed

At 12 cycles 16/25 (64%) patients had reached MMR and CCyR. With regard to MMR by time point, 64% of the patients had gained MMR by cycle 12, while 68% had gained MMR by data cut-off. Only 1/17 patients lost MMR by data cut-off. The CCyR rate was 84% by the time of data cut-off. Median time to first complete cytogenetic response was 5.55 months. The KM estimated rate of CCyR was 90.6% by 6 months. Only 1/21 had a loss of CCyR at the time of data cut-off.

3.3. Uncertainties and limitations about favourable effects

No data are available in paediatric patients with newly diagnosed CML in chronic phase below the age of 10 years and there are limited data in paediatric CML-CP patients below 6 years of age in the resistant/refractory setting. Taking into account the rareness of the disease, it is considered acceptable that the clinical pharmacology data and the data provided from the literature support the conclusion that nilotinib at the dose of 230 mg/m^2 BID is efficacious and safe in newly diagnosed and resistant/intolerant CML-CP patients from 2 to 18 years of age. The product information has been updated to reflect it.

3.4. Unfavourable effects

There was no Grade 5 AE, while the number of Grade 3-4 AEs was 43.2% and 64% in cohort 1 and 3 respectively.

The most common AEs were related to skin/subcutaneous tissue disorders, infections, GI disorders, investigations, nervous system, respiratory and musculoskeletal disorders. More specifically, the most common AEs were headache, rash, liver enzyme increase, pyrexia, nausea, upper respiratory infection, vomiting, and pain. Overall, the most commonly observed AEs in the paediatric population are similar to the observed safety profile of nilotinib in the adult population.

In total 10 patients (8 (18.2%) patients in cohort 1 and 2(8.0%) patients in cohort 3) experienced SAEs. The SAE are mostly related to GI.

With regard to laboratory findings, as expected the majority of the patients experienced haematological abnormalities. Most common AEs were thrombocytopenia, neutropenia and anaemia. Nilotinib is known for its myelosuppressive effects. The type and severity of AEs in paediatric patients were generally similar to those seen in adults.

Hepatotoxicity as reflected in rates of increased ALT, AST, and bilirubin is significantly more frequent in the paediatric patients compared with that reported in adults. This is clearly reflected in the SmPC, section 4.4.

3.5. Uncertainties and limitations about unfavourable effects

Currently, there is limited information regarding the side effects of nilotinib in paediatric patients treated for duration longer than 18 months. Although data on growth and development was collected in Study A2203, the duration of follow-up at the time of the 18-month data cut-off is too short to allow

any definite conclusions to be drawn. The final report of study A2203 will be submitted post authorisation.

3.6. Effects Table

Table 60 Effects Table for Tasigna for the treatment of paediatric patients with newly diagnosed Philadelphia chromosome positive chronic myelogenous leukaemia (CML) in the chronic phase, and with resistance or intolerance to prior therapy including imatinib (data cut-off: 1 June 2016)

Effect	Short Description	Unit	Imatinib/dasatinib resistant/intolerant	Newly diagnosed	Uncertainties/ Strength of evidence	References
Favourable Effects						
MMR rate		N(%)	13 (39.4%)	16 (68%)		
Unfavourable Effects						
Headache		N(%)	17(38.9%)	14(56%)		
Rash		N(%)	11(25%)	11(44%)		
Blood bilirubin increased		N(%)	14(31.8%)	7(28%)		
ALT increased		N(%)	11(25%)	9(36%)		
AST increased		N(%)	9(20.5%)	7(28%)		
Pyrexia		N(%)	12(27.3%)	7(28.0%)		
Nausea		N(%)	10(22.7%)	7(28.0%)		

Abbreviations: MMR: Major molecular response; ALT: alanine aminotransferase; AST: aspartate aminotransferase

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

In imatinib/dasatinib resistant paediatric population, approximately 40% of the patients in cohort 1 were in MMR at 6 cycles, however, it should be noted that 6 out of 13 patients were already in MMR at baseline. Nonetheless, the results are encouraging, since treatment with nilotinib keeps these 6 patients in MMR and further patients are brought into MMR. Although 14 patients did not obtain MMR, reflecting the resistant/refractory patient population, the observed results are nevertheless considered clinically highly relevant. Regarding secondary endpoints, median time to first MMR was 2.79 months and by 18 months and onwards the MMR rate was 64.9%. Once a patient gained MMR they continued to stay in MMR by the time of data cut-off date. These clinically relevant findings support the primary endpoint.

In newly diagnosed paediatric patients, 68% of them had gained MMR by cycle 18, while 68% had gained MMR by data cut-off. Only 1/17 patients lost MMR by data cut-off. Therefore, deep and prolonged responses are achieved in newly diagnosed patients treated with nilotinib.

Overall, clinically relevant and meaningful results have been shown in resistant/refractory and newly diagnosed paediatric patients with Ph+ CML.

With regard to AEs, the safety profile of nilotinib in a paediatric population is similar that observed in an adult population. There were no new safety findings. The majority of AEs were clinically manageable. However, as for a life-long treatment, particularly long-term safety risks have to be carefully considered, patients in newly diagnosed PH+CML-CP should receive the drug with the lowest safety risk, while in patients with no treatment alternatives, e.g. those in second or later line, the benefit of TKI-treatment in CML will outweigh also higher toxicities.

3.7.2. Balance of benefits and risks

The overall benefit-risk balance of nilotinib administered at 230 mg/m^2 bid in paediatric patients with CML-CP resistant/intolerant to prior TKI (including imatinib) and in newly diagnosed CML-CP is positive. Due to the lack of treatment alternatives, the safety risks are outweighed by the observed efficacy.

3.7.3. Additional considerations on the benefit-risk balance

N/A

3.8. Conclusions

The overall B/R of Tasigna is positive.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Tasigna is not similar to Sprycel (dasatinib), Bosulif (bosutinib) and Iclusig (ponatinib) within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See Appendix 1.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Tasigna 50 mg hard capsules is favourable in the following indications:

Tasigna is indicated for the treatment of:

- adult and paediatric patients with newly diagnosed Philadelphia chromosome positive chronic myelogenous leukaemia (CML) in the chronic phase,
- adult patients with chronic phase and accelerated phase Philadelphia chromosome positive CML with resistance or intolerance to prior therapy including imatinib. Efficacy data in patients with CML in blast crisis are not available,

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

The CHMP therefore recommends the extension of the marketing authorisation for Tasigna subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

The MAH shall ensure that prior to launch, all doctors who intend to prescribe the medicinal product, and all pharmacists who may dispense the medicinal product, are provided with a healthcare professional information pack containing the following:

- Educational brochure
- Summary of Product Characteristics (SPC) and Package Leaflet and Labelling

Key elements to be included in the educational brochure

- Brief background on Tasigna, its authorised indication and posology

- Information on the cardiac risks associated with the use of Tasigna
    - That Tasigna can cause prolongation of the QT interval and that Tasigna should be used with caution in patients who have or who are at significant risk of developing prolongation of QTc. Concomitant use of Tasigna with anti arrhythmics or other medicinal products that may prolong the QT interval should be undertaken with caution
    - Caution in prescribing to patients with a history of or risk factors for coronary heart disease
    - That Tasigna may cause fluid retention, cardiac failure and pulmonary oedema

- That Tasigna is metabolised by CYP3A4 and that strong inhibitors or inducers of this enzyme may significantly affect exposure to Tasigna.
    - That inhibitors may increase the potential for adverse drug reactions in particular QT interval prolongation.
    - To warn patients about OTC medicines in particular St John's Wort

- The need to inform patients about the effects of food on Tasigna
    - Not to eat within two hours before and one hour after taking Tasigna
    - The need to avoid foods such as grapefruit juice which inhibit CYP3A4 enzymes

Obligation to conduct post-authorisation measures

The MAH shall complete, within the stated timeframe, the below measures:

Description	**Due date**
Post authorisation efficacy study (PAES): In order to investigate the efficacy of nilotinib in paediatric patients with Ph+ CML CP resistant or intolerant to either imatinib or dasatinib and in newly diagnosed patients the MAH should submit the final results of the phase II CAMN107A2203 study.	Final CSR: April 2021

In addition, CHMP recommends the variation(s) to the terms of the marketing authorisation, concerning the following change(s):

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Extension of Indication to include treatment of paediatric patients with newly diagnosed Philadelphia chromosome-positive chronic myelogenous leukaemia in chronic phase (Ph+ CML-CP), or with Ph+ CML-CP resistant or intolerant to prior therapy including imatinib, based on results from two clinical studies in paediatric patients conducted in accordance with the approved Tasigna Paediatric Investigation Plan (PIP); the Phase I PK study CAMN107A2120 and the Phase II safety and efficacy study CAMN107A2203. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have

been updated and Annex II and the package leaflet have been updated accordingly. In addition, the MAH took the opportunity to implement minor editorial changes and to align the annexes with the latest QRD template. An updated RMP version 20.0 was agreed during the procedure.

The variation leads to amendments to the Summary of Product Characteristics, Annex II, labelling and Package Leaflet and to the RMP.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0297/2015 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

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