CLINICAL REVIEW

Application Type	505(b)(1) NDA
Application Number(s)	NDA 022068: Supplement 27
Priority or Standard	Priority
Submit Date(s)	25 September 2017
Received Date(s)	25 September 2017
PDUFA Goal Date	25 March 2018
Division/Office	DHP/OHOP
Reviewer Name(s)	Nicholas C. Richardson, DO, MPH
Review Completion Date	16 February 2018
Established/Proper Name	Nilotinib
(Proposed) Trade Name	Tasigna
Applicant	Novartis
Dosage Form(s)	Capsule, for oral use
Applicant Proposed Dosing Regimen(s)	230 mg/m^2 twice daily, rounded to the nearest 50mg dose (to a maximum single dose of 400 mg)
Applicant Proposed Indication(s)/Population(s)	- Treatment of newly diagnosed pediatric patients with Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase (CP). - Treatment of Ph+ CML-CP pediatric patients resistant or intolerant to prior tyrosine-kinase inhibitor (TKI) therapy.
Recommendation on Regulatory Action	Regular Approval
Recommended Indication(s)/Population(s) (if applicable)	- Treatment of pediatric patients with newly diagnosed Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase (CP). - Treatment of pediatric patients with Ph+ CML-CP resistant or intolerant to prior tyrosine-kinase inhibitor (TKI) therapy.

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Glossary

AC	Advisory committee
AE	Adverse event
ALL	Acute lymphoblastic leukemia
ALT	Alanine aminotransferase
AP	Accelerated phase
AR	Adverse reaction
AST	Aspartate aminotransferase
AUC	Area under the curve
$AUC_{0-\infty}$	Area under the serum concentration-time curve to infinity
BC	Blast crisis
CCyR	Complete cytogenetic response
CDER	Center for Drug Evaluation and Research
CHR	Complete hematologic response
CL/F	Systemic clearance
Cmax	Maximum observed concentration
CMC	Chemistry, manufacturing, and controls
CML	Chronic myeloid leukemia
CP	Chronic phase
ECG	Electrocardiogram
ELN	European Leukemia Net
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good clinical practice
ICH	International Council for Harmonization
MCyR	Major cytogenetic response
MMR	Major molecular response
MedDRA	Medical Dictionary for Regulatory Activities
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	New drug application
PD	pharmacodynamics
Ph+	Philadelphia chromosome positive
PK	Pharmacokinetics
PMR	Postmarketing requirement
PRO	Patient reported outcome

PSUR	Periodic Safety Update report
SAE	Serious adverse event
$T_{1/2}$	Terminal elimination half-life
TEAE	Treatment emergent adverse event
TKI	Tyrosine kinase inhibitor
Tmax	Time to reach the maximum concentration after drug administration
USPI	United Stated Prescribing Information
Vd/F	Volume of distribution
XRT	External beam radiation therapy

1. Executive Summary

1.1. Product Introduction

Established Name: Nilotinib
Trade Name: Tasigna
Applicant: Novartis
Drug Class: Tyrosine kinase inhibitor (second generation)

Nilotinib is currently approved for the following indications:

- Treatment of newly diagnosed adult patients with Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase.
- Treatment of chronic phase or accelerated phase Ph+ CML in adult patients resistant to or intolerant to prior therapy that included imatinib.

Applicant's Proposed Indications:

- Treatment of newly diagnosed adult and pediatric patients with Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase (CP).
- Treatment of Ph+ CML-CP pediatric patients resistant or intolerant to prior tyrosine-kinase inhibitor (TKI) therapy

Applicant's Proposed Dosage and Administration: 230 mg/m^2 twice daily, orally, rounded to the nearest 50mg dose (to a maximum single dose of 400 mg). Table 1.

Table 1 Pediatric dosing of nilotinib (230 mg/m^2 twice daily, maximum single dose of 400mg)

Body Surface Area (BSA)	Single Dose	Total Daily Dose
Up to 0.32 m^2	50 mg	100 mg
0.33 – 0.54 m^2	100 mg	200 mg
0.55 – 0.76 m^2	150 mg	300 mg
0.77 – 0.97 m^2	200 mg	400 mg
0.98 – 1.19 m^2	250 mg	500 mg
1.20 – 1.41 m^2	300 mg	600 mg
1.42 – 1.63 m^2	350 mg	700 mg
≥ 1.64 m^2	400 mg	800 mg

1.2. Conclusions on the Substantial Evidence of Effectiveness

The information submitted by the Applicant provides substantial evidence for the effectiveness of nilotinib for the treatment of pediatric patients with resistant or intolerant Ph+ CML in chronic phase and newly diagnosed Ph+ CML in chronic phase. The efficacy of nilotinib has been established by two open-label, single arm studies in pediatric patients with Ph+ CML in chronic phase. The primary efficacy endpoint evaluated was major molecular response (MMR) rate, which was defined as ≤ 0.1% BCR-ABL/control gene (ABL) % by international scale, or equivalent to ≥ 3 log reduction of BCR-ABL transcript from standardized baseline. Of the 44 patients with Ph+ CML-CP resistant or intolerant to either imatinib or dasatinib, 21 patients (48%) achieved a major molecular response by 12 cycles. The median duration of response was not reached as none of the 21 patients experienced a loss of MMR, with a median follow-up of 11.3 months. Of the 25 patients with newly diagnosed Ph+ CML-CP, 16 patients (64%) achieved a major molecular response by 12 cycles. The median duration of response was not reached as only one patient experienced a confirmed loss of MMR, with a median follow-up of 11.1 months. The magnitude of the achieved rates of MMR and the durability of the responses support the establishment of efficacy of nilotinib treatment in pediatric patients with Ph+ CML-CP. Further, nilotinib is currently approved for the treatment of adult patients with resistant or intolerant Ph+ CML in chronic phase and newly diagnosed Ph+ CML in chronic phase. The pathogenic mechanism, the BCR-ABL fusion gene, that is the underlying biologic driver in patients with CML is similar between pediatric and adult populations. Therefore, the efficacy of nilotinib demonstrated in adults with Ph+ CML-CP can be extrapolated to pediatric patients with Ph+ CML-CP, further supporting the efficacy of nilotinib treatment for Ph+ CML in chronic phase. Taken together, the evidence of efficacy forms a strong basis for regular approval.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

The benefit-risk assessment supports regular approval of nilotinib for the treatment pediatric patients with Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase resistant or intolerant to prior tyrosine-kinase inhibitor therapy and newly diagnosed Ph+ CML in chronic phase (CP).

The efficacy of nilotinib is based on the results of two open-label, single arm studies in pediatric patients with Ph+ CML in chronic phase. In the analysis of the primary efficacy endpoint major molecular response rate, 21 patients (48%) of the 44 patients with resistant or intolerant Ph+ CML-CP and 16 patients (64%) of the 25 patients with newly diagnosed Ph+ CML-CP achieved a major molecular response by 12 cycles. The median duration of response was not reached for either pediatric cohort as there was only one patient with newly diagnosed Ph+ CML-CP that experienced a loss of MMR. In addition, the efficacy of nilotinib demonstrated in adults with Ph+ CML-CP can be extrapolated to pediatric patients with Ph+ CML-CP because the underlying biologic driver, the BCR-ABL fusion gene, is similar between pediatric and adult patients with CML. Nilotinib is currently approved for the treatment adult patients with newly diagnosed Ph+ CML in chronic phase and Ph+ CML in chronic phase resistant or intolerant to prior therapy that included imatinib.

The safety profile of nilotinib in pediatric patients is tolerable and manageable. The safety of nilotinib 230 mg/m^2 twice daily was evaluated in 69 pediatric patients with Ph+ CML in chronic phase. Common adverse reactions in greater than 10% of patients included hyperbilirubinemia, rash, ALT increased, headache, AST increased, nausea, neutropenia, thrombocytopenia, vomiting, and fatigue. The most common serious adverse events were gastroenteritis, neutropenia, and hyperbilirubinemia. Adverse events resulting in treatment discontinuation were reported in 13% of patients. Adverse events leading to dose reduction of nilotinib therapy occurred in 38% of patients. There were no deaths reported and no reports of progressive or irreversible drug-induced liver injury. Overall, the safety profile in pediatric patients with Ph+ CML is similar to the known safety profile in adults with Ph+ CML treated with nilotinib. The identified risks with nilotinib can be managed and mitigated with appropriate labeling.

The conclusion for substantial evidence of effectiveness is supported by the durable major molecular response rate of 48% and 64% in pediatric patients with resistant or intolerant Ph+ CML-CP and newly diagnosed Ph+ CML-CP, respectively. The safety profile is similar to the known profile in adult patients and was demonstrated to be tolerable and manageable in pediatric patients. Overall, the risk-benefit assessment of

nilotinib is favorable for the treatment pediatric patients with Ph+ CML in chronic phase.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Pediatric patients with Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) account for 3% of newly diagnosed pediatric leukemias, with an annual incidence of 1 case per million in children younger than 15 years of age and 2.2 cases per million in adolescents between 15 and 19 years of age.	Pediatric chronic myeloid leukemia is a rare, but serious and life-threatening disease.
Current Treatment Options	• Imatinib is the recommended first-line therapy and is FDA approved for pediatric patients with Ph+ CML in chronic phase (CP). Dasatinib is a second-generation BCR-ABL tyrosine kinase inhibitor approved for pediatric patients with Ph+ CML in chronic phase. These therapies are intended to be given as life-long therapy. • Around 10 to 40% of patients discontinue imatinib or dasatinib due to intolerance, declining response, or progressive disease. • Allogeneic hematopoietic stem cell transplantation is the only curative treatment option available for pediatric patients with Ph+ CML in chronic phase.	The optimal treatment strategy for pediatric patients with Ph+ CML in chronic phase remains uncertain. New treatment options are needed for pediatric patients with Ph+ CML.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• Study CAMN107A2120 and CAMN107A2203 were open-label, single-arm studies of nilotinib in pediatric patients with resistant or intolerant Ph+ CML in chronic phase and newly diagnosed Ph+ CML in chronic phase. • Twenty-one patients (48%) with resistant or intolerant Ph+ CML-CP achieved a major molecular response by 12 cycles. • Sixteen patients (64%) with newly diagnosed Ph+ CML-CP achieved a major molecular response by 12 cycles. • The median duration of response was not reached in either, patients with resistant or intolerant Ph+ CML-CP or newly diagnosed Ph+ CML-CP.	Nilotinib is effective in treating pediatric patients with Ph+ CML in chronic phase. The magnitude and duration of major molecular response are clinically meaningful. Further, nilotinib has demonstrated efficacy in adult patients with resistant or intolerant Ph+ CML-CP and newly diagnosed Ph+ CML-CP and is approved for these indications. The efficacy of nilotinib in adults can be extrapolated to pediatric patients because the underlying biologic driver, the BCR-ABL fusion gene, is similar between pediatric and adult patients with Ph+ CML.
Risk and Risk Management	• The most common adverse reactions in greater than 10% of patients include hyperbilirubinemia, rash, ALT increased, headache, AST increased, nausea, neutropenia, thrombocytopenia, vomiting, and fatigue. • The most common Grade 3-4 adverse reactions include neutropenia, hyperbilirubinemia, rash, and ALT increased. • The adverse reactions of Grade 3-4 hyperbilirubinemia (13%) and transaminase elevation (AST Grade 3-4: 1%, ALT Grade 3-4: 9%) were reported a higher frequency in pediatric patients than in adult patients. • The study protocol included monitoring for risks and instruction for	Overall, the safety profile in pediatric patients is consistent with the safety profile in adult patients. The safety profile of nilotinib in pediatric patients is tolerable and manageable. Long-term safety information is needed in the pediatric population since nilotinib is intended for prolonged use and there may be potential for cumulative toxicity and effects on growth and development. The risk associated with nilotinib in pediatric

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	intervention. Interventions included dose interruption, reduction, or discontinuation, which were sufficient to mitigate the majority of treatment-related toxicities. • The proposed labeling includes warnings and dose modifications for myelosuppression, QT prolongation, elevated lipase or amylase, elevated bilirubin, and elevated hepatic transaminases for pediatric patients.	patients can be adequately addressed with labeling. Labeling should include warnings and precautions, along with instruction for monitoring and dose modification, for myelosuppression, QT prolongation, and hepatotoxicity.

1.4. Patient Experience Data

There were no patient experience data collected during the conduct of the 2 clinical trials supporting this NDA application.

Patient Experience Data Relevant to this Application (check all that apply)

□	The patient experience data that was submitted as part of the application include:	Not applicable
	□ Clinical outcome assessment (COA) data, such as	Not applicable
	□ Patient reported outcome (PRO)	
	□ Observer reported outcome (ObsRO)	
	□ Clinician reported outcome (ClinRO)	
	□ Performance outcome (PerfO)	
	□ Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	Not applicable
	□ Patient-focused drug development or other stakeholder meeting summary reports	Not applicable
	□ Observational survey studies designed to capture patient experience data	Not applicable
	□ Natural history studies	Not applicable
	□ Patient preference studies (e.g., submitted studies or scientific publications)	Not applicable
	□ Other: (Please specify)	
□	Patient experience data that were not submitted in the application, but were considered in this review:	
	□ Input informed from participation in meetings with patient stakeholders	Not applicable
	□ Patient-focused drug development or other stakeholder meeting summary reports	Not applicable
	□ Observational survey studies designed to capture patient experience data	Not applicable
	□ Other: (Please specify)	
X	Patient experience data was not submitted as part of this application.	

2. Therapeutic Context

2.1. Analysis of Condition

Pediatric patients with chronic myeloid leukemia account for 3% of newly diagnosed pediatric leukemias, with an annual incidence of 1 case per million in children younger than 15 years of age and 2.2 cases per million in adolescents between 15 and 19 years of age.[1] The incidence of CML in the pediatric population increases with age. Pediatric patients with CML typically present with high white blood cell count, fatigue, weight loss, and splenomegaly.[2-3] Signs and symptoms consistent with bone marrow infiltration can be seen in more advanced cases of CML. Further, the natural history of pediatric CML progresses through 3 phases that include 1) chronic phase, 2) accelerated phase, and 3) blast crisis. Chronic phase is defined by less than 10% leukemic blasts in the bone marrow. Accelerated phase is defined by 10% to 19% leukemic blasts in the bone marrow, peripheral blood basophils more than 20%, persistent thrombocytopenia (platelets < 100 x 10^9/L) or thrombocytosis (platelets > 1000 x 10^9/L), increasing spleen size or increasing white blood cell count unresponsive to therapy, or cytogenetic clonal evolution. Blast crisis is defined as more than 20% leukemic blasts in the bone marrow consistent with overt leukemia.[4] Approximately 95% of pediatric patients present with CML in chronic phase.[2] Adult share a similar natural history and the majority of adult patients with CML also present in chronic phase.

The molecular features of pediatric CML is similar to that of adult CML. Both populations feature the translocation between the long arms of chromosomes 9 and 22, t(9;22), which results in the fusion gene BCR-ABL, also known as the Philadelphia chromosome. BCR-ABL encodes a constitutively active tyrosine kinase that is the underlying biologic driver in patients with CML. Although, it has recently been demonstrated that the breakpoints on chromosome 22 for the BCR gene are different in pediatric CML versus adult CML.[5] This may contribute to the more aggressive clinical characteristics seen in pediatric CML, such as higher white blood cell count, increased splenomegaly, more advanced stage of disease, and decreased response to therapy, compared to adults with CML.[2, 6-9]

The treatment for pediatric patients with CML has evolved over time. Before the advent of BCR-ABL tyrosine kinase inhibitor therapies, pediatric patients with CML were treated with hydroxyurea and interferon-alpha with or without cytarabine, followed by autologous hematopoietic stem cell transplantation. Since 2006, the recommended first-line therapy for pediatric patients with newly diagnosed CML is imatinib, the first BCR-ABL tyrosine kinase inhibitor approved by the Food and Drug Administration (FDA). Despite imatinib being the established first-line therapy, 10% to 40% of patients become resistant or intolerant to imatinib

therapy.[10-11] The second-generation TKIs, dasatinib and nilotinib, have demonstrated impressive efficacy in adult patients with CML.[12-13] In November 2017, dasatinib was approved by the FDA for the treatment of pediatric patients with Ph+ CML in chronic phase. However, the optimal treatment strategy for pediatric patients with CML remains uncertain. This is due to emerging data supporting the conclusion that pediatric patients with CML have more aggressive features in CML presentation, CML progression, and response to treatment. Allogeneic hematopoietic stem cell transplantation (HSCT) remains the only curative option for pediatric patients with CML, which raises the question of the role of transplantation in the era of chronic treatment with TKI therapy. Additionally, pediatric patients have a long life expectancy and the risks with long-term TKI therapy need to be considered. Therefore, the collective evidence supports the need for alternative treatment options and clinical studies in pediatric patients with CML.

2.2. Analysis of Current Treatment Options

There are 2 currently available agents approved for the treatment of pediatric patients with CML in chronic phase. This includes dasatinib, a second generation, BCR-ABL tyrosine kinase inhibitor. The drugs and indications relevant to this application are listed in Table 2.

Table 2 FDA Approved Drugs for Pediatric Patients with CML

Drug	Year of Initial Approval	Excerpted Indication
Imatinib	2001	• Treatment of pediatric patients with Philadelphia chromosome positive chronic myeloid leukemia in chronic phase. • Patients with Philadelphia chromosome positive chronic myeloid leukemia in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy.
Dasatinib	2006	• Treatment of pediatric patients with Philadelphia chromosome positive chronic myeloid leukemia in chronic phase.
Source: FDA table, created from review of drug labeling		

In clinical practice, treatment regimens for pediatric patients with CML includes BCR-ABL tyrosine kinase inhibitor therapy or combination chemotherapy in preparation for an allogeneic HSCT.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Nilotinib was first approved in the United States in October 2007 for the treatment of chronic phase and accelerated phase Philadelphia chromosome positive CML in adult patients resistant to or intolerant to prior therapy that included imatinib. In June 2010, nilotinib was approved for the treatment of newly diagnosed adult patients with Ph+ CML in chronic phase.

Nilotinib carries a boxed warning for an increased risk of QT prolongation and sudden death, and to avoid drugs known to prolong the QT interval and strong CYP3A4 inhibitors.

3.2. Summary of Presubmission/Submission Regulatory Activity

The pediatric development plan for nilotinib started in December 2008 with the submission of a formal proposed pediatric study request to the FDA. Based on the proposed pediatric study request, the FDA issued a Written Request on June 19, 2009. The Written Request included 2 studies:

- Study 1: Dose escalation, safety and tolerability, pharmacokinetic study of nilotinib administered orally twice daily in pediatric patients with imatinib-resistant or intolerant chronic or accelerated phase CML and relapsed or refractory Ph+ acute lymphoblastic leukemia (ALL).
- Study 2: Study to assess the activity, pharmacokinetics, and safety of nilotinib administered orally twice daily in pediatric patients with imatinib-resistant or intolerant chronic or accelerated phase CML and newly diagnosed chronic phase CML.

The Written Request underwent Amendment 1 in March 2014, which allowed for the extrapolation of efficacy from adults to pediatrics given the underlying biologic driver, the BCR-ABL fusion oncogene, is similar in adults and pediatrics. Additionally, children less than 1 year of age were excluded from the Written Request because CML does not occur in children less than 1 year. Study 1 added eligibility for pediatric patients with newly diagnosed chronic phase Ph+ CML and Study 1 and 2 added eligibility for pediatric patients that are dasatinib resistant or intolerant. The endpoint for Study 1 was changed to be the recommended Study 2 dose (versus maximum tolerated dose) and the endpoint for Study 2 was changed to rate of major molecular response (versus major cytogenetic response).

The Written Request underwent Amendment 2 in August 2015, which required that 15 patients out of at least 50 evaluable patients must be within the age of 1 to < 10 years of age in Study 2.

The Written Request underwent Amendment 3 in February 2016, which altered amendment 2 to be 15 patients out of at least 50 evaluable patients must be within the age of 1 to < 12 years of age in Study 2.

A pre-NDA meeting was held on August 26,2009 that was a written response only that addressed filing determinations, case report forms and narratives, the statistical analysis plan, dataset format and content, the content of the Summary of Clinical Safety and the Summary of Clinical Efficacy, and the 120-day safety update.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

No sites were inspected by the FDA Office of Scientific Investigations for this review. Previous inspections of clinical sites by the FDA as part of the review of prior supplemental new drug applications for nilotinib revealed no concerns regarding clinical trial data.

4.2. Product Quality

The Applicant submitted a request for approval of a new 50 mg capsule strength as part of this supplemental NDA application. The chemistry, manufacturing, and controls (CMC) review team did not identify any significant issues. Please see the CMC review for further information.

4.3. Nonclinical Pharmacology/Toxicology

There are no new pharmacology/toxicology issues. Please see the nonclinical review for further information.

4.4. Clinical Pharmacology

There were no significant issues identified by the clinical pharmacology review team. Please see the clinical pharmacology review for further information.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

The Applicant submitted data from 2 clinical studies of single agent nilotinib in pediatric patients with Ph+ CML and Ph+ ALL. Table 3 lists the safety and efficacy studies analyzed in this review.

Table 3 Clinical Studies

Study identity	Design	Treatment regimen	Study population	Study endpoint	No. of patients enrolled
Studies to support efficacy and safety					
A2120	Phase 1, pharmacokinetic, single-arm study	230 mg/m^2 twice daily	Imatinib or dasatinib resistant or intolerant Ph+ CML in chronic phase and relapsed or refractory Ph+ ALL	RP2D	15 (4 patients with Ph+ ALL)
A2203	Phase 2, open-label, single-arm study	230 mg/m^2 twice daily	Imatinib or dasatinib resistant or intolerant Ph+ CML in chronic phase and newly diagnosed Ph+ CML in chronic phase	MMR	58 (33 patients resistant or intolerant, 25 newly diagnosed)

CML: Chronic myeloid leukemia, MMR: Major Molecular Response, Ph+: Philadelphia chromosome positive, RP2D: Recommended Phase 2 Dose
Source: Summary of Clinical Safety, Section 1.1.2

5.2. Review Strategy

The key material used for the review of efficacy and safety included:

- NDA datasets (raw and derived), clinical study reports, and responses to the review teams information requests
- Relevant published literature
- Relevant information in the public domain

The clinical review of efficacy and safety was primarily based on an analysis of pooled data from Study A2120 and Study A2203 in pediatric patients with Ph+ CML in chronic phase.

All major efficacy and safety analyses were reproduced or audited. Statistical analyses by the reviewer was performed using JMP 12 (SAS Institute, Inc., Cary, NC) and MedDRA-Based Adverse Event Diagnostics (MAED) 1.6 (enterprise Performance and Lifecycle System Design).

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. CAMN107A2120

6.1.1. Study Design

Overview and Objective

Study A2120 is a multicenter, open-label study to characterize the pharmacokinetics of nilotinib 230 mg/m^2 twice daily in pediatric patients with newly diagnosed chronic phase Ph+ chronic myeloid leukemia, with chronic phase or accelerated phase Ph+ CML resistant or intolerant to imatinib or dasatinib, or refractory or relapsed Ph+ acute lymphoblastic leukemia.

Primary Objective

- Characterize the pharmacokinetics of nilotinib in pediatric patients

Secondary Objectives

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

Trial Design

Study A2120 is a multicenter, open-label study to characterize the pharmacokinetics of nilotinib 230 mg/m^2 twice daily in pediatric patients enrolled into 2 age groups: ages 1 year to < 10 years and ages ≥ 10 years to < 18 years.

Pharmacokinetics (PK) will be assessed in Cycle 1 (Days 1 – 28). The PK parameters of maximum observed concentration (Cmax) and time to reach the maximum concentration after drug administration (Tmax) will be calculated from the individual concentration-time profiles following single oral dose on Day 1. Pharmacokinetic parameters of area under the serum concentration-time curve to infinity ($AUC_{0-\infty}$), terminal elimination half-life ($T_{1/2}$), volume of distribution (Vd/F), and the apparent systemic (or total body) clearance (CL/F) will be estimated based on the Day1 concentration-time data, if appropriate. Nilotinib steady-state area under the serum concentration-time curve from time zero to the end of dosing interval ($AUC_{0-\tau}$) and CL/F were derived based on full concentration-time profiles of nilotinib obtained on Day 1 as well as steady-state trough concentrations of nilotinib on Day 8 , 15, 22, and 28. Steady-state PK parameters were then compared with reference data obtained in adult patients with Ph+ CML. The reference data used from the adult study will consist of patients who received 400 mg twice daily and had steady state PK parameters on Cycle 1, Day 15.

Study Endpoints

Primary

- Pharmacokinetic parameters of nilotinib, i.e. AUC0-∞, Cmax, Tmax, $T_{1/2}$, Vd/F, $AUC_{0-\tau}$, and CL/F.

Secondary

- Safety and tolerability: measures such as incidence and severity of adverse events and abnormal blood laboratory tests
- Activity: hematological, cytogenetic, and molecular response
- Mutational assessments of BCR-ABL

Eligibility Criteria

All patients must meet all of the inclusion and exclusion criteria. Patient selection must be established at screening.

Inclusion criteria

- Age less than 18 and more than 1 year of age
- Patients must have newly diagnosed Ph+ CML in chronic phase, chronic phase or accelerated phase Ph+ CML resistant or intolerant to imatinib or dasatinib or Ph+ ALL

either relapsed after or refractory to standard therapy
    - Imatinib or dasatinib resistance in Ph+ CML is defined as:
        - Increasing white blood cell count or platelet count while on imatinib or dasatinib therapy indicative of a hematological relapse or primary resistance to imatinib or dasatinib
        - Cytogenetic or molecular response consistent with suboptimal response or failure from European Leukemia Net (ELN) recommendations
        - Progression to accelerated phase or blast crisis while on imatinib or dasatinib therapy
        - Reappearance of Ph+ bone marrow cells after a complete cytogenetic response to imatinib or dasatinib
        - A greater than 30% increase in Ph+ cells on peripheral blood or bone marrow cytogenetics while on imatinib or dasatinib therapy
        - Loss of molecular response on imatinib or dasatinib therapy
    - Imatinib or dasatinib intolerance is defined as the development of adverse events requiring discontinuation of imatinib or dasatinib therapy
    - Newly diagnosed Ph+ CML is defined as:
        - Patients with Ph+ CML-CP within 6 months of diagnosis
- Performance status: Karnofsky ≥ 50% for patients > 10 years of age, and Lansky ≥ 50 for patients ≤ 10 years of age
- Patients must have adequate renal, hepatic, and pancreatic function and normal electrolytes defined as:
    - Creatinine clearance or glomerular filtration rate at least 70 ml/min/1.73m^2, or a serum creatinine based on age as follows

Age (Years)	Maximum Serum Creatinine (mg/dL)
1< age £ 5	0.8
5< age £ 10	1.0
10 < age £ 15	1.2
> 15	1.5

    - Total bilirubin ≤ 1.5 x upper limit normal (ULN) for age
    - Serum amylase and lipase ≤ 1.5 x ULN
    - ALT and AST ≤ 2 x ULN for age
- Adequate contraception for patients of childbearing potential
- Patients must have adequate laboratory values:
    - Potassium, magnesium, phosphorus, total calcium ≥ lower limit of normal

Exclusion criteria
- Patients actively receiving therapy with strong CYP3A4 inhibitors and inducers and the treatment cannot be either discontinued or switched to a different medication at least 14 days prior to starting study drug

- Patients who are currently receiving treatment with any medications that have a known risk or potential risk to prolong the QT interval and the treatment cannot be either discontinued or switched to a different mediation prior to starting study drug
- Impairment of gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of study drug
- Acute or chronic liver, pancreatic, or severe renal disease considered unrelated to disease
- History of pancreatitis within 12 months prior to starting study drug or past medical history of chronic pancreatitis
- No active or systemic bacterial, fungal, or viral infection
- 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
    - History of or presence of clinically significant ventricular or atrial tachyarrhythmia
    - Clinically significant resting bradycardia (< 50 beats per minute)
    - QTcF > 450 msec on baseline ECG
    - History of clinically documented myocardial infarction within 12 months prior to study drug
    - History of unstable angina within 12 months prior to study drug
    - Other clinically significant heart disease
- Patients who will have received dasatinib therapy within 3 days prior to study drug
- Patients who will have received imatinib therapy within 5 days prior to study drug
- Patients who will have received myelosuppressive chemotherapy within 21 days prior to study drug
- Patients who will not have recovered from all acute toxicities from all prior myelosuppressive chemotherapy to Grade ≤ 1 prior to study drug
- Patients receiving greater than 14 days of hydroxyurea for the treatment of Ph+ CML or corticosteroids for the treatment of Ph+ ALL and has not been discontinued at least one week after the initiation of nilotinib
- Patients who will have received a hematopoietic growth factor within 7 days prior to study drug
- Patients who will have received Pegfilgrastim within 14 days prior to study drug
- Stem cell transplant or rescue without total body irradiation: Evidence of active graft versus host disease and < 3 months since stem cell transplant
- External beam radiation therapy (XRT):
    - < 2 weeks after local palliative XRT

  - < 3 months after prior total body irradiation, or craniospinal radiation
  - ≥ 50% radiation of pelvis
  - < 6 weeks after other substantial bone marrow irradiation
- Patients with a known T315I mutation in BCR-ABL
- Patients with known HIV, Hepatitis B or C
- Patients who are breastfeeding
- Patients with a known hypersensitivity to the active ingredient or any other excipients including lactose

Treatment Regimen
Nilotinib will be administered at a dose of 230 mg/m^2 orally twice daily rounded to the nearest 50mg dose with a maximum single dose of 400mg. Nilotinib will be administered in 28-day cycles. Treatment will continue until completion of 24 cycles, unacceptable toxicity, or study withdrawal.

Only a single dose of 230 mg/m^2 of nilotinib will be administered on Day 1 of Cycle 1. Twice daily dosing will be initiated on Day 2 after the 24 hour trough sample from Day 1 is obtained.

Nilotinib will be supplied in 50mg, 150mg, and 200mg capsules. Apple sauce may be used as a vehicle for dosing where capsules cannot be swallowed whole.

Statistical Analysis Plan

Analysis populations
Full analysis set (FAS): All enrolled patients. Patient may or may not have taken study drug. This population will be used for all demographic and baseline characteristics.

Pharmacokinetic set: All patients who receive the nilotinib dose on Day 1, have an evaluable Day 1 PK profile or provide at least one steady state trough concentration. This population will be used for all PK parameter summaries.

Safety set: All patients who receive at least one dose of nilotinib. This population will be used for all core safety summaries.

Primary objective
Characterize the pharmacokinetics of nilotinib in pediatric patients

The primary focus of the statistical analysis is to characterize single and multiple dose PK of nilotinib. The geometric means for area under the curve (AUC) and CL/F at steady state for both

pediatric age groups will be compared to reference data in adults to determine if additional patients are required to characterize the PK for this pediatric population.

For each group, once 7 patients have been enrolled and completed Cycle 1 or have adequate PK sampling for PK characterization, an interim analysis will be performed to decide whether the PK characteristics of the group differ from adult reference data. If the interim study results do not show at least a 2-fold difference in geometric means of steady state AUC or CL/F from the adult reference data for either age group, then PK data will be pooled and summarized. The geometric means for steady state AUC and CL/F will also be calculated based on a model that includes age as a covariate.

If either of the age groups shows a difference in geometric means of steady state AUC or CL/F of at least 2-fold from the adult population, 5 additional patients will be enrolled in that age group, for a total of 12 patients. PK profiles will then be summarized separately for both age groups.

Summary statistics will be presented for nilotinib PK parameters.

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

The assessment of safety will be based on the frequency of adverse events and on the number of laboratory values that fall outside pre-determined ranges. Safety data will presented with descriptive statistics.

Clinical activity will be presented descriptively and no statistical tests will be conducted. Hematological, cytogenetic, and molecular responses will be summarized by descriptive statistics.

The Ph+ CML response criteria can be found in Appendix 13.3 (Table 26)

Sample size
The sample size is based on a 2-fold difference in PK parameters, AUC, or CL/F, between the pediatric data and the adult reference data. In adult CML patients (Study CAMN107A2101) the inter-patient variability was found to be 32% to 64% for AUC and 34% to 72% for Cmax. The inter-patient variability of nilotinib at the recommended clinical dose of 400mg twice daily is 48.1% for Cmax and 44.5% for AUC. There are no estimates of variability available for the PK

parameters in the pediatric population. Therefore the sample size calculation assumes that the variability in the pediatric population will be similar to the adult population.

With inter-patient variability of 48.1%, at least 12 patients provides sufficient precision (0.237 in log scale) to characterize the mean AUC. The sample size will be reached by pooling the two age groups together or enrolling 5 additional patients if the difference is observed during interim analysis. On the other hand, with inter-patient variability of 48% and 7 patients per age group, the half width of the 90% confidence interval for the pediatric versus adult population difference for PK parameters (in log scale) will be approximately 0.335. This precision allows an estimated difference between pediatric and adult PK parameters within a reasonable range. See Section 10.7 of the A2120 protocol for further details.

Protocol Amendments

The study protocol was amended four times.

1. Amendment 1 further enhanced the safety parameters prior to any patient enrollment. Additional ECG monitoring, additional clarification on assessments for disease monitoring, and addition of a washout period for CYP3A4 inhibitors and inducers were implemented.
2. Amendment 2 extended the duration of the study to 24 cycles (versus 12) and updated language regarding pregnancy.
3. Amendment 3 expanded the patient population to include newly diagnosed Ph+ CML in chronic phase and chronic phase or accelerated phase Ph+ CML resistant or intolerant to imatinib or dasatinib. The change to the patient population was incorporated into the Written Request.
4. Amendment 4 updated guidelines for management of ischemic vascular or cardiovascular events based on the update nilotinib Investigator's Brochure (version 9 and 10).

6.1.2. Study Results

Compliance with Good Clinical Practices

The protocol, protocol amendments, and patient or legal representative consent forms for Study A2120 were reviewed and approved by the Institutional Review Boards and Independent Ethics Committees of the participating study centers.

Study A2120 was conducted in accordance with the International Council for Harmonization guideline for Good Clinical Practice, the principles of the Declaration of Helsinki, and the US

Code of Regulations, Title 21, Parts 50, 56, and 312 providing the protection of the rights and welfare of human patients participating in biomedical research. All patients or their legal representative voluntarily consented prior to trial enrollment. Assent was also obtained from age-appropriate patients able to provide signature or able to provide verbal assent.

Financial Disclosure

The Applicant submitted financial disclosure information from 296 investigators from two studies (A2120 and A2203) indicating that none of the investigators had disclosable financial interests or arrangements. For details, refer to the Clinical Investigator Financial Disclosure Review in Section 13.2. None of the disclosures submitted revealed a potential conflict of interest.

Patient Disposition

An overview of patient disposition is shown in Table 4 below. Of the 15 pediatric patients, 7 patients (47%) completed treatment as per protocol and 8 patients discontinued treatment. The reasons for discontinuing treatment included new cancer therapy (40%), adverse event (7%) and disease progression (7%). Eight patients (53%) completed the follow-up phase per protocol while 6 patients (40%) completed the study due to initiation of a new cancer therapy and 1 patient (7%) because of disease progression.

Table 4 Patient Disposition for Study A2120

Patient Disposition	**N = 15 n (%)**
Reason for end of treatment	
Treatment completed	7 (46.7)
New cancer therapy	6 (40.0)
Adverse event	1 (6.7)
Disease progression	1 (6.7)
Reason for study evaluation completion	
Follow-up completed	8 (53.3)
New cancer therapy	6 (40.0)
Disease progression	1 (6.7)
Source: FDA analysis of AIDENT dataset	

Protocol Violations/Deviations

There were a small number of protocol violations. The majority included procedure deviations such as altered or missed dose prior to PK trough sampling or missing vital signs. There were 3 patients that experienced adverse events that warranted drug interruption per protocol, but were continued on treatment. The adverse events included hyperbilirubinemia and neutropenia.

Reviewer Comment: The protocol violations reported do not appear to have introduced bias into the clinical study.

Demographic Characteristics

Refer to Table 5 for a tabular summary of patients demographics and disease characteristics in the full analysis set.

Table 5 Demographic and Patient Characteristics in Study A2120

Characteristic	N = 15
Age, (years)	
Median	9
Min, Max	5, 17
Sex, n (%)	
Female	7 (46.7)
Male	8 (53.3)
Race, n (%)	
Caucasian	12 (80.0)
Asian	2 (13.3)
Missing	1 (6.7)
Body mass index (kg/m^2)	
Median	17.3
Min, Max	15.0, 24.2
Body surface area (m^2)	
Median	0.99
Min, Max	0.70, 1.95
Diagnosis, n (%)	
Ph+ CML	11 (73.3)
Ph+ ALL	4 (26.7)
Number prior regimens, n (%)	
1	15 (100.0)
2	12 (80.0)
3	8 (53.3)
≥ 4	3 (20.0)
Source: FDA analysis of AIDENT and APTMTKI dataset	

The study population consisted of 11 patients with Ph+ CML-CP resistant or intolerant to either imatinib or dasatinib. The median age was 9 years with the majority of patients being Caucasian. At least 80% of the study population had received 2 prior systemic treatment regimens and half of the patients had received 3 prior regimens.

Treatment Compliance and Concomitant Medications

In the 15 patients enrolled on the study, the median actual dose intensity was 453.9 mg/m^2/day and the median relative dose intensity was 98.7%. Six patients (40%) required concomitant medications that included antibacterials, calcium compounds, opioids, corticosteroids, and anti-emetics.

Key Efficacy Results

The primary objective of the study was to evaluate the pharmacokinetic parameters in pediatric patients with newly diagnosed Ph+ chronic myeloid leukemia in chronic phase, chronic phase or accelerated phase Ph+ CML resistant or intolerant to imatinib or dasatinib, or refractory or relapsed acute lymphoblastic leukemia. The pharmacokinetic data demonstrated similarity between pediatric patients age 1 year to < 10 years and age ≥ 10 years to < 18 years. The PK data also demonstrated similarity between the pediatric population and the adult reference population. Thus, confirming a dose of 230 mg/m^2 twice daily in pediatric patients.

The activity of nilotinib was assessed by evaluating hematologic, cytogenetic, and molecular responses. Of the 11 patients with Ph+ CML-CP resistant or intolerant to either imatinib or dasatinib, 3 patients (27%) achieved a major molecular response, 4 patients (36%) achieved a complete cytogenetic response, and 10 (91%) patients achieved a complete hematological response. In the 4 patients with refractory or relapsed Ph+ acute lymphoblastic leukemia, complete remission was achieved in 3 patients (75%). There were no patients with Ph+ CML that progressed to accelerated phase or blast crisis.

Refer to Section 7 for a comprehensive, integrated review of effectiveness in pediatric patients with newly diagnosed Ph+ CML-CP or Ph+ CML-CP resistant or intolerant to imatinib or dasatinib.

6.2. CAMN107A2203

6.2.1. Study Design

Overview and Objective

Study A2203 is a multicenter, open-label, Phase 2 study to evaluate the efficacy and safety of oral nilotinib in pediatric patients with newly diagnosed Ph+ chronic myeloid leukemia in chronic phase or with Ph+ CML in chronic phase or accelerated phase (AP) resistant or intolerant to either imatinib or dasatinib.

Primary Objectives

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

Secondary Objectives

- To further characterize the efficacy and the pharmacokinetic profile of nilotinib in

pediatric patients with Ph+ CML
- To characterize the safety and tolerability of nilotinib in pediatric patients with Ph+ CML
- To assess the long term effect on growth, development, and maturation while on nilotinib treatment in pediatric patients with Ph+ CML
- To identify emerging signs of resistance to nilotinib

Exploratory
- Assess long term effect of nilotinib on bone metabolism

Trial Design

Study A2203 is a multicenter, open-label study to assess efficacy, safety, and PK parameters of 230 mg/m^2 twice daily nilotinib in pediatric patients. Three patient cohorts were planned based on disease classification:
- Cohort 1: Ph+ CML-CP patients resistant or intolerant to either imatinib or dasatinib
- Cohort 2: Ph+ CML-AP patients resistant or intolerant to either imatinib or dasatinib
- Cohort 3: Newly diagnosed Ph+ CML in chronic phase

A minimum number of 50 pediatric patients (from age 1 to < 18 years) should be enrolled in the study. Of them, at least 15 patients should be Ph+ CML-CP patients resistant or intolerant to either imatinib or dasatinib, and at least 15 patients should be newly-diagnosed Ph+ CML-CP patients in chronic phase. There is no minimum number of patients required for Ph+ CML-AP patients resistant or intolerant to either imatinib or dasatinib.

Patients who complete the study will be treated with nilotinib for a total of 66 cycles of 28 days unless the patient prematurely discontinued study treatment. The primary analysis cut-off will be the date by which all patients enrolled in the trial have either completed their visit for treatment cycle 12 or have discontinued study treatment early.

Study Endpoints

Primary Endpoints
Pediatric patients with Ph+ CML-CP resistant or intolerant to either imatinib or dasatinib
- Rate of major molecular response at 6 cycles by PCR analysis. MMR is defined as ≤ 0.1% BCR-ABL/control gene (ABL) % by international scale, or equivalent to ≥ 3 log reduction of BCR-ABL transcript from standardized baseline, measured by RQ-PCR

Pediatric patients with newly diagnosed Ph+ CML-CP
- Rate of major molecular response by 12 cycles by PCR analysis. MMR is defined as ≤ 0.1% BCR-ABL/control gene (ABL) % by international scale, or equivalent to ≥ 3 log reduction of BCR-ABL transcript from standardized baseline, measured by RQ-PCR

- Rate of complete cytogenetic response (CCyR) at 12 cycles

Secondary Endpoints

- Rate of major cytogenetic response (MCyR) and CCyR in patients with newly diagnosed Ph+ CML-CP by 6, 12, 18, 24, 36, 48, and 66 cycles
- Rate of each cytogenetic response category (complete, partial, major, minor, minimal, and no response) in patients with Ph+ CML-CP resistant or intolerant to either imatinib or dasatinib by 6, 12, 18, 24, 36, 48, and 66 cycles
- Rate of MMR and complete hematologic response (CHR) by 3, 6, 9, 12, 18, 24, 36, 48, and 66 cycles in patients with newly diagnosed Ph+ CML-CP
- Time to response and duration of response, time to disease progression, overall survival, and event free survival
- Population PK parameters of nilotinib
- Pharmacodynamics (BCR-ABL transcript levels determined with standard protocols in peripheral blood)
- Safety and tolerability: incidence and severity of adverse events
- Assessment of development (growth and sexual maturation), and thyroid function
- Mutational assessments of BCR-ABL to assess emerging signs of resistance to nilotinib

Exploratory

- Effect on bone metabolism: alteration of bone biochemical markers, DEXA, and x-ray

Eligibility Criteria

Inclusion criteria

Patients eligible for inclusion in this study have to meet all of the following criteria:

- Age 1 year to less than 18 years
- Patients must have a diagnosis of 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 is defined as:
        - Patients with CML-CP within 6 months of diagnosis (date of initial diagnosis is the date of first cytogenetic analysis)
        - Diagnosis of CML in chronic phase with cytogenetic confirmation of Philadelphia chromosome (9;22) translocation. Standard conventional cytogenetic analysis must be done on bone marrow. FISH cannot be used
    - Ph+ CML-CP will meet all the criteria defined by:
        - < 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 x 10^9/L platelets
        - No evidence of extramedullary leukemic involvement, with the exception of hepatosplenomegaly
    - Imatinib or dasatinib resistant Ph+ CML is defined by any of the following:
        - Increasing white blood cell or platelet count while on imatinib or dasatinib therapy indicative of a hematological 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 (2009 ELN; 2013 ELN)
        - Appearance of accelerated phase or blast crisis while on imatinib or dasatinib
        - 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
- Performance status: Karnofsky ≥ 50% for patients > 10 years of age, and Lansky ≥ 50 for patients ≤ 10 years of age
- Patients must have adequate renal, hepatic, and pancreatic function defined as:
    - Creatinine clearance or a serum creatinine based on age/gender as follows:

Age	**Maximum Serum Creatinine (mg/dL)**	
	Male	Female
1 to < 2 years	0.6	0.6
2 to < 6 years	0.8	0.8
6 to < 10 years	1	1
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
≥ 16 years	1.7	1.4

    - Total bilirubin ≤ 1.5 x upper limit normal (ULN) for age
    - Serum lipase ≤ 1.5 x ULN
    - ALT and AST ≤ 2.5 x ULN for age
- Patients must have adequate laboratory values:
    - Potassium, magnesium, phosphorus, total calcium ≥ lower limit of normal

Exclusion criteria
Patients eligible for this study must not meet any of the following criteria:

- Female patients who are pregnant, of childbearing potential without a negative hCG pregnancy test prior to baseline, those who do not agree to adequate contraception

- Patients actively receiving therapy with strong CYP3A4 inhibitors and inducers and the treatment cannot be either discontinued or switched to a different medication at least 14 days prior to starting study drug
- Patients who are currently receiving treatment with any medications that have a known risk or potential risk to prolong the QT interval and the treatment cannot be either discontinued or switched to a different medication prior to starting study drug
- Impairment of gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of study drug
- Acute or chronic liver, pancreatic, or severe renal disease considered unrelated to disease
- History of pancreatitis within 12 months prior to starting study drug or past medical history of chronic pancreatitis
- No active or systemic bacterial, fungal, or viral infection
- Impaired cardiac function including any one of the following:
    - Inability to determine the QT interval on 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 bradycardia (< 50 beats per minute)
    - QTcF > 450 msec on baseline ECG
    - Shortening fraction of < 27% by echocardiogram, or ejection fraction of < 50% by MUGA scan
    - Other clinically significant heart disease
- Patients with documented T315I mutation in BCR-ABL
- Previous treatment with more than one TKI for imatinib or dasatinib resistant or intolerant Ph+ CML patients. Previous treatment with any TKI for newly diagnosed Ph+ CML patients is not permitted unless the patients has 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
- Patients who will have received dasatinib therapy within 3 days prior to study drug
- Patients who will have received imatinib therapy within 5 days prior to study drug
- Patients who will have received myelosuppressive chemotherapy within 21 days prior to study drug
- Patients who will not have recovered from all acute toxicities from all prior myelosuppressive chemotherapy prior to study drug
- Patients receiving greater than 21 days of hydroxyurea 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
- Patients who will have received a hematopoietic growth factor within 7 days prior to

study drug
- Patients who will have received Pegfilgrastim within 14 days prior
- Stem cell transplant or rescue without total body irradiation: Evidence of active graft versus host disease and < 3 months since stem cell transplant
- External beam radiation therapy:
  - < 2 weeks after local palliative XRT
  - < 3 months after prior total body irradiation, or craniospinal radiation
  - ≥ 50% radiation of pelvis
  - < 6 weeks after other substantial bone marrow irradiation
- Patients with known HIV, Hepatitis B or C
- Patients who are breastfeeding
- Patients with a known hypersensitivity to the active ingredient or any other excipients including lactose

Treatment Regimen

Nilotinib will be administered at a dose of 230 mg/m^2 orally twice daily rounded to the nearest 50mg dose with a maximum single dose of 400mg. Nilotinib will be administered in 28-day cycles. Treatment will continue until completion of 66 cycles, unacceptable toxicity, or study withdrawal.

Nilotinib will be supplied in 50mg, 150mg, and 200mg capsules. Apple sauce may be used as a vehicle for dosing where capsules cannot be swallowed whole.

Statistical Analysis Plan

The cut-off date for primary analysis will be the date by which all enrolled patients completed their visit for treatment cycle 12 or have discontinued study treatment early. A second analysis will be performed when all patients have completed their visit for treatment cycle 24 or discontinued study treatment early. At trial end, a final evaluation of all data collected will be completed.

Full Analysis Set
The Full Analysis Set consists of all patients who receive at least one dose of study medication. The FAS will be used for efficacy analyses, including split by cohort.

Safety Set
The Safety Set includes all patients who received at least one dose of study medication.

Patient, Disease, and Treatment Characteristics
Demographics, disease characteristics, and other baseline data will be summarized descriptively and listed by cohort. Time on treatment, duration of exposure, percentage of days on treatment, average dose intensity, actual daily dose, relative dose intensity, and concomitant medications will be summarized.

Primary Objective

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

The Ph+ CML response criteria can be found in Appendix 13.3 (Table 26)

The primary efficacy variables are defined below:

- In patients with newly diagnosed Ph+ CML-CP:
    - Rate of major molecular response by 12 cycles by PCR analysis. A patients will be counted as MMR by 12 cycles if the MMR criteria is met at least once any time between first study drug intake and Cycle 12 visit
    - Rate of complete cytogenetic response at 12 cycles. A patients will be counted as CCyR at 12 cycles if CCyR criteria is met at Cycle 12 visit
- In patients with Ph+ CML-CP resistant or intolerant to either imatinib or dasatinib:
    - Rate of major molecular response at 6 cycles. A patients will be counted as MMR at 6 cycles if the MMR criteria are met at Cycle 6 visit

Analyses of primary endpoints will be performed by cohort using the FAS, in a descriptive manner, without hypothesis testing. Response rates will be provided with 95% confidence intervals using the Pearson-Clopper method by cohort. Response rates will also be summarized by age groups.

Patients not providing at least one post baseline primary efficacy assessment because of early dropout or for any other reason will be considered as early discontinuation or not evaluable, respectively, and will be included in the FAS analysis as non-responders.

Secondary Objectives

- To further characterize the efficacy and the pharmacokinetic profile of nilotinib in pediatric patients with Ph+ CML
- To characterize the safety and tolerability of nilotinib in pediatric patients with Ph+ CML
- To assess the long term effect on growth, development, and maturation of nilotinib treatment in pediatric patients with Ph+ CML
- To identify emerging signs of resistance to nilotinib

The secondary efficacy time to event variables are defined below:

- Time to response is defined as the time from the date of first study drug intake to the date of the first specified response.
- Duration of response is defined as the time between date of the first specified response to either the date for the confirmed loss of the response or progression to AP or blast crisis (BC) or CML-related death, whichever is earlier.
- Time to disease progression is defined as the time from the date of first study drug intake to the date of the event defined as first progression to AP or BC or CML-related death, whichever is earlier.
- Overall survival is defined as the time from the date of first study drug intake to the date of death due to any cause during the study, including the follow-up period after discontinuation of treatment.
- Event free survival is defined as the time from the date of first study drug intake to the first occurrence of any of the following: loss of CHR, loss of MCyR, progression to AP or BC, or death from any cause.

Analyses of secondary endpoints will be performed using the FAS. All the time to event variables will be analyzed using Kaplan-Meier method by cohort. BCR-ABL transcript levels will be summarized by cohort and time point. Response rates will be provided with 95% confidence intervals using Pearson-Clopper method by cohort. Descriptive statistics will be used to summarize mutation assessments of BCR-ABL by cohort.

For all safety analyses, the Safety Set will be used. The overall observation period will be divided into the pre-treatment period, on-treatment period, and post-treatment period. Safety data will be summarized with descriptive statistics.

Sample Size
There is no formal power-based calculation for this single arm trial. The total of 50 patients (including a minimum of 15 patients with newly diagnosed Ph+ CML-CP and 15 patients with Ph+ CML-CP resistant or intolerant to either imatinib or dasatinib) was selected on the basis of operational and feasibility criteria.

Protocol Amendments

The study protocol was amended 5 times:

- Amendment 1 extended the study duration from 24 cycles to 66 cycles in order to evaluate long-term safety and efficacy. Additionally, long term assessment of

development (growth and sexual maturation), thyroid function, and bone metabolism were added as endpoints. The primary endpoint definitions were modified for patients with Ph+ CML-CP resistant or intolerant to either imatinib or dasatinib to rate of MCyR at 6 cycles from rate of MCyR by 12 months and for patients with newly diagnosed Ph+ CML-CP to rate of MMR and CCyR at 12 cycles from rate of MCyR by 12 months.

- Amendment 2 was a reduction in the sample size from 65 total patients with at least 50 being patients with newly diagnosed Ph+ CML-CP to a total of 50 patients with at least 15 being patients with newly diagnosed Ph+ CML-CP. Additionally, information was included that confirmed the dose in patients aged 1 to < 10 years.

- Amendment 3 changed the primary endpoint based on recent data concerning Ph+ CML response evaluation. The primary efficacy variable for patients with Ph+ CML-CP resistant or intolerant to either imatinib or dasatinib was changed to rate of MMR at 6 cycles from rate of MCyR at 6 cycles. Other response endpoints were revised accordingly.

- Amendment 4 included hepatitis B virus testing to identify patients at risk or hepatitis B reactivation.

- Amendment 5 clarified the assessment of development and growth and updated discontinuation criteria for QT prolongation.

6.2.2. Study Results

Compliance with Good Clinical Practices

The protocol, protocol amendments, and patient or legal representative consent forms for Study A2203 were reviewed and approved by the Institutional Review Boards and Independent Ethics Committees of the participating study centers.

Study A2203 was conducted in accordance with the International Council for Harmonization guideline for Good Clinical Practice, the principles of the Declaration of Helsinki, and the US Code of Regulations, Title 21, Parts 50, 56, and 312 providing the protection of the rights and welfare of human patients participating in biomedical research. All patients or their legal representative voluntarily consented prior to trial enrollment. Assent was also obtained from age-appropriate patients able to provide signature or able to provide verbal assent.

Financial Disclosure

The Applicant submitted financial disclosure information from 296 investigators from two studies (A2120 and A2203) indicating that none of the investigators had disclosable financial interests or arrangements. For details, refer to the Clinical Investigator Financial Disclosure Review in Section 13.2. None of the disclosures submitted revealed a potential conflict of interest.

Patient Disposition

An overview of patients disposition is shown in Table 6 below. Of the 33 pediatric patients with Ph+ CML-CP resistant or intolerant to imatinib or dasatinib, 25 patients (76%) remain on treatment as of a data cut-off of 01 June 2016. Eight patients (24%) with resistant or intolerant Ph+ CML-CP discontinued treatment with the most common reason being adverse events in 5 patients (15%). Of the 25 patients with newly diagnosed Ph+ CML-CP, 19 patients (76%) remain on treatment as of the data cut-off and 6 patients (24%) discontinued treatment. Four patients (16%) discontinued treatment due to an adverse event.

Table 6 Patient Disposition for Study A2203

Patient Disposition	**Resistant or intolerant Ph+ CML-CP N = 33 n (%)**	**Newly diagnosed Ph+ CML-CP N = 25 n (%)**
Treatment ongoing	25 (75.8)	19 (76.0)
End of treatment	8 (24.2)	6 (24.0)
Reason for end of treatment		
Adverse event	5 (15.1)	4 (16.0)
New cancer therapy	1 (3.0)	1 (4.0)
Disease progression	1 (3.0)	0
Withdrew consent	0	1 (4.0)
Protocol deviation	1 (3.0)	0
Source: FDA analysis of AIDENT dataset		

Protocol Violations/Deviations

There were a small number of protocol violations. The majority included treatment not administered according to protocol which included a missed dose, dose not changed

accordingly, and nilotinib not taken as instructed. Several patients took medication with a risk of prolonging the QT interval. There were no protocol deviations that excluded patients from the full analysis set.

Reviewer Comment: The protocol violations reported do not appear to have introduced bias into the clinical study.

Demographic Characteristics

Refer to Table 7 for a tabular summary of patients demographics and disease characteristics in the full analysis set.

Table 7 Demographic and Patient Characteristics in Study A2203

Characteristic	Resistant or intolerant Ph+ CML-CP N = 33	Newly diagnosed Ph+ CML-CP N = 25
Age, (years)		
Median	13	13
Min, Max	2, 17	10, 16
Sex, n (%)		
Female	12 (36.4)	12 (48.0)
Male	21 (63.6)	13 (52.0)
Race, n (%)		
Asian	16 (48.5)	7 (28.0)
Caucasian	12 (36.4)	18 (72.0)
Black	3 (9.1)	0
Native American	1 (3.0)	0
Other	1 (3.0)	0
Body mass index (kg/m^2)		
Median	18.1	19.3
Min, Max	12.6, 32.2	13.6, 27.5
Body surface area (m^2)		
Median	1.37	1.54
Min, Max	0.49, 1.92	1.06, 2.01
Imatinib resistant, n (%)		NA
Yes	28 (84.8)	

Characteristic	Resistant or intolerant Ph+ CML-CP N = 33	Newly diagnosed Ph+ CML-CP N = 25
Imatinib intolerant, n (%)		NA
Yes	3 (9.1)	
Dasatinib resistant, n (%)		NA
Yes	2 (6.1)	
Dasatinib intolerant, n (%)		NA
Yes	0	
Baseline BCR-ABL ratio, n (%)		
≤ 0.0032%	1 (3.0)	0
> 0.0032 to ≤ 0.01%	1 (3.0)	0
> 0.01% to ≤ 0.1%	5 (15.2)	0
> 0.1% to ≤ 1%	10 (30.3)	0
> 1% to ≤ 10%	9 (27.3)	0
> 10%	5 (15.2)	25 (100.0)
Other[1]	2 (6.1)	0

[1] One patient with an atypical transcript at baseline and one patient with missing information
Source: FDA analysis of AIDENT and APTMTKI datasets

The study population consisted of 33 patients with Ph+ CML-CP resistant or intolerant to either imatinib or dasatinib. The median age was 13 years with the majority of patients being Asian and Caucasian. The majority of the population was imatinib resistant (85%), with 3 patients (9%) imatinib intolerant, and 2 patients (6%) dasatinib resistant. In the patients with resistant or intolerant Ph+ CML-CP, 7 patients (21%) had BCR-ABL ratios ≤ 0.1%, which meets criteria for a major molecular response. For the patients with newly diagnosed Ph+ CML-CP, the median age was 13 years and the majority were Caucasian.

Treatment Compliance and Concomitant Medications

In the 33 patients with resistant or intolerant Ph+ CML-CP enrolled on the study, the median actual dose intensity was 438.9 mg/m^2/day and the median relative dose intensity was 95.4%. Thirty patients (91%) required concomitant medications after the start of nilotinib that included stomatitis-related medications, systemic antihistamines, corticosteroids, analgesics, antipyretics, and ophthalmological preparations.

In the 25 patients with newly diagnosed Ph+ CML-CP, the median actual dose intensity was 384.5 mg/m^2/day and the median relative dose intensity was 83.6%. Twenty-three patients (92%) used concomitant medications after the start of nilotinib that included analgesics, antipyretics, systemic antihistamines, and stomatitis-related medications.

Key Efficacy Results – Primary Endpoint

In patients with resistant or intolerant Ph+ CML-CP, the primary efficacy endpoint was the rate of major molecular response at 6 cycles. MMR is defined as ≤ 0.1% BCR-ABL/control gene (ABL) % by international scale, or equivalent to ≥ 3 log reduction of BCR-ABL transcript from standardized baseline. The MMR rate was 39.4% (95% CI: 22.9, 57.9) at 6 cycles with 13 of 33 patients achieving a MMR. Although, 6 of the 13 patients met the criteria for MMR at baseline. The cumulative incidence of MMR was 57.6% (95% CI: 39.2, 74.5) at 12 cycles with a total of 19 patients achieving MMR by the end of cycle 12. The median time to MMR was 2.8 months (range 0 to 11.3 months). Of the 19 patients in MMR, no patients had a loss of MMR by the time of the data cut-off and thus the median duration of MMR was not reached. For cytogenetic response, 27 patients (82%) achieved a complete cytogenetic response by cycle 12. On patient with imatinib resistant Ph+ CML-CP progressed to AP/BC around 10.1 months of treatment.

In patients with newly diagnosed Ph+ CML, the primary efficacy endpoint was the rate of major molecular response at 12 cycles. MMR is defined as ≤ 0.1% BCR-ABL/control gene (ABL) % by international scale, or equivalent to ≥ 3 log reduction of BCR-ABL transcript from standardized baseline. The MMR rate at 12 cycles was 64.0% (95% CI 42.5, 82.0) with 16 patients achieving MMR. The cumulative incidence of MMR was 68.0% (95% CI: 46.5, 85.1) at 17 months with a total of 17 patients achieving MMR. The median time to MMR was 5.6 months (range 2.7 to 16.6 months). Of the 17 patients who achieved MMR, one patient had loss of MMR at the time of data cut-off (01 June 2016) and thus the median duration of MMR was not reached. By 12 cycles, 6 patients (24%) achieved a BCR-ABL ratio ≤ 0.0032 or a 4.5 log reduction of BCR-ABL transcript. For cytogenetic response, 21 patients (84%) achieved a complete cytogenetic response by cycle 6 and maintained to cycle 12. Two patients with newly diagnosed Ph+ CML-

CP had disease progression. On patient experienced an increased basophil count, which met criteria for progression to accelerated phase, after one month of treatment with nilotinib. The patient remained on treatment and the disease went back to chronic phase and the patient achieved a complete cytogenetic response. The other patient experienced a clonal evolution while on treatment and discontinued therapy due to lack of efficacy.

Refer to Section 7 for a comprehensive, integrated review of effectiveness in pediatric patients with newly diagnosed Ph+ CML-CP or Ph+ CML-CP resistant or intolerant to imatinib or dasatinib.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

The pooled data from Study A2120 and Study A2203 comprise the efficacy data used to support the establishment of efficacy for pediatric patients with Ph+ CML in chronic phase. The pooled efficacy database is comprised of pediatric patients with Ph+ CML-CP resistant or intolerant to imatinib or dasatinib and newly diagnosed Ph+ CML-CP (Table 8).

Table 8 Summary of Pooled Efficacy and Safety Database

Study	Resistant or intolerant Ph+ CML-CP	Newly diagnosed Ph+ CML-CP
A2120	11	0
A2203	33	25
Total	44	25

Patient Disposition

An overview of patient disposition is shown in Table 9 below. Of the 44 pediatric patients with Ph+ CML-CP resistant or intolerant to imatinib or dasatinib, 25 patients (57%) remain on treatment as of a data cut-off of 01 June 2016. Nineteen patients (43%) with resistant or intolerant Ph+ CML-CP discontinued treatment with the most common reasons being initiation of a new cancer therapy (14%), treatment duration completed per protocol (Study A2120) and adverse events (11% each). Of the 25 patients with newly diagnosed Ph+ CML-CP, 19 patients (76%) remain on treatment as of the data cut-off and 6 patients (24%) discontinued treatment. Four patients (16%) discontinued treatment due to an adverse event.

Table 9 Patient Disposition for Pooled Efficacy Population

Patient Disposition	Resistant or intolerant Ph+ CML-CP N = 44 n (%)	Newly diagnosed Ph+ CML-CP N = 25 n (%)
Treatment ongoing	25 (56.8)	19 (76.0)
End of treatment	19 (43.2)	6 (24.0)
Reason for end of treatment		
New cancer therapy	6 (13.6)	0
Adverse event	5 (11.4)	4 (16.0)
Treatment complete per protocol	5 (11.4)	0
Disease progression	2 (4.5)	1 (4.0)
Withdrew consent	0	1 (4.0)
Protocol deviation	1 (2.3)	0
Source: FDA analysis of AIDENT dataset		

Demographic Characteristics

The patient demographics and disease characteristics for the pooled efficacy population is shown in Table 10 below.

Table 10 Patient Demographics and Disease Characteristics in Pooled Efficacy Population

Characteristic	Resistant or intolerant Ph+ CML-CP N = 44	Newly diagnosed Ph+ CML-CP N = 25
Age, (years)		
Median	12	13
Min, Max	2, 17	10, 16
Sex, n (%)		
Female	17 (38.6)	12 (48.0)
Male	27 (61.4)	13 (52.0)
Race, n (%)		
Caucasian	21 (47.7)	18 (72.0)
Asian	17 (38.6)	7 (28.0)
Black	3 (9.1)	0
Native American	1 (3.0)	0
Other	1 (3.0)	0

Characteristic	Resistant or intolerant Ph+ CML-CP N = 44	Newly diagnosed Ph+ CML-CP N = 25
Body mass index (kg/m^2)		
Median	17.8	19.3
Min, Max	12.6, 32.2	13.6, 27.5
Body surface area (m^2)		
Median	1.34	1.54
Min, Max	0.49, 1.95	1.06, 2.01
Imatinib resistant, n (%)		NA
Yes	37 (84.1)	
Imatinib intolerant, n (%)		NA
Yes	5 (11.4)	
Dasatinib resistant, n (%)		NA
Yes	2 (4.5)	
Dasatinib intolerant, n (%)		NA
Yes	0	
Baseline BCR-ABL ratio, n (%)		
> 0.01% to ≤ 0.1%	8 (18.2)	0
> 0.1% to ≤ 1%	15 (34.1)	0
> 1% to ≤ 10%	11 (25.0)	0
> 10%	7 (15.9)	25 (100.0)
Other[1]	3 (6.8)	0

[1] Two patients with atypical transcripts at baseline and one patient with missing information
Source: FDA analysis of AIDENT and APTMTKI datasets

The pooled study population consisted of 44 patients with Ph+ CML-CP resistant or intolerant to either imatinib or dasatinib. The median age was 12 years with the majority of patients being Caucasian and Asian. The majority of the population was imatinib resistant (84%), with 5 patients being imatinib intolerant (11%), and 2 patients being dasatinib resistant (5%). In patients with Ph+ CML-CP resistant or intolerant to either imatinib or dasatinib, 8 patients (18%) had BCR-ABL ratios ≤ 0.1%, which meets criteria for a major molecular response. For the patients with newly diagnosed Ph+ CML-CP, the median age was 13 years and the majority were Caucasian.

Reviewer Comment: The demographics and disease characteristics of the pooled efficacy population are representative of a general pediatric population with Ph+ CML in chronic phase. The 8 patients with resistant or intolerant Ph+ CML-CP that met criteria for major molecular

response at baseline will need to considered in the evaluation of efficacy.

Efficacy Results

The review of the efficacy endpoints focuses on the two patient populations, newly diagnosed Ph+ CML-CP and Ph+ CML-CP resistant or intolerant to either imatinib or dasatinib. The database cutoff date was 01 June 2016.

Table 11 summarizes the analysis results of the primary efficacy endpoint major molecular response. In patients with Ph+ CML-CP resistant or intolerant to imatinib or dasatinib, 21 patients (48%) achieved a major molecular response at or before cycle 12. In patients with newly diagnosed Ph+ CML-CP, 16 patients (64%) achieved a major molecular response at or before cycle 12.

Table 11 Major Molecular Response Rate by Treatment Cycle

Major Molecular Response Rate by Cycle	**Resistant or intolerant Ph+ CML-CP N = 44**	**Newly diagnosed Ph+ CML-CP N = 25**
Cycle 3		
MMR, n (%)	14 (31.8)	3 (12.0)
95% Confidence Interval (CI)	18.6, 47.6	2.5, 31.2
Cycle 6		
MMR, n (%)	17 (38.6)	13 (52.0)
95% CI	24.4, 54.5	31.3, 72.2
Cycle 12		
MMR, n (%)	21 (47.7)	16 (64.0)
95% CI	32.5, 63.3	42.5, 82.0
Source: FDA analysis of AEFFSBJ dataset		

BCR-ABL Ratio
In December 2017, nilotinib was approved for treatment discontinuation in adult patients with newly diagnosed Ph+ CML-CP and Ph+ CML-CP resistant or intolerant to imatinib who have received nilotinib for at least 3 years and have achieved a sustained molecular response. The molecular response was defined as ≤ 0.0032% BCR-ABL/control gene (ABL) % by international scale, or equivalent to ≥ 4.5 log reduction of BCR-ABL transcript from standardized baseline. Therefore, an analysis was conducted within the pediatric patients to determine which patients were able to achieve a 4 or 4.5 log reduction of BCR-ABL transcript. In patients with resistant or intolerant Ph+ CML-CP, 3 patients (7%) achieved a 4 log reduction or BCR-ABL ratio ≤ 0.01% - > 0.0032% and 2 patients (5%) achieved a 4.5 log reduction or BCR-ABL ratio ≤ 0.0032%. In patients with newly diagnosed Ph+ CML-CP, 1 patient (4%) achieved a 4 log reduction or BCR-

ABL ratio ≤ 0.01% - > 0.0032% and 7 patients (28%) achieved a 4.5 log reduction or BCR-ABL ratio ≤ 0.0032%.

Reviewer Comment: In patients with resistant or intolerant Ph+ CML-CP, 8 patients started nilotinib treatment with a BCR-ABL ratio that met criteria for a major molecular response. MMR was defined as ≤ 0.1% BCR-ABL/control gene (ABL) % by international scale, or equivalent to ≥ 3 log reduction of BCR-ABL transcript from standardized baseline. If the 8 patients are excluded from the efficacy analysis, the MMR rate by 12 cycles is 36.1% (13/36, 95% CI: 20.8, 53.8). A MMR rate of 36% in patients with resistant or intolerant Ph+ CML-CP may be clinically meaningful if the response is durable and the overall benefit-risk evaluation remains favorable. Nevertheless, the 8 patients with resistant or intolerant Ph+ CML-CP all had prior imatinib therapy and 7 patients were classified as imatinib resistant and one patient was imatinib intolerant. The most common reason reported for enrolling on the study was an inadequate response to imatinib therapy. Although, the baseline assessment of the BCR-ABL ratio for these patients at baseline demonstrated achievement of a major molecular response prior to starting therapy with nilotinib. All 8 patients remained in MMR through cycle 24 with nilotinib treatment, demonstrating durability of the molecular response. Of the 8 patients, 1 patient at baseline had a 4-log reduction of the BCR-ABL transcript and 1 patients had a 4.5 log reduction or 0.0032% BCR-ABL ratio. These patients accounted for 1 of 3 patients that achieved a 4 log reduction BCR-ABL transcript and 1 of 2 patients that achieved a 4.5 log reduction BCR-ABL transcript. Though, the evidence suggests that nilotinib therapy is able to maintain durable molecular remissions in patients with a low disease burden at the onset of treatment. Despite the 8 patients being in MMR at baseline, labeling should reflect efficacy in the intention to treat population as this is the current labeling practice and most importantly, it is reflective of patients that will be encountered in clinical practice.

Duration of Major Molecular Response

Almost all patients that achieved MMR remained in MMR during follow-up. In patients with Ph+ CML-CP resistant or intolerant to either imatinib or dasatinib and newly diagnosed Ph+ CML-CP, the median duration of response was not reached. None of the 21 patients with resistant or intolerant Ph+ CML-CP who achieved MMR, had loss of MMR. Of the 17 patients with newly diagnosed Ph+ CML-CP who achieved MMR, one patient (6%) had loss of MMR. The median follow-up for patients with resistant or intolerant Ph+ CML-CP and newly diagnosed Ph+ CML-CP who achieved MMR was 11.3 months and 11.1 months, respectively.

Reviewer Comment: For patients that achieve MMR, the durability of the molecular remission is sustained for nearly 12 months in all patients except for one. The ability to interpret duration of MMR after 11 to 12 months is uncertain due to the median follow-up of the those patients that achieved MMR. Although, a duration of response of 11 to 12 months and possibly greater remains clinically meaningful in the resistant or intolerant Ph+ CML-CP and newly diagnosed

Ph+ CML-CP population.

Time to MMR
The time to MMR was defined as the time from the start of treatment to the first observed MMR. In patients with resistant or intolerant Ph+ CML-CP, the median time to response was 2.8 months (range 0 to 11.2 months). In patients with newly diagnosed Ph+ CML-CP, the median time to response was 5.5 months (range 2.7 to 16.6 months).

Reviewer Comment: In patients with resistant or intolerant Ph+ CML-CP, there were 8 patients that met criteria for MMR at baseline. These patients introduce bias in the time to MMR. Excluding the 8 patients, the median time to MMR for the other 13 patients that achieved MMR becomes 5.5 months (range 1.0 to 11.3 months), which is consistent with the median time to MMR in patients with newly diagnosed Ph+ CML-CP. Labeling will reflect the data as evaluated in the intention to treat analysis as this is representative of patients that will be treated in clinical practice.

Cytogenetic Response in Patients with Newly Diagnosed Ph+ CML-CP
In Study A2203, complete cytogenetic response was evaluated as a secondary endpoint in patients with newly diagnosed Ph+ CML-CP. Among the 25 patients with newly diagnosed CML-CP, 21 patients (84%) achieved a complete cytogenetic response. Of the 21 patients, one patient had loss of complete cytogenetic response, thus the median duration of complete cytogenetic response was not reached. The median time to complete cytogenetic response was 5.6 months (range 2.8 to 5.8 months)

Subgroup Analyses
Subgroup analyses were performed for age, gender, and race. The 3 categories evaluated for age included 2 to ≤ 6 years, > 6 to < 12 years, and 12 to < 18 years. Table 12 displays the MMR rate by cycle 12 in the different age groups.

Table 12 Rate of Major Molecular Response by Cycle 12 by Age Group

	Age 2 to ≤ 6 years n (%)	Age > 6 to < 12 years n (%)	Age 12 to < 18 years n (%)
Resistant or Intolerant Ph+ CML-CP	N = 6	N = 12	N = 26
MMR	1 (16.7)	7 (58.3)	13 (50.0)
Newly Diagnosed Ph+ CML-CP	N = 0	N = 6	N = 19
MMR		4 (66.7)	13 (68.4)

CML-CP: Chronic myeloid leukemia in chronic phase, MMR: Major molecular response
Source: FDA analysis of AEFFSBJ dataset

The MMR rate between the age groups of < 6 to < 12 years and 12 to < 18 years were similar. The rates of MMR between males and females were similar overall. For patients with resistant or intolerant Ph+ CML-CP, male and female patients had a MMR rate of 48% (13/27) and 47% (8/17), respectively. For patients with newly diagnosed Ph+ CML-CP, male patients had a MMR rate of 77% (10/13) and female patients had a MMR rate of 50% (6/12). For race, Asian patients tended to have higher MMR rates than Caucasians in both, resistant or intolerant Ph+ CML-CP (65% versus 33%) and newly diagnosed Ph+ CML-CP (86% versus 61%).

Reviewer Comment: Overall, the sample size of the patient population is small with a total of 69 patients with Ph+ CML-CP. The subgroup analyses exhibit very small sample sizes and the results are exploratory and no meaningful conclusion can be made from the data.

7.2. Integrated Assessment of Effectiveness

The efficacy of nilotinib was assessed in Study CAMN107A2120 and Study CAMN107A2203, which were open-label, single arm, multicenter studies of nilotinib in pediatric patients with Ph+ CML-CP resistant or intolerant to either imatinib or dasatinib and newly diagnosed Ph+ CML-CP.

The primary efficacy endpoint was major molecular response rate by 12 cycles, which was analyzed with descriptive statistics. Of the 44 patients with Ph+ CML-CP resistant or intolerant to either imatinib or dasatinib, 21 patients (48%) achieved a major molecular response by 12 cycles. The median duration of response was not reached as none of the 21 patients experienced a loss of MMR, with a median follow-up of 11.3 months. Of the 25 patients with newly diagnosed Ph+ CML-CP, 16 patients (64%) achieved a major molecular response by 12 cycles. The median duration of response was not reached as only one patient experienced a

confirmed loss of MMR, with a median follow-up of 11.1 months.

The effectiveness of nilotinib treatment for pediatric patients with Ph+ CML-CP resistant or intolerant to either imatinib or dasatinib or newly diagnosed Ph+ CML-CP is established by the major molecular response rate by 12 cycles and the durability of the responses. Since nilotinib treatment is intended for chronic use, data on long-term use greater than 1 year is needed to support an expectation of long-term benefit. Nevertheless, the effectiveness of nilotinib treatment in pediatric patients with Ph+ CML in chronic phase is clinically meaningful.

8. Review of Safety

8.1. Safety Review Approach

The safety population is defined as all patients assigned to study treatment with at least one study drug administration. The safety review for this supplemental NDA will focus on the pediatric patients with Ph+ CML-CP. There were 4 patients with Ph+ ALL that were included in the safety database and a review of their safety data demonstrates no change in the overall safety results. Thus, the data from the 4 patients with Ph+ ALL will not be presented in this safety review.

The clinical review of safety for this NDA is based on the following:

- Clinical study report for study CAMN107A2120 and A2203
- Protocol and statistical analysis plan for study CAMN107A2120 and A2203
- Integrated datasets from the two pediatric studies
- Case report forms and safety narratives
- Summary of Clinical Safety
- Proposed labeling for nilotinib

The safety review was conducted using the integrated datasets provided by the Applicant from clinical studies CAMN107A2120 and CAMN107A2203. A data pool included pediatric patients with newly diagnosed Ph+ CML-CP and pediatric patients with Ph+ CML-CP resistant or intolerant to either imatinib or dasatinib. The safety review will evaluate the patient groups separately (newly diagnosed Ph+ CML-CP and resistant or intolerant Ph+ CML-CP) and as a pooled population.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

Pediatric patients were treated with nilotinib 230 mg/m^2 twice daily, rounded to the nearest 50mg dose (to a maximum single dose of 400mg) in both pediatric studies, A2120 and A2203. The median exposure duration for the total Ph+ CML-CP population was 13.4 months (range 0.5 to 30.9 months). Table 13 displays a summary of duration of nilotinib treatment by patient group.

Table 13 Duration of Treatment with Nilotinib

Exposure	Resistant or intolerant Ph+ CML-CP N = 44	Newly diagnosed Ph+ CML-CP N = 25	Total Ph+ CML-CP population N = 69
Duration of exposure (months)			
Median	12.5	13.4	13.4
Min, Max	0.5, 30.9	0.7, 27.6	0.5, 30.9
Relative dose intensity			
Mean (SD)	89.2 (18.5)	79.7 (20.0)	85.8 (19.5)
Median	95.6	83.6	94.7
Min, Max	42, 112	32, 102	32, 112
Months of treatment, n (%)			
≥ 3 months	42 (95.5)	24 (96.0)	66 (95.7)
≥ 6 months	38 (86.4)	23 (92.0)	61 (88.4)
≥ 9 months	36 (81.8)	21 (84.0)	57 (82.6)
≥ 12 months	22 (50.0)	15 (60.0)	36 (52.2)
≥ 18 months	14 (31.8)	9 (36.0)	22 (31.9)
≥ 24 months	8 (18.2)	2 (8.0)	10 (14.5)
SD: Standard deviation Source: FDA analysis of AIDENT dataset			

The median relative dose intensity, compared to the planned dose of 230 mg/m^2 twice daily, was 96% and 84% for patients with resistant or intolerant Ph+ CML-CP and newly diagnosed Ph+ CML-CP, respectively. Overall, 50% or more patients received nilotinib for greater than or equal to 12 months.

Reviewer Comment: The overall exposure and dose intensity is sufficient to provide meaningful information on the safety of nilotinib in pediatric patients. The decreased median relative dose

intensity, compared to the planned dose of 230 mg/m^2 twice daily, in the newly diagnosed patients is likely due to dose reductions (10 patients with dose reductions due to adverse events and 2 patients due to dosing errors).

8.2.2. Relevant characteristics of the safety population:

The demographics and patient characteristics of the 44 patients with resistant or intolerant Ph+ CML-CP and 25 patients with newly diagnosed Ph+ CML-CP are shown in Table 14 and Table 15.

Table 14 Patient Demographics

Characteristic	Resistant or intolerant Ph+ CML-CP N = 44	Newly diagnosed Ph+ CML-CP N = 25
Age (years)		
Median	13	13
Min, Max	2, 17	10, 16
Age group, n (%)		
2 to ≤ 6 years	6 (13.6)	0
> 6 to < 12 years	12 (27.3)	6 (24.0)
≥ 12 to < 18 years	26 (59.1)	19 (76.0)
Gender, n (%)		
Female	17 (38.6)	12 (48.0)
Male	27 (61.4)	13 (52.0)
Race, n (%)		
Caucasian	21 (47.7)	18 (72.0)
Asian	17 (38.6)	7 (28.0)
Black	3 (6.8)	0
Native American	1 (2.3)	0
Other/Missing	2 (4.5)	0
Body surface area		
Median	1.34	1.54
Min, Max	0.49, 1.95	1.06, 2.01
Source: FDA analysis of AIDENT dataset		

The patient demographics display a mostly adolescent population with a median age of 13 and a population that is primarily Caucasian and Asian.

Table 15 Patient Disease-Related Characteristics

Characteristic	Resistant or intolerant Ph+ CML-CP N = 44	Newly diagnosed Ph+ CML-CP N = 25
Time since diagnosis (days)		
Median	667.5	14
Min, Max	113, 4131	1, 51
Imatinib or dasatinib resistant, n (%)		
Imatinib	37 (84.1)	N/A
Dasatinib	2 (4.5)	
Time since resistance (days)		
Median	77	N/A
Min, Max	5, 1037	
Number of prior regimens, n (%)		
1	31 (70.5)	N/A
2	7 (15.9)	
≥ 3	6 (13.6)	
Source: FDA analysis of AIDENT dataset		

Reviewer Comment: The study population is consistent with the general population of pediatric patients with Ph+ CML-CP. The resistant Ph+ CML-CP population primarily consists of patients previously treated with imatinib.

Patient Disposition

An overview of patients disposition is shown in Table 16 below. Of the 44 pediatric patients with Ph+ CML-CP resistant or intolerant to imatinib or dasatinib, 25 patients (57%) remain on treatment as of a data cut-off of 01 June 2016. Fourteen patients (32%) with resistant or intolerant Ph+ CML-CP discontinued treatment with the most common reason being new cancer therapy in 6 patients (14%) and adverse events in 5 patients (11%). Of the 25 patients with newly diagnosed Ph+ CML-CP, 19 patients (76%) remain on treatment as of the data cut-off and 6 patients (24%) discontinued treatment. Four patients (16%) discontinued treatment due to an adverse event.

Table 16 Patient Disposition

Patient Disposition	Resistant or intolerant Ph+ CML-CP N = 44 n (%)	Newly diagnosed Ph+ CML-CP N = 25 n (%)	Total Ph+ CML-CP population N = 69 n (%)
Completed treatment in A2120	5 (11.4)	-	5 (7.2)
Treatment ongoing	25 (56.8)	19 (76.0)	44 (63.8)
End of treatment	14 (31.8)	6 (24.0)	20 (29.0)
Reason for end of treatment			
Adverse event	5 (11.4)	4 (16.0)	9 (13.0)
New cancer therapy	6 (13.6)	0	6 (8.7)
Disease progression	2 (4.5)	0	2 (2.9)
Lack of efficacy	0	1 (4.0)	1 (1.4)
Withdrew consent	0	1 (4.0)	1 (1.4)
Protocol deviation	1 (2.3)	0	1 (1.4)
Source: FDA analysis of AIDENT dataset			

8.2.3. Adequacy of the safety database:

The size of the safety database for pediatric patients with Ph+ CML-CP is small with a total of 69 patients. Although, the exposure in combination with the size of the safety database may be sufficient to provide an estimate of adverse reactions observed in pediatric patients with Ph+ CML-CP treated with nilotinib. The population in the safety database is representative of the general pediatric Ph+ CML-CP population.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

The data submitted to this NDA were of adequate quality to perform the safety review. Overall, there were no concerns regarding the integrity of the NDA submission.

8.3.2. Categorization of Adverse Events

Adverse events (AE) were coded using the Medical Dictional for Regulatory Activities (MedDRA), version 19. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 4.03. Treatment-emergent adverse events were defined as any event arising or worsening after the start of

study drug administration until 30 days after the last study drug administration.

8.4. Safety Results

8.4.1. Deaths

There were no deaths during the conduct of either study, A2120 or A2203, or after treatment discontinuation as of the data cut-off of 01 June 2016 (Table 17).

8.4.2. Serious Adverse Events

A serious adverse event (SAE) during treatment or within 30 days after the end of treatment occurred in 10 patients (14%). All grades and Grade 3-4 serious adverse events were more common is those patients with resistant or intolerant Ph+ CML-CP compared to patients with newly diagnosed Ph+ CML-CP. Table 17 provides a summary of the serious adverse events that occurred in pediatric patients with Ph+ CML-CP.

Table 17 Deaths and Serious Adverse Events in Pediatric Patients with Ph+ CML-CP

	Resistant or intolerant Ph+ CML-CP N = 44 n (%)	Newly diagnosed Ph+ CML-CP N = 25 n (%)	Total Ph+ CML-CP population N = 69 n (%)
Deaths	0	0	0
Serious Adverse Events (SAE)			
Any SAE	8 (18.2)	2 (8.0)	10 (14.5)
Grade 3/4	5 (11.4)	1 (4.0)	6 (8.7)
Most common SAEs			
Gastroenteritis	2 (4.5)	1 (4.0)	3 (4.3)
Neutropenia	2 (4.5)	0	2 (2.9)
Hyperbilirubinemia	0	1 (4.0)	1 (1.4)
Source: FDA analysis of AAEV dataset			

Reviewer Comment: The increased incidence of serious adverse events, including Grade 3-4, in patients with resistant or intolerant Ph+ CML-CP is expected given the prior treatment received

by those patients. The most common serious adverse events are consistent with the known safety profile with nilotinib in adults and labeling provides appropriate information regarding these safety issues.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Table 18 provides a summary of discontinuations, dose reductions, and dose interruptions due to treatment emergent adverse events in pediatric patients with Ph+ CML-CP.

Table 18 Summary of Discontinuations, Dose Reductions, and Dose Interruptions due to Treatment Emergent Adverse Events

	Resistant or intolerant Ph+ CML-CP N = 44 n (%)	Newly diagnosed Ph+ CML-CP N = 25 n (%)	Total Ph+ CML-CP population N = 69 n (%)
Discontinuation due to AE	5 (11.4)	4 (16.0)	9 (13.0)
Hyperbilirubinemia	4 (9.0)	2 (8.0)	6 (8.7)
Rash	2 (4.5)	1 (4.0)	3 (4.3)
Dose reduction due to AE	16 (36.4)	10 (40.0)	26 (37.7)
Dose interruption due to AE	22 (50.0)	17 (68.0)	39 (56.5)
AEs requiring interruption or dose reduction			
Hyperbilirubinemia	10 (22.7)	10 (40.0)	20 (29.0)
Rash	6 (13.6)	3 (12.0)	9 (13.0)
ALT increased	3 (6.8)	4 (16.0)	7 (10.1)
AE: Adverse event Source: FDA analysis of AAEV dataset			

The most common treatment emergent adverse events leading to permanent discontinuation of nilotinib were hyperbilirubinemia (9%) and rash (4%). The treatment emergent adverse events leading to dose reduction or interruption included hyperbilirubinemia (29%), rash (13%), and increase ALT (10%).

Reviewer Comment: The number of pediatric patients that discontinued nilotinib due to an adverse event was relatively low, suggesting that dose interruption or dose reduction are reasonable strategies to allow most patients to continue or resume treatment with nilotinib following an adverse event. Labeling will need to include appropriate dose modifications for identified adverse events such as hyperbilirubinemia, increased transaminases, and other non-

hematologic toxicity.

8.4.4. Significant Adverse Events

The Applicant identified adverse events of special interest based on some of the identified or potential risks for nilotinib or within the class of drugs. The adverse events of special interest include:

- Transaminase and bilirubin elevations
- Drug-induced liver injury
- Myelosuppression
- Rash
- Renal events
- QT prolongation
- Bleeding events
- Pancreatitis
- Fluid retention (edema)
- Cardiovascular events
- Blood cholesterol or glucose increased

Table 19 displays a summary of the adverse events of interest experienced by pediatric patients with Ph+ CML-CP treated with nilotinib. There were no cases of cardiovascular events, renal events, pancreatitis, significant fluid retention, or significant bleeding (central nervous system bleeding or gastrointestinal bleeding).

Table 19 Summary of Adverse Events of Special Interest

Adverse Events of Interest	Resistant or Intolerant Ph+ CML-CP N = 44 n (%)		Newly Diagnosed Ph+ CML-CP N = 25 n (%)		Total Ph+ CML-CP population N = 69 n (%)	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Transaminase elevation	35 (79.5)	3 (6.8)	23 (92.0)	3 (12.0)	58 (84.1)	6 (8.7)
Hyperbilirubinemia	35 (79.5)	5 (11.4)	19 (76.0)	4 (16.0)	54 (78.3)	9 (13.0)
Rash	21 (47.7)	5 (11.4)	15 (60.0)	2 (8.0)	36 (52.2)	7 (10.1)
Thrombocytopenia	8 (18.2)	0	22 (88.0)	3 (12.0)	30 (43.5)	3 (4.3)
QT prolongation	6 (13.6)	0	3 (12.0)	0	9 (13.0)	0
Source: FDA analysis of AAEV dataset						

In pediatric patients with Ph+ CML-CP, 84% and 78% experienced an adverse event of transaminase elevation and hyperbilirubinemia, respectively. Nine to thirteen percent of patients experienced a Grade 3 or greater event of transaminase elevation or hyperbilirubinemia. Rash and thrombocytopenia were common amongst patients treated with nilotinib. Lastly, a small number of patients had QT prolongation or edema. The adverse events of transaminase elevation, hyperbilirubinemia, and thrombocytopenia will be further reviewed in Section 8.4.6. QT prolongation with be reviewed in Section 8.4.9. A brief description of the adverse events of rash is presented below.

Rash
In pediatric patients with Ph+ CML-CP, 52% experienced an adverse event of rash, with 7% of patients experiencing a Grade 3 event. The most common rash description included a macular or maculo-papular rash on the head, neck, trunk, and arms. In pediatric patients with resistant or intolerant Ph+ CML-CP, an adverse event of rash led to discontinuation of nilotinib in 1 patient (2%) and dose interruption or reduction in 6 patients (14%). In pediatric patients with newly diagnosed Ph+ CML-CP, an adverse event of rash led to discontinuation in 2 patients (8%) and dose interruption or reduction in 4 patients (12%). Concomitant medications were commonly used for patients experiencing an adverse event of rash with the most common being topical preparations (moisturizing agents, hydrocortisone, topical anti-histamine) and systemic anti-histamines.

Reviewer Comment: The incidence of the identified adverse events of interest were consistent with the known safety profile in adults with Ph+ CML-CP.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Treatment Emergent Adverse Events
Treatment emergent adverse events were assessed from the start of study drug until 30 days after the last study drug administration. Treatment emergent adverse events were reported in all pediatric patients and 51% experienced Grade 3 to 4 adverse events. The number of pediatric patients with treatment emergent adverse events (≥ 13% of patients) is displayed in Table 20 in decreasing order of incidence.

Table 20 Treatment Emergent Adverse Events in ≥ 13% of Patients

Preferred Term	Resistant or Intolerant Ph+ CML-CP N = 44 n (%)		Newly Diagnosed Ph+ CML-CP N = 25 n (%)		Total Ph+ CML-CP Population N = 69 n (%)	
	All Grades	Grade 3-4	All Grades	Grade 3-4	All Grades	Grade 3-4
Any adverse event	44 (100)	19 (43.2)	25 (100)	16 (64.0)	69 (100)	35 (50.7)
Hyperbilirubinemia[1]	22 (50.0)	4 (9.1)	13 (52.0)	4 (16.0)	35 (50.7)	8 (11.6)
Rash[2]	20 (45.5)	5 (11.4)	14 (56.0)	2 (8.0)	34 (49.3)	7 (10.1)
Headache	17 (38.6)	1 (2.3)	14 (56.0)	0	31 (44.9)	1 (1.4)
ALT increased	11 (25.0)	3 (6.8)	9 (36.0)	3 (12.0)	20 (29.0)	6 (8.7)
Pyrexia	12 (27.3)	0	7 (28.0)	0	19 (27.5)	0
Abdominal pain[3]	8 (18.2)	0	9 (36.0)	0	17 (24.6)	0
Nausea	10 (22.7)	0	7 (28.0)	0	17 (24.6)	0
URI	11 (25.0)	1 (2.3)	6 (24.0)	0	17 (24.6)	1 (1.4)
AST increased	9 (20.5)	1 (2.3)	7 (28.0)	0	16 (23.2)	1 (1.4)
Vomiting	8 (18.2)	0	7 (28.0)	1 (4.0)	15 (21.7)	1 (1.4)
Pain in extremity	9 (20.5)	0	4 (16.0)	0	13 (18.8)	0
Nasopharyngitis	7 (15.9)	0	5 (20.0)	0	12 (17.4)	0
Arthralgia	7 (15.9)	0	4 (16.0)	0	11 (15.9)	0
Thrombocytopenia[4]	3 (6.8)	0	8 (32.0)	3 (12.0)	11 (15.9)	3 (4.3)
Diarrhea	6 (13.6)	0	4 (16.0)	0	10 (14.5)	0
Fatigue[5]	3 (6.8)	0	7 (28.0)	0	10 (14.5)	0
Rhinitis[6]	6 (13.6)	0	3 (12.0)	0	9 (13.0)	0
Cough[7]	5 (11.4)	0	4 (16.0)	0	9 (13.0)	0
Neutropenia[8]	4 (9.1)	4 (9.1)	5 (20.0)	5 (20.0)	9 (13.0)	9 (13.0)

AR: Adverse reaction, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase URI: Upper respiratory tract infection

[1]Hyperbilirubinemia preferred terms (PT): Hyperbilirubinemia, blood bilirubin increased, bilirubin conjugated increased, bilirubin unconjugated increased

[2]Rash PTs: Rash, rash follicular, rash generalized, rash macular, rash maculo-papular, rash papular, rash pruritic, exfoliative rash

[3]Abdominal pain PTs: Abdominal pain, abdominal pain upper, abdominal pain lower, abdominal tenderness

[4]Thrombocytopenia PTs: Thrombocytopenia, platelet count decreased

[5]Fatigue PTs: Asthenia, fatigue

[6]Rhinitis PTs: Rhinitis, rhinitis allergic

[7]Cough PTs: Cough, productive cough

[8]Neutropenia PTs: Neutropenia, neutrophil count decreased

Preferred Term	Resistant or Intolerant Ph+ CML-CP N = 44 n (%)	Newly Diagnosed Ph+ CML-CP N = 25 n (%)	Total Ph+ CML-CP Population N = 69 n (%)
Source: FDA analysis of AAEV dataset			

The most frequently reported adverse events in all pediatric patients with Ph+ CML-CP were hyperbilirubinemia (51%), rash (49%), headache (45%), ALT increased (29%), pyrexia (28%) abdominal pain, nausea, and upper respiratory tract infection (25% each).

The most common Grade 3 to 4 adverse events reported in the total population were neutropenia (13%), hyperbilirubinemia (12%), rash (10%), and ALT increased (9%).

Adverse Drug Reactions
Adverse drug reactions were identified by the Applicant in pediatric patients with Ph+ CML-CP. Adverse events were evaluated by the investigator to determine whether there was a relationship between nilotinib and the adverse event in order to categorize the event as suspected to be drug-related (i.e., an adverse reaction) or not drug-related. The number of pediatric patients with adverse drug reactions (≥ 5% of patients) is displayed in Table 21 in decreasing incidence.

Table 21 Adverse Drug Reactions in ≥ 5% of Patients with Ph+ CML-CP

Preferred Term	Resistant or Intolerant Ph+ CML-CP N = 44 n (%)		Newly Diagnosed Ph+ CML-CP N = 25 n (%)		Total Ph+ CML-CP Population N = 69 n (%)	
	All Grades	Grade 3-4	All Grades	Grade 3-4	All Grades	Grade 3-4
Any AR	38 (86.4)	16 (36.4)	22 (88.0)	16 (64.0)	60 (87.0)	32 (46.4)
Hyperbilirubinemia[1]	21 (47.7)	4 (9.1)	13 (52.0)	4 (16.0)	34 (49.3)	8 (11.6)
Rash[2]	18 (40.9)	5 (11.4)	8 (32.0)	2 (8.0)	26 (37.7)	7 (10.1)
ALT increased	11 (25.0)	3 (6.8)	9 (36.0)	3 (12.0)	20 (29.0)	6 (8.7)
Headache	10 (22.7)	1 (2.3)	8 (32.0)	0	18 (26.1)	1 (1.4)
AST increased	9 (20.5)	1 (2.3)	7 (28.0)	0	16 (23.2)	1 (1.4)
Nausea	4 (9.1)	0	5 (20.0)	0	9 (13.0)	0
Neutropenia[3]	4 (9.1)	4 (9.1)	5 (20.0)	5 (20.0)	9 (13.0)	9 (13.0)

Preferred Term	Resistant or Intolerant Ph+ CML-CP N = 44 n (%)		Newly Diagnosed Ph+ CML-CP N = 25 n (%)		Total Ph+ CML-CP Population N = 69 n (%)	
Thrombocytopenia[4]	2 (4.5)	0	6 (24.0)	1 (4.0)	8 (11.6)	3 (4.3)
Vomiting	2 (4.5)	0	5 (20.0)	1 (4.0)	7 (10.1)	1 (1.4)
Fatigue[5]	1 (2.3)	0	6 (24.0)	0	7 (10.1)	0
QT prolonged	4 (9.1)	0	2 (8.0)	0	6 (8.7)	0
Pain in extremity	5 (11.4)	0	0	0	5 (7.2)	0
Abdominal pain[6]	1 (2.3)	0	4 (16.0)	0	5 (7.2)	0
Arthralgia	2 (4.5)	0	2 (8.0)	0	4 (5.8)	0
Decreased appetite	3 (6.8)	0	1 (4.0)	0	4 (5.8)	0

AR: Adverse reaction, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase
[1]Hyperbilirubinemia preferred terms (PT): Hyperbilirubinemia, blood bilirubin increased, bilirubin conjugated increased, bilirubin unconjugated increased
[2]Rash PTs: Rash, rash follicular, rash generalized, rash maculo-papular, rash papular, rash pruritic, exfoliative rash
[3]Neutropenia PTs: Neutropenia, neutrophil count decreased
[4]Thrombocytopenia PTs: Thrombocytopenia, platelet count decreased
[5]Fatigue PTs: Asthenia, fatigue
[6]Abdominal pain PTs: Abdominal pain, abdominal pain upper
Source: FDA analysis of AAEV dataset

The adverse drug reactions reported for at least 10% of pediatric patients with Ph+ CML-CP were hyperbilirubinemia (49%), rash (38%), ALT increased (29%), headache (26%), AST increased (23%), nausea, and neutropenia (13% each). The most common Grade 3 to 4 adverse reactions included neutropenia (13%), hyperbilirubinemia (12%), rash (10%), and ALT increased (9%).

Reviewer Comment: The most common adverse reactions are similar to the most common treatment emergent adverse events. The most common adverse reactions, excluding laboratory abnormalities, in pediatric patients with Ph+ CML-CP are similar to those in adults. The most common adverse reactions reported in labeling for adults captures the appropriate adverse reactions in pediatric patients Per the USPI, the adverse reactions most common in adults (>20%) include: nausea, rash, headache, fatigue, pruritus, vomiting, diarrhea, cough, constipation, arthralgia, nasopharyngitis, pyrexia, and night sweats. Hematologic adverse reactions include: myelosuppression, thrombocytopenia, neutropenia, and anemia.

Labeling will need to reflect the incidence of hyperbilirubinemia and transaminase elevation in pediatric patients to ensure healthcare providers are informed and able to monitor patients

appropriately.

Hypersensitivity
FDA conducted an evaluation for hypersensitivity that demonstrated no reported cases of anaphylaxis or severe hypersensitivity reactions. Two patients experienced Grade 1 hypersensitivity reactions, both of which were not suspected to be related to nilotinib by the investigator.

Reviewer Comment: In the current USPI, there is a single event listed for an adult patient who experienced a hypersensitivity reaction during a nilotinib clinical trial. The pediatric data support the adult data that hypersensitivity is a rare occurrence with nilotinib treatment.

8.4.6. Laboratory Findings

The Applicant included an analysis of laboratory parameters that included pediatric patients with changes from baseline with respect to the reference ranges of laboratory values. The FDA was able to independently reproduce the analysis and the results were consistent with those of the Applicant.

Table 22 displays the hematology laboratory abnormalities in pediatric patients treated with nilotinib.

Table 22 Summary of Hematology Laboratory Abnormalities

Hematology laboratory abnormality	Resistant or Intolerant Ph+ CML-CP N = 44 n (%)		Newly Diagnosed Ph+ CML-CP N = 25 n (%)		Total Ph+ CML-CP Population N = 69 n (%)	
	All Grades	Grade 3-4	All Grades	Grade 3-4	All Grades	Grade 3-4
Platelets decreased	8 (18.2)	0	22 (88.0)	3 (12.0)	30 (43.5)	3 (4.3)
Neutrophils decreased	16 (36.4)	5 (11.4)	12 (48.0)	7 (28.0)	28 (40.6)	12 (17.4)
Lymphocytes decreased	13 (29.5)	1 (2.3)	9 (36.0)	1 (4.0)	22 (31.9)	2 (2.9)
Hemoglobin decreased	13 (29.5)	1 (2.3)	8 (32.0)	1 (4.0)	21 (30.4)	2 (2.9)
Source: FDA analysis of ALRS dataset						

Cytopenias were common during treatment with nilotinib. In pediatric patients with Ph+ CML-CP, neutropenia was the most common cytopenia at 17%. Patients with newly diagnosed Ph+ CML-CP experienced a higher incidence of cytopenias overall and Grade 3-4 events. Although, this difference did not translate into a higher incidence of infections or bleeding events in

patients with newly diagnosed Ph+ CML-CP.

Table 23 displays the chemistry laboratory abnormalities in pediatric patients with Ph+ CML-CP treated with nilotinib.

Table 23 Summary of Biochemical Laboratory Abnormalities

Biochemical laboratory abnormality	Resistant or Intolerant Ph+ CML-CP N = 44 n (%)		Newly Diagnosed Ph+ CML-CP N = 25 n (%)		Total Ph+ CML-CP Population N = 69 n (%)	
	All Grades	Grade 3-4	All Grades	Grade 3-4	All Grades	Grade 3-4
Increased ALT	35 (79.5)	3 (6.8)	23 (92.0)	3 (12.0)	58 (84.1)	6 (8.7)
Hyperbilirubinemia	35 (79.5)	5 (11.4)	19 (76.0)	4 (16.0)	54 (78.3)	9 (13.0)
Increased AST	28 (63.6)	1 (2.3)	17 (68.0)	0	45 (65.2)	1 (1.4)
Hyperglycemia	19 (43.2)	0	12 (48.0)	0	31 (44.9)	0
Hypercholesterolemia	14 (31.8)	0	12 (48.0)	1 (4.0)	26 (37.7)	1 (1.4)
Hypertriglyceridemia	15 (34.1)	1 (2.3)	7 (28.0)	0	22 (31.9)	1 (1.4)
Hypophosphatemia	13 (29.5)	1 (2.3)	7 (28.0)	0	20 (29.0)	1 (1.4)
Hypermagnesemia	13 (29.5)	2 (4.5)	4 (16.0)	0	17 (24.6)	2 (2.9)
Hyponatremia	9 (20.5)	0	6 (24.0)	0	15 (21.7)	0
Hypokalemia	10 (22.7)	1 (2.3)	5 (20.0)	0	15 (21.7)	1 (1.4)
Increased alkaline phosphatase	5 (11.4)	0	7 (28.0)	0	12 (17.4)	0
Increased lipase	8 (18.2)	3 (6.8)	3 (12.0)	2 (8.0)	11 (15.9)	5 (7.2)
Source: FDA analysis of ALRS dataset						

The majority of pediatric patients experienced hyperbilirubinemia (78%) and transaminase elevation (84%), with 13% and 9% being Grade 3-4 events, respectively. The other Grade 3-4 event that was common was increased lipase (7%), but no patients has clinical pancreatitis. The other biochemical abnormalities were mostly of low grade, but the common abnormalities included hyperglycemia, hypercholesterolemia, hypertriglyceridemia, hypophosphatemia, hypermagnesemia, hyponatremia, and hypokalemia. The electrolyte abnormalities were not a common cause of dose interruption or dose reduction.

Hyperbilirubinemia and Transaminase Elevation
Nilotinib causes an unconjugated hyperbilirubinemia because of inhibition of UGT1A1, the key enzyme for bilirubin conjugation. Thus, bilirubin metabolism is impaired and this causes an

increase in the total bilirubin concentration. In adults, studies have been conducted that support the conclusion that UGT1A1 inhibition is the leading mechanism of nilotinib-induced hyperbilirubinemia and is not necessarily a result of liver injury. Nilotinib-induced hyperbilirubinemia is typically benign, clinically manageable, and reversible. Nevertheless, it is important to assess patients for evidence of nilotinib-associated hepatic injury.

As mentioned, the majority of pediatric patients experienced transaminase elevation (84%) and hyperbilirubinemia (78%). The incidence of all-grade and Grade 3-4 transaminase elevation and hyperbilirubinemia is higher in the pediatric population versus the adult population. Per the Tasigna United States Prescribing Information (USPI), 72% of adult patients experienced transaminase elevation and 59% of adult patients experienced hyperbilirubinemia. In pediatric patients, the incidence of Grade 3-4 transaminase elevation and hyperbilirubinemia is nearly double the incidence seen in adult patients with Ph+ CML-CP treated with nilotinib, as shown in Table 24.

Table 24 Comparison of Grade 3-4 Hyperbilirubinemia and Transaminase Elevation in Pediatrics and Adults

Adverse Events of Interest	Pediatric Ph+ CML-CP (%)	Adult Ph+ CML-CP (%)
	Grade 3/4	Grade 3/4
Hyperbilirubinemia	11 - 16	4 - 7
Transaminase elevation	7 - 12	3 - 4
Source: FDA analysis of ALRS dataset and nilotinib USPI		

Reviewer Comment: The increased incidence of hyperbilirubinemia and transaminase elevation in the pediatric population should be reflected in labeling to ensure that pediatric providers are aware of the increased incidence of Grade 3-4 events. The underlying reason for the disparity is uncertain. However, nilotinib is a known inhibitor of UGT1A1 which causes an unconjugated hyperbilirubinemia. The degree of hyperbilirubinemia can be explained by different UGT1A1 genotypes, TA(6)/TA(6), TA(6)/TA(7), and TA(7)/TA(7). Patients with the homozygous TA(7)/TA(7) genotype have an increased risk of nilotinib-induced hyperbilirubinemia compared to the other genotypes. For instance, in adults with resistant or intolerant Ph+ CML, the frequency of Grade 3-4 hyperbilirubinemia for those with the TA(6)/TA(6) genotype, TA(6)/TA(7) genotype, and TA(7)/TA(7) genotype were 6%, 12%, and 48%. Therefore, a better understanding of the genotype variation in pediatric patients may help explain a possible reason for the increased incidence of hyperbilirubinemia.

Hy's Law

The Applicant performed an analysis for Hy's Law cases and used a definition of AST or ALT values >3 times the upper limit of normal, total bilirubin value >2 times the upper limit of normal, and alkaline phosphatase ≤ 2 times the upper limit of normal. Table 25 displays the liver-related laboratory parameters greater than the specified upper limit of normal.

Table 25 Liver Laboratory Abnormalities

Liver Laboratory Parameter	Resistant or Intolerant Ph+ CML-CP N = 44		Newly Diagnosed Ph+ CML-CP N = 25		Total Ph+ CML-CP Population N = 69	
	Event #/ Subject #	% of Subjects	Event #/ Subject #	% of Subjects	Event #/ Subject #	% of Subjects
AST or ALT						
AST or ALT > 3x ULN	12/44	27.3	7/25	28.0	19/69	27.5
AST or ALT > 5x ULN	3/44	6.8	3/25	12.0	6/69	8.7
AST or ALT > 8x ULN	2/44	4.5	2/25	8.0	4/69	5.8
AST or ALT > 10x ULN	0/44	0	2/25	8.0	2/69	2.9
AST or ALT > 20x ULN	0/44	0	0/25	0	0/69	0
Total Bilirubin						
TB > 2x ULN	17/44	38.6	12/25	48.0	29/69	42.0
TB > 3x ULN	5/44	11.4	4/25	16.0	9/69	13.0
Combination						
AST or ALT > 3x ULN, TB > 2x ULN, ALP ≤ 2x ULN	3/44	6.8	2/25	8.0	5/69	7.2

ALP: Alkaline phosphatase, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, TB: Total bilirubin, ULN: Upper limit of normal
Source: FDA analysis of ALRS dataset

There were 5 patients that met the definition of Hy's law using the definition AST or ALT values >3 times the upper limit of normal, total bilirubin value >2 times the upper limit of normal, and alkaline phosphatase ≤ 2 times the upper limit of normal. Overall, the 5 patients did not exhibit progressive or irreversible drug-induced liver injury and the cases were driven by an unconjugated hyperbilirubinemia. The patients were managed with close observation and dose reduction or discontinuation as appropriate. The 5 patients are briefly discussed below.

Case 1: A 6 year old female with resistant Ph+ CML-CP developed AST and ALT greater than 3 times the upper limit of normal and total bilirubin greater than 2 times the upper limit of

normal during cycle 2 of treatment. She continued treatment with nilotinib and the increased transaminases resolved, but the hyperbilirubinemia persisted, which was due to an unconjugated hyperbilirubinemia consistent with UGT1A1 inhibition. The patient continued treatment for 9 cycles before discontinuing therapy in order to receive a hematopoietic stem cell transplantation.

Case 2: A 13 year old male with resistant Ph+ CML-CP on nilotinib 350 mg twice daily developed ALT greater than 3 times the upper limit of normal and total bilirubin greater than 2 times the upper limit of normal toward the end of cycle 1. The patient continued treatment with nilotinib with no changes to dose or dose schedule. The patient continued to have intermittent periods of hyperbilirubinemia for a prolonged period of time with no associated increase in transaminases. The patient did have another occurrence of increased ALT and bilirubin consistent with Hy's law at the end of cycle 21. The dose of nilotinib was reduced to 350 mg once daily at this time for a total of 40 days. The increased ALT and hyperbilirubinemia resolved and the patients was resumed on nilotinib 350 mg twice daily. The patient had a recurrence of hyperbilirubinemia but no AST or ALT increase greater than 3 times the upper limit of normal. The patient received a total of 30 cycles of nilotinib and was continuing treatment at the time of data cut-off.

Case 3: A 13 year old male with intolerant Ph+ CML-CP on nilotinib 350 mg twice daily developed ALT greater than 3 times the upper limit of normal and total bilirubin greater than 2 times the upper limit of normal at the end of cycle 6. This event also included a rash which had been occurring off and on since cycle 1. Nilotinib was interrupted at the end of cycle 6 for 12 days and was restarted at 350mg once daily once the transaminase elevation and hyperbilirubinemia and rash resolved. The patient developed ALT greater than 3 times the upper limit of normal and total bilirubin greater than 2 times the upper limit of normal at the end of cycle 7. Nilotinib was increased on the same day to 350mg twice daily as synthetic liver function remained intact. The ALT elevation improved and the patients continue nilotinib for a total of 8 cycles. The patient discontinued nilotinib due to persistent rash and persistent hyperbilirubinemia.

Case 4: 12 year old female with newly diagnosed Ph+ CML-CP on nilotinib 350 mg twice daily developed ALT greater than 3 times the upper limit of normal and total bilirubin greater than 2 times the upper limit of normal on day 8 of therapy. Nilotinib was continued with no changes in dose or dose schedule. The increased ALT and hyperbilirubinemia persisted and nilotinib was interrupted at the end of cycle 1 for 13 days. The event resolved and nilotinib was restarted at 300 mg once daily. The patient continued with persistent transaminase elevation, but was able to increase the dose of nilotinib to 350mg once daily at the start of cycle 5. Transaminase elevation persisted but there were no concerns regarding synthetic liver function reported. The dose of nilotinib was further increased to 350mg twice daily at the start of cycle 6. The patient

developed ALT greater than 3 times the upper limit of normal and AST greater than 2 times the upper limit of normal by the end of cycle 6. Nilotinib was permanently discontinued at the end of cycle 6 due to elevated transaminases and rash.

Case 5: A 11 year old male with newly diagnosed Ph+ CML-CP on nilotinib 250mg twice daily developed ALT greater than 3 times the upper limit of normal and total bilirubin greater than 2 times the upper limit of normal at the end of cycle 9. Nilotinib was interrupted for 10 days due to the event. The event resolved and nilotinib was restarted at 250mg once daily. The dose of nilotinib was further increased to 250mg twice daily after 48 days on the once daily dosing. At the end of cycle 15, the patient developed total bilirubin greater than 2 times the upper limit of normal and AST and ALT elevation greater than the upper limit of normal but less than 3 times the upper limit of normal. Nilotinib was reduced to 250mg once daily at that time and continued for 33 days. At the start of cycle 17, the dose was increased back to 250mg twice daily. The patient received a total of 18 cycles of nilotinib and was continuing treatment at the time of data cut-off.

Reviewer Comment: The cases described above reflect the increased risk of hyperbilirubinemia and increased AST or ALT with nilotinib therapy. However, the underlying mechanisms causing the hyperbilirubinemia and increased transaminases does not appear to affect synthetic liver function as patients did not develop signs and symptoms of coagulopathy or acute liver injury or failure. Further, patients were able to continue treatment with close monitoring of clinical status and laboratory parameters. Nilotinib is intended for prolonged use so it will be important to continue to monitor for signs and symptoms of hepatotoxicity because a cumulative toxicity effect may be possible. Healthcare providers should be aware of the risk of hyperbilirubinemia (UGT1A1 inhibition) and increased transaminases. Labeling should provide a warning and precaution for hepatotoxicity and instructions for monitoring and dose modifications for hyperbilirubinemia and increased transaminases.

8.4.7. Vital Signs

The Applicant provided a record of the vital signs and a description of the changes in vital signs during treatment with nilotinib. A review of the weight, heart rate, and temperature did not reveal any identified safety signals.

8.4.8. Electrocardiograms (ECGs)

Electrocardiograms were performed at baseline, during Days 1, 8 and 28 of Cycle 1 and then on Day 1 or 28 of Cycle 3, 6, 9, 12, 15, 18, 21, 24, 30, 36, 42, 48, 54, and 60. Treatment emergent adverse events related to ECG changes were reviewed along with all cardiac events.

The majority of patients (84%, 48/57) had an abnormal ECG during treatment. The most common findings in all 69 patients with Ph+ CML-CP were sinus bradycardia (49%), sinus tachycardia (31%) and a junctional rhythm (25%). Nine patients (16%) had a prolonged QTcF during treatment with nilotinib. There was one patients with a prolonged QT interval that required hospitalization resulting in a serious adverse event. Otherwise, there were no ECG-related abnormalities that resulted in clinical abnormalities.

8.4.9. QT

In the 69 patients with Ph+ CML-CP, none of the patients experienced a QTcF > 500 md or QTcF increase > 60 ms from baseline. Three patients (4%) with Ph+ CML-CP developed a QTcF > 480 ms during treatment with nilotinib. Seventeen patients (25%) had a QTcF increase > 30 ms from baseline. There were no cases of ventricular arrhythmia or torsade de pointes. One patient experienced an adverse event of syncope, but had a normal QTcF at the time of the event.

The Applicant evaluated the QTc prolongation potential with a linear mixed effects model and population PK prediction of Cmax for the change from baseline in QTc. The results demonstrated a positive correlation between the trough concentration and change from baseline QTcF interval. In patients with resistant or intolerant Ph+ CML-CP, exposure greater than 1800 ng/mL resulted in an estimated QTcF interval increase greater than 10 ms from baseline. In patients with newly diagnosed Ph+ CML-CP, exposure greater than 1100 ng/mL resulted in an estimated QTcF interval increase greater than 10 ms from baseline (in patients 12 to <18 years of age).

Reviewer Comment: Nilotinib contains a boxed warning for QT prolongation. The QT prolongation in pediatric patients in the study did not result in syncope, seizures, or torsade de pointes. However, healthcare providers need to be aware of the risk of QT prolongation and appropriately monitor. Labeling should reflect the risk and the need for monitoring and appropriate dose modifications.

8.5. Analysis of Submission-Specific Safety Issues

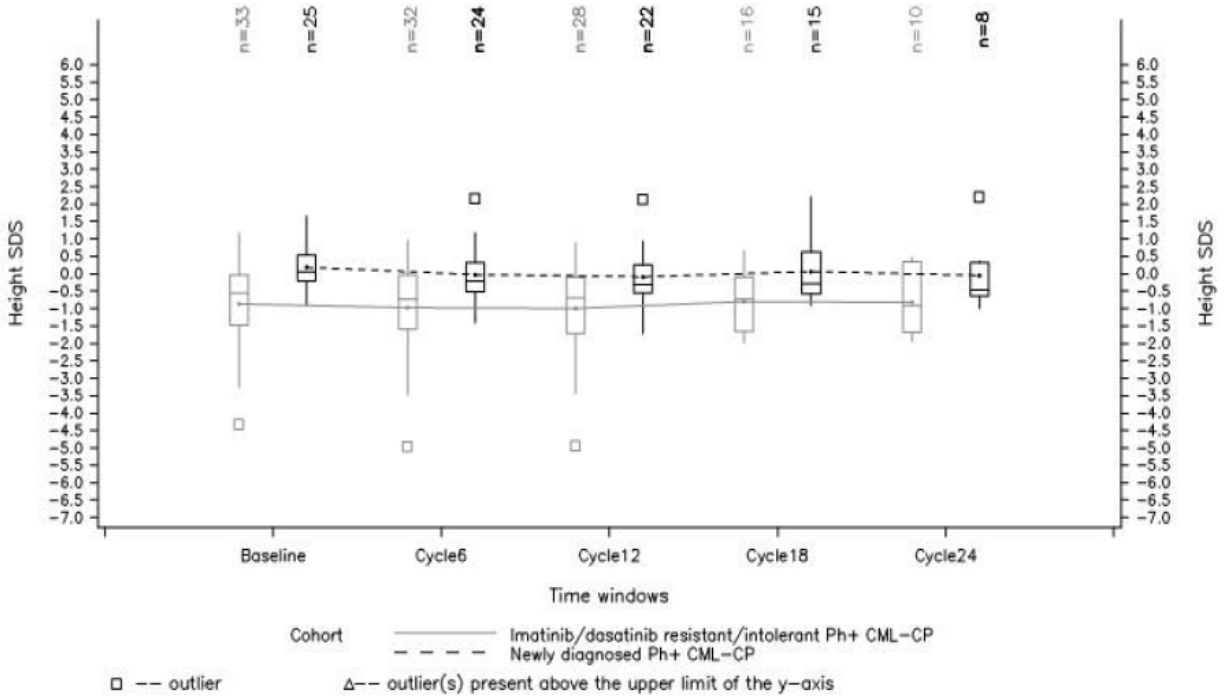
8.5.1. Growth and Development

Growth
Delayed growth and development has been reported in pediatric patients treated with BCR-ABL tyrosine kinase inhibitors. During the conduct of the nilotinib pediatric study A2203, the Applicant collected data on growth and development that included standard deviation scores for height, height velocity, body mass index, weight velocity, bone biochemical markers (serum

C-telopeptide and bone specific alkaline phosphatase), and bone mineral density, chronological age versus bone age, and Tanner staging.

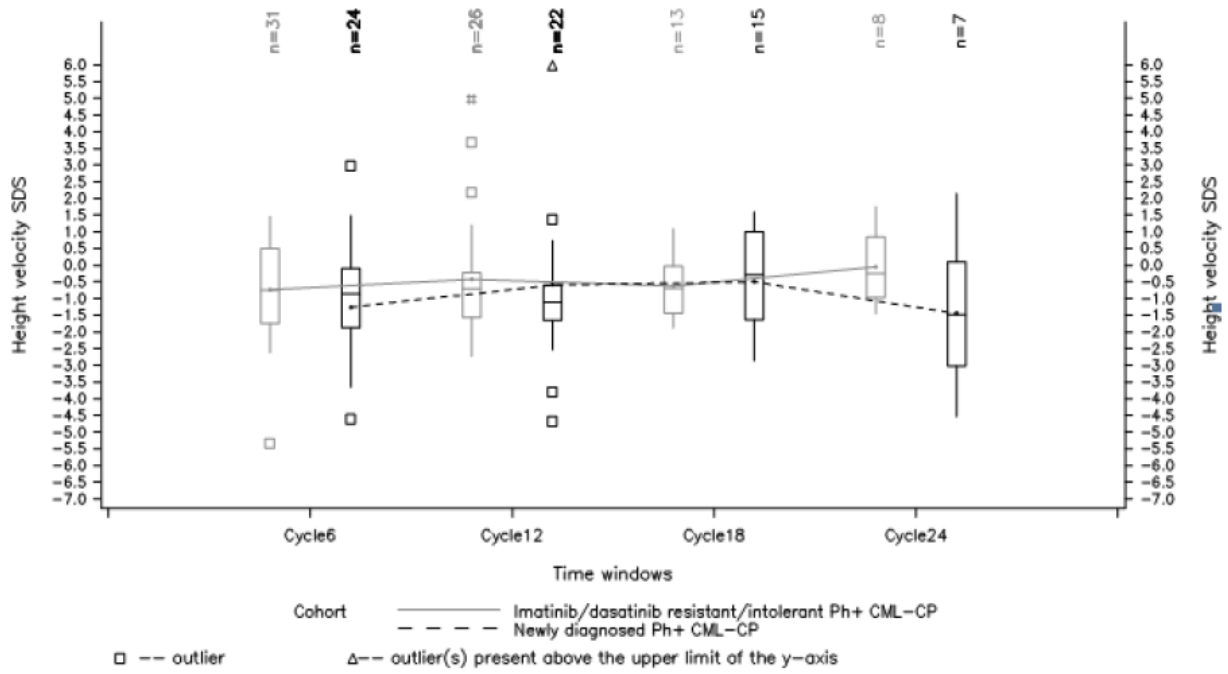
By the data cut-off, there were no meaningful changes in growth parameters or development. The standard deviation scores for height, height velocity, weight velocity were similar at baseline and throughout treatment in all 58 patients enrolled in Study A2203. Figure 1, Figure 2, and Figure 3 shown below demonstrate stable growth parameters in pediatric patients with CML-CP treated with nilotinib.

Figure 1 Height Standard Deviation Scores by Treatment Cycle and Cohort



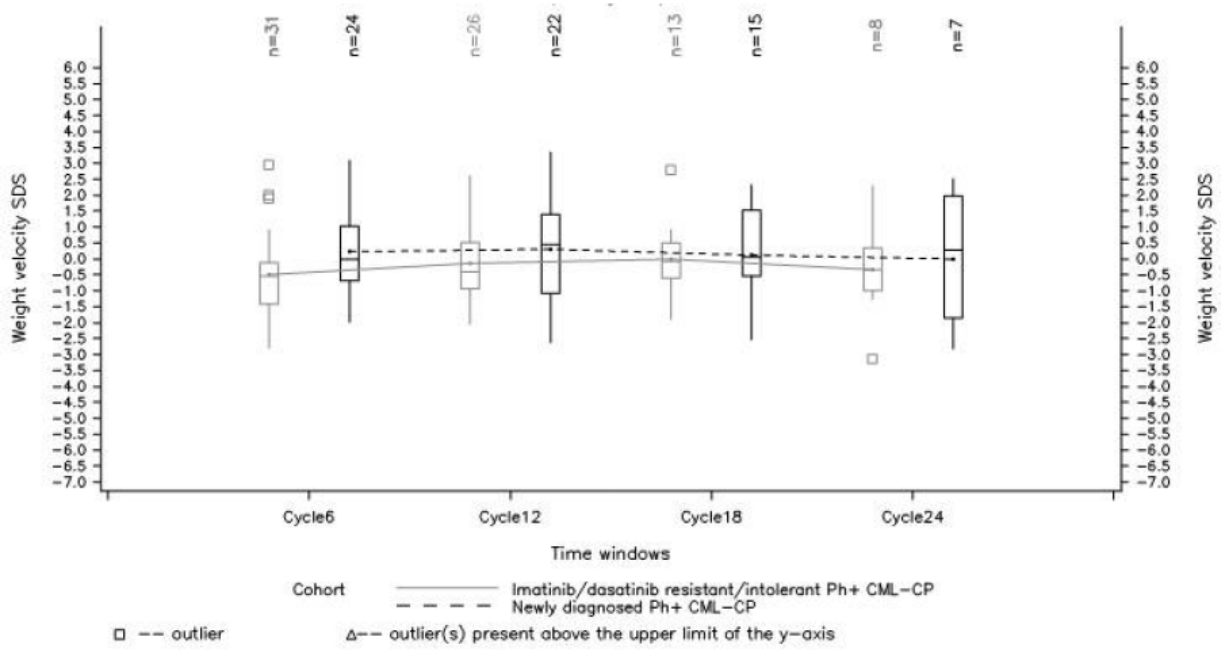
Source: Study A2203 Study Report Section 12.5.4.2

Figure 2 Height Velocity Standard Deviation Scores by Treatment Cycle and Cohort



Source: Study A2203 Study Report Section 12.5.4.2

Figure 3 Weight Velocity Standard Deviation Scores by Treatment Cycle and Cohort



Source: Study A2203 Study Report Section 12.5.4.2

An evaluation of bone biochemical markers, serum C-telopeptide and bone specific alkaline phosphatase, x-rays for bone age, and DEXA scans were also performed. There were no relevant changes in any of the above parameters during treatment with nilotinib for 12 cycles.

Development

The Applicant utilized physician documentation of a patient's sexual maturity rating staging of sexual development, also known as Tanner staging, which provides a means of documenting a child's progression through puberty by inspection. Separate scales are used for breast (female), genital (male), and pubic hair (both sexes) development. By definition, Tanner stage 1 is prepubertal. Pubertal development of the gonads is indicated specifically by thelarche (subareolar breast bud – Tanner stage 2) in girls and testicular enlargement (Tanner stage 2) in boys. Stage 2 pubic hair is classified as sparse, fine straight pubic hair. Pubertal development is ongoing at stage 3 (girls: elevation of breast contour and enlargement of areola, long, dark, curly pubic hair; boys: continued enlargement of the testes and scrotum along with penile growth, long, dark, curly pubic hair), nearly complete by stage 4 (girls: areola form a secondary mound over the contour of the breast, pubic hair resembles adult pubic hair in quality but not distribution [no spread to medial thighs]; boys: continued growth of the testes, scrotum, and penis, with enlargement of the glans, pubic hair resembles adult pubic hair in quality but no

distribution), and complete and adultlike at stage 5 (mature adult breast, mature adult genitalia, and mature pubic hair). See Appendix 13.4 for Tanner staging scales and estimates of age of onset of pubertal milestones.[14]

The normal age for the onset of puberty in girls is between 8 and 13 years of age and in boys is between 9 and 14 years of age.

Delayed puberty is defined as lack of breast development by age 13 years in girls and lack of pubertal testicular development (genital Tanner stage 2) by age 14 in boys.[14] Delayed puberty is typically accompanied by delayed linear growth velocity.

The patients enrolled on Study A2203 were monitored for sexual development. At the time of data cut-off, there were no reported cases of delayed development or puberty. Among the patients in Tanner stage 1 (prepubertal) at baseline, Tanner stage 2 for breast development was achieved in 2 of 5 female patients and Tanner stage 2 for genital development was achieved in 3 of 8 male patients. The patients that did not achieve Tanner stage 2 were less than 13 years at the time of data cut-off.

Reviewer Comment: The growth and development data are immature to adequately evaluate whether nilotinib treatment has an effect on growth and development in pediatric patients. The median follow-up in pediatric patients with resistant or intolerant Ph+ CML-CP is 18.8 months and newly diagnosed Ph+ CML-CP is 16.5 months. Long-term data is needed to evaluate if there is an effect on growth and development. A safety PMR was developed to ensure to continued collection of growth and development data to determine the effect of nilotinib treatment on growth and development in pediatric patients. In addition, BCR-ABL tyrosine kinase inhibitors as a class are associated with growth delay and possibly delayed development. Labeling will need to include a warning and precaution for this class effect since the data is insufficient to determine if nilotinib therapy has an effect.

8.6. Safety Analyses by Demographic Subgroups

Subgroup analyses were performed for age, gender, and race. The 3 categories evaluated for age included 2 to ≤ 6 years, > 6 to < 12 years, and 12 to < 18 years. Overall, there were no relevant differences in exposure, safety, or tolerability in patients with Ph+ CML-CP when evaluated according to age, gender, and race.

Reviewer Comment: Overall, the sample size of the patient population is small with a total of 69 patients with Ph+ CML-CP. The subgroup analyses exhibit very small sample sizes and the results are exploratory and no meaningful conclusion can be made from the data.

8.7. Additional Safety Explorations

8.7.1. Human Carcinogenicity or Tumor Development

Section 13.1 of the Tasigna U.S. Prescribing Information describes the carcinogenicity studies in animals that demonstrates the development of skin neoplastic lesions.

8.7.2. Human Reproduction and Pregnancy

Section 8.1 and 8.3 of the Tasigna U.S. Prescribing Information describes the information for the risk of fetal harm while taking Tasigna.

8.7.3. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There was no experience with overdose reported in the pediatric clinical studies of nilotinib. Section 10 of the Tasigna U.S. Prescribing Information discuss that in adults, Tasigna was ingested in combination with alcohol and other drugs, which resulted in events including neutropenia, vomiting, and drowsiness. In the event of overdose, the patient or caregiver should seek appropriate medical guidance.

8.8. Safety in the Postmarket Setting

8.8.1. Safety Concerns Identified Through Postmarket Experience

Development Safety Update Report (DSUR): 01 February 2016 through 31 January 2017

The estimated cumulative exposure to nilotinib from marketing of the product since 31 January 2005 is approximately (b) (4) patient treatment years.

During this reporting period, safety information was added to the Tasigna Prescribing Information related to hepatitis B virus infection reactivation. All ongoing studies underwent protocol amendments to identify patients at risk for reactivation and dear healthcare provider letter was also issued. In July 2016, an adverse drug reaction describing increased musculoskeletal pain after Tasigna discontinuation was added to the Tasigna Prescribing Information.

Important identified risks associated with the use of Tasigna include:

- QT prolongation
- Myelosuppression
- Cardiovascular events
- Significant bleeding

- Severe infections
- Hepatic transaminase and bilirubin elevations
- Pancreatitis, lipase and amylase elevations
- Fluid retention
- Blood glucose increased
- Blood cholesterol increased
- Use in patients with hepatic impairment
- Interaction with strong CYP3A4 inhibitors or inducers
- Interaction with sensitive CYP3A4 substrates
- Interaction with food

Important potential risks associated with the use of Tasigna include:

- Sudden death
- Cardiac failure
- Drug induced liver injury
- Reproductive toxicity/pregnancy
- Skin malignancy
- Interaction with P-gp inhibitors
- Interaction with drugs that may prolong the QT interval
- Interaction with drugs eliminated by CYP2C8, CYP2C9, CYP2D6 or substrates of UGT1A1, and P-gp, OATP1B1 and OCT1 transporters

8.8.2. Expectations on Safety in the Postmarket Setting

Safety in the postmarket setting is expected to be similar to that observed in the clinical studies reviewed in this application and what is known from adult postmarketing safety data.

8.9. Integrated Assessment of Safety

The safety of nilotinib was evaluated in 69 pediatric patients with resistant or intolerant Ph+ CML-CP or newly diagnosed Ph+ CML-CP. Patients received nilotinib 230 mg/m^2 twice daily continuously for 28-day treatment cycles. The median duration of exposure was 13.4 months.

- There were no patient deaths reported during or after the pediatric clinical studies, as of the data cut-off.

- The most common treatment emergent adverse events in pediatric patients include were hyperbilirubinemia (51%), rash (49%), headache (45%), ALT increased (29%), pyrexia (28%) abdominal pain, nausea, and upper respiratory tract infection (25% each).

- The most frequently reported Grade 3-4 treatment emergent adverse events were neutropenia (13%), hyperbilirubinemia (12%), rash (10%), and ALT increased (9%).

- Serious adverse events were reported in 15% of patients. The most common serious adverse events were gastroenteritis (4%), neutropenia (3%), and hyperbilirubinemia (1%).

- Adverse events resulting in treatment discontinuation were reported in 13% of patients. Adverse events leading to dose reduction of nilotinib therapy occurred in 38% of patients.

A comprehensive review of the safety data demonstrates that the safety profile of nilotinib is tolerable and management in pediatric patients with Ph+ CML-CP. Further, the safety profile in pediatric patients is similar to the known safety profile in adult patients with Ph+ CML.

9. Advisory Committee Meeting and Other External Consultations

This application was not presented to the Oncologic Drug Advisory Committee or any other external consultants because the application did not raise significant efficacy or safety issues for the proposed indications.

10. Labeling Recommendations

10.1. Prescribing Information

The following are recommended major clinical changes to the proposed nilotinib prescribing information based on this review:

1. INDICATIONS AND USAGE: Revised language to state “adult and pediatric patietns with newly diagnosed Ph+ CML in chronic phase” and “pediatric patients with Ph+ CML-CP resistant or intolerant to prior tyrosine-kinase inhibitor therapy” to reflect current practice in describing a patient population. The lower age was decreased from 2 years of age to 1 year of age because efficacy and safety were able to be extrapolated from young children to patients that would be 1 year or greater.
2. WARNINGS AND PRECAUTIONS: Added a Warning and Precaution for “Effect on Growth and Development” because BCR-ABL tyrosine kinase inhibitors have been associated with adverse growth and development in pediatric patients and patients need to be monitored. Recommended to add a comparative statement on hepatotoxicity because

pediatric patients experienced a higher incidence of Grade 3-4 hyperbilirubinemia and AST or ALT elevation.

3. ADVERSE REACTIONS: Added a statement specifying the most common adverse reactions and the most common Grade 3-4 adverse reaction in pediatric patients with Ph+ CML.
4. USE IN SPECIFIC POPULATIONS: Per the Pediatric labeling Guidance, Section 8.4 was updated to include any significant differences between pediatric and adults with regard to efficacy and safety.
5. CLINICAL STUDIES: The NCT numbers for the clinical studies were added. The information on dose intensity was moved to Section 6. The actual number of patients, in addition to the proportion, that achieved MMR were added to provide context. Possible misleading statement regarding deaths and progression of disease were removed.

11. Risk Evaluation and Mitigation Strategies (REMS)

There are no additional risk management strategies needed beyond recommended labeling. The review teams agreed that labeling is sufficient to address safety concerns for treatment with nilotinib.

12. Postmarketing Requirements and Commitments

The following Postmarketing Requirements (PMRs) are recommended:

1. To characterize the long-term safety of treatment with Tasigna in pediatric patients with Philadelphia chromosome positive chronic myeloid leukemia in chronic phase, submit annual interim and final reports and analysis datasets from Study CAMN107A2203 until at least 5 years of follow-up.

2. To characterize the effect of treatment with Tasigna on growth and development in pediatric patients with Philadelphia chromosome positive chronic myeloid leukemia in chronic phase, submit the final report and analysis datasets that include long-term follow-up of patients enrolled on CAMN107A2203. For pre-pubertal patients and those who have not completed pubertal development, include growth parameters, sexual maturation, bone metabolism parameters, and endocrine and reproductive toxicities in the safety evaluation. The growth and development safety data should include patients with at least 5 years of follow-up or until pubertal development is complete in at least 90% of patients, whichever is longer.

13. Appendices

13.1. References

1. Ries, L.A.G., et al., *Cancer incidence and survival among children and adolescents: United States SEER Program 1975-1995*. 1999, Bethesda: National Cancer Institute (NCI). 179 pp.

2. Millot, F., et al., *Clinical and biological features at diagnosis in 40 children with chronic myeloid leukemia.* Pediatrics, 2005. **116**(1): p. 140-3.

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4. Vardiman, J.W., N.L. Harris, and R.D. Brunning, *The World Health Organization (WHO) classification of the myeloid neoplasms.* Blood, 2002. **100**(7): p. 2292-302.

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7. Hijiya, N., F. Millot, and M. Suttorp, *Chronic myeloid leukemia in children: clinical findings, management, and unanswered questions.* Pediatr Clin North Am, 2015. **62**(1): p. 107-19.

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9. Millot, F., et al., *The International Registry for Chronic Myeloid Leukemia (CML) in Children and Adolescents (I-CML-Ped-Study): Objectives and Preliminary Results.* Blood, 2012. **120**(21): p. 3741.

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12. Kantarjian, H., et al., *Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia.* N Engl J Med, 2010. **362**(24): p. 2260-70.

13. Saglio, G., et al., *Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia.* N Engl J Med, 2010. **362**(24): p. 2251-9.

14. Bordini, B. and R.L. Rosenfield, *Normal Pubertal Development: Part II: Clinical Aspects of Puberty.* Pediatrics in Review, 2011. **32**(7): p. 281.

13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): A2120 and A2203

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 303		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)

Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 7		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

13.3. Ph+ CML Response Criteria

Response criteria utilized in Study A2120 and A2203.

Table 26 Ph+ CML Response Criteria

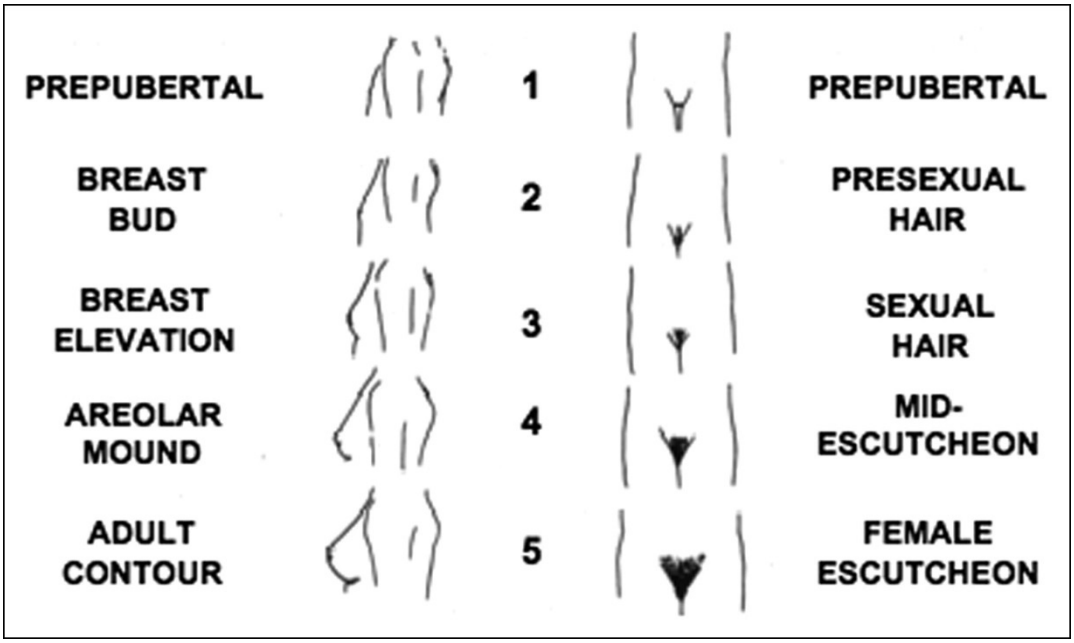
Response	Criteria
Complete Hematologic Response (CHR)	CHR is defined as all of the following present for ≥ 4 weeks (which means present at least at 2 visits 4-week apart, with no intermediate visit showing no CHR): • WBC count < 10 x 10^9/L • Platelet count < 450 x 10^9/L • Basophils <5% • No blasts and promyelocytes in peripheral blood • Myelocytes + metamyelocytes < 5% in peripheral blood • No evidence of extramedullary disease, including spleen and liver
Cytogenetic Response	Cytogenetic response will be assessed as the percentage of Ph+ metaphases in the bone marrow. At least 20 metaphases are required for determination of response. Cytogenetic response is defined as follows • Complete (CCyR) - 0% Ph+ metaphases • Partial (PCyR) - >0 to 35% Ph+ metaphases • Major* (MCyR) - 0 to 35% Ph+ metaphases • Minor (mCyR) - >35 to 65% Ph+ metaphases • Minimal - >65 to 95% Ph+ metaphases • None - >95 to 100% Ph+ metaphases *A major response (0 to 35% Ph+ metaphases) combines both complete and partial responses.
Major Molecular Response	A Major Molecular Response (MMR) is defined as at least 3.0 log reduction of BCR-ABL transcript from standardized baseline value, or 0.1% or less BCR-ABL/control gene (ABL) % by international scale, measured by RQ-PCR
Loss of CHR	Defined by the appearance of any of the following criteria, if this criterion is confirmed at least 4 weeks apart: • WBC count > 20 x 10^9/L • Platelet count ≥ 600 x 10^9/L • Appearance of myelocytes + metamyelocytes ≥ 5% in peripheral blood • Appearance of blasts or promyelocytes in peripheral blood • Progressive splenomegaly refractory to therapy CML-related death or progression to AP/BC will be considered as confirmed loss of CHR in any case.

Response	Criteria
Loss of MCyR	Defined as an increase in the Ph+ bone marrow cells to > 35% in two cytogenetic assessments obtained at least four weeks apart. For patients with response = PCyR, this would constitute loss of PCyR. One of the two assessments must be based on at least 20 metaphases, while the other assessment should be based on at least 5 metaphases. If there is any assessment in between, based on 20 or more metaphases and with Ph+ ≤ 35%, then the initial indication of loss of MCyR cannot be confirmed. However, an assessment indicating (unconfirmed) loss of MCyR will be considered as confirmed loss of MCyR if the patient also had confirmed loss of CHR after achievement of MCyR. CML-related death or progression to AP/BC will be considered as confirmed loss of MCyR in any case.
Loss of CCyR	Defined as an increase in the Ph+ bone marrow cells to >0% in 2 cytogenetic assessments at least 4 weeks apart (regardless of the total number of metaphases examined). If there was any assessment in-between based on 20 or more metaphases and with Ph+ = 0%, then the initial indication of loss of CCyR cannot be confirmed. However, an assessment indicating (unconfirmed) loss of CCyR will be considered as confirmed loss of CCyR if the patient had confirmed loss of CHR after achievement of CCyR. CML-related death or progression to AP/BC will be considered as confirmed loss of CCyR in any case.
Loss of MMR	Defined as confirmed loss of a greater than or equal to 3.0 log reduction in BCR-ABL transcript levels compared to the standardized baseline value, or confirmed loss of a less than or equal to 0.1% (BCR-ABL/control gene (ABL) %) by international scale in association with a ≥ 5-fold rise in BCR-ABL from the lowest value achieved on study treatment. This result has to be confirmed by a subsequent sample at least 4 weeks apart unless it is associated with confirmed loss of CHR or loss of CCyR or progression to AP/BC or CML-related death.
Disease Progression	1. CML-related death as determined by investigator. 2. Progression to Accelerated phase (AP) as defined by any of the following: • ≥ 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, but < 30% blast in peripheral blood or bone marrow aspirate • ≥ 20% basophils in the peripheral blood • Thrombocytopenia (<100 x 10^9/L) unrelated to therapy 3. Progression to blast crisis (BC) defined by any of the following: • ≥ 30% blasts in peripheral blood or bone marrow aspirate • Appearance of extramedullary involvement other than hepato-/ splenomegaly proven by biopsy (i.e., chloroma) Any value of AP or BC within the first 4 weeks of study treatment is not defined as progression to AP/BC within the study unless the patient discontinues study treatment due to progression or the treating physician determines there is unsatisfactory therapeutic effect within the first 8 weeks.

Response	Criteria
Progressive splenomegaly	The absolute measurement is not possible because children are growing individuals, therefore progressive splenomegaly must be individually defined by investigator. Progressive splenomegaly is defined as a spleen progressively extending below the left costal margin and possibly well into the left lower quadrant or pelvis, and/or which has crossed the midline of the abdomen. This assessment is made at the discretion of the investigator taking into account the patient's age and progression over time.
Progressive leukocytosis	A continued increase in WBC count above $>10x10^9$/L or assessed at the discretion of the investigator taking into account the patient's age and progression over time.

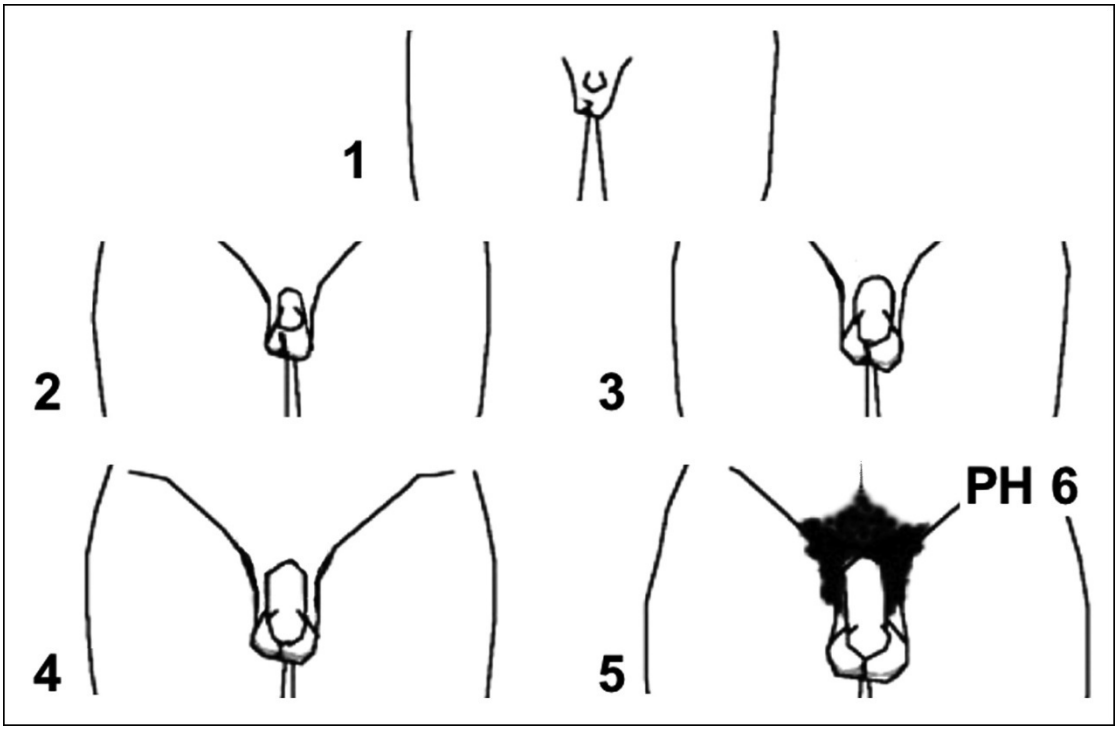
13.4. Tanner Staging (Sexual Maturity Rating)

Figure 4 Tanner Stages of Breast and Pubic Hair Development



Stages of breast and pubic hair development. Stage 1 is prepubertal. Breast stages (left panel): 2–a subareolar breast bud, 3–elevation of the breast contour and enlargement of the areolae, 4–the areolae form a secondary mound above the contour of the breast, 5–mature female breast with recession of the secondary mound and a dependent breast contour. Pubic hair stages (right panel): 2–sparse, fine, straight pubic hair; 3—long, dark, curly hair; 4–pubic hair resembles adult pubic hair in quality but not distribution, having not yet spread to the thighs; 5–pubic hair has adult quality and distribution, with spread to the medial thighs. Males go through the same pubic hair stages and on to stage 6 (male escutcheon, an inverted triangular extension of pubic hair up the midline) at maturity.

Figure 5 Tanner Stages of Male Genital Development



Genital stages in males. Stage 1 is prepubertal. Stage 2 is characterized by enlargement of the testes and scrotum but no enlargement of the penis. Stage 3 involves continued enlargement of the testes and scrotum along with penile growth, first in length and later in diameter. Stage 4 involves continued growth of the testes, scrotum, and penis, with enlargement of the glans. Stage 5 is mature male genitalia, which are shown with mature pubic hair (stage 6, PH6).

Current Best Estimates for Age of Onset of Pubertal Milestones in Normal Children in the United States General Population†

	Age of Onset	
Stage	**Mean**	**Range (5th to 95th)**
Girls		
Breast Buds (B2)	10.2	8.2 to 12.1*
Pubic Hair (PH3)	11.6	9.3 to 13.9**
Menarche	12.6	11.0 to 14.1***
Boys		
Testes length 2.6 cm (4 cc) (G2)	11.5	9.5 to 13.3
Pubic Hair (PH3)	12.6	10.7 to 14.5
Testes length 3.8 cm (12 cc) (G5)	14.0	11.5 to 16.5

- B2=breast stage 2, G2/5=genital stage 2/5, PH3=pubic hair stage 3
- ↲† Overweight girls' puberty is about 0.5 years earlier
- ↲* Thelarche is normal in the 7th year in non-Hispanic African American and Mexican American girls.
- ↲** Pubarche is approximtely 0.5 to 1.0 years earlier in non-Hispanic African American and Mexican American girls.
- ↲*** Menarche is approximately 0.5 years earlier in non-Hispanic African American and intermediate in Mexican American girls.

Bordini, B. and R.L. Rosenfield, *Normal Pubertal Development: Part II: Clinical Aspects of Puberty.* Pediatrics in Review, 2011. **32**(7): p. 281.

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