Pharmacokinetics of Nilotinib in Pediatric Patients with Philadelphia Chromosome–Positive Chronic Myeloid Leukemia or Acute Lymphoblastic Leukemia

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ABSTRACT

Purpose: We investigated nilotinib exposure in pediatric patients with chronic myeloid leukemia (CML) or Philadelphia chromosome–positive (Ph^+) acute lymphoblastic leukemia (ALL) resistant to, relapsed on, refractory to, or intolerant of previous treatment.

Patients and Methods: Fifteen patients (aged 1–<18 years) with CML resistant to or intolerant of imatinib and/or dasatinib ($n = 11$) or Ph^+ ALL relapsed on or refractory to standard therapy ($n = 4$) enrolled in this phase I study. Nilotinib (230 mg/m^2 twice daily; equivalent to the adult 400-mg twice-daily dose) was administered orally in 12 or 24 cycles of 28 days. The primary objective was to characterize the pharmacokinetics of nilotinib in pediatric patients.

Results: The area under the concentration–time curve at steady state was slightly lower in pediatric patients versus adults (14,751.4 vs. 17,102.9 ng/h/mL); the geometric mean ratio (GMR; pediatric:adult) was 0.86 [90% confidence interval (CI), 0.70–1.06]. Body surface area–adjusted systemic clearance was slightly higher in pediatric versus adult patients (GMR, 1.30; 90% CI, 1.04–1.62). Nilotinib was generally well tolerated. The most common adverse events were headache, vomiting, increased blood bilirubin, and rash. Three patients with CML achieved major molecular response, and three with Ph^+ ALL achieved complete remission.

Conclusions: Nilotinib 230 mg/m^2 twice daily in pediatric patients provided a pharmacokinetics and safety profile comparable with the adult reference dose; clinical activity was demonstrated in both CML and Ph^+ ALL. This dose is recommended for further evaluation in pediatric patients. The safety profile was consistent with that in adults.

Introduction

The development of BCR-ABL1 tyrosine kinase inhibitors (TKI) has profoundly improved the prognosis of patients with Philadelphia chromosome–positive (Ph^+) chronic myeloid leukemia (CML; refs. 1, 2). However, prior to 2017, imatinib was the only approved treatment for pediatric patients with CML in chronic phase (CP), and it remains the only approved treatment for those with CML in accelerated phase (AP) or blast crisis (BC; ref. 3). Some patients are resistant to or intolerant of imatinib, and the long-term adverse effects of treatment are still being explored (3–5). Thus, the second-generation TKIs nilotinib and dasatinib were investigated in pediatric CML-CP, and both recently received regulatory approval (6–8).

Prior to this study, nilotinib was indicated only for the treatment of adults with newly diagnosed CML-CP or with CML-CP/AP resistant to or intolerant of prior therapy, including imatinib (9). In the Evaluating Nilotinib Efficacy and Safety in Clinical Trials–Newly Diagnosed Patients study, adults with newly diagnosed CML-CP had higher rates and faster achievement of molecular response with nilotinib than with imatinib (10). Nilotinib also demonstrated activity in adults with Ph^+ acute lymphoblastic leukemia (ALL) in phase I and II studies (11, 12).

To evaluate the dosing of nilotinib in pediatric patients, we conducted a multicenter, open-label, phase I pharmacokinetic study (NCT01077544) in pediatric patients with Ph^+ CML or Ph^+ ALL. The study aimed to evaluate whether a fixed dose of 230 mg/m^2 twice daily achieved a nilotinib exposure similar to that observed in adults receiving the recommended dose of 400 mg twice daily, with the ultimate goal of identifying a dose for use in future pediatric studies. This method was preferred over the traditional dose escalation

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Translational Relevance

The development of BCR-ABL1 tyrosine kinase inhibitors has profoundly improved the prognosis of Philadelphia chromosome–positive (Ph$^+$) leukemias. In this phase I study, we investigated the pharmacokinetics of nilotinib in pediatric patients with chronic myeloid leukemia (CML) or Ph$^+$ acute lymphoblastic leukemia (ALL) resistant to, relapsed on, refractory to, or intolerant of previous treatment for comparison with the pharmacokinetics of nilotinib in adult patients. Our results showed that a dose of nilotinib 230 mg/m^2 twice daily in pediatric patients provided a pharmacokinetic and safety profile comparable with that of the adult reference dose, and clinical activity was demonstrated in both CML and Ph$^+$ ALL. Following our study, nilotinib 230 mg/m^2 twice daily was approved for the treatment of pediatric patients with CML in chronic phase.

approach to minimize the chance of exposing pediatric patients to ineffective doses of a drug known to benefit adult patients with a shared disease pathology (13–16).

Patients and Methods

Study design and patient eligibility criteria

Eligible patients (aged 1–<18 years) had CML-CP or AP and were resistant to or intolerant of imatinib and/or dasatinib or had Ph$^+$ ALL that had relapsed on or was refractory to standard therapy (see Supplementary Table S1 for key terms and abbreviations). A protocol amendment was made to include patients with newly diagnosed CML-CP, reflecting the approval of nilotinib for adult patients with newly diagnosed CML-CP as well as preliminary information from an interim analysis of this study; however, no patients with newly diagnosed disease were enrolled in the study. For patients with CML, resistance to imatinib/dasatinib was defined as increasing white blood cell or platelet counts (indicative of primary resistance or hematologic relapse), cytogenetic or molecular response consistent with suboptimal response or failure, progression to AP/BC, reappearance of Ph$^+$ bone marrow cells following achievement of complete cytogenetic response (CCyR), increase of >30% in Ph$^+$ cells in peripheral blood or bone marrow, or loss of molecular response. Intolerance of imatinib/dasatinib was defined as the development of adverse events (AE) requiring discontinuation of therapy. Patients must have had adequate heart, renal, hepatic, and pancreatic function as well as normal electrolyte levels. Patients receiving medications that inhibit or induce cytochrome P450 3A4 or that may prolong the QT interval and those who had received myelosuppressive chemotherapy within 3 weeks prior to study entry were not eligible. In the case of prior stem cell transplant or rescue without total body irradiation, patients with evidence of active GVHD and patients within 3 months of stem cell transplant were not eligible.

Patients were required to have a Karnofsky performance status of $\geq$50% (aged >10 years) or a Lansky performance status of $\geq$50% (aged $\leq$10 years). To evaluate the potential differences in pharmacokinetic parameters between younger and older pediatric patients, enrolled patients were assigned to 1 of 2 cohorts: aged 1 to <10 years or aged $\geq$10 to <18 years.

Study treatment

Nilotinib was administered orally in 50-, 150-, and/or 200-mg hard gelatin capsules at a dose of 230 mg/m^2 twice daily rounded to the nearest 50 mg (Supplementary Table S2), up to a maximum single dose of 400 mg. This dose was based on the recommended dose for adults of 400 mg twice daily, scaled to body surface area (BSA; ref. 11). Patients were not to consume food for $\geq$2 hours before the dose was taken, and no oral intake other than water was to be consumed for $\geq$1 hour after the dose was taken. Capsules were to be swallowed whole with water; patients with difficulty swallowing the capsule could disperse the contents in 1 teaspoon of applesauce (to be taken within 15 minutes of preparation; ref. 17).

Patients received a total of up to 12 or 24 cycles of nilotinib (28 days/cycle), depending on the protocol amendment under which they enrolled. On cycle 1 day 1, a single dose of nilotinib 230 mg/m^2 was administered to obtain a full 24-hour pharmacokinetic profile. Patients who completed $\geq$12 cycles of treatment and were benefiting from nilotinib could continue treatment in a rollover or compassionate-use study.

Study endpoints

The primary objective was to characterize the pharmacokinetic profile of nilotinib in pediatric patients, with a goal of identifying a dose for further pediatric studies to provide a nilotinib exposure with a dose equivalent to 400 mg twice daily in adult patients. Secondary objectives included assessment of safety and tolerability, evaluation of activity, and mutational analysis of peripheral blood by qRT-PCR.

Pharmacokinetic assessments

Single-dose pharmacokinetic parameters were calculated from full pharmacokinetic profiles obtained via serial sampling following a single administration of nilotinib 230 mg/m^2 on cycle 1 day 1. Steady-state pharmacokinetic parameters were calculated on the basis of trough concentrations of nilotinib on cycle 1 days 8, 15, 22, and 28 following twice-daily administration of nilotinib 230 mg/m^2. Serum concentrations of nilotinib were determined using a validated LC/MS-MS method (lower limit of quantification, 2.5 ng/mL). To assess steady-state pharmacokinetic parameters following multiple nilotinib doses, a sparse sampling approach (vs. more frequent serial sampling) was used to reduce the total blood sample volume required from pediatric patients.

Calculation of steady-state pharmacokinetic parameters

Area under the serum concentration–time curve (AUC) from time 0 to the end of the dosing interval at steady state (AUC_{SS}) was calculated as follows:

$$AUC_{tau} = AUC_{SS} = (C_{12h,SS}/C_{12h,1st\,dose}) \times AUC_{0-12h,1st\,dose},$$

where AUC_{tau} is the AUC from time 0 to the end of the dosing interval at steady state, $C_{12h,SS}$ is the average of the steady-state trough concentrations available on or after day 8, and AUC_{0-12h} is the AUC from 0 to 12 hours. Steady-state apparent systemic clearance (CL/F) was calculated as follows:

$$\text{steady-state } CL/F = dose/AUC_{tau}$$

Steady-state CL/F was then scaled according to BSA to obtain the BSA-adjusted CL/F.

Efficacy assessments for CML

Response assessments were performed through the end of the study, and best responses on treatment were reported. In patients with CML, activity was evaluated on the basis of hematologic, cytogenetic, and molecular responses, with best responses reported per category. Complete hematologic response (CHR) was defined as white blood cell

count of <10 × 10^9/L, platelet count of <450 × 10^9/L, basophils <5%, no blasts or promyelocytes in peripheral blood, myelocytes plus metamyelocytes <5% in peripheral blood, and no extramedullary involvement. Confirmed CHR was defined as CHR confirmed in 2 consecutive assessments ≥4 weeks apart.

Cytogenetic parameters included CCyR (0% Ph^+ metaphases), partial cytogenetic response (PCyR; >0%–35% Ph^+ metaphases), major cytogenetic response (0%–35% Ph^+ metaphases; i.e., CCyR or PCyR), minor cytogenetic response (>35%–65% Ph^+ metaphases), minimal cytogenetic response (>65%–95% Ph^+ metaphases), and no cytogenetic response (>95% Ph^+ metaphases). Evaluation of cytogenetic response required examination of ≥20 metaphases in each bone marrow sample.

Molecular response was assessed using a validated qRT-PCR assay for the e13a2/e14a2 *BCR-ABL1* transcript; results were reported as a ratio of *BCR-ABL1* transcripts to *ABL1* control transcripts, standardized to the International Scale (*BCR-ABL1*^{IS}). Major molecular response (MMR) was defined as a 3-log reduction in *BCR-ABL1* transcripts from a standardized baseline, or *BCR-ABL1*^{IS} ≤ 0.1%. If the e13a2/e14a2 transcript was not detected at baseline, samples were tested for the e1a2 transcript, although no molecular response on the IS could be determined; patients with e1a2 transcripts were monitored for treatment response based on changes in the *BCR-ABL1*/*ABL1* ratio over time and via hematologic and cytogenetic responses.

Efficacy assessments for Ph^+ ALL

Response assessments were performed through the end of the study, and best responses on treatment were reported. Complete remission with platelet recovery was defined as <5% blasts in bone marrow (M1 status), no blasts in peripheral blood, and platelet count of ≥100 × 10^9/L. Complete remission with incomplete platelet recovery was defined as M1 status, no blasts in peripheral blood, and platelet count of <100 × 10^9/L. Partial remission was

Table 1. Patient characteristics.

Parameter	All patients[a] (*N* = 15)	By age group		By disease	
		1–<10 years (*n* = 8)	≥10–<18 years (*n* = 7)	CML (*n* = 11)	Ph^+ ALL (*n* = 4)
Age, median (range), years	9 (5–17)	7 (5–9)	15 (10–17)	10 (5–17)	7 (7–10)
Male, *n* (%)	8 (53.3)	5 (62.5)	3 (42.9)	6 (54.5)	2 (50.0)
Race, *n* (%)					
White	12 (80.0)	6 (75.0)	6 (85.7)	9 (81.8)	3 (75.0)
Asian	2 (13.3)	1 (12.5)	1 (14.3)	1 (9.1)	1 (25.0)
Missing data	1 (6.7)	1 (12.5)	0	1 (9.1)	0
BSA, median (range), m^2	0.99 (0.70–1.95)	0.92 (0.70–1.03)	1.50 (0.98–1.95)	1.03 (0.70–1.95)	0.99 (0.97–1.18)
Patients with CML, *n*	NA	5	6	11	NA
Baseline disease status, *n* (%)[b]					
Newly diagnosed	NA	0	0	0	NA
Resistant/intolerant	NA	5 (100.0)	6 (100.0)	11 (100.0)	NA
Chronic phase	NA	5 (100.0)	6 (100.0)	11 (100.0)	NA
Accelerated phase	NA	0	0	0	NA
Time since initial diagnosis, median (range), months	NA	45.2 (11.4–84.9)	22.9 (3.7–35.6)	25.3 (3.7–84.9)	NA
Patients with Ph^+ ALL, *n*	NA	3	1	NA	4
Baseline disease status, *n* (%)[c]					
Active leukemia	NA	2 (66.7)	0	NA	2 (50.0)
Morphologic remission with evolving relapse	NA	1 (33.3)	1 (100.0)	NA	2 (50.0)
Time since initial diagnosis, median (range), months	NA	42.7 (33.1–46.0)	14.8	NA	37.9 (14.8–46.0)
No. of prior TKIs among patients with CML, *n* (%)[b,d]					
1	NA	2 (40.0)	3 (50.0)	5 (45.5)	NA
2	NA	3 (60.0)	2 (33.3)	5 (45.5)	NA
≥3	NA	0	1 (16.7)	1 (9.1)	NA
No. of prior antineoplastic medication regimens among patients with Ph^+ ALL, *n* (%)[c,e]					
1	NA	1 (33.3)	0	NA	1 (25.0)
2	NA	0	0	NA	0
≥3	NA	2 (66.7)	1 (100.0)	NA	3 (75.0)
Prior radiotherapy, *n* (%)	1 (6.7)	1 (12.5)	0	0	1 (25.0)
Prior stem cell transplant, *n* (%)	2 (13.3)	0	2 (28.6)	1 (9.1)	1 (25.0)
Other prior therapies, *n* (%)	1 (6.7)[f]	0	1 (14.3)[f]	1 (9.1)[f]	0

Abbreviations: NA, not applicable; No., number.

[a]For the adult reference population (*N* = 17), the median age was 49 years (range, 21–72 years); 9 (52.9%) were male; and 13 (76.5%) were white, 1 (5.9%) was black, and 3 (17.6%) were categorized as other. The median BSA was 1.95 m^2 (range, 1.42–2.47 m^2).

[b]Percentages are based on the number of patients with CML.

[c]Percentages are based on the number of patients with Ph^+ ALL.

[d]Prior TKIs received by patients with CML included imatinib, dasatinib, and nilotinib; other prior antineoplastic medications included hydroxyurea/hydroxycarbamide, interferon, cytarabine, and investigational drug (not specified).

[e]Prior antineoplastic medications received by patients with Ph^+ ALL included imatinib, dasatinib, antithymocyte immunoglobulin, asparaginase, busulfan, clofarabine, crisantaspase, cyclophosphamide, cyclosporine, cytarabine, daunorubicin, dexamethasone, doxorubicin, etoposide, fludarabine, hydrocortisone, ifosfamide, mercaptopurine, methotrexate, methylprednisolone, prednisolone, prednisone, treosulfan, vincristine, and vindesine.

[f]This patient underwent thrombapheresis.

defined as ≥5% to ≤25% blasts in bone marrow with adequate cellularity (M2 status) and complete disappearance of circulating blasts. Progressive disease was defined as >25% increase in blasts in bone marrow or peripheral blood, extramedullary involvement, >30% increase in Ph$^+$ metaphases in bone marrow, or central nervous system involvement. Stable disease was defined as lack of complete remission, partial remission, or progressive disease.

Mutational analyses

Mutational analyses were performed via sequencing of peripheral blood and bone marrow samples collected at baseline and the end of treatment; samples collected at other time points were also assessed if clinically indicated. Emerging mutations were reported for the following 12 key BCR-ABL1 amino acid residues: M244, G250, Q252, Y253, E255, V299, F311, T315, F317, M351, F359, and H396. Mutations were classified as follows: resistant (T315I), less sensitive (Y253H, F359V, E255K, and E255V), or sensitive (all other mutations except T315I, Y253H, F359V, E255K, and E255V).

Safety assessments

Safety and tolerability were assessed through the end of the study and 30 days after study drug discontinuation based on AEs and clinical laboratory evaluations. AEs were graded using the NCI Common Terminology Criteria for Adverse Events version 3.0.

Statistical analyses

At least 14 pediatric patients were planned for initial enrollment (≥7/age group). Based upon moderate to high interpatient variability in nilotinib pharmacokinetic values (32%–64% for the AUC) and the safety profile of nilotinib in adult patients (7, 11), a 2-fold difference in the AUC or CL/F between pediatric and adult patients would be considered clinically meaningful. An interim analysis was performed to compare pharmacokinetic data from the first 7 patients in each group with data from a subset of adult patients in a phase 1 dose escalation study (11) who received nilotinib 400 mg twice daily. If a ≥2-fold difference in the AUC or CL/F was observed between a group and the reference data, 5 additional patients would be enrolled in that

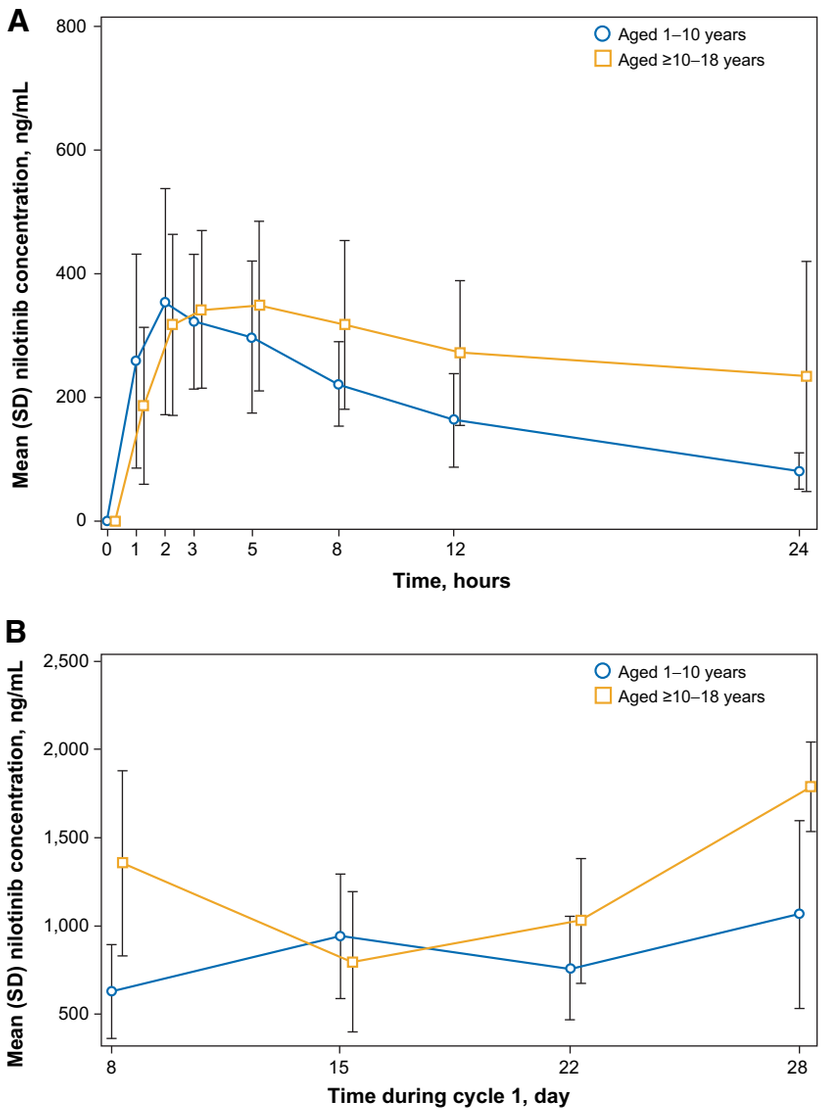

Figure 1.
Arithmetic mean nilotinib serum concentration–time profile on cycle 1 day 1 (**A**) and trough serum concentration-time profile at steady state by cohort (**B**).

group because a sample size of ≥12 patients would be required to provide sufficient precision (0.237 in log scale) to characterize the mean AUC. Pharmacokinetic analyses included all patients who received nilotinib on cycle 1 day 1 and had an evaluable pharmacokinetic profile (defined as having completed cycle 1 and/or had pharmacokinetic sampling sufficient for pharmacokinetic characterization) or ≥1 evaluable steady-state trough concentration. Single-dose pharmacokinetic parameters following administration of nilotinib on cycle 1 day 1 were estimated using noncompartmental analysis based on individual concentration–time profiles. AUC_{SS} and CL/F were derived from drug accumulation ratios based on steady-state trough concentrations of nilotinib on cycle 1 days 8, 15, 22, and 28. Geometric means for AUC_{SS} and BSA-adjusted CL/F at steady state were compared with the reference data from adult patients treated with nilotinib 400 mg twice daily. Because the terminal phases of the concentration–time profiles on cycle 1 day 1 were not attainable due to the limitations of 24-hour sampling, some parameters (e.g., AUC to infinity) could not be determined. AUC_{0-12h} and AUC from time 0 to the last quantifiable concentration point (AUC_{last}; where last is 24 hours) for cycle 1 day 1 were reported instead. Because full concentration–time profiles after a single dose or at steady state were not available, steady-state parameters such as AUC_{tau} and CL/F could not be calculated using noncompartmental analysis, and population pharmacokinetic analysis could not be used to estimate these parameters due to the small sample size. Demographic and baseline characteristics and response parameters were summarized using descriptive statistics for all patients. Safety analyses included all patients who received ≥1 dose of nilotinib.

Ethics

This study was conducted in accordance with the principles of the Declaration of Helsinki as well as local laws and regulations. Written informed consent was provided by each patient's parent or legal guardian prior to participation in the study; in addition, assent was obtained from patients who were able to provide a signature or verbal assent. The study protocol and amendments were reviewed by an independent ethics committee or Institutional Review Board of each study center.

Data sharing statement

Novartis will not provide access to patient-level data if there is a reasonable likelihood that individual patients could be reidentified. Phase I studies, by their nature, present a high risk of patient reidentification; therefore, individual patient results for phase I studies cannot be shared. In addition, clinical data, in some cases, have been collected subject to contractual or consent provisions that prohibit transfer to third parties. Such restrictions may preclude granting access under these provisions. Where codevelopment agreements or other legal restrictions prevent companies from sharing particular data, companies will work with qualified requestors to provide summary information where possible.

Results

Patient disposition

Fifteen patients aged 5 to 17 years with CML-CP or CML-AP resistant to or intolerant of imatinib and/or dasatinib or with Ph^+ ALL that had relapsed on or was refractory to standard therapy were enrolled and assigned to 2 cohorts: aged 1 to <10 years ($n = 8$, including 5 patients with CML and 3 with Ph^+ ALL) or aged ≥10 to <18 years ($n = 7$, including 6 with CML and 1 with Ph^+ ALL; **Table 1**). The median age (range) among all patients was 9 (5–17) years [younger group: 7 (5–9) years; older group: 15 (10–17) years]. All 11 patients with CML were resistant to or intolerant of imatinib and/or dasatinib and were in CP at study entry (median time from diagnosis, 25.3 months). Of the 4 patients with Ph^+ ALL (median time from diagnosis, 37.9 months), 2 had relapsed and 2 were in complete morphologic remission at study entry but met the eligibility criteria because they were experiencing an increase in levels of minimal residual disease. All patients had received ≥1 prior regimen of antineoplastic medication. In the younger group, all 5 patients with CML had previously received imatinib, while 3 also had received

Table 2. Nilotinib single-dose PK parameters for cycle 1 day 1.

Parameter	All patients ($N = 14$)[a]	Aged 1–<10 years ($n = 7$)[a]	Aged ≥10–<18 years ($n = 7$)[a]
C_{max}, ng/mL			
Mean (SD)	428.1 (146.5)	433.3 (163.1)	422.9 (140.8)
Median (range)	402.0 (222.0–669.0)	407.0 (222.0–669.0)	397.0 (231.0–636.0)
Geometric mean (CV, %)	403.9 (37.3)	405.1 (42.5)	402.7 (35.2)
T_{max}, h			
Mean (SD)	NA	NA	NA
Median (range)	2.53 (1.02–7.88)	2.00 (1.02–7.08)	3.00 (2.00–7.88)
Geometric mean (CV, %)	NA	NA	NA
AUC_{last}, ng/h/mL			
Mean (SD)	5,355.1 (2,595.1)	4,397.1 (1,500.8)	6,313.1 (3,193.4)
Median (range)	4,727.2 (2,116.9–12,625.5)	4,374.3 (2,116.9–6,820.3)	5,704.0 (2,759.8–12,625.5)
Geometric mean (CV, %)	4,873.2 (46.8)	4,161.0 (38.5)	5,707.4 (51.2)
AUC_{0-12h}, ng/h/mL			
Mean (SD)	3,231.7 (1,042.0)	2,932.3 (917.1)	3,531.0 (1,141.1)
Median (range)	3,087.4 (1,490.1–5,755.0)	2,895.7 (1,490.1–4,098.2)	3,331.8 (2,316.2–5,755.0)
Geometric mean (CV, %)	3,080.0 (33.5)	2,795.8 (35.7)	3,393.2 (30.4)

Abbreviations: AUC_{0-12h}, area under the serum concentration–time curve from 0 to 12 hours; AUC_{last}, area under the serum concentration–time curve from time 0 to the last quantifiable concentration point; C_{max}, maximum concentration observed; CV, coefficient of variation; NA, not applicable; PK, pharmacokinetics; T_{max}, time to reach maximum concentration.

[a]Includes patients with available PK data (1 patient aged 1–<10 years had unevaluable PK samples due to a storage temperature excursion).

dasatinib. In the older group, all 6 patients with CML had previously received imatinib, 1 also had received dasatinib, and another had received both dasatinib and nilotinib (sequentially) and also had a history of stem cell transplant and donor lymphocyte infusion. Among those with Ph$^+$ ALL, all 3 patients in the younger group had previously received imatinib in combination with other therapies (1 also received total-body radiotherapy prior to stem cell transplant); the patient in the older group had previously received imatinib and dasatinib (sequentially) and prior stem cell transplant.

Seven patients (46.7%) completed the study treatment period per protocol (2 received 24 cycles and 5 received 12 cycles of treatment), and 8 patients discontinued treatment (Supplementary Fig. S1). Of the 6 patients who discontinued due to new cancer therapy, 5 with CML (2 aged 1–<10 years, 3 aged ≥10–<18 years) had inadequate responses as determined by the investigator (due to lack of an MMR or lack of a substantial decrease in *BCR-ABL1*), 4 subsequently underwent stem cell transplant, and 1 received dasatinib, while 1 patient with Ph$^+$ ALL in the younger group achieved complete remission at the end of treatment and subsequently underwent stem cell transplant followed by treatment with chimeric antigen receptor T cells. Of the remaining 2 patients (both aged ≥10–<18 years), 1 with CML discontinued due to increasing blasts and 1 with Ph$^+$ ALL discontinued due to AEs. Of the 7 patients who completed the study treatment period, 5 were benefiting from nilotinib and continued treatment in a rollover study ($n = 4$) or compassionate-use study ($n = 1$); information regarding the 2 remaining patients is not available.

Pharmacokinetics

The arithmetic mean serum concentration–time profiles for nilotinib on cycle 1 day 1 are shown in **Fig. 1A**, and pharmacokinetic parameters following a single dose of nilotinib are summarized in **Table 2**. Nilotinib exposure following a single dose was comparable between patients in both age groups. The maximum concentration observed and time to reach the maximum concentration were similar between groups. Differences between groups in the geometric mean AUC_{last} and AUC_{0-12h} were small, with coefficients of variation of ≥30%. The arithmetic mean trough serum concentration–time profiles for nilotinib at steady state are shown in **Fig. 1B**, while the steady-state pharmacokinetic parameters are summarized in **Table 3**. Steady-state nilotinib exposure was similar in both age groups, with differences of <10% observed between groups in AUC_{SS} and BSA-adjusted CL/F. AUC_{SS} was slightly lower in pediatric versus adult patients (14,751.4, 15,129.2, and 14,383.1 ng/h/mL in all pediatric patients, those aged 1–<10 years, and those aged ≥10–<18 years, respectively, vs. 17,102.9 ng/h/mL in adult patients). Geometric mean ratios (pediatric:adult) were 0.86, 0.89, and 0.84 in all pediatric patients, the younger group, and the older group, respectively. BSA-adjusted CL/F was slightly higher in pediatric versus adult patients (15.64, 15.36, and 15.92 L/h/m^2 in all pediatric patients, the younger group, and the older group, respectively, versus 12.03 L/h/m^2 in adult patients). Geometric mean ratios (pediatric:adult) were 1.30, 1.28, and 1.32 in all pediatric patients, the younger group, and the older group, respectively. Overall, differences between pediatric and adult patients in AUC_{SS} and BSA-adjusted CL/F were ≈30% or less, and the lower and upper bounds of the 90% CIs for the geometric mean ratios were within a predefined 2-fold range of the data from the adult reference population for both AUC_{SS} and BSA-adjusted CL/F.

Clinical activity

Best responses to treatment in patients with CML or Ph$^+$ ALL are presented in **Table 4**. Of the 11 patients with CML, all were assessed for hematologic and molecular responses and 10 were assessed for cytogenetic response (1 patient discontinued from the study before an evaluable on-treatment cytogenetic assessment was obtained). Best responses during study treatment included MMR in 27.3% of patients (3/11) and CCyR in 36.4% of patients (4/11). Ten patients had a CHR and 1 had a CHR not confirmed at a subsequent visit. For the cytogenetic assessment, the best responses were CCyR in 4 patients

Table 3. Nilotinib steady-state PK parameters estimated from noncompartmental analysis.

Parameter	All patients ($N = 14$)[a]	Aged 1–<10 years ($n = 7$)[a]	Aged ≥10–<18 years ($n = 7$)[a]
AUC_{SS}, ng/h/mL			
Mean (SD)	15,521.6 (5098.2)	16,036.2 (6,017.9)	15,007.0 (4,414.0)
Median (range)	14,268.4 (7,943.9–26,984.9)	14,420.1 (9,032.5–26,984.9)	14,046.4 (7,943.9–19,807.2)
Geometric mean (CV, %)			
Pediatric patients	14,751.4 (34.5)	15,129.2 (38.0)	14,383.1 (33.6)
Adult reference population ($N = 17$)	17,102.9	NA	NA
Geometric mean ratio (90% CI) vs. adults	0.86 (0.70–1.06)	0.89 (0.68–1.15)	0.84 (0.65–1.09)
BSA-adjusted CL/F, L/h/m^2			
Mean (SD)	16.58 (6.14)	16.23 (5.48)	16.93 (7.18)
Median (range)	16.33 (7.94–32.11)	16.13 (7.94–22.99)	16.53 (11.72–32.11)
Geometric mean (CV, %)			
Pediatric patients	15.64 (36.3)	15.36 (38.7)	15.92 (37.0)
Adult reference population ($N = 17$)	12.03	NA	NA
Geometric mean ratio (90% CI) vs. adults	1.30 (1.04–1.62)	1.28 (0.97–1.68)	1.32 (1.01–1.74)
C_{min}, ng/mL			
Mean (SD)	967.1 (270.5)	842.3 (270.1)	1,091.9 (221.7)
Median (range)	979.8 (549.0–1,435.0)	877.0 (549.0–1,236.7)	1,055.7 (835.7–1,435.0)
Geometric mean (CV, %)	929.2 (30.9)	804.8 (33.7)	1,072.9 (20.5)
Geometric mean ratio (90% CI) vs. adults	ND	ND	ND

Abbreviations: AUC_{SS}, area under the serum concentration–time curve from time 0 to the end of the dosing interval at steady state; CL/F, apparent systemic clearance; C_{min}, lowest trough concentration observed (average of evaluable C_{trough} values from cycle 1 days 8, 15, 22, and 28); CV, coefficient of variation; NA, not applicable; ND, not done; PK, pharmacokinetic.

[a]Includes patients with available PK data (1 patient aged 1–<10 years had unevaluable PK samples due to a storage temperature excursion).

Table 4. Best responses on treatment in patients with CML or Ph$^+$ ALL.

Response category	All patients ($N = 15$)	Aged 1–<10 years ($n = 8$)	Aged ≥10–<18 years ($n = 7$)
Patients with CML, *n*	11	5	6
Assessed for hematologic response, *n*	11	5	6
Confirmed CHR, *n* (%)[a]	10 (90.9)[b]	5 (100.0)[c]	5 (83.3)[b,d]
Assessed for cytogenetic response, *n*	10[e]	5	5[e]
CCyR, *n* (%)[a]	4 (40.0)	2 (40.0)[f]	2 (40.0)[g]
PCyR, *n* (%)[a,h]	1 (10.0)	0	1 (20.0)
mCyR, *n* (%)[a,h]	1 (10.0)	0	1 (20.0)
Absence of Ph$^+$ at baseline, *n* (%)[a,i]	4 (40.0)	3 (60.0)	1 (20.0)
Assessed for molecular response, *n*	11	5	6
MMR, *n* (%)[a,j]	3 (27.3)	1 (20.0)	2 (33.3)
Patients with Ph$^+$ ALL, *n*[k]	4	3	1
CR with platelet recovery, *n* (%)	3 (75.0)	2 (66.7)	1 (100.0)
Stable disease, *n* (%)[l]	1 (25.0)	1 (33.3)	0

Abbreviations: CR, complete remission; mCyR, minor cytogenetic response; MMR, major molecular response (*BCR-ABL1* ≤ 0.1% on the International Scale).
[a]Percentages are based on the number of patients assessed for each response category.
[b]One additional patient with CML aged ≥10–<18 years met the criteria for CHR, but the result was not confirmed at a subsequent visit within 4 weeks; this patient had an MMR and CCyR on treatment.
[c]Of these 5 patients, 1 also had an MMR and no Ph$^+$ at baseline, 2 also had a CCyR, and 2 had no Ph$^+$ at baseline.
[d]Of these 5 patients, 1 also had an MMR and CCyR, 1 each also had a PCyR and mCyR, 1 had no Ph$^+$ at baseline, and 1 discontinued due to new cancer therapy before an evaluable cytogenetic assessment was obtained.
[e]Cytogenetic response data were not available for 1 additional patient (aged ≥10–<18 years) who was Ph$^+$ at baseline and discontinued due to new cancer therapy before an evaluable cytogenetic assessment was obtained.
[f]These 2 patients received 336 and 72 days of treatment, respectively, without achieving an MMR.
[g]These 2 patients also had an MMR (661 and 336 days of treatment, respectively).
[h]The patients with a PCyR and mCyR received 185 and 107 days of treatment, respectively, without achieving a CCyR or MMR.
[i]These patients had a CCyR at baseline and were not counted as having achieved a CCyR on treatment; hence, they were classified as having no Ph$^+$ at baseline to distinguish from patients who achieved a CCyR during treatment.
[j]Of the 8 patients who did not have an MMR, best responses were CCyR ($n = 2$), PCyR ($n = 1$), mCyR ($n = 1$), and CHR ($n = 4$; 3 were not Ph$^+$ at baseline and 1 discontinued due to new cancer therapy before an evaluable cytogenetic assessment was obtained).
[k]All patients with Ph$^+$ ALL were assessed for treatment response.
[l]This patient received 324 days of nilotinib without achieving partial or complete remission.

and partial and minor cytogenetic responses in 1 patient each; 4 additional patients had a CCyR at baseline and were not counted as having achieved a CCyR on treatment; they were thus conservatively counted in a stand-alone category as "absence of Ph$^+$ at baseline." For the molecular assessment, 3 patients had an MMR on treatment. No patient with CML progressed to either AP or BC.

Of the 2 patients with Ph$^+$ ALL who were in remission at baseline, 1 relapsed to stable disease and later regained complete remission with platelet recovery by the end of treatment, while the other relapsed and stayed in stable disease for the duration of the study. The 2 remaining patients with Ph$^+$ ALL who were not in remission at baseline achieved complete remission with platelet recovery during the study. Thus overall, of the 4 patients with Ph$^+$ ALL, 3 achieved a complete remission with platelet recovery and 1 had stable disease.

Mutational analyses

Nine patients with CML and 2 patients with Ph$^+$ ALL had evaluable mutational assessments at baseline. One patient with CML had an H396P mutation (the patient had an MMR on treatment) and 1 patient with Ph$^+$ ALL had a Y253F mutation (the patient achieved complete remission with platelet recovery on treatment); neither patient had an evaluable end-of-treatment mutational assessment. Only 4 patients had evaluable mutational assessments at the end of treatment; these 4 patients were among the 9 with CML who had evaluable baseline assessments, and no mutations were reported for these patients at either baseline or the end of treatment. One of these 4 patients had an MMR at the end-of-treatment response assessment, whereas the other 3 patients did not achieve an MMR but had either CCyR and CHR ($n = 1$), CHR only ($n = 1$), or neither CCyR nor CHR ($n = 1$).

Safety

All 15 patients had ≥1 AE (regardless of relationship to study drug; **Table 5**); overall, the most common AEs were headache and vomiting [6 patients (40.0%) each] and increased blood bilirubin and rash [5 patients (33.3%) each]. Grade 3/4 AEs were reported in 6 patients (40.0%), 4 with CML and 2 with Ph$^+$ ALL. Of the 4 patients with CML, 2 aged ≥10 to <18 years had neutropenia and 2 aged 1 to <10 years had elevated blood bilirubin (reported events were increased blood bilirubin and hyperbilirubinemia). Of the 2 patients with Ph$^+$ ALL, 1 aged 1 to <10 years had an appendix disorder (appendicitis) and 1 aged ≥10 to <18 years had increased blood urea. These grade 3/4 AEs did not lead to treatment discontinuation. Five patients (33.3%) had serious AEs; these included the 2 patients with CML who had grade 3/4 neutropenia and the 1 patient with Ph$^+$ ALL who had grade 3 appendicitis. Another 2 patients with Ph$^+$ ALL had influenza-like illness/pyrexia (aged 1–< 10 years) and renal failure (aged ≥10–<18 years), respectively. One patient with Ph$^+$ ALL aged ≥10 to <18 years discontinued due to multiple AEs (increased blood bilirubin, blood creatinine, blood urea, and blood uric acid); all of these AEs were grade ≤2, considered unrelated to study drug, and resolved.

In assessments based on groupings of AE terms, 8 patients (53.3%) had AEs related to hepatic transaminase and bilirubin elevations, and 7 (46.7%) had rash-related AEs (Supplementary Table S3). Hy's law comprises thresholds for alanine aminotransferase and total bilirubin levels that suggest whether a patient is at high risk of drug-induced liver injury (excluding other potential causes). No cases of Hy's law or potential Hy's law occurred, and there were no deaths. Grade 3/4 shifts from baseline in newly occurring or worsening clinical laboratory abnormalities were observed in absolute neutrophils, bilirubin, and phosphate. Three patients (20.0%; all aged ≥10–<18 years) had decreased absolute neutrophils with a grade 0 to grade 3 shift. Two patients (13.3%; both aged 1–<10 years) had increased bilirubin with a grade 0/1 to grade 3 shift. One patient (6.7%; aged ≥10–<18 years) had decreased phosphate with a grade 0 to grade 3 shift.

Discussion

In this phase I study of nilotinib in pediatric patients with CML or Ph$^+$ ALL, nilotinib 230 mg/m^2 twice daily provided AUC_{SS} and BSA-

Table 5. AEs of any grade reported in ≥3 patients overall (regardless of relationship to study drug).

MedDRA preferred term	All patients ($N = 15$)	By age group		By disease	
		1–<10 years ($n = 8$)	≥10–<18 years ($n = 7$)	CML ($n = 11$)	Ph$^+$ ALL ($n = 4$)
Any AE, *n* (%)	15 (100.0)	8 (100.0)	7 (100.0)	11 (100.0)	4 (100.0)
Headache	6 (40.0)	4 (50.0)	2 (28.6)	4 (36.4)	2 (50.0)
Vomiting	6 (40.0)	3 (37.5)	3 (42.9)	4 (36.4)	2 (50.0)
Blood bilirubin increased[a]	5 (33.3)	2 (25.0)	3 (42.9)	3 (27.3)	2 (50.0)
Rash	5 (33.3)	3 (37.5)	2 (28.6)	5 (45.5)	0
ALT increased	4 (26.7)	3 (37.5)	1 (14.3)	3 (27.3)	1 (25.0)
Cough	4 (26.7)	2 (25.0)	2 (28.6)	2 (18.2)	2 (50.0)
Diarrhea	4 (26.7)	1 (12.5)	3 (42.9)	2 (18.2)	2 (50.0)
Hyperbilirubinemia[a]	4 (26.7)	2 (25.0)	2 (28.6)	3 (27.3)	1 (25.0)
Nasopharyngitis	4 (26.7)	4 (50.0)	0	2 (18.2)	2 (50.0)
Pain in extremity	4 (26.7)	3 (37.5)	1 (14.3)	3 (27.3)	1 (25.0)
Rhinitis	4 (26.7)	3 (37.5)	1 (14.3)	3 (27.3)	1 (25.0)
Abdominal pain	3 (20.0)	1 (12.5)	2 (28.6)	3 (27.3)	0
Arthralgia	3 (20.0)	0	3 (42.9)	3 (27.3)	0
AST increased	3 (20.0)	3 (37.5)	0	2 (18.2)	1 (25.0)
Eczema	3 (20.0)	2 (25.0)	1 (14.3)	3 (27.3)	0
Nausea	3 (20.0)	0	3 (42.9)	3 (27.3)	0

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; MedDRA, Medical Dictionary for Regulatory Activities.
[a]A total of 9 patients had AEs of blood bilirubin increased ($n = 5$) or hyperbilirubinemia ($n = 4$).

adjusted CL/F values that were within 2-fold of the reference data from adult patients with CML treated with nilotinib 400 mg twice daily. This suggests that the steady-state nilotinib exposure in pediatric patients receiving a dose of 230 mg/m^2 twice daily is comparable with that observed in adult patients receiving 400 mg twice daily. For single-dose pharmacokinetic parameters, the small differences in AUC_{last} and AUC_{0-12h} observed between age groups were not considered meaningful given the small sample size and high coefficients of variation. Similarly, no notable differences were seen between age groups in AUC_{SS} or CL/F. These findings support a nilotinib dose of 230 mg/m^2 twice daily in pediatric patients aged 1 to <18 years.

Overall, nilotinib 230 mg/m^2 was associated with a good safety profile in pediatric patients. Few patients experienced grade 3/4 AEs, all serious AEs resolved, and only 1 patient discontinued due to AEs. Safety findings were generally similar between patients in the 2 age groups. No deaths were reported, which is notable given that 4 of the 15 patients had relapsed/refractory Ph$^+$ ALL. These safety results are generally consistent with those observed in adult patients treated with nilotinib 400 mg twice daily (10, 18, 19), and no new safety signals were identified. Despite somewhat high rates of bilirubin elevations, no cases of Hy's law or potential Hy's law were reported.

Nilotinib demonstrated activity in pediatric patients with CML or Ph$^+$ ALL. Among patients with CML, the best response during study treatment was MMR in 27.3% (3/11) and CCyR in 36.4% (4/11); no progressions to AP/BC were observed. In a phase II study of nilotinib 400 mg twice daily in adult patients resistant to or intolerant of imatinib, the MMR rate was 28% and the CCyR rate was 44% based on a follow-up of ≥24 months (20). Of the 4 patients with Ph$^+$ ALL, 3 achieved complete remission with platelet recovery and 1 had stable disease. Although the numbers of patients are small, these findings are encouraging given that the patients with CML were resistant to or intolerant of imatinib/dasatinib, and the patients with Ph$^+$ ALL had relapsed/refractory disease. No notable differences in activity were observed between the 2 age groups.

In summary, these findings confirm 230 mg/m^2 twice daily as the recommended nilotinib dose for further studies in pediatric patients. Because patients are required to receive treatment twice daily ≥2 hours after and ≥1 hour before food, challenges of this dosing schedule should be addressed when considering meal planning for young children and families. Because the age range of patients enrolled in this study was 5 to 17 years, future studies/analyses may be needed to evaluate the pharmacokinetics of nilotinib in younger patients (e.g., those aged <5 years), although the prevalence of these diagnoses in younger patients is low. Further investigations of dosing in patients who are close to adulthood (e.g., 15–18 years) would also be of interest. The efficacy and safety of nilotinib in pediatric patients with newly diagnosed CML-CP or CML-CP/-AP and resistance to or intolerance of imatinib/dasatinib are being further evaluated in an ongoing phase II study (NCT01844765).

Disclosure of Potential Conflicts of Interest

N. Hijiya is an unpaid consultant/advisory board member for Novartis. J. Landman-Parker reports receiving commercial research grants from Boehringher. X. Tian is an employee/paid consultant for and holds ownership interest (including patents) in Novartis. A. Buchbinder is an employee/paid consultant for Novartis and holds ownership interest (including patents) in Equity. No potential conflicts of interest were disclosed by the other authors.

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