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Section designation: Scientific section, clinical trials and observations

Title: A phase 1/2, open-label, dose-escalation study of midostaurin in children with relapsed or refractory acute leukemia (116 characters, limit 120)

Short title: MIDOSTAURIN IN PEDIATRIC R/R ACUTE LEUKEMIA (43 characters, limit 50)

Submitted [date]; accepted [date]. Prepublished online as Blood First Edition Paper, [date]; DOI 10.1182/blood-YYYY-MM-NNNNNN.

Presented as a poster at the 57th annual meeting of the American Society of Hematology, Orlando, FL, December 6, 2015 (abstract 2564).

The online version of the article contains a data supplement.

Key Points

- Midostaurin monotherapy was adequately tolerated in children with *FLT3*-mutated AML or *MLL*-rearranged ALL, and the safety profile was consistent with that of adult studies (*186 characters*)
- The observed single agent activity indicates that future trials evaluating midostaurin pediatric acute leukemia should be in combination with standard chemotherapy (*164 characters*)

Abstract (249 words)

FLT3-mutated acute myeloid leukemia (AML) and *MLL*-rearranged acute lymphoblastic leukemia (*MLL*r-ALL) are associated with activation or increased expression of FLT3, respectively. This multicenter, dose-escalation study evaluated oral midostaurin solution (doses ≤60 mg/m^2 twice daily [bid]) in pediatric patients with relapsed or refractory *FLT3*-mutated AML or *MLL*r-ALL. The primary objective was to determine the recommended dose for expansion (RDE) for 2 age groups (3 months to 2 years; >2 to <18 years). Secondary objectives included response rate, overall survival (OS), and safety. Among 22 patients, 9 had *FLT3*-mutated AML (all older), and 13 had *MLL*r-ALL (11 younger, 2 older). For patients with *FLT3*-mutated AML and *MLL*r-ALL, the rate of best clinical response (mostly blast reductions) was 55.6% (1 patient achieved an incomplete remission) and 23.1%, respectively. The median OS was 3.7 months and 1.4 months, respectively. No dose-limiting toxicities (DLTs) occurred with the 30 mg/m^2 bid dose (0/6); 1 DLT occurred with the 60 mg/m^2 bid dose (1/11). The most common adverse events (AEs) were vomiting, pyerexia, thrombocytopenia, diarrhea, and nausea; grade 3/4 AEs were more common in the 60 mg/m^2 cohort. Midostaurin in combination with induction/consolidation chemotherapy significantly improved survival compared with placebo in adult patients with *FLT3*-mutated AML. Evaluation of midostaurin in combination with chemotherapy in pediatric *FLT3*-mutated AML is warranted. The RDE for midostaurin in combination with chemotherapy was set at 30 mg/m^2 bid, given the known toxicities of standard chemotherapy in combination with midostaurin in adult patients with AML. (Funded by Novartis Pharmaceuticals; ClinicalTrials.gov number, NCT00866281)

Introduction

Acute leukemias comprise approximately 27% of childhood cancers, and among these the most frequent are acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML).[1] *Mixed lineage leukemia* gene rearrangements (*MLL*r) occur more frequently in infants (53%-80% of patients with ALL aged <1 year) than in children (5% of children with ALL aged >1 year).[2,3] Patients with *MLLr*-ALL have a worse prognosis than patients without *MLLr*-ALL.[3,4] The outcome of childhood AML has improved over the past several decades.[1] In recent collaborative group studies both the median event-free survival (EFS) and overall survival (OS) have ranged between 3 and 8 years, and the percentage of patients who relapse has declined to approximately 30% (reviewed in Zwaan 2015).[5]

FLT3

Fms-like tyrosine kinase 3 (FLT3), a receptor tyrosine kinase that is an important mediator of signal transduction in normal hematopoiesis,[6] is highly expressed in hematologic malignancies, including AML and ALL.[7] High levels of *FLT3* gene expression have been associated with an increased risk of relapse in pediatric patients with AML[8] and in infant ALL.[9] Activating mutations in FLT3, such as internal tandem duplications (ITD) and tyrosine kinase domain (TKD) point mutations have also been identified in 12% to 18% and 3% to 7% of pediatric patients with AML, respectively.[10-12] The frequency of *FLT3* mutations in children with AML increases with age.[13] In general, *FLT3* mutations are rare in patients with ALL,[14] but they occur at a higher frequency in patients with *MLL*r-ALL, particularly *FLT3*-TKD mutations.[14-16]

The presence of a *FLT3*-ITD mutation confers a poorer prognosis in pediatric AML, and the presence of a *FLT3*-ITD allelic ratio (AR) >0.4 is a significant and independent prognostic factor for relapse.[12] In a recent report of 54 children with newly diagnosed *FLT3*-ITD AML who were treated in the AIEOP AML-2002 study, the presence of this mutation was associated with older age, higher WBC, and a higher probability of relapse.[17] Among these patients, 51% had an ITD mutation with a high AR that was

associated with poorer prognosis (3-year EFS 19.2% compared to 63.5% for low AR patients). Patients with a less than 2 log reduction in *FLT3*-ITD minimal residual disease (MRD) after one cycle of induction chemotherapy had a lower EFS and increased cumulative incidence of relapse (CIR) compared to those with a greater than 2 log reduction.[17] Likewise, *FLT3* overexpression is also associated with poor prognosis in patients with *MLL*r-ALL.[18,19]

Midostaurin

Midostaurin (PKC412, CGP41251), an N-benzoylated staurosporine derivative, is amutlikinase inhibitor that was recently approved by the US Food and Drug Administration for use in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation chemotherapy in adult patients with *FLT3*-mutated AML.[20] Midostaurin inhibits the FLT3 tyrosine kinase that serves a key signaling role in normal hematopoiesis and in the pathogenesis of leukemias.[16,21] Midostaurin also inhibits protein kinase C and the mutated tyrosine kinases KIT-D816V, KIT-D816Y and FGFR3-K650E in mastocytosis and multiple myeloma.[22-24]

Patients and methods

Study design

This was a multicenter dose-escalation and dose-expansion study (NCT00866281), oral midostaurin solution was administered to children aged 3 months to <18 years in 2 age groups: younger and older (**Figure 1**). The bioequivalency of the oral midostaurin solution to that of the soft gel capsules used in adult patients was evaluated in healthy volunteers prior to the initiation of this study (**Supplemental Information**). The first cohort received the starting dose of midostaurin 30 mg/m^2 bid, equivalent to the adult dose of 50 mg bid; patients with a body surface area ≥1.67 received midostaurin 50 mg bid. Each subsequent cohort received increasing doses until the maximum dose (60 mg/m^2 bid, equivalent to the 100 mg bid adult dose) was reached or until the stopping rules were met due to dose-limiting toxicity

(DLT), which was defined as a nonhematologic grade 3/4 AE or drug-related abnormal laboratory value or an AE leading to study discontinuation within 14 days of starting treatment. Exceptions to DLT were grade 3/4 alkaline phosphatase elevations, grade 3/4 AEs related to disease progression, alopecia, and febrile neutropenia lasting up to 3 days. Grade 3/4 nausea and vomiting was considered to be a DLT if it persisted despite appropriate anti-emetic treatment.

Oral midostaurin was administered as an oral solution every 12 hours in 14-day cycles. Patients could receive >1 cycle of midostaurin if considered clinically appropriate by the investigator and in the absence of safety concerns. The starting dose of midostaurin for each age strata was 30 mg/m^2 bid (or 50 mg bid for patients with a body surface area ≥1.67 m^2).

Patients

Eligible patients had a documented diagnosis of *FLT3*-mutated AML or *MLL*r-ALL and an expected survival of ≥8 weeks. *MLL*r-ALL was either refractory to standard induction therapy or in first or subsequent relapse. *FLT3*-mutated AML was refractory to at least two different induction regimens, refractory to re-induction at first relapse, or in second or greater relapse. A performance status (PS) of ≥60 was required; Lansky PS was used for patients ≤12 years and Karnofsky PS was used for patients >12 years. Patients had adequate organ function, as assessed by aspartate transaminase (AST) and alanine transaminase (ALT) ≤5× the upper limit of normal (ULN), serum total bilirubin ≤1.5×ULN, and serum creatinine ≤2× ULN. Patients with isolated extramedullary leukemia or symptomatic leukemic central nervous system involvement were excluded, as were patients who had received prior treatment with a FLT3 inhibitor or investigational agent, except for sorafenib.

Objectives

The primary objective of this study was to determine the maximum tolerated dose (MTD) or recommended dose for expansion (RDE) of oral midostaurin solution in this pediatric population. Secondary objectives included characterizing the population pharmacokinetics (PK) of midostaurin and its metabolites, assessing the safety and tolerability of midostaurin, and determining overall response rates (ORR) per modified Cheson criteria (see **Supplemental Table 2**),[28] time to relapse, and OS.

Assessments

Safety was monitored continuously throughout treatment and up to 28 days after discontinuation according to the Common Toxicity Criteria for AEs (CTCAE), version 3.0. Bone marrow aspirate/biopsy were performed at baseline, on the first day of cycles 2 and 3, the beginning of every other cycle thereafter, and at the end of treatment. Response was assessed weekly beginning on cycle 1, day 8 through cycle 3, day 1; therafter, the assessments occurred at the discretion of the investigator in order to confirm clinical benefit, but at least once every 3 months.

FLT3 mutation status and *FLT3* expression levels in the bone marrow and peripheral blood (including FLT3 phosphorylation data and in vitro midostaurin sensitivity) was assessed locally at baselineand this assessment of *FLT3* mutation-positivity was allowed for enrollment, if the sample was taken within 30 days of starting midostaurin therapy for patients with relapsed AML or 90 days for patients with refractory AML; *FLT3* mutation status was later confirmed in a central laboratory (Erasmus University Medical Center, Rotterdam, Netherlands) using samples collected at baseline.

Samples for pharmacokinetic analyses were collected on day 1 cycle 1 after the first dose of midostsaurin (patients were randomized to have samples taken at 1, 2, and 3 hours after the first dose; all patients had samples taken at 12 hours, immediately prior to the second dose), predose on days 5 and 7 of cycle 1,

day 1 of cycle 2, day 1 of cycle 3, and on day 1 of every other cycle thereafter until study drug discontinuation. The plasma concentrations of midostaurin and its metabolites (CGP62221 and CGP52421) were summarized by timepoint, age group and dose. The modeling of the population PK analysis of the pediatric data was based on an available model developed for adult patients with AML.

Statistics

In the dose-escalation phase, a single 3-parameter Bayesian logistic regression model (BLRM) was used, allowing separate dose escalation and estimation of the MTD and/or RDE in each age group. Information on probabilities of toxicity for each dose were updated after each patient cohort was completed using all available data from both age groups. Recommendations were based on the posterior probabilities of DLT being in underdosages (0% to <16%), targeted toxicity (16% to <33%), or excessive toxicity (33% to 100%). The escalation with overdose control (EWOC) principal[29,30] required that any dose of midostaurin with >25% chance of being in the excessive toxicity category was not considered for the next dose cohort. Following the EWOC principal,[29,30] after each cohort of patients, the recommended dose was the one with the highest posterior probability of DLT in the target interval (16%-33%) among the doses fulfilling the overdose criteria. Time-to-event assessments, including OS, were described using Kaplan-Meier analysis.

Ethics

This study was conducted in accordance with the Declaration of Helsinki, and was reviewed and approved by the institutional review boards at each study center prior to initiation of the study. Written informed consent was provided by the parent or legal guardian and/or the patient in accordance to local laws and regulations.

Results

Baseline characteristics

Twenty-two patients were enrolled from September 2009 to 2013. Baseline characteristics by diagnosis are presented in **Table 1**. In the AML cohort (n=9), all patients were in the older age group and had a median age of 15.8 years (range, 10.5-17.1 years). French-American-British (FAB) classification of these patients was M1 (n=1), M2 (n=4), M4 (n=2), M5 (n=1), and missing (n=1). Most patients (78%) were female and 67% had a performance status of 80 to 100. Baseline disease status was first relapse with salvage attempt (n=1), second relapse with salvage attempt (n=1), refractory to second induction therapy (n=4), and other (n=3). The median number of prior therapies was 4 (range, 3-9) with a best response of CR (n=6), marrow response (n=1), minor response (n=1), or partial response (n=1). One patient received a previous allogeneic bone marrow stem cell transplant (SCT). The median time from diagnosis to study treatment was 9.0 (range, 3.3-45.7) months, the median time from diagnosis to first relapse or recurrence was 8.4 (range, 2.0-43.8) months, and the median time from last relapse or recurrence to starting this study was 1.4 (range, 0.5-4.3) months.

Baseline samples for central laboratory analysis of *FLT3* mutations were available for all 22 patients, but were only evaluable in 13 samples (7 samples were not evaluable and 2 samples were missing; **Supplemental Table 3**). *FLT3*-ITD was confirmed in only 5 out of 9 patients in the AML cohort; 1 patient had *FLT3*-WT*,* and information was not obtained for 3 patients. One of the patients with missing *FLT3* mutation status at baseline was found to have *FLT3*-ITD at a subsequent timepoint assessed by the central laboratory.

Among patients with ALL (n=13; 11 younger and 2 older), the median age was 1.6 (range, 0.5-13.8) years, 10 patients (77%) were female, nine patients (69%) had a performance status of 80 to 100, and all 13 patients had *MLL*r-ALL. Baseline disease status was first relapse (n=6; 2 with salvage attempt), refractory to second induction therapy (n=1), second relapse with salvage attempt (n=3), and other (n=3).

The median number prior therapies was 3 (range, 1-8), with a best response of CR (n=8) or hematologic improvement (n=1). One patient received a previous allogeneic stem cell transplant. The median time from diagnosis to treatment was 11.0 (range, 3.1-17.7) months, the median time from diagnosis to first relapse or recurrence was 7.4 (1.4-14.8) months, and he median time from last relapse or recurrence to starting the study was 0.5 (range, 0.1-3.9) months. Central laboratory analysis of *FLT3* mutation status in baseline samples identified *FLT3*-WT in 7 out of 13 patients, and *FLT3*-TKD in 1 patient (see **Supplemental Table 3**). For the remaining 5 patients with missing baseline assessment, peripheral blood samples collected post-baseline were used for central laboratory analysis, and *FLT3*-WT was identified in 4 patients. High levels of phosphorylated FLT3 were not detected in any patient sample at baseline; thus, no interpretable data were generated on phosphorylated FLT3 (see **Supplemental Table 4**).

Determination of MTD and RDE

Of the 22 enrolled patients, 7 patients (3 with *FLT3*-mutated AML and 4 with *MLL*r-ALL per local assessment) received the starting dose (30 mg/m^2 bid) and 15 patients (6 with *FLT3*-mutated AML and 9 with *MLL*r-ALL per local assessment) received the maximum dose (60 mg/m^2 bid). All patients discontinued treatment (**Figure 2**). No DLTs or significant safety concers were experienced among the 6 patients (2 younger and 4 older) who received the 30 mg/m^2 dose. Dose escalation proceeded to 60 mg/m^2 bid in 11 patients (younger, n=5; older, n=6), with a DLT reported in 1 patient in the younger group (grade 3 ALT elevation). One patient with *FLT3*-mutated AML in the 60 mg/m^2 bid cohort completed the per-protocol follow-up; the remaining 21 patients died. The median duration of exposure to midostaurin for all patients was 16 (range, 3-64) days. No patients in the younger group and 8 patients (72.7%) in the older group had an exposure to midostaurin ≥28 days. Given that the study design did not allow dosing beyong 60 mg/m^2 bid, a true MTD beyond 60 mg/m^2 bid could not be determined using the BLRM model for either age cohort. The 60 mg/m^2 bid dose was chosen as the RDE given that it was safely administered in each age group. Using a three-parameter BLRM, the mean posterior probability of a DLT

at the 60 mg/m^2 bid dose were 10% (95% CI, 1%-33%) for the younger patient group and 8% (95% CI, 1%-26%) for the older patient group (see **Supplemental Table 5**).

Efficacy

The rates of best clinical response were 55.6% (95% CI, 21.2%-86.3%) and 23.1% (95% CI, 5.0%-53.8%) for patients with *FLT3*-mutated AML and *MLL*r-ALL per local assessment, respectively (

Figure 3). Of the 5 patients with AML who responded, 1 patient achieved a CR with incomplete count recovery (CRi), 2 patients had a bone marrow blast response (BR), and 1 patient each achieved a peripheral blood blast response (BRp) and a minor BRp. The patient who achieved a CRi was a 14-year-old female with *FLT3*-mutated AML, who had multiple relapses on prior chemotherapy regimens; she achieved a CRi on day 14 and remained in remission until her last response assessment on day 67. This patient discontinued midostaurin therapy (on day 64) prior to receiving a hematopoietic SCT on day 76 and was alive at the time of the per-protocol survival follow-up on day 960. *FLT3*-ITD expression was not assessed in this patient. In the *MLL*r-ALL group, 3 patients achieved a best response of BRp.

Of the 8 patients who responded overall, 4 patients (1 with *FLT3*-mutated AML and 3 with *MLL*r-ALL per local assessment) experienced disease progression or died within 2 months of achieving a response; the remaining patients were censored due to the start of subsequent antineoplastic therapy. The median time to response was 14.0 (range, 8-22) days for patients with *FLT3*-mutated AML and 8.0 (range, 3-8) days for patients with *MLL*r-ALL. The median OS was 3.7 (95% CI, 2.7-8.3) and 1.4 (95% CI, 1.0-2.9) months for patients with *FLT3*-mutated AML and *MLL*r-ALL, respectively (**Supplemental Figure 1**). At the time of the last data cutoff, 1 patient (with AML) was alive; all other patients died.

Safety

The majority of patients (95.5%) in the safety set experienced ≥1 AE on treatment or during the 28-day follow-up period (**Table 2**). The most common any-grade AEs (occurring in ≥30% of patients) were vomiting (68.2%), pyrexia (40.9%), thrombocytopenia (40.9%), diarrhea (36.4%), and nausea (31.8%). Grade 3/4 AEs were more common in the 60 mg/m^2 bid cohort than in the 30 mg/m^2 bid cohort (86.7% vs 57.1%). The most frequent grade 3/4 AEs (occurring in ≥10% of patients) reported more frequently in the 60 mg/m^2 bid cohort than in the 30 mg/m^2 bid cohort (86.7% vs 57.1%) included, thrombocytopenia (53.3% vs 0%), ALT elevation (26.7% vs 14.3%), anemia (26.7% vs 0%), and hypokalemia (26.7% vs

0%). Overall, 77.3% of patients experienced grade 3/4 AEs (72.7% and 81.8% in the younger and older cohorts, respectively).

No DLTs were reported at the 30 mg/m^2 bid dose. In 60 mg/m^2 bid cohort, 1 DLT was reported (grade 3 ALT elevation) in a patient in the younger group, whereas no DLTs were reported in patients in the older group. AEs suspected to be study treatment related were reported in 16 patients (72.7%), including 13 grade 1/2 and 3 grade 3/4 AEs. The 3 patients (13.6%) with suspected treatment-related grade 3/4 AEs included 2 patients with grade 3 ALT increase, and 1 patients with grade 4 neutropenia and leukopenia. Of the 21 patients who died, 5 died on treatment (ie, while receiving midostaurin or within 28 days of receiving the final midostaurin dose) due to the underlying malignancy (*FLT3*-mutated AML, n=4; *MLL*r-ALL, n=1).

Pharmacokinetics

Plasma concentrations of midostaurin were analyzed in a population PK analysis. Exposure to midostaurin and its metabolites in children, based on a model that had been developed for adult patients andt that was adjused for a more rapid absorption in children, fell within the ranges predicted using data from adults. Weight, age, and body surface area were highly correlated in children; exposure decreased with increasing weigth at both midostaurin doses. Midostaurin exposure was predicted to peak around day 3 and then decline, reaching steady-sate levels at half day-1 levels (**Supplemental Figure 2**). CGP62221 exposure was predicted to peak around day 5 and then decline to steady-state levels that were 1.5-fold to 2.0-fold higher than day 1 levels. CGP52421 exposure was predicted to increase from day 1 to steady-state levels that were approximately 15-fold higher than day 1 levels.

Discussion

This study was the first to evaluate the safety, efficacy, and PK of oral midostaurin solution in children. The primary objective of the study was to estimate the MTD or RDE for the 2 age groups. The MTD for

single-agent midostaurin was not determined. According to the BLRM, the 60 mg/m^2 bid dose was tolerable in both the young and older patient groups. The study design and slow patient recruitment did not allow dosing beyond 60 mg/m^2 bid. The safety profile of single-agent midostaurin was similar for patients in the younger and older patients groups, but a higher frequency of grade 3/4 AEs was reported in patients who received the 60 mg/m^2 bid dose vs the 30 mg/m^2 bid dose.

Single-agent midostaurin showed limited clinical activity in children with *FLT3*-mutated AML or *MLL*r-ALL. These results are in line with single-agent midostaurin in adult patients with *FLT3*-mutated AML; despite an ORR of 71%, none of the patients achieved a CR and the majority of patients had varying degrees of blast response.[25] Nevertheless, in adult patients with *FLT3*-mutated AML midostaurin therapy was associated with rapid blast response and inhibition of FLT3 autophosphorylation.[31] Preliminary data from patient-derived samples suggested that midostaurin sensitivity was similar in MLLr-ALL overexpressing *FLT3* and *FLT3*-mutated AML,[15] which was not confirmed by the clinical data here.

These single-agent studies, in combination with preclinical and clinical data support the use of sequential chemotherapy and TKI therapy for patients with *FLT3*-mutant AML and *MLL*r-ALL. Combining chemotherapy with subsequent TKI therapy has a synergistic effect in *MLL*r-ALL and *FLT3*-ITD AML cell lines and patient-derived samples; this effect was not seen when the exposure sequence between the 2 therapies was reversed (ie, TKI followed by chemotherapy).[2,32] Midostaurin in combination with chemotherapy has shown clinical activity in adult patients (aged 18-60 years) with newly diagnosed *FLT3*-mutated AML.[26,27] A dose of midostaurin equivalent to the 30 mg/m^2 bid dose evaluated here (50 mg bid) was determined to be both safe and effective for use in combination with chemotherapy in adult patients with *FLT3*-mutated AML; patients on the 50 mg bid dose schedule showed high response rates and a lower frequency of grade 3/4 AEs than patients on a 100 mg bid dose schedule.[26] Results from the phase 3, placebo-controlled RATIFY study evaluating midostaurin 50 mg bid in combination with chemotherapy

in adult patients (aged 18-60 years) with newly diagnosed *FLT3*-mutant AML showed significant improvement in OS and EFS for patients who received midostaurin compared with patients who received placebo.[27]

Given that FLT3 inhibitors have demonstrated clinical benefit in combination with chemotherapy in adults[27] and elderly patients,[33] and as single-agent maintenance therapy in pediatric patients,[34] it is not surprising that additional ongoing studies are evaluating FLT3 inhibitors in combination therapies in pediatric patients. Sorafenib, a FLT3 inhibitor, demonstrated clinical benefit as maintenance therapy following SCT in children with *FLT3*-ITD–positive AML, particularly in patients with minimal residual disease.[34] In children with relapsed AML or *MLL*r-ALL, the FLT3 inhibitor quizartinib, 4 of 17 patients responded, including 2 with complete response.[35] Results from a phase 3 study evaluating lestaurtinib in combination with chemotherapy in pediatric patients with *MLL*r-ALL (NCT00557193) were recently reported; the addition of lestaurtinib did not improve outcomes in this patient population.[36] There are currently 2 trials underway investigating the safety and efficacy of a TKI plus chemotherapy or targeted agents in children and younger adults (<40 years) with newly diagnosed (sorafenib and bortezomib in patients aged ≤29 years [NCT01371981]) or relapsed/refractory (crenolanib and sorafenib aged ≤39 years [NCT02270788]) *FLT3*-mutant AML. Thus, further clinical evaluation of midostaurin in pediatric patients should be done in combination with established chemotherapeutic regimens.

According to our central laboratory determination, of the 13 patients with available baseline *FLT3* mutation status, 5 patients with AML had *FLT3*-ITD mutations and 1 patient with *MLL*r-ALL had a *FLT3*-TKD mutation, while the remaining 7 samples were *FLT3*-WT. *FLT3*-ITD was not identified in patients with *MLL*r-ALL, which is consistent with prior studies that identified *FLT3*-TKD as the only activating mutation in *MLL*r-ALL.[15,16] *FLT3* mutation status was determined after baseline for 6 additional patients, of which only 1 patient had *FLT3*-ITD. Having a documented *FLT3* mutation was an inclusion criterion for patients

with AML; however, not all patients with AML with known mutation status had *FLT3*-mutant AML per our central laboratory assessment. *FLT3* mutation status could have changed from the time of diagnosis to relapse[38] or the diagnostic technique may not have been sensitive enough to detect the *FLT3* mutation.[39] For example, Cloos and collaborators determined that approximately 18% of pediatric and adult patients with AML had a change in *FLT3*-ITD status between diagnosis and relapse.[38] Determining the *FLT3* mutation status of patients with AML is important because *FLT3*-ITD conveys a worse prognosis than *FLT3*-WT.[10-12] A recent epigenetic study of B-cell ALL showed that MLL fusion proteins directly target the *FLT3* promoter and activate transcription, explaining why FLT3 overexpression is associated with *MLL*r-ALL.[40]

Despite these preclinical models, single-agent midostaurin did not show clinical activity in children with *MLL*r-ALL, possibly because overexpression of FLT3 alone is not sufficient to drive the disease or because FLT3 was not inhibited enough at the doses tested to elicit responses. However, without additional data on changes in FLT3 phosphorylation status of patients at baseline and on-treatment, it is difficult to draw a conclusion. The unmet need for pediatric patients with R/R *FLT3*-mutant AML or *MLL*r-ALL is high. Although single-agent midostaurin showed limited activity in pediatric patients with *FLT3*-mutated AML or *MLL*r-ALL, midostaurin was generally well tolerated and should be evaluated in combination with chemotherapy in this patient population. In addition, future studies should also seek to understand the kinetics of *FLT3* mutations between diagnosis and relapse, as they present such an important prognostic factor for patients with AML.

Acknowledgements

We thank the patients enrolled in this trial and their families for their participation. We also acknowledge all of the investigators at the study sites that participated in the trial: Erasmus MC/Sophia Children's Hospital, Rotterdam, the Netherlands; Karolinska Institutet, and Karolinska University Hospital Stockholm,

Sweden; Hôpital Robert-Debré, Paris, France; IRCCS Ospedale Pediatrico Bambino Gesù, Rome, Italy; Fondazione MBBM, Azienda Ospedaliera San Gerardo, Monza, Italy; Pediatric Onco-Hematology, Stem Cell Transplantation and Cellular; Therapy Division, A.O.U. Città della Salute e della Scienza di Torino, Ospedale Infantile Regina Margherita, Torino, Italy; Seattle Children's Hospital, Seattle, WA; Hematology Unit, IRCCS Instituto Giannina Gaslini, Genova, Italy; Princess Máxima Center for Pediatric Oncology, Utrecht, the Netherlands. We would also like to thank Katherine Mills-Luján, PhD, CMPP, and Pamela Tuttle, PhD, CMPP, of ArticulateScience, LLC for medical editorial assistance, which was funded by Novartis Pharmaceuticals Corporation.

Authorship

Contribution: the study was designed by the sponsor (Novartis Pharmaceuticals) and the study steering committee (CMZ, ML and RP); CMZ, SS, BB, ML, CR, RS, FF, PH, CDufour, and RP enrolled patients; data was collected and analyzed by the sponsor in conjunction with the authors who had full access to the data; CMZ and RP wrote the manuscript with medical support from ArticulateScience LLC; all authors contributed to draft revisions and approved the final version of the manuscript.

Conflicts-of-interest disclosure: this clinical study was sponsored and funded by Novartis Pharmaceuticals. In addition, the authors declare the following conflicts of interest: CMZ is a consultant for and has received funding from Novartis Pharmaceuticals; CDufour is a consultant for Pfizer and has participated in advisory committees for Novartis Pharmaceuticals; PH is a former employee of Seattle Genetics and has equity ownership in Seattle Genetics; DS, EB, and CDutreix are current employees of Novartis Pharmaceuticals.

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Tables and figures

Table 1. Baseline characteristics of the full analysis set

Parameter		AML (n=9), n (%)		ALL (n=13), n (%)		Total (N=22), n (%)	
Median age (range), years		15.8 (10.5-17.1)		1.6 (0.5-13.8)		2.0 (0.5-17.1)	
Sex	Male	2 (22)		5 (38)		7 (32)	
	Female	7 (78)		8 (62)		15 (68)	
Race	White	9 (100)		8 (62)		17 (77)	
	Other	0		5 (38)		5 (23)	
Performance status[a]		**>12 y**	**≤12 y**	**>12 y**	**≤12 y**	**>12 y**	**≤12 y**
		8 (89)	**1 (11)**	**1 (8)**	**12 (92)**	**9 (41)**	**13 (59)**
Performance status	100	0	1 (100)	0	2 (17)	0	3 (23)
	90	1 (13)	0	1 (100)	5 (42)	2 (22)	5 (38)
	80	4 (50)	0	0	2 (17)	4 (44)	2 (15)
	70	2 (25)	0	0	2 (17)	2 (22)	2 (15)
	60	1 (13)	0	0	1 (8)	1 (11)	1 (8)
	First relapse	1 (11)		6 (46)		7 (32)	
	Without salvage attempt	0		4 (31)		4 (18)	
	With salvage attempt	1 (11)		2 (15)		3 (14)	
	Refractory to second induction therapy	4 (44)[b]		1 (8)		5 (23)	
	Second relapse	1 (11)		3 (23)		4 (18)	
	With salvage attempt	1 (11)		3 (23)		4 (18)	
	Other	3 (33)		3 (23)		6 (27)	
Number of prior therapies (range)		4 (3-9)		3 (1-8)		4 (1-9)	
Best response to prior therapy	Complete remission	6 (67)		8 (62)		14 (64)	
	Partial remission	1 (11)		0		1 (5)	
	Hematologic improvement	0		1 (8)		1 (5)	
	Marrow response	1 (11)		0		1 (5)	
	Minor response	1 (11)		0		1 (5)	
	Progressive disease	0		2 (15)		2 (9)	
	Unknown/not applicable	0		2 (15)		2 (9)	
Patient received previous SCT	Yes	1 (11)		1 (8)		2 (9)	
	Allogeneic BM SCT	1 (11)		1 (8)		2 (9)	
	No	8 (89)		12 (92)		20 (91)	
Median time since initial diagnosis of primary disease (range), months		9.0 (3.3-45.7)		11.0 (3.1-17.7)		9.4 (3.1-45.7)	
Median time from initial diagnosis to first recurrence or relapse (range), months		8.4 (2.0-43.8)		7.4 (1.4-14.8)		7.8 (1.4-43.8)	

Median time since most recent recurrence or relapse (range), months	1.4 (0.5-4.3)	0.5 (0.1-3.9)	0.7 (0.1-4.3)

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; BM, bone marrow; SCT, stem cell transplant.

[a] Lansky performance status and Karnofsky performance status used for patients ≤ 12 years old and >12 years old, respectively.

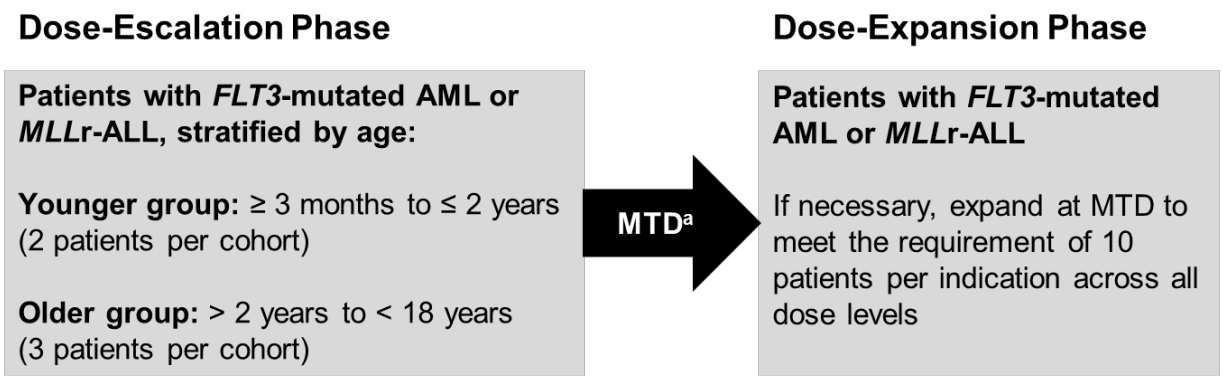
[b] Note that 1 patient with AML who was eligible as refractory to second induction at the time of enrollment due to having received prior antineoplastic therapies, was initially incorrectly identified as previously untreated.

Table 2. Most common adverse events (occurring in ≥10% patients)

Preferred Term	30 mg/m^2 bid (n=7), n (%)		60 mg/m^2 bid (n=15), n (%)		Total (N=22), n (%)	
	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Total	6 (85.7)	4 (57.1)	15 (100)	13 (86.7)	21 (95.5)	17 (77.3)
Vomiting	3 (42.9)	0	12 (80.0)	1 (6.7)	15 (68.2)	1 (4.5)
Pyrexia	2 (28.6)	1 (14.3)	7 (46.7)	2 (13.3)	9 (40.9)	3 (13.6)
Thrombocytopenia	0	0	9 (60.0)	8 (53.3)	9 (40.9)	8 (36.4)
Diarrhea	2 (28.6)	1 (14.3)	6 (40.0)	2 (13.3)	8 (36.4)	3 (13.6)
Nausea	0	0	7 (46.7)	0	7 (31.8)	0
ALT increased	1 (14.3)	1 (14.3)	4 (26.7)	4 (26.7)	5 (22.7)	5 (22.7)
Anemia	0	0	5 (33.3)	4 (26.7)	5 (22.7)	4 (18.2)
Anxiety	0	0	5 (33.3)	0 (0.0)	5 (22.7)	0
AST increased	1 (14.3)	0	4 (26.7)	1 (6.7)	5 (22.7)	1 (4.5)
Headache	1 (14.3)	0	4 (26.7)	0	5 (22.7)	0
Decreased appetite	1 (14.3)	1 (14.3)	3 (20.0)	0	4 (18.2)	1 (4.5)
Hypocalcaemia	1 (14.3)	0	3 (20.0)	1 (6.7)	4 (18.2)	1 (4.5)
Hypokalemia	0	0	4 (26.7)	4 (26.7)	4 (18.2)	4 (18.2)
Neutropenia	1 (14.3)	1 (14.3)	3 (20.0)	2 (13.3)	4 (18.2)	3 (13.6)
Cough	0	0	3 (20.0)	0	3 (13.6)	0
Febrile neutropenia	1 (14.3)	1 (14.3)	2 (13.3)	2 (13.3)	3 (13.6)	3 (13.6)
Hyperbilirubinemia	1 (14.3)	0	2 (13.3)	1 (6.7)	3 (13.6)	1 (4.5)
Hyponatremia	0	0	3 (20.0)	0	3 (13.6)	0
Mood altered	0	0	3 (20.0)	0	3 (13.6)	0
Alopecia	0	0	2 (13.3)	0	2 (9.1)	0

bid, twice daily.

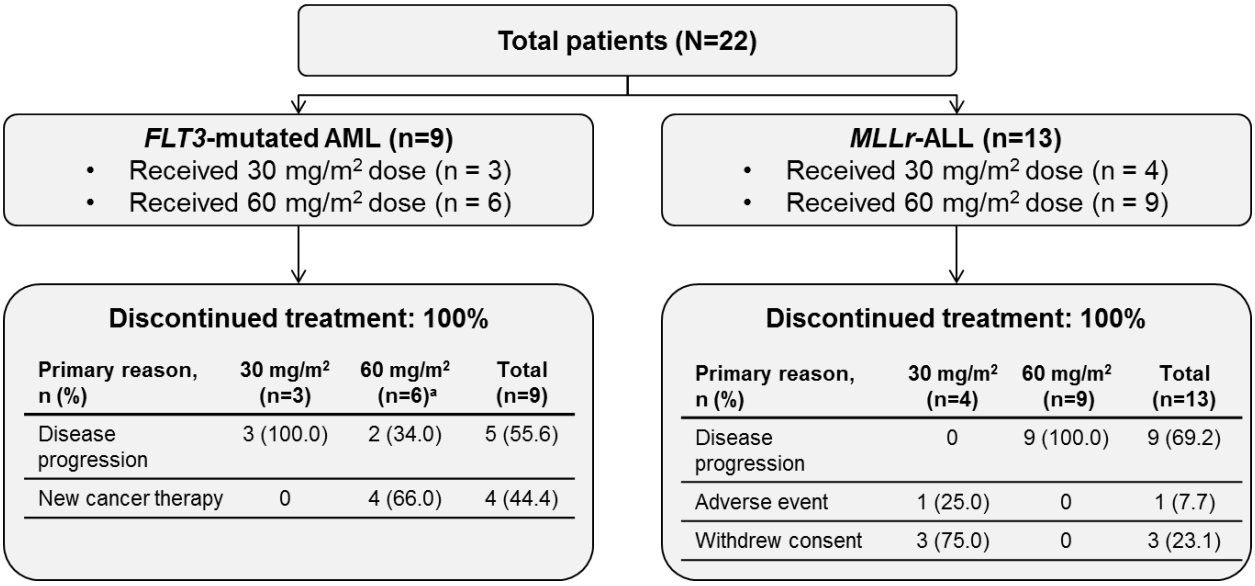
Figure 1. Trial design



ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; FLT3, Fms-like tyrosine kinase 3; ITD, internal tandem duplication; MLLr, mixed lineage leukemia gene rearrangements; MTD, maximum tolerated dose.

[a] If an MTD could not be established within an age group because escalation to a dose >60 mg/m^2 was required, then the MTD was not reached, and the recommended phase 2 dose was evaluated during dose expansion.

Figure 2. Patient disposition



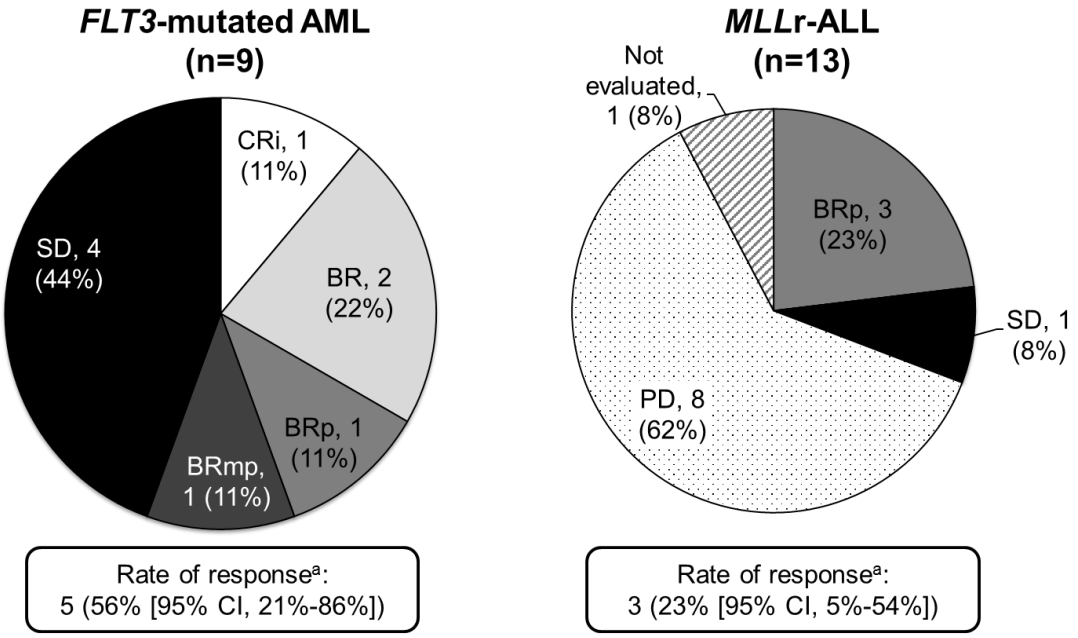
Primary reason, n (%)	30 mg/m² (n=3)	60 mg/m² (n=6)[a]	Total (n=9)
Disease progression	3 (100.0)	2 (34.0)	5 (55.6)
New cancer therapy	0	4 (66.0)	4 (44.4)

Primary reason, n (%)	30 mg/m² (n=4)	60 mg/m² (n=9)	Total (n=13)
Disease progression	0	9 (100.0)	9 (69.2)
Adverse event	1 (25.0)	0	1 (7.7)
Withdrew consent	3 (75.0)	0	3 (23.1)

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; bid, twice daily; FLT3, fms-like tyrosine kinase 3; MLLr, mixed lineage leukemia rearranged.

[a] One patient in the *FLT3*-mutated AML 60 mg/m^2 bid cohort completed the follow-up phase per protocol. This 12-year-old female patient discontinued midostaurin treatment for a new cancer therapy (stem cell transplant). All other patients died after discontinuing treatment.

Figure 3. Best overall response in patients with *FLT3*-mutated AML and *MLL*r-ALL



ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; BR, bone marrow blast response; BRm, minor bone marrow blast response; BRmp, minor peripheral blood blast response; BRp, peripheral blood blast response; CR, complete remission; CRi, complete remission with incomplete count recovery; FLT3, Fms-like tyrosine kinase 3; ITD, internal tandem duplication; LFS, leukemia-free state; MLLr, mixed lineage leukemia gene rearrangements; PD, progressive disease; SD, stable disease.

[a] Best clinical response includes LFS, CR, CRi, PR, BR, BRm, BRp, and BRmp.

Supplementary Appendix

Supplemental Bioequivalency Methods and Results

The relative bioavailability and safety of midostaurin given in 3 different formulations (clinical service formulation [CSF], final market imagine [FMI], and drink solution [DS]) was investigated in a phase 1, single-center, open-label, randomized study in healthy adult volunteers. Of the 54 healthy volunteers enrolled, 18 subjects were randomized to each formulation; the median age for the entire cohort was 34 years (range, 18-50 years). Pharmacokinetic parameters of midostaurin and its metabolites, CGP52421 and CGP62221, were assessed following a single oral dose of midostaurin 50 mg under fasting conditions. For the CSF and FMI formulations, subjects received two 25-mg capsules; for the DS, subjects received 2 mL of 25 mg/mL solution. Samples were collected pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, 96, and 120 post-dose. Safety was evaluated for the 120-hour study time period and for 1 month therafter.

After a single oral dose of midostaurin 50 mg, on average, the bioavailability of midostaurin was ≈ 9% lower with the DS formulation than with the CSF formulation (as measured by the $AUC_{0-\infty}$ geometric mean; **Supplemental Table 1**), whereas the absoption of midostaurin was ≈ 6% higher with the DS formulation than with the CSF formulation (as measured by the C_{max} geometric mean). Similarly, the absorption of CGP52421 and CGP62221 were ≈ 14% and ≈ 12% higher, respectively, in the DS vs CSF formulation, but there was little change in the the $AUC_{0-\infty}$ geometric mean (≈ 5% higher for CGP52421; ≈ 2% lower for CGP62221). Compared with the DS formulation, FMI capsules showed a higher AUC_{0-inf} for midostaurin, CGP62221 and CGP52421 by 26%, 29% and 21%, respectively, and produced little change for C_{max}.

Comparing DS with CSF for midostaurin, CGP52421 and CGP62221 the mean ratios of AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} varied from 0.91 to 1.14 and all of their 90% CIs are within or very close to the traditional bioequivalence boundary of 0.8 to 1.25. Comparing FMI with drinking solution the 90% CIs for C_{max} of midostaurin, CGP52421 and CGP62221 are all within the traditional bioequivalence boundary of 0.8 to 1.25. For midostaurin, CGP52421 and CGP62221 the mean ratios of AUC_{0-t} and $AUC_{0-\infty}$ varied from 1.05

to 1.29 with their 90% CI covered by the range of 0.90 to 1.65. Based on these observations, the FMI, drinking solution and CSF formulations were considered very similar from a pharmacological perspective.

Gastrointestinal adverse events (AEs) were the most frequently reported AEs overall. Of these, nausea was more common in subjects who received the DS formulation than the CSF formulation or the FMI formulation (38.9% vs 5.6% vs 22.2%). Diarrhea occurred in 16.7% of subjects treated with the DS and FMI formulations vs 0% in the CSF formulation group. Vomiting occurred in 11.1% of subjects in the FMI group and 5.6% of subjects in the DS and CSF formulation groups. No other AE occurred in more than 1 patient in any of the treatment groups. Considering the small number of volunteers with AEs, no clinically relevant differences between the 3 formulations can be derived.

Supplemental Table 1. Bioavailability and Safety of Midostaurin Oral Drink and Capsule Formulations in Healthy Volunteers in Study A2108.

	Oral Midostaurin Formulation				
	Capsule/CSF (n=18)[a]	**Capsule/FMI (n=18)[b]**	**Drink Solution (n=18)[c]**	**Geometric Mean Ratio (90% CI)[d]**	**Geometric Mean Ratio (90% CI)[e]**
Pharmacokinetic Parameters[a]					
Midostaurin					
Mean $AUC_{0-\infty}$ (CV%), h×ng/mL	14365.5 (60.9)	16463.2 (46.42)	13016.7 (35.1)	0.91 (0.70-1.17)	1.26 (0.98-1.63)
Mean AUC_{0-t} (CV%), h×ng/mL	13630.6 (59.24)	15504.9 (40.80)	12568.4 (35.28)	0.92 (0.72-1.18)	1.23 (0.97-1.57)
Mean C_{max} (CV%), ng/mL	1183.2 (27.2)	1296.2 (21.11)	1258.0 (24.6)	1.06 (0.93-1.22)	1.03 (0.90-1.18)
Median T_{max} (range), hours	1.3 (1.0-4.0)	1.00 (1.0-3.0)	1.0 (0.5-2.0)	0.00 (-3.5-1.0)	0.00 (-1.0-2.5)
Mean $t_{1/2}$ (CV%), hours	19.3 (53.21)	21.4 (62.68)	13.3 (36.00)	N/A	N/A
Mean Cl/F (CV%), L/hour	3480.5 (60.89)	3037.0 (46.42)	3841.2 (35.09)	N/A	N/A
Mean Vz/F (CV%), L	97047.0 (34.85)	93973.8 (34.18)	74141.5 (33.08)	N/A	N/A
Mean Lambda Z (CV%), /hour	0.035 (53.2140)	0.032 (62.6871)	0.051 (36.0066)	N/A	N/A
CGP52421					
Mean $AUC_{0-\infty}$ (CV%), h×ng/mL	36604.3 (26.1)	49308.1 (57.78)	38291.9 (48.2)	1.05 (0.82-1.34)	1.29 (1.01-1.65)
Mean AUC_{0-t} (CV%), h×ng/mL	14948.0 (16.32)	17084.6 (11.46)	16339.2 (21.87)	1.09 (0.99-1.20)	1.05 (0.95-1.15)
Mean C_{max} (CV%), ng/mL	217.9 (16.9)	258.9 (22.70)	248.6 (20.0)	1.14 (1.02-1.28)	1.04 (0.93-1.17)
Median T_{max} (range), hours	4.0 (2.0-8.0)	4.0 (3.0-8.0)	4.0 (1.5-8.0)	0.00 (-6.50-6.00)	0.00 (-5.00-6.50)
Mean $t_{1/2}$ (CV%), hours	136.4 (30.52)	167.2 (79.26)	129.8 (62.55)	N/A	N/A
Mean Lambda Z (CV%), /hour	0.005 (30.5285)	0.004 (79.2596)	0.005 (62.5572)	N/A	N/A
CGP62221					
Mean $AUC_{0-\infty}$ (CV%), h×ng/mL	23904.4 (58.2)	28295.0 (42.63)	23372.0 (30.0)	0.98 (0.77-1.24)	1.21 (0.95-1.54)
Mean AUC_{0-t} (CV%), h×ng/mL	21034.7 (45.21)	24444.7 (28.91)	22007.3 (28.00)	1.05 (0.87-1.26)	1.11 (0.92-1.34)
Mean C_{max} (CV%), ng/mL	531.7 (23.4)	616.6 (16.85)	593.3 (16.5)	1.12 (1.00-1.24)	1.04 (0.93-1.16)
Median T_{max} (range), hours	3.0 (2.0-6.0)	4.0 (2.0-6.0)	3.0 (1.5-8.0)	0.00 (-4.50-6.00)	0.00 (-6.00-4.50)
Mean $t_{1/2}$ (CV%), hours	30.3 (59.15)	34.9 (53.24)	25.7 (29.42)	N/A	N/A
Mean Lambda Z (CV%), /hour	0.022 (59.1524)	0.019 (53.2468)	0.026 (29.4279)	N/A	N/A
Adverse events, n (%)	**Capsule/CSF (n=18)[a]**	**Capsule/FMI (n=18)[b]**	**Drink Solution (n=18)[c]**	**All (n=54)**	
Nausea	1 (5.6)	4 (22.2)	7 (38.9)	12 (22.2)	
Diarrhea	0	3 (16.7)	3 (16.7)	6 (11.1)	
Vomiting	1 (5.6)	2 (11.1)	1 (5.6)	4 (7.4)	

Headache	0	1 (5.6)	1 (5.6)	2 (3.7)	
Rash	0	2 (11.1)	0	2 (3.7)	
Blood bilirubin increased	0	1 (5.6)	0	1 (1.9)	
Constiption	0	0	1 (5.6)	1 (1.9)	
Dizziness	0	1 (5.6)	0	1 (1.9)	
Dyspnea	0	1 (5.6)	0	1 (1.9)	
Flatulence	0	0	1 (5.6)	1 (1.9)	
Protozoal infection	1 (5.6)	0	0	1 (1.9)	
Oral herpes	0	0	1 (5.6)	1 (1.9)	
Viral infection	0	0	1 (5.6)	1 (1.9)	

$AUC_{0-\infty}$, area under the curve from time 0 to infinity; C_{max}, maximum (peak) observed plasma concentration; CSF, clinical service formulation; CV, coefficient of variation; FMI, final market image; NA, not applicable; $t_{1/2}$, half life; T_{max}, time to reach maximum (peak) plasma concentration.

[a] Used in early phase clinical trials.

[b] Used in phase 3 (RATIFY) trial.

[c] Used in the pediatric trial.

[d] Geometric mean ratio between the drinking solution and CSF.

[e] Geometric mean ratio between the drinking solution and FMI.

Supplemental Table 2. Modified Cheson Criteria for Response

		Definition
Response	LFS	<5% BM blasts (minimum count 200 with marrow spicules), no Auer rods in patients with AML, no persistent extramedullary disease, no circulating blasts in the PB
	CR	Met the definition of LFS, absolute neutrophil count ≥ 1000/μL, and platelets ≥ 100,000/μL
	CRi	Met the definition of CR except for either residual neutropenia (<1000/μL) or thrombocytopenia (<100,000/μL) and platelet transfusion independent
	PR	A decrease in BM blasts from ≥ 50% to between 5% and 25%
	BR	Absolute BM blast percentage >25% and ≥ 50 % decrease in BM blasts from baseline
	BRm	≥ 25% decrease in BM blasts from baseline
	BRp	≥ 50 % decrease in PB blasts from baseline
	BRmp	≥ 25 % decrease in PB blasts from baseline
No response	SD	Failure to achieve any of the above responses without meeting the definition of PD
	PD	• If <40% BM blasts at baseline, a ≥ 100% increase in BM blast percentage from baseline • If >40% BM blasts at baseline, a ≥ 50% increase in BM blast percentage from baseline • If leukocyte count >20 × 106 at baseline, a PB blast count increase of ≥ 50% • If leukocyte count <20 × 106 at baseline, a PB blast count increase of ≥ 50% and an absolute increase of ≥ 2000 PB blasts

BM, bone marrow; BR, bone marrow blast response; BRmp, minor peripheral blood blast response; BRp, peripheral blood blast response; CR, morphological complete remission; CRi, morphological complete remission with incomplete count recovery; LFS, morphological leukemia-free state; mBR, minor blast response; PB, peripheral blood; PD, progressive disease; PR, partial remission; SD, stable disease.

Supplemental Table 3. *FLT3* Mutation Status According to Central Laboratory Assessment

***FLT3* Mutation by Disease Type**	**Central Laboratory Assessment of *FLT3* Mutation Status**		
	Baseline Assessment[a]	**Post-Baseline Assessment[b]**	**Overall Assessment**
Patients with AML, n %	**(n=9)**	**(n=3)**	**(n=9)**
FLT3-ITD-positive	5 (56)	1 (33)	**6 (67)**
FLT3-TKD-positive	0	0	**0**
FLT3-mutant–negative[c]	1 (11)	0	**1 (11)**
Missing	3 (33)	2 (67)	**2 (22)**
Patients with *MLL*r-ALL, n %	**(n=13)**	**(n=5)**	**(n=13)**
FLT3-ITD-positive	0	0	**0**
FLT3-TKD-positive	1 (7)	0	**1 (7)**
FLT3-mutant–negative[c]	7 (54)	4 (80)	**11 (84)**
Missing	5 (39)	1 (20)	**1 (7)**

[a] *FLT3* mutation status was evaluated using bone marrow aspirate samples in all patients, except in 1 patient with AML for whom a peripheral blood sample was used (this patient was *FLT3*-mutant–negative).

[b] Peripheral blood samples were used in all post-baseline assessments of *FLT3* mutation status; post-baseline assessment were done in a patients with missing baseline assessments.

[c] Patients negative for both *FLT3*-ITD and *FLT3*-TKD.

Supplemental Table 4. FLT3 Expression and Phosphorylation Analysis

	Pt #	FLT3 Mutation Status	FLT3 Expression at Baseline		FLT3 Expression at End of Treatment		FLT3 Phosphorylation at Baseline		FLT3 Phosphorylation After Baseline	
			Bone Marrow	Peripheral Blood	Bone Marrow	Peripheral Blood	Bone Marrow	Peripheral Blood	Bone Marrow	Peripheral Blood
Patients with AML	1	WT	Low	Intermediate	ND	High	ND	ND	ND	Very low/ absent
	2	ITD	Intermediate	High	ND	ND	Low	ND	ND	ND
	3	ITD	Intermediate	Intermediate	ND	ND	Very low	Very low	ND	Very low
	4	ITD	Low	Intermediate	ND	Int	Very low	Low	ND	Low
	5	ITD	Low	Intermediate	ND	High	Very low	Very low	ND	Low
	6	ITD	Low	ND	ND	Low	ND	ND	ND	Very low/ absent
	7	Missing[a]	ND	ND	ND	ND	ND	ND	ND	High
	8	Missing	ND	ND	ND	ND	ND	ND	ND	ND
	9	Missing	ND	ND	ND	ND	ND	ND	ND	ND
Patients with ALL	10	TKD	Low	ND	ND	Low	Absent	Absent	ND	Very low/ absent
	11	WT	High	High	ND	ND	Average	Low	ND	High
	12	WT	High	High	ND	High	Absent	Absent	ND	Average/high
	13	WT	Intermediate	ND	ND	ND	Low/average	ND	ND	ND
	14	WT	Intermediate	ND	ND	ND	ND	ND	ND	ND
	15	WT	Low	ND	ND	ND	ND	ND	ND	ND
	16	WT	ND	ND	ND	ND	Average	ND	ND	ND
	17	WT	Not detected	ND	ND	Int	Very low	ND	ND	Average
	18	Missing[b]	ND	ND	ND	Int	ND	ND	ND	ND
	19	Missing[b]	ND	ND	ND	ND	ND	ND	ND	ND
	20	Missing[b]	ND	ND	ND	ND	ND	ND	ND	ND
	21	Missing[b]	ND	ND	ND	High	Average	ND	ND	High
	22	Missing	ND	ND	ND	ND	ND	ND	ND	ND

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; FLT3, fms-like tyrosine kinase 3; ITD, internal tandem duplication; ND, not done; TKD, tyrosine kinase domain; WT, wildtype.

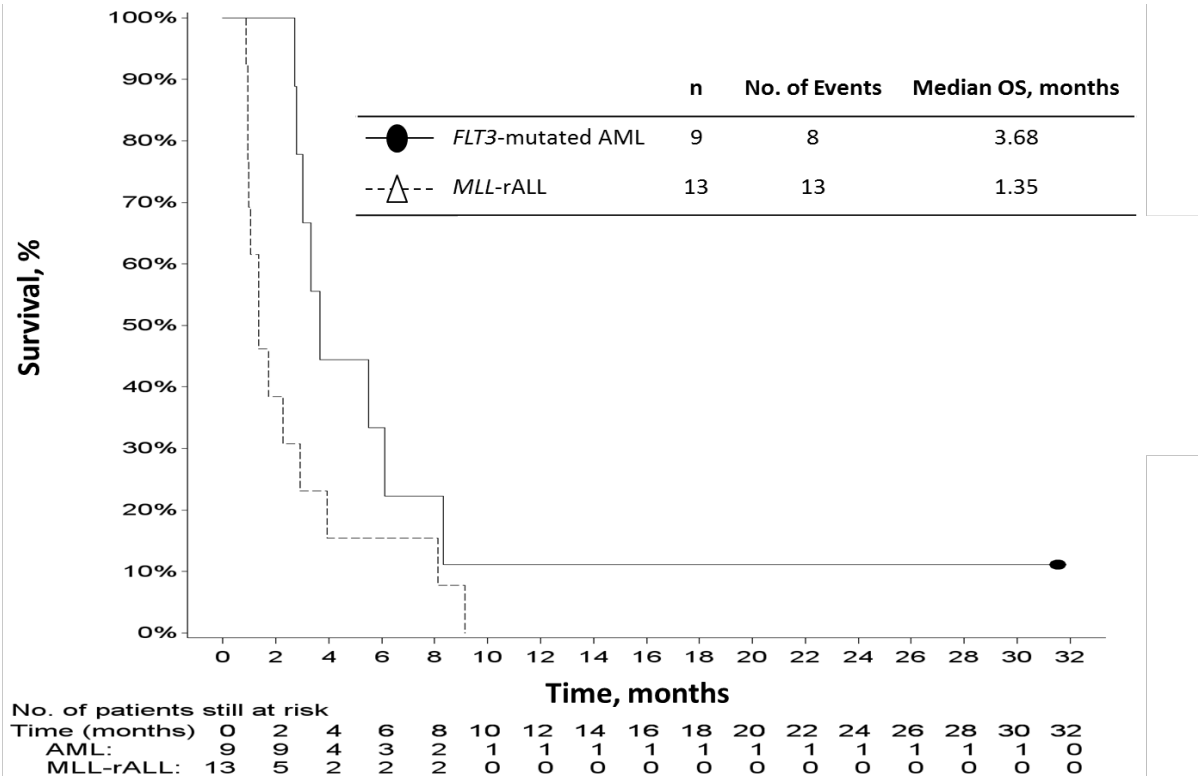
[a] Patient was later found to have FLT3-ITD. [b] Patient was later found to have FLT3-WT.

Supplemental Table 5. Posterior Probabilities of Dose-Limiting Toxicity by Age Strata and Dose

Dose-Determining Set (n=17)	Younger Group (≥3 months to ≤2 years)		Older Group (>2 to <18 years)	
	30 mg/m² bid (n=2)	60 mg/m² bid (n=5)	30 mg/m² bid (n=4)	60 mg/m² bid (n=6)
Posterior probability of dose-limiting toxicity				
Underdosage: 0% to <16%	0.973	0.806	0.987	0.879
Targeted toxicity: 16% to <33%	0.026	0.171	0.012	0.115
Excessive toxicity: 33% to 100%	0.002	0.023	0.000	0.007
Mean (95% probability estimates), %	3 (0-16)	10 (1-33)	3 (0-13)	8 (1-26)

bid, twice daily.

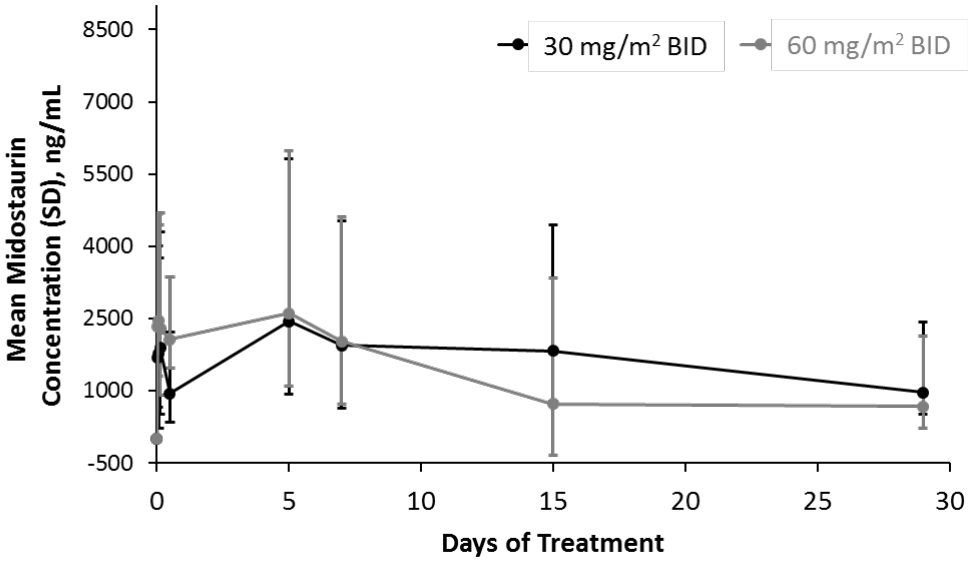
Supplemental Figure 1. Overall survival



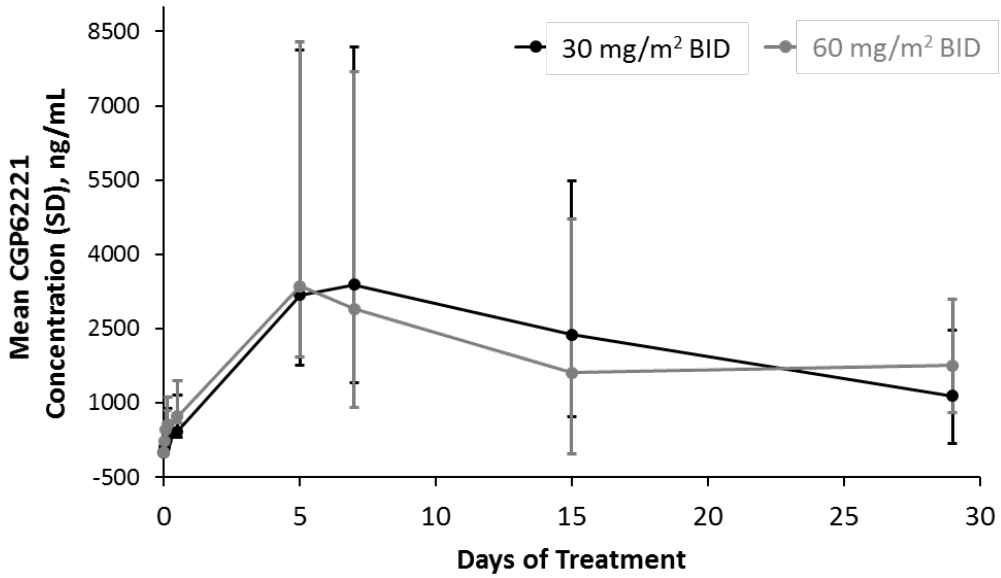
ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; FLT3, Fms-like tyrosine kinase 3; ITD, internal tandem duplication; MLLr, mixed lineage leukemia gene rearrangements; OS, overall survival.

Supplemental Figure 2. Pharmacokinetics of midostaurin (A) and its metabolites: CGP62221 (B) and CGP52421 (C)

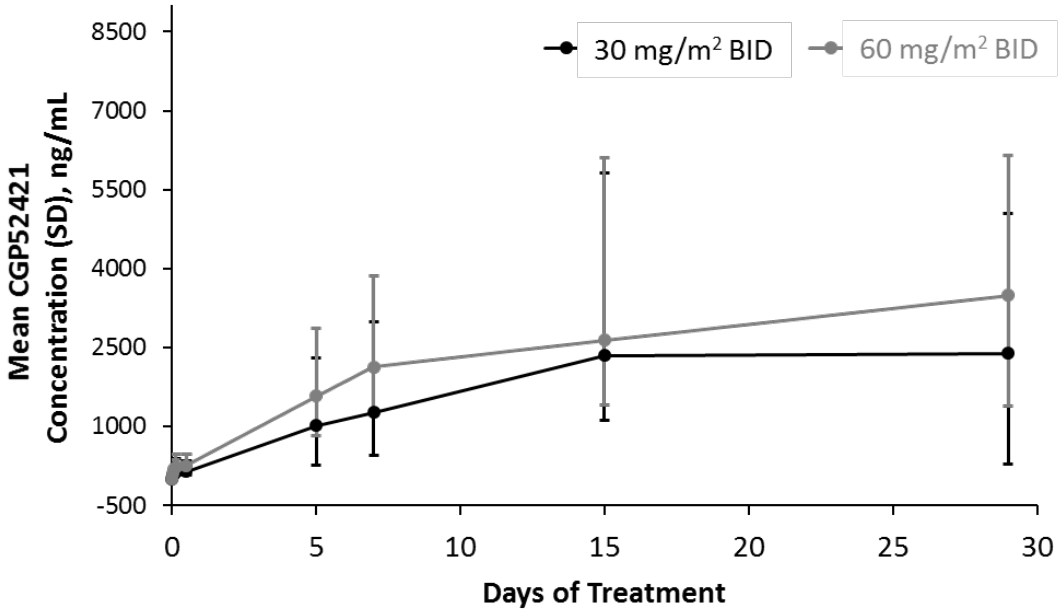
A



B



C



Data are only from patients with non-missing values. Data shown at each point are the mean ± SD from 2-6 patients in the 30 mg/m^2 bid cohort and 5-13 patients in the 60 mg/m^2 bid cohort.

SD, standard deviation; bid, twice daily.