Clinical Development & Medical Affairs

PKC412/midostaurin

Clinical Trial Protocol CPKC412A2114

A phase I/II, open-label, dose-escalating study to evaluate the safety, tolerability and pharmacokinetics of twice daily oral midostaurin and to evaluate the preliminary clinical and pharmacodynamic response in pediatric patients with relapsed or refractory leukemia


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2. Medication Instructions for Use

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List of abbreviations

AE  adverse event
ALL  Acute Lymphoblastic Leukemia
ALT  alanine aminotransferase/glutamic pyruvic transaminase/GPT
AML  Acute Myeloid Leukemia
Ara-c  cytarabine
AST  aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
b.i.d.  *bis in die* / twice a day
BM  Bone Marrow
BSA  Body surface area
CLL  Chronic lymphocytic leukemia
CNS  Central Nervous System
CRF  Case Report/Record Form
CS&E  Clinical Safety and Epidemiology
CR  Complete Remission
CRD  Clinical Research and Development
CRO  Contract Research Organization
CTCAE  Common Terminology Criteria for Adverse Events v3.0
CYP450  Cytochrome P 450
DLT  Dose Limiting Toxicity
DNA  Deoxyribonucleic acid
eCRF  Electronic Case Report/Record Form
ECG  electrocardiogram
FLK2  Fetal liver tyrosine kinase 2
FLT3  fms-like tyrosine kinase 3
G-CSF  Granulocyte colony stimulating factor
GM-CSF  Granulocyte macrophage colony stimulating factor
hERG  Human Ether-a-go-go related gene
ICH  International Conference on Harmonization
IEC  Independent Ethics Committee
IL-3  Interleukin 3
i.v.  intravenous(ly)
IRB  Institutional Review Board
ITD  Internal Tandem Duplication
IVRS  Interactive Voice Response System
kg  kilograms
LLN  Lower Limit of Normal
MDS  Myelodysplastic syndrome
mg  milligrams
MLL  Mixed Lineage Leukemia (gene) rearranged ALL, or MLL-rearranged ALL
mRNA  Messenger ribonucleic acid
MTD  Maximum Tolerated Dose
MUGA  Multi Gated Acquisition scan
NHL  Non-hodgkins lymphoma
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>o.d.</td>
<td>Omni die/once a day</td>
</tr>
<tr>
<td>p.o.</td>
<td>Per os/by mouth/orally</td>
</tr>
<tr>
<td>PD</td>
<td>Pharmacodynamics</td>
</tr>
<tr>
<td>Pgp</td>
<td>P-glycoprotein</td>
</tr>
<tr>
<td>PK</td>
<td>Pharmacokinetics</td>
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<tr>
<td>REB</td>
<td>Research Ethics Board</td>
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<tr>
<td>SAE</td>
<td>Serious adverse event</td>
</tr>
<tr>
<td>SOP</td>
<td>Standard Operating Procedure</td>
</tr>
<tr>
<td>STK1</td>
<td>Stem cell tyrosine kinase 1</td>
</tr>
<tr>
<td>t.i.d.</td>
<td>Three times per day</td>
</tr>
<tr>
<td>TKD</td>
<td>Tyrosine Kinase Domain</td>
</tr>
<tr>
<td>ULN</td>
<td>Upper limit of normal</td>
</tr>
<tr>
<td>WT</td>
<td>Wild-type</td>
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# Oncology clinical study protocol synopsis

<table>
<thead>
<tr>
<th>Investigational drug</th>
<th>Midostaurin (PKC412)</th>
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<tr>
<td>Protocol no.</td>
<td>CPKC412A2114</td>
</tr>
<tr>
<td>Study phase</td>
<td>I/II</td>
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<tr>
<td>Study title</td>
<td>A phase I/II, open-label, dose-escalating study to determine the safety, tolerability, and pharmacokinetics of twice daily oral midostaurin and to determine the preliminary clinical and pharmacodynamic response in pediatric patients with relapsed or refractory leukemia</td>
</tr>
<tr>
<td>Background</td>
<td>The presence of a mutation in FLT3 in childhood acute myeloid leukemia and the over-expression of wild-type FLT3 in childhood MLL-rearranged acute lymphoblastic leukemia, or MLL, are associated with an unfavorable prognosis. Midostaurin inhibits a number of tyrosine kinases, such as the class III tyrosine protein kinase FLT3, and has documented antiproliferative and pro-apoptotic activities in cell systems expressing and depending on mutated FLT3 receptor signaling or in wild-type FLT3 over-expressing cells. In vitro cytotoxicity studies on samples derived from pediatric patients showed that cells from MLL patients were significantly ~5 fold more sensitive to midostaurin than cells from children with conventional ALL, although a subgroup of these other ALL group showed the same sensitivity. In addition to its activity as a single agent, [Study CPKC412A2104], midostaurin can be combined with standard chemotherapeutic agents used in leukemia resulting in synergism or additivity [Study CPKC412A2106]. In order to support dosing pediatric patients a drink solution has been developed. The relative bioavailability of the drink solution was demonstrated to be bio comparable to the oral capsule in [Study CPKC412A2108], with no conversion factor required.</td>
</tr>
<tr>
<td>Purpose/rationale</td>
<td>The survival of children with refractory or relapsed MLL-rearranged ALL or with refractory or second relapse of AML is poor (Pieters 2007, Kaspers 2006). The prognosis remains the same if the patients are treated with intensive chemotherapy protocols, including an allogeneic stem-cell transplantation, if this has not been performed in first or second complete remission. Further intensification of upfront therapy is not possible because it leads to very high toxic-death rates in these children (Slats 2005, Creutzig 2004). Thus, there is need to develop new modalities of treatment for these subtypes of leukemia, which may be added to standard chemotherapy, to further reduce relapse rate without increasing toxicity. As noted above, FLT3 activation plays a role in the development of leukemias and is related to a poor outcome. The addition of a targeted agent against FLT3 may offer the possibility for significant therapeutic advantage as demonstrated in adult AML patients expressing FLT3 (Gilliland 2002). Childhood MLL shows over-expression of FLT3 compared to other types of leukemia (Stam 2005), and AML shows activating FLT3 mutations in a significant percentage of patients (Zwaan 2003). Therefore, FLT3 has the potential to be a promising target for therapy in these subtypes of childhood leukemia. So far, no other FLT3 inhibitors have been developed for use in children in Europe. This is a phase I/II pediatric dose-ranging study that will evaluate the safety, tolerability and pharmacokinetics of midostaurin in children &lt;18 years of age and ≥ 3 months who have relapsed or refractory leukemias that may benefit from administration of midostaurin including MLL-rearranged ALL and AML. Treatment with single agent midostaurin may have potential therapeutic benefit in pediatric AML patients similar to the response seen in adults with</td>
</tr>
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the disease, as was shown in [Study CPKC412A2104] which is summarized in Section 1.3.4.2. A similar effect may be seen in MLL cases, although there are no adult data to support this, as high FLT3-overexpression in the absence of mutations is mainly limited to infant ALL. Since the main issue in the tolerability of midostaurin is nausea and vomiting, the IMP will be administered with standard anti-emetics to improve tolerability and to minimize side-effects. Given midostaurin’s limited potential to induce CRs in adults with AML, it is anticipated that in future protocols, midostaurin will be used mainly in combination with regular chemotherapy. This will be addressed in future phase II trials in MLL and AML. However, before doing so, sufficient background data are needed on its safety and preliminary evidence of activity/efficacy as a single agent, at the same time limiting the number of patients exposed to single-agent midostaurin. Therefore, only a limited number of dose-levels will be assessed, based on availability of adult data, and non-eficacious dose-levels will be avoided.

### Objectives

**Primary**
- To determine the maximum tolerated dose (MTD) for two age groups (≥3 months to ≤2 years: >2years to <18 years) of pediatric patients with AML or MLL based on the rate of dose-limiting toxicity (DLT) of midostaurin administered orally in dose ranges studied in adults.

**Secondary**
- To characterize the safety and tolerability of midostaurin, including acute and chronic toxicities
- To characterize the population PK and trough of single and repeated doses of midostaurin and its metabolite(s)
- To determine the response rates, time to relapse and overall survival of patients treated with midostaurin
- To determine the presence of activating mutations or WT-overexpression of the FLT3 gene in MLL-rearranged ALL and AML samples
- To correlate baseline levels of FLT3 phosphorylation with FLT3 expression levels and clinical outcome in MLL patients
- To correlate baseline levels of FLT3 phosphorylation with activating FLT3 mutations and clinical outcome in AML patients
- To evaluate changes in FLT3 phosphorylation following treatment with midostaurin, and correlate changes with clinical outcome
- To evaluate changes in FLT3 phosphorylation following treatment with midostaurin, and correlate with pharmacokinetic data

### Endpoints (efficacy, safety)

**Primary endpoints:**
- Safety: Occurrence of dose-limiting toxicities (DLTs)

**Secondary endpoints:**
- Safety: Adverse drug reactions and serious adverse drug reactions, changes in hematology and chemistry values, vital signs and electrocardiograms
- Pharmacokinetics: Population PK and trough levels of midostaurin and metabolites.
- Efficacy: Best clinical response; bone marrow and peripheral blood status; time to response; duration of response; overall survival
- Biomarker: FLT3 expression, FLT3-phosphorylation, mutational status of FLT3
### Study design

This is a phase I/II, open-label, dose-escalating study to determine the safety, tolerability, and pharmacokinetics of twice daily oral midostaurin and to determine the preliminary clinical and pharmacodynamic response in pediatric patients with relapsed or refractory leukemia. The dose escalation will be stratified into two age groups, patients aged greater than 2 years and less than 18 years, and those 2 years or younger but greater than or equal to 3 months. The maximum treatment dose administered in the adult population on monotherapy is 100 mg b.i.d., and for this reason the maximum of midostaurin in the pediatric population will not exceed 60 mg/m², equivalent to 100 mg b.i.d.

Once the MTD has been established in each stratum of the dose-escalation part additional patients might need to be included in order to have a total of 10 patients within each of the two indications (AML/MLL). The eligibility criteria and assessments for patients enrolled in this dose-expansion phase will be the same as those used during the dose-escalation phase (Refer to Figure 4-1).

It is expected approximately 22 patients would be enrolled during the dose-escalation/expansion. The respective MTD cohorts may have to be expanded until up to approximately 10 evaluable patients with AML and 10 patients with MLL are treated. A minimum of 6 patients per indication will be enrolled at the MTD. The number of patients may vary depending on replacement of dropouts and expansion of cohorts, under Novartis and Principal Investigator decision on estimated risk.

An exploratory analysis will be performed in which the dose-blast response relationship is modeled. The results for this analysis will be used to determine the optimal dose based on maximizing the probability of blast response in the absence of DLT. This model could be used to assist decision making within the dose escalation.

### Population

Pediatric patients (≥ 3 months and <18 years old) with one of the following relapsed or refractory leukemias:

- MLL-rearranged ALL, who are either refractory to standard induction treatment or who are in first or subsequent relapse
- FLT3 mutated AML, refractory to standard induction (after failure of at least 2 different induction chemotherapy regimens) or refractory to re-induction at 1st relapse (after failure of the first re-induction course), or in second or subsequent relapse

### Inclusion/exclusion criteria

**Inclusion**

1. Patients must have a documented diagnosis of one of the following leukemias:
   - MLL-rearranged ALL, refractory to standard induction treatment or in first or subsequent relapse
   - FLT3-mutated AML refractory to standard induction (after failure of at least 2 different induction chemotherapy regimens) or refractory to re-induction at 1st relapse (after failure of the first re-induction course), or in second or greater relapse
2. Patients must be less than 18 years of age and ≥3 months of age.
3. Patients must have a Lansky/Karnofsky performance status ≥ 60.
4. Patients must have the following laboratory values reflecting appropriate organ function:
   - AST and ALT ≤ 5x Upper Limit of Normal (ULN),
   - Serum Bilirubin ≤ 1.5 x ULN,
| Exclusion |  
| --- | --- |
| 1. Patients with symptomatic leukemic CNS involvement. |  
| 2. Patients with isolated extramedullary leukemia. |  
| 3. Patients must have recovered from prior cytotoxic chemotherapy, with a minimum wash-out time of previous chemotherapy of 72 hours. For intrathelial chemotherapy, the minimum wash-out time is 48 hours (other exceptions for intrathelial chemotherapy are noted in Section 6.6.5) |  
| 4. Patients who had prior allogeneic, syngeneic or autologous bone marrow or stem cell transplant less than 2 months from Day 1 |  
| 5. Patients who have received any investigational agent within 30 days or 5 2 half lives, whichever is greater, prior to Day 1. An investigational agent is an agent with no approved medical uses in adults or pediatrics. |  
| 6. Patients who have had prior treatment with a FLT3 inhibiting drug or investigational agent. |  
| 7. Use of CYP3A4/5 enzyme inducing or inhibiting drugs or herbal supplements while on study treatment |  
| 8. The use of corticosteroids while on study drug (exceptions are noted in Section 6.6.5) |  
| 9. Patients who have had any surgical procedure, excluding central venous catheter placement or other minor procedures (e.g. skin or bone marrow biopsy), within 14 days of Day 1. |  
| 10. Patients with any other known disease concurrent severe and/or uncontrolled medical condition (e.g. cardiovascular disease including congestive heart failure or active uncontrolled infection) which could compromise participation in the study. |  
| 11. Patients with an abnormal chest X-ray and/or any pulmonary infiltrate including those suspected to be of infectious origin. In particular, patients with resolution of clinical symptoms of pulmonary infection but with residual pulmonary infiltrates on chest x-ray are not eligible until pulmonary infiltrates have completely resolved. |  
| 12. Patients with known impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of midostaurin, including active graft-versus-host disease of the liver or the gut. |  
| 13. Patients with a known confirmed diagnosis of HIV infection or active viral hepatitis. |  
| 14. Patients with a left ventricular shortening fraction < 27% as determined by MUGA scan or echocardiogram |  
| 15. Patients with abnormal ECG including: |  
| • QTcF ≥ 450 ms, PR ≥ 200 msec, QRS complex ≥ 110 msec, at screening or prior to first dosing |  
| • Any cardiac conduction abnormality |  
| • Any morphologic abnormality |  
| • Any ST/T wave abnormality |  
| • Any atrial or ventricular arrhythmia |  

- Serum Creatinine ≤ 2 x ULN.
16. Female patients who are pregnant or breast feeding or patients of reproductive potential not employing an effective method of birth control. Barrier contraceptives must be used throughout the trial by both sexes, if applicable.

17. Males of reproductive potential unwilling to comply with contraceptive requirements.

18. Patients/parents unwilling or unable to comply with the protocol.

**Patient numbering**

Each patient in the study is uniquely identified by a 9 digit patient number which is a combination of his/her 4-digit center number and 5-digit subject number. The center number is assigned by Novartis to the investigative site.

**Investigational and control drugs**

Study drug refers to any Novartis investigational drug(s) being used for an unapproved indication. For this study, the term “Study drug” refers to midostaurin (PKC412) 25 mg/mL oral solution, 50mL bottles.

**Dose, regimen, treatment cycle**

Midostaurin will be given as an oral solution twice daily. The drug will be used continuously, unless uninterrupted is required to manage toxicity or for progressive disease. Cycles will consist of 14 days, and are mainly defined in order to assess safety at an earlier time point. There will be no break between cycles. Following Cycle 1, patients may receive additional cycles of study drug as clinically appropriate, according to investigator discretion, and in the absence of safety concerns.

Patients will be assigned to a particular dose cohort by the Novartis clinical team. The starting dose will be the approximate dose that was well tolerated in the adult combination chemotherapy (Study CPKC412A2106), 50 mg b.i.d. or approximately 30 mg/m² b.i.d. In patients with BSA ≥ 1.67, midostaurin will be dosed at 50 mg b.i.d. Midostaurin will be dosed per m², but in children weighing less than 10 kg, midostaurin will be dosed by body weight. The starting dose in children weighing less than 10 kg will be calculated based on the assumption that 1 m² equals approximately 30 kg, or at the dose of 1 mg/kg b.i.d.

At all dose levels, an adaptive Bayesian logistic model (BLRM) permits alterations in the dose increments based on the observed, clinically relevant, toxicities. In general, dose escalation will occur in increments of 15 mg/m². At each dose level, the clinical response, PK and pharmacodynamic response will be determined. Three patients from < 18 years old to > two years old and two patients ≥ 3 months to ≤ 2 years old will be initially treated and evaluated for DLT assessment at the starting dose. Based on results from adult studies where the primary toxicity has been gastro-intestinal, especially nausea and vomiting, the escalation will not exceed the equivalent of the adult dose of 100 mg b.i.d.

After completion of a given dose cohort within a given stratum, the decision to dose escalate and actual dose chosen will depend on a calculation of risk assessment using the described BLRM and a medical review of available clinical and laboratory data. Details of the statistical methodology are provided in Section 10. The BLRM estimates the MTDs by updating estimates of probability of observing a DLT for each dose level in both strata of the study as patient information becomes available. A dose-limiting toxicity (DLT) is defined as a CTCAE grade 3 or 4 non hematological adverse event or abnormal laboratory value assessed as study treatment-related and that occurs within 14 days starting from day 1 dosing of midostaurin or that results in treatment discontinuation within the first 14 days.

Upon determination of MTD, or establishing that there is no DLT at the 60
mg/m² b.i.d. dose level, additional patients may be enrolled to establish a more robust assessment of preliminary clinical response. Enrollment may be expanded to include up to approximately 10 evaluable patients per indication. A minimum of 6 patients per indication will be enrolled at the MTD.

Supply, preparation, and administration

Tear off the flip-off cap from the midostaurin oral solution bottles, and assemble the dispensing system as described in the separate instructions for use of the dispensing system. For the dosing process, carefully follow the handling/dispensing instructions as described in Post text supplement 2.

Visit schedule and assessments

See Table 7-1.

Efficacy assessment(s)

Patients should be assessed for response based on the following criteria and must meet all of the criteria listed (adapted from Cheson 2003):

**Morphologic leukemia free state (LFS)**
- < 5% bone marrow blasts (minimum count 200 with marrow spicules)
- No Auer rods (in AML patient)
- No persistent extramedulary disease
- No circulating blasts in the peripheral blood
  - Note: The presence of a unique phenotype (by flow cytometry) identical to what was found in the pretreatment specimen (e.g., CD34, CD7 coexpression) should be viewed as persistence of leukemia.

**Morphologic complete remission (CR)**
- Meets definition of Morphological leukemia free state
- Absolute neutrophil count (ANC) ≥ 1000 / µL
- Platelets ≥ 100,000 / µL

**Morphologic complete remission with incomplete count recovery (CRi)**
- Meets definition of CR except for either residual neutropenia (< 1000 / µL or thrombocytopenia (< 100,000 / µL)
- **Platelet** transfusion independent

**Partial remission (PR)**
- a decrease in bone marrow blasts of ≥ 50% to between 5 and 25%

**Bone marrow blast response (BR)**
- absolute bone marrow blast percentage >25%
- ≥ 50% decrease in bone marrow blasts from baseline

**Minor bone marrow blast response (BRm)**
- ≥ 25% decrease in bone marrow from baseline

**Peripheral blood blast response (BRp)**
- ≥ 50% decrease in peripheral blood blasts from baseline

**Minor peripheral blood blast response (BRmp)**
- ≥ 25% decrease in peripheral blood blasts from baseline

**Stable disease (SD)**
- Failure to achieve any response (CR, CRi, LFS, PR, BR, BRm, BRp, BRmp) without meeting the definition of Progressive disease

**Progressive disease (PD)**
- In patients with < 40% bone marrow blasts at baseline: A ≥ 100% increase in bone marrow blast percentage from baseline
- In patients with > 40% bone marrow blasts at baseline: A ≥ 50% increase in bone marrow blast percentage from baseline
- In patients with a leucocyte count > 20,000 x 10^6 at baseline, a peripheral blood blast count increases of ≥50%
- In patients with a leucocyte count < 20,000 x 10^6 at baseline, an increase in peripheral blood blasts of ≥ 50% AND an absolute increase of ≥ 2000 peripheral blood blasts

**Relapse**
- After meeting the criteria of Morphologic CR, reappearance of leukemic blasts in the peripheral blood, or ≥ 5 % blasts in the bone marrow not attributable to any other cause
- In the setting of recent treatment, if the marrow contains 5-20 % blasts, a repeat bone marrow performed at least one week later is necessary to distinguish from bone marrow regeneration unless flowcytometric confirmation of leukemia.

### Special safety assessment(s)

- Patients will be evaluated for safety as described in Section 7.5, including adverse events, physical examination, vital signs, performance status, hematology, biochemistry, thyroid function test, pregnancy (where applicable), chest x-ray, electrocardiogram, and cardiac imaging. All assessments should be performed prior to the morning dose unless otherwise specified.

### Patient reported outcomes

- Not applicable

### Pharmacokinetics

- Blood samples for pharmacokinetic assessment will be collected on all subjects of the study. If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed before the next scheduled dose.

  Blood samples (2 mL per sample) will be collected on day 1 at either 1, 2, or 3 hours following a randomization schema. Blood samples collection will also occur at predose on day 5 or day 7, following a randomization schema, and on day 14. Additional samples will be requested, but not required, in patients ≥ 10 years old. The pharmacokinetic assessments are described in Section 7.9.

  Morning spot urine samples will be collected, if available, prior to dosing on day 1, on day 5 or 7 and on day 14 to explore the potential CYP3A4 induction by midostaurin by measuring urine ratio of 6β-hydroxycortisol to cortisol as an in vivo marker for assessment of CYP3A4 induction activity.

### Biomarker assessments

- Patient bone marrow (3 ml) and peripheral blood (5 ml for patients ≥ 3 months and ≤ 2 years and 10 mL for patients > 2 and < 18 years) will be collected at baseline for isolation of blast cells. Blast cells will be characterized for FLT3 gene overexpression (MLL) and for FLT3 mutations (all patients).

### Exploratory Biomarker pharmacodynamic studies involving tumor samples

- Pharmacodynamic effects of midostaurin will be tested using peripheral blood blast cells collected at baseline, at cycle 1 day3, and at end of treatment. FLT3 phosphorylation will be measured by immunoprecipitation/western blot analysis. Changes in FLT3 phosphorylation will be correlated with clinical response and pharmacokinetic data. If sample quantity is sufficient, blast cells will be used for expression profiling and in ex vivo experiments testing effects of midostaurin on FLT3 phosphorylation and cell killing.

### Optional Biomarker studies on additional or remaining samples

- To facilitate exploratory biomarker efforts, we also request that unused / leftover blood plasma (EDTA), serum, and tumor from other mandatory assessments is saved and shipped to Novartis for retention up to 15 years. The optional signature line included in the main consent will cover the use of this “retention” material for the future analysis of biomarkers that may help to
better understand the disease and/or the study drug in relation to cancer.

DSMB | Not applicable
--- | ---

**Statistical methods and data analysis**

The full analysis set (FAS) consists of all patients who received at least one dose of midostaurin. The full analysis set will be the primary population for all analyses unrelated to safety endpoints.

The safety set will consist of all patients who received at least one dose of midostaurin and had at least one post-baseline safety assessment (where the statement that a patient had no adverse event (on the Adverse Events eCRF) constitutes a safety assessment). The safety set will be the primary population for all safety related endpoints except determination of the dose-DLT relationship.

**The dose-determining set (DDS)** consists of all patients from the safety set who either meet the following minimum exposure criterion and have sufficient safety evaluations, or discontinue earlier due to DLT. This constitutes an evaluable patient for the determination of the MTD. Patients in the expansion phase are not included in this population.

A patient is considered to have met the minimum exposure criterion if they have received $\geq 75\%$ of the planned doses of midostaurin within the first 14 days of dosing. Patients who do not experience DLT during the first 14 days are considered to have sufficient safety evaluations if they have been observed for $\geq 14$ days following the first dose, and have completed all required safety evaluations. Patients who do not meet these minimum safety evaluation requirements will be regarded as ineligible for inclusion into the DDS and will be replaced. A patient can be counted for a DLT at any time point in the first 14 days, if the patient has received at least 75% of the treatment planned at the day the DLT was observed.

The data cutoff date for the final analysis for the study will be when all patients continuing treatment have been followed for at least one cycle or have been discontinued from the study.

Data will be summarized with respect to demographic and baseline characteristics, efficacy measurements, safety measurements, and all relevant pharmacokinetic and pharmacodynamic measurements using descriptive statistics (quantitative data) and contingency tables (qualitative data) by dose and stratum.

The safety analysis will consist of (i) AE summaries (frequency tables based on CTCAE grades) and listings, (ii) laboratory abnormalities summary CTCAE shift tables summary statistics tables and flagging of notable values in listings, and (iii) listing of other tests (e.g., electrocardiogram, vital signs). All analyses will be displayed by dose and stratum as well patients treated with the recommended Phase II dose or MTD in the expansion phase for either stratum will be analyzed with the patients in the dose-escalation phase treated at the same dose level.

Midostaurin pharmacokinetic and biomarker parameters will be listed and summarized by dose and stratum using descriptive statistics.

**Pharmacokinetic:** The concentration-time data will be tabulated together with descriptive statistics for each dose level. Individual as well as mean, concentration-time plots will be generated. Descriptive statistics will be computed and tabulated for all pharmacokinetic parameters evaluated in this study. Formal statistical analyses will not be performed because the study is not powered for such evaluations.

**Biomarker:** FLT3 message overexpression, FLT3 gene mutations phosphorylation status of FLT3 will be correlated with one another and with
clinical response to see if baseline activation of FLT3 correlates with response to midostaurin.

**Dose-escalation phase**

An adaptive 3 parameter Bayesian logistic regression model (BLRM) (Bailey 2009) guided by the escalation with overdose control (EWOC) principle will be used in the dose-escalation phase. The use of Bayesian response adaptive models for Phase I studies has been advocated by the (EMEA guideline on small populations 2006) and by (Rogatko 2007).

Standardized doses will be used such that one of the doses (d*) equals 1, i.e., doses are rescaled as d/d*. As a consequence $\alpha$ is equal to the odds of the probability of toxicity at d* for patients older than 2 years. A covariate is also included in the model for the age group. It takes the value zero if a patient is older than 2 years and the value one otherwise. The respective parameter, $\gamma$, may be interpreted as the log-odds ratio of the probability of DLT for a patient $\geq$ 3 months and $\leq$ 2 yrs old, versus a patient <18 and > 2 yrs old.

Information on probabilities of toxicity for each dose will be updated after each patient cohort is completed using all available data from both strata. Recommendations will be based on the posterior probabilities of DLT being in [0,16%) under-dosing [16%,33%) targeted toxicity [33%,100%) excessive toxicity

The escalation with overdose control (EWOC) principle (Babb 1998), (Neuenschwander 2008) mandates that any dose of midostaurin that has more than a 25% chance of being in the excessive toxicity category is not considered for the next dose cohort. A clinical synthesis of the available toxicity information (including adverse events that are not DLTs), PK, PD, and efficacy information as well as the recommendations from the Bayesian model for the stratum being investigated will be reviewed by the investigators and Novartis trial personnel and will be used to determine the dose for the next cohort in that stratum at a dose-escalation teleconference.

The frequency of DLTs as well as additional information will be tabulated by dose and stratum.

**Sample size**

During the dose escalation, a minimum of 3 evaluable patients will typically be treated per cohort in the stratum for patients < 18 years old and > 2 years old. A minimum of 2 patients will typically be treated per cohort in the stratum for patients $\leq$ 2 years old and $\geq$ 3 months old to assess the log-odds ratio, $\gamma$. At least six evaluable patients must be treated at the doses declared to be the MTD in each stratum. It is estimated that at least 22 patients should be enrolled in total, (12 in the <18 year old and > 2 year old stratum and 10 in the $\leq$ 2 year old and $\geq$ 3 month old stratum) for the model to have reasonable operating characteristics.

**Dose-expansion phase**

Once the MTD or recommended phase II doses have been declared if there are not a total of 10 patients in each indication group additional patients would be enrolled at this dose level to meet this requirement.
1 Background

1.1 Leukemia and FLT 3

The fms-like tyrosine kinase 3 (FLT-3), also known as stem cell tyrosine kinase-1 (STK1) or fetal liver tyrosine kinase-2 (FLK-2) belongs to the group of class III receptor tyrosine kinases. FLT3 and its ligand FL play an important role in survival and self-renewal of early hematopoietic progenitors, of monocytic precursors and in early lymphoid development. FLT3 is expressed on early progenitor cells in the bone marrow (BM), has an extracellular domain and a cytoplasmic domain that carries a tyrosine kinase motif (Zwaan 2003). The FLT3 ligand is produced in the BM and stimulates the proliferation of hematopoietic cells by activating the tyrosine kinase activity of the receptor. It acts in a synergistic way with other growth factors and interleukins such as G-CSF, GM-CSF, IL-3 and SCF (Rosnet 1996, Lyman 1995, Drexler 1999, Lisovsky 1996, Turner 1996). The fact that mice, engrafted with gene-modified bone marrow cells encoding murine FLT3, developed hematological malignancies, suggests that dysregulated expression of FLT3 contributes to leukemogenesis (Hawley 1998). FLT3 is expressed on the surface of leukemia blasts from > 80% of patients with AML (Birg 1992, Carow 1996, Rosnet 1996). FLT3 mRNA is expressed in virtually all pediatric leukemias. In AML, the FLT3 receptor may be constitutively activated either by wild-type (WT) over-expression or by activating mutations in the gene encoding FLT3. Mutations usually are divided in 2 types, as they occur either in the tyrosine kinase domain (TKD mutations) or in the juxtamembrane domain of the gene (so called internal tandem duplications (FLT3/ITD), also referred to as length mutations). Constitutively activated FLT3 provides leukemic cells with a growth advantage and transforming capacity, and hence may well represent a step in the multi-step process of leukemic transformation.

1.2 Overview of childhood leukemia

In childhood, acute leukemias comprise approximately 25% of childhood cancers, and mainly consists of acute leukemias. They can be subdivided in acute lymphoblastic (ALL) and acute myeloid leukemia (AML). ALL is more common than AML in childhood, as only 15-20% of acute leukemias comprise AML.

1.2.1 Acute Myeloid Leukemia (AML)

The outcome of childhood acute myeloid leukemia (AML) has also improved over the last decades. About 85-90% of children with AML achieve complete remission and about 60% of children with AML stay in continuous complete remission (Creutzig 2005, Gibson 2005). However, in case of refractory AML or following relapse, the outcome is still poor. For this reason, several years ago the International AML-BFM Study Group initiated a protocol for relapsed/refractory pediatric AML, Study Relapsed/Refractory AML 2001/01 (Kaspers 2006). Poor response to the 1st course of therapy (>20% of blasts in the BM shortly before the 2nd course), was seen in 23% of patients, more often in early relapses (31%) than in late relapses (15%). Early death occurred in 6% of patients. Complete remission (CR) was achieved in 63% of patients after 2 courses, and they have a probability of survival at 3 years of 47%, compared to 33% for the total group, and 8% for patients not achieving CR. Compared to
early relapses, patients with late relapse had higher CR rates (76 vs. 51%), and higher 3-yr probability of survival 42% vs. 23%. Clearly, the induction therapy or the consolidation phase are not effective enough - and we need more effective treatment options for these children (Kaspers 2006).

1.2.1.1 FLT3 and AML

Both internal tandem duplications (ITD) as well as point mutations can be found in pediatric AML cells (Meshinchi 2006, Stirewalt 2006, Zwaan 2003, Meshinchi 2003). FLT3 gene ITDs were originally reported in AML in 1996 (Nakao 1996). Somatic mutations involving a set of in-frame ITDs occur at the juxtamembrane part of the FLT3 gene, resulting in the duplication of a small segment of this domain. The JM domain mutations have been confirmed in a number of large studies, with an overall incidence of about 10-20% of pediatric AML patients, but are not detectable in normal hematopoiesis (Nakao 1996, Rombouts 2000, Kondo 1999, Kiyoi 1997, Meshinchi 2003, Meshinchi 2006, Zwaan 2003, Hollink 2008). ITD mutations of FLT3 (FLT3-ITD) have oncogenic potential, and their presence on AML blasts indicates a poor prognosis in both adult and pediatric AML (Kondo 1999, Kiyoi 1997, Kiyoi 1999, Zwaan 2003, Meshinchi 2001, Kondo 1999, Iwai 1999, Xu 1999, Arrigoni 2003). This urged the AMLBFM collaborative group to stratify patients based on FLT3/ITD in their ongoing 2004 study. The FLT3-ITD appears to result in constitutively activated FLT3 kinase activity. Although increased tyrosine phosphorylation (i.e. activation) of FLT3 is not a consistent feature of FLT3 point mutations, expression of most of the FLT3-ITD mutants in hematopoietic cell lines is associated with increased tyrosine phosphorylation of the receptor, and of other cellular proteins known to be involved in FLT3 signaling (Fenski 2000, Hayakawa 2000, Kiyoi 1998). Furthermore, expression of a FLT3-ITD mutant in a factor-dependent cell line such as 32D results in factor independent proliferation (Yamamoto 2001).

Several studies suggest that FLT3/ITD may not always be stable between diagnoses and relapse, which might be explained by their presence in sub-clones of the leukemia-cell population, especially the stem-cell population that drives the leukemia. (Cloos 2006, Pollard 2006).

Point mutations in FLT3 have been reported in up to 5-10 % of pediatric AML cases, however they seem to lack prognostic significance (Meshinchi 2003). In a recent adult AML study it was even suggested that these patients have improved outcome (Mead 2007). Several papers have shown that there are differences in activated downstream signaling pathways between ITDs and tyrosine kinase domain mutations (TKD), that may explain this difference in biological behavior (Choudhary 2005, Mead 2007). Additionally, the high level expression of wild-type FLT3 is associated with a poor outcome and selective sensitivity to FLT 3 inhibitors in childhood AML (Brown 2008).

Taken together, it appears that FLT3 might be a therapeutic target in a subset of pediatric acute myeloid leukemia patients (Brown 2004).

1.2.2 MLL-rearranged ALL

The outcomes of children with acute lymphoblastic leukemia (ALL) have improved tremendously over the last decades. Current therapies result in a 70-80% survival rate in the Western countries. However, 20-30% of the children with ALL die from the disease, and as
ALL comprises about 20-25% of childhood cancer cases, this renders this type of cancer a major cause of childhood death in absolute numbers.

Rearrangements at chromosome 11q23 involving the MLL (mixed lineage leukemia) gene are associated with a poor outcome. Children with an MLL-rearranged ALL, hereafter called MLL, have only ~40% event-free survival with contemporary intensive combination chemotherapies, which may include allogeneic stem cell transplantation. About 80% of children with ALL < 1 year of age at diagnosis (infants) have MLL rearrangements, while this type of leukemia is found in only 2% of children above 1 year of age (Biondi 2000). An international collaboration was started in 1999 to treat infants with ALL on a single treatment protocol, the Interfant-99 protocol. The complete remission rate in this study of patients with MLL is 94%. As opposed to more common types of childhood ALL, where relapses may occur up to 6 years after first diagnosis, relapses in MLL occur early, usually when patients are still on therapy and about 70% take place within a year after diagnosis (Pieters 2007). The outcome for relapsed MLL, and for MLL refractory to initial induction therapy, is dismal. Therefore, development of new treatment modalities for this specific subtype of childhood ALL is necessary.

1.2.2.1 FLT3 and MLL-rearranged ALL

In addition to mutations of FLT3, over-expression of WT FLT3 also may contribute to the pathogenesis of leukemia (Stam 2006, Brown 2005). Over-expression of FLT3 was originally identified as a common feature of MLL-rearranged acute lymphoblastic leukemia in infants, and later confirmed by other investigators (Armstrong 2002, Brown 2005, Yeoh 2002, Armstrong 2003). RT-PCR analysis confirmed the over-expression of FLT3 detected by gene expression profiling using micro-arrays (Armstrong 2003, Stam Blood 2003, Stam 2005). Further evaluation demonstrated that the mechanism of constitutively activated FLT3 in MLL is due to either activating mutations or over-expression of WT FLT3. D835 mutations and the newly described deletions of I836 in the activation loop of FLT3 were found in up to 17% of MLL (Armstrong 2003, Stam 2005). FLT3 ITD mutations have not been reported in MLL-rearranged ALL (Stam 2005). It has also been demonstrated that high-level expression levels of FLT3 is associated with receptor activation and is of unfavorable prognostic value in MLL-rearranged ALL (Stam 2005, Stam Haematoligica 2007). Because of these observations, it was hypothesized that FLT3 might be a therapeutic target in MLL-rearranged leukemias (Brown 2006).

Taken together, it appears that FLT3 might be a therapeutic target in a pediatric MLL patients, mainly occurring in infants, whose ALL-cells are characterized by FLT3 overexpression.

1.3 Overview of midostaurin

Midostaurin (PKC412, CGP41251), an N-benzoylated staurosporine derivative, is chemically designated as (9S,10R,11R,13R)-N-(2,3,10,11,12,13-hexahydro-10-methoxy-9-methyl-1-oxo-9,13-epoxy-1H,9H-diindolo[1,2,3-gh:3',2',1'-lm]pyrrolo[3,4-j][1,7]benzodiazaizin-11-yl)-N-methyl-benzamide. The chemical structure of midostaurin is shown in Figure 1-1 below.
Midostaurin (PKC412, formerly CGP 41251), is an inhibitor of protein kinase C (PKC). In addition, midostaurin inhibits a number of tyrosine kinases such as, the class III tyrosine protein kinase Flt-3 that is involved in hematopoiesis and leukemia (Weisberg 2002), (Armstrong 2003). Midostaurin inhibits PDGF-Rα that occurs as a fusion protein FIP1L-PDGFR-α and causes hypereosinophilic syndrome (HES) (Cools 2003) Midostaurin inhibits also the ZNF198-FGFR1 fusion kinase which has been implicated in myeloproliferative disorder (MPS) (Chen 2004) In addition, midostaurin inhibits the mutated tyrosine kinases KIT-D816V, KIT-D816Y and FGFR-3K650E that contribute to the clinical pattern of AML, mastocytosis and multiple myeloma (Goemans 2005, Gotlib 2005, Growney 2005).

Midostaurin is currently being developed as an antileukemic agent in AML, based on its well-documented antiproliferative and pro-apoptotic activities in cell systems expressing and depending on mutated FLT3 receptor signaling or in wild-type FLT3 overexpressing cells. Activity of midostaurin against various PKC isoforms may also contribute directly or indirectly to the antileukemic activity (i.e. inhibition of Pgp activation), (Hunter 2004). In addition to its activity as single agent [Study CPKC412A2104], midostaurin can exert enhanced antiproliferative effects against AML cells in vitro when combined with other antiproliferative agents (Bali 2004, George 2004). More importantly, midostaurin can be combined with standard chemotherapeutic agents used in AML (daunorubicin and Ara-C) resulting in synergism or additivity [Study CPKC412A2106].
1.3.1 Preclinical data

1.3.1.1 In-vitro pharmacology - FLT3

Activating mutations in FLT3 and wild type FLT3 over-expression are likely to contribute to the deregulated growth and viability of AML and/or MLL-rearranged cells. Accordingly, an inhibitor of FLT3 would be expected to reduce growth and viability in those leukemia cells, expressing constitutively activated FLT3 by a number of mechanisms including mutations (ITD, point mutations) and high-level of WT FLT3.

Midostaurin has been identified as an inhibitor of FLT3 (Weisberg, Cancer Cell, 2002). Ba/F3 cells expressing a mutant of FLT3 and growing in the absence of growth factors were found to be substantially more sensitive to midostaurin than were Ba/F3 cells expressing (but not overexpressing) WT FLT-3, growing in the presence of IL-3, or Ba/F3 cells not expressing FLT3. The cytotoxic effect of midostaurin is reversed by addition of IL-3 suggesting that midostaurin affects FLT3 directly or affects the signaling pathway of the mutant FLT3. Midostaurin potently inhibits recombinant FLT3 using an in vitro kinase assay, and inhibits tyrosine phosphorylation of mutant FLT3, both ITD mutants and D835Y point mutants. These data suggest that midostaurin directly blocks the kinase activity of mutant FLT3, thereby interfering with its transforming functions. Expression of a mutant FLT3 receptor (FLT3-ITD or FLT3-D835) in murine marrow cells results in a lethal myeloproliferative syndrome, which is cured with the administration of midostaurin (Stam Blood 2003).

As with Ba/F3 cells transfected with FLT3 mutations, FLT3-ITD and FLT3-D835, midostaurin is also differentially cytotoxic to primary leukemia cells with MLL translocations that exhibit FLT3 that is constitutively activated by over-expression of the wild-type receptor (Stam 2005). Moreover, midostaurin appeared to be differentially cytotoxic to MLL cells that carry either a mutated FLT3 or a wild-type overexpressed FLT3 protein as compared to leukemia cell lines that had a normal expression of WT FLT3. Thus, high-level FLT3 expression predicts sensitivity to midostaurin. Cell lines expressing high FLT3 levels also show high levels of phosphorylated (activated) FLT3. The other cell lines showed no or minimal phosphorylated FLT3. Target validation was shown by the fact that treatment with midostaurin resulted in inhibition of FLT3 phosphorylation. The cytotoxic effect was related to induction of apoptosis in the MLL cells, whereas the control cell lines did not show apoptosis upon midostaurin incubation. Additionally, Armstrong et al developed a xenograft mouse model of MLL in which leukemia burden was quantitated by bioluminescence imaging (Armstrong 2003). In this model, they demonstrated significant antitumor activity of midostaurin against FLT3 over-expressing MLL cells in vivo. Finally, in vitro cytotoxicity studies on samples derived from patients showed that cells from MLL-rearranged ALL patients were significantly ~5-fold more sensitive to midostaurin than cells from older children with conventional ALL although a subgroup of these other ALL group showed the same sensitivity (Stam Erasmus 2003). Thus there is both in vitro and in vivo preclinical data supporting the hypothesis that FLT3 kinase inhibitors in general, and midostaurin in particular, may have activity against wild-type over-expressing, as well as mutant FLT3 receptors in MLL-rearranged ALL.
1.3.1.2 Preclinical toxicology

The toxic effects of midostaurin observed in preclinical safety studies were essentially limited to those expected from an inhibitor of cell proliferation, and were in part predictive of the adverse events in the early clinical studies. The no observable effect (NOEL) in the 12-month toxicity studies was 3 mg/kg in rat and 1 mg/kg in dog. In vitro and in vivo mutagenicity tests revealed no genotoxicity. There was no teratogenic effect noted from embryo-fetal development studies in rats and rabbits. Developmental toxicity was seen at 10 mg/kg or higher. NOEL for fertility and general reproductive toxicity was defined at 30 mg/kg.

Treatment with midostaurin at doses $\geq$ 3 mg/kg in dogs and $\geq$ 10 mg/kg in rats at durations up to 12 months was associated with effects on proliferating tissues, especially the intestine (mucosal alteration), testes (degenerated spermatogonia), and bone marrow (hypocellularity). The effect on the bone marrow was accompanied by hematological changes (decreased total white cells, lymphocytes and erythrocytic parameters). In rats, treatment was consistently associated with changes of liver enzymes (increased ALT and AST) although not accompanied by pathological changes. In dogs, effects on the cardiovascular system were seen after 3 months of treatment and characterized by a decrease in heart rate in individual animals (10 and 30 mg/kg) and correlated with a prolongation of the P-Q interval; however, no associated morphological changes in the heart were found. Inhibition of spermatogenesis was seen in dogs at all doses (3, 10 and 30 mg/kg) after 3 months' treatment and confirmed after 12 months' treatment at 10 mg/kg.

In vitro, midostaurin did not inhibit hERG channels stably expressed in HEK293 cells at its highest soluble concentration of 12 µM (6.8 µg/mL). The two metabolites of midostaurin, hydroxy-PKC412 and desmethyl-PKC412, had an inhibition of hERG channels about 26.4% and 11.5% at the highest soluble concentrations of 4.74 and 1.21 µM, respectively.

1.3.2 Pharmacokinetic and pharmacodynamic data

The metabolism and pharmacokinetics of midostaurin have been extensively studied in rats and dogs. Absorption from a microemulsion formulation was >90% in rats and 47-67% in dogs. In both rats and dogs, the exposure after multiple doses was slightly higher (<2-fold) compared to that after a single dose. Radioactivity derived from $^{14}$C midostaurin was extensively distributed into tissues in the rat. After multiple doses, the radioactivity in tissues was 2-10-fold higher than that after a single dose. Plasma protein binding in the rat and dog was high, ranging from 98.0-99.2% and independent of concentration over the concentration range of 0.1 to 5 µg/mL.

Midostaurin was extensively metabolized in rats and dogs and the majority $^{14}$C midostaurin related radioactivity after p.o. dosing was excreted almost exclusively in feces in the form of metabolites. The major circulating components in the rat plasma included midostaurin and the two epimers of CGP52421. In the dog, the major circulating components were midostaurin, CGP52421 (the two epimers) and CGP62221 (the O-demethylation product). In in vitro postmitochondrial liver fractions, there were some qualitative and quantitative interspecies differences in metabolism, but the major metabolites appeared to be common among the species studied including mouse, rat, rabbit, dog, marmoset, cynomolgus monkey, baboon and man.
Based on recombinant enzymes and human liver microsomes, CYP3A4 was the major enzyme involved in midostaurin oxidative metabolism. Therefore, concomitant medications which interfere with CYP3A4 activity (inhibition or induction) could lead to changes in the systemic exposure to midostaurin. Midostaurin appeared to have little inhibitory effect on in vitro activities associated with CYP enzymes, 1A2, 2C8, 2C9, 2C19, 2D6, and 2E1. However, inhibition of CYP3A4 (midazolam 1'-hydroxylation) was observed with an IC50 value of about 1.5 µM. Overall the available results suggest that the potential for drug-drug interactions is highest with comediations metabolized by CYP3A4, assuming that midostaurin reaches sufficiently high concentrations (≥1.5 µM) therapeutically. Although midostaurin appears to be not a good substrate of Pgp, the drug is a potent Pgp inhibitor with an IC50 value of 1.7 µM. The excretion of radioactivity was rapid and virtually complete in rats but not in dogs (80%). In both species, radioactivity was mainly excreted via bile into feces and renal excretion was very minor (<2%).

1.3.3 Clinical data

1.3.3.1 Pharmacokinetic and pharmacodynamic data

The pharmacokinetics of midostaurin has been extensively studied, including single dose PK and ADME studies in healthy subjects, multiple doses PK studies in subjects with diabetes mellitus, solid tumors, progressive CLL or NHL, metastatic melanoma, Stage IIIb and IV non-small cell lung cancer, and AML. In these studies, midostaurin was given alone or in combination with standard chemotherapeutic agents.

Following single oral administration, midostaurin was rapidly absorbed with T_max at 1-3 hours. C_max and AUC increase with dose, but under-proportionally especially following a long-term treatment of multiple doses. The oral bioavailability of Midostaurin is estimated to be high (>90%), since only 3.43% of the parent drug is found in the feces and the compound is stable in the gut. The mean apparent volume of distribution during the terminal phase (Vz/f, 111 L) was higher than the total body water (42 L) indicating a high tissue distribution. Midostaurin is metabolized into two major active metabolites, the O-demethylated compound, CGP62221 and the hydroxylated compound, CGP52421 (epimer 2). Midostaurin is predominantly metabolized by cytochrome P4503A (CYP3A) iso-enzymes to form two major active circulating metabolites, CGP62221 (via O-demethylation) and CGP52421 (via hydroxylation) in human. The relative potency of these metabolites (Midostaurin: CGP62221: CGP52421) is approximately 1 : 1.4 : 0.1 in FLT3 based cellular assays. Following multiple oral doses, midostaurin and CGP62221 concentrations accumulated significantly in the first 3-5 days, and then declined by approximately 40-80% prior to reach a new steady state between 2-3 weeks post dose, whereas CGP52421 concentrations accumulated continuously through day 28 and remained stable thereafter, being roughly 7-times higher than that of either the parent drug or CGP62221 [Study CPKC412A2106]. In the ADME study [Study CPKC412A2107], the terminal half-life of midostaurin was found to be about 25 hours (ranging 10-50 hours) following a single oral dose of 50 mg [14C] midostaurin to 6 healthy volunteers. CGP62221 exhibited a similar elimination half-life as midostaurin, with a mean value of 39 hours. However, the elimination half-life of CGP52421 was much longer, ranging from 16 to 31 days. The time-dependent kinetics of midostaurin was probably resulted from an induction of CYP3A4 by midostaurin and/or its metabolites as shown at in vitro
conditions. The mean apparent plasma clearance (CL/f) of PKC412 was low (3.71 L/h) compared to the human hepatic blood flow (87 L/h), suggesting that PKC412 has a low hepatic extraction. Because midostaurin and its major metabolites are all highly bound to plasma proteins including albumin and alpha-acid glycoprotein, a protein binding interaction between midostaurin and its metabolites could be an alternative mechanism for the time-dependent kinetics of midostaurin following multiple doses.

In-vitro and ex vivo studies have shown that midostaurin is a potent Pgp inhibitor P-gp expression is absent in most pediatric AML samples, and a study aiming at its inhibition with cyclosporine A did not improve outcome (Zwaan 2006, Becton 2006).

In [Study CPKC412A2104], the midostaurin dose of 75 mg t.i.d. was efficacious in patients with FLT3 mutated AML. Preliminary PK/PD analysis from this study showed that the plasma level of midostaurin following 75 mg t.i.d. seems to be well above the IC50 value for FLT3 ITD/D835 inhibition. Analysis of FLT3 phosphorylation of patient leukemic cells pre- and post-treatment with midostaurin indicated that phosphorylation of FLT3 was inhibited in most patients at 4 and/or 24 hours after the first dose of drug. Because of the long half-life of midostaurin and its active metabolites, b.i.d. instead of t.i.d. dosing regimen is reasonable and convenient for patients. The b.i.d. dosing regimen, 100 mg b.i.d. or the reduced 50 mg b.i.d. dose level, has recently been tested in [Study CPKC412A2106] (midostaurin in combination with chemotherapeutic agents: daunorubicin and cytarabine).

The purpose of [Study CPKC412A2108] was to compare the relative bioavailability of midostaurin from Marketed Formulation (MF), final market image (FMI) and drinking solution (DS) following a single oral dose of midostaurin in healthy subjects. In addition, a drinking solution (DS) is also being developed for the convenience of administration, especially in the special patient populations such as the critically ill adult patients and pediatric patients who have difficulties to swallow the capsules. Preliminary results showed that the three formulations are biocomparable, with no conversion factor required.

### 1.3.4 Clinical Safety and efficacy

Midostaurin has been studied as a single agent and in combination with standard chemotherapeutic regimens in over 800 human subjects, including healthy volunteers, patients with solid and hematological malignancies, and patients with diabetic macular edema.

#### 1.3.4.1 Healthy volunteers

The safety and tolerability of midostaurin was first evaluated in healthy adult males with single ascending oral doses up to 25 mg prior to the first meal of the day. Treatment was well tolerated with no drug-related changes in clinical laboratory parameters or vital signs. In the human ADME study [Study PKC412A2107] where a single oral dose of 50 mg [14C] midostaurin was given to 6 healthy subjects, no serious or severe adverse events were reported during the study. Minor adverse events reported included headache, gassy, loose stool, constipation and light headedness.

#### 1.3.4.2 Cancer patients

The first clinical Phase IB study in patients with advanced solid cancers [Study 002] assessed the safety, tolerability and pharmacokinetics of continuous dosing with midostaurin at one of
seven dose levels (ranging from 12.5 to 300 mg daily). A total of 32 patients were treated and received a total of 68 cycles. The most common adverse events were fatigue, nausea and vomiting. Both the incidence and severity of most common adverse events were increased at higher dose levels. Prophylactic treatment with anti-emetics was found to control these side effects in most patients. The average treatment duration was one to two treatment cycles (one treatment cycle is 28 days daily dosing plus 1 week without treatment). Most patients (26/32) withdrew from the study because of disease progression.

Two exploratory Phase II clinical studies assessed the safety, tolerability and biological activity of midostaurin as a single agent in CLL/NHL [Study 006] and metastatic melanoma [Study 011]. Mild to moderate nausea / vomiting and diarrhea were the most frequently reported adverse events in both studies. Transient increases in serum amylase were observed in 5/21 CLL/NHL patients. Mild and transient increases in liver enzymes were also observed in two patients in this study. There was a single report of “hot flushes” lasting for one day in a melanoma patient. There were also two occurrences of severe nausea and one of each of diarrhea and lethargy in the melanoma trial.

**Study CPKC412A2104 Core and Amendments**

The [Study CPKC412A2104 Core], of midostaurin in FLT3 mutated patients with relapsed or refractory AML or MDS was completed in 2003, and twenty patients had been treated. The median age was 62 years (range 29 to 78). Patients were treated with midostaurin at a dose of 75 mg orally three times a day. Of the 20 patients enrolled, 18 had AML, 1 patient each had MDS and CMML. FLT-3 status at baseline included 18 ITD’s and 2 D835Y.

All patients experienced at least one AE. The most frequent were nausea and vomiting (experienced by 70% and 60% of patients, respectively). Two patients experienced AEs with a maximum severity of grade 1 or 2, all others experienced at least one AE of grade 3 (10 patients, 50%) or grade 4 (8 patients, 40%). Nineteen patients (95%) experienced at least one AE related to study drug. The most frequent adverse events are described in Table 1-1.

**Table 1-1 Most frequent adverse events in patients with FLT3 mutated AML [Study CPKC412A2104 core]**

<table>
<thead>
<tr>
<th>System organ class affected</th>
<th>Preferred term</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Anemia NOS</td>
<td>6 (30.0)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea</td>
<td>14 (70.0)</td>
</tr>
<tr>
<td></td>
<td>Vomiting NOS</td>
<td>12 (60.0)</td>
</tr>
<tr>
<td></td>
<td>Diarrhea NOS</td>
<td>6 (30.0)</td>
</tr>
<tr>
<td></td>
<td>Gingival bleeding</td>
<td>5 (25.0)</td>
</tr>
<tr>
<td>General disorders and admin. site disorders</td>
<td>Fatigue</td>
<td>8 (40.0)</td>
</tr>
<tr>
<td></td>
<td>Edema peripheral</td>
<td>8 (40.0)</td>
</tr>
<tr>
<td></td>
<td>Pyrexia</td>
<td>8 (40.0)</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Anorexia</td>
<td>5 (25.0)</td>
</tr>
<tr>
<td></td>
<td>Hypokalemia</td>
<td>5 (25.0)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache</td>
<td>7 (35.0)</td>
</tr>
</tbody>
</table>
Eight patients (reported in Argus database) died in the safety follow-up within 28 days following study drug discontinuation. SAEs were reported for 12 patients (60%). In 3 of the patients, the investigator rated the SAEs as related to study drug: these were febrile neutropenia, bronchopneumonia NOS, troponin NOS, hypoxia, pulmonary edema NOS, respiratory failure, and urticaria NOS.

None of the 20 patients experienced a complete or partial clinical response. The median time to treatment failure was 29 days (95% CI: 29 to 33 days). All patients who had failed treatment did so by 55 days. Sixteen of the 20 patients (70%) had a ≥ 50% decrease in peripheral blood blast counts. Six (30%) minor responses occurred (defined as a significant improvement in hematologic parameters by standard criteria).

The study was then amended to include up to an additional 100 patients with either wild-type or FLT-3 mutated AML [CPKC412A2104A3]. Patients were randomized to single-agent oral midostaurin at 50 mg b.i.d. or 100 mg b.i.d. Patients were discontinued if they did not respond by two months, or for disease progression or unacceptable toxicity.

The frequency of AEs was similar for both dose regimens and for both FLT3 groups. The most frequent AEs were nausea, vomiting, diarrhea and fatigue. SAEs regardless of study drug relationship were reported for 26 patients (74.3%) in the FLT3 mutated group and for 38 patients (63.3%) in the FLT3 wild type group. The most common SAEs regardless of relationship to study drug were febrile neutropenia (18.9%), pneumonia (15.8%), pyrexia (13.7%), dyspnea (7.4%), disease progression (5.3%), hypoxia (5.3%) and hypotension (5.3%). Among these, 7 (20.0%) in the FLT3 mutated group and 6 (10.0%) in the FLT3 wild type group were thought to be drug related. The most common SAEs considered to be related to study drug by investigators are ALT increase (3.2%), AST increase (2.1%), and pulmonary edema (2.1%). Seven deaths occurred, five in the FLT3 mutated patient group and two in the FLT3 wild type patient group. The causes of death were sepsis (two patients), splenic infarction, cardiac failure, general health deterioration, septic shock and AML (one patient each). As reported in the survival follow up a total of 28 patients died within 28 days of last dose of study drug.

Response was defined as complete, partial or minor using standard criteria, and biologic activity was defined as at least a 50% decrease in blood and/or bone marrow blasts. A total of 95 patients were enrolled from 7 study centers (2 in Germany, 5 in the US) into the study (85 AML, 10 MDS) with either FLT3 WT (n=60) or mutated (n=35) AML. Median duration of drug exposure was 46 days for mutated patients and 52.5 days for wild type patients.

The blast responses in the ITT population for [Study CPKC412A2104 Core and A3] are summarized in the Table 1-2 given below.
Table 1-2: CPKC412A2104 core through A3 blast response

<table>
<thead>
<tr>
<th>Blast reduction</th>
<th>Patients n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FLT3 mutated</td>
</tr>
<tr>
<td>75 mg i.d.</td>
<td>16 (80.0)</td>
</tr>
<tr>
<td>(N=20)</td>
<td></td>
</tr>
<tr>
<td>50 mg b.i.d.</td>
<td>12 (66.7)</td>
</tr>
<tr>
<td>(N= 18)</td>
<td></td>
</tr>
<tr>
<td>100 mg b.i.d.</td>
<td>13 (76.5)</td>
</tr>
<tr>
<td>(N= 17)</td>
<td></td>
</tr>
<tr>
<td>50 mg b.i.d.</td>
<td></td>
</tr>
<tr>
<td>(N= 31)</td>
<td></td>
</tr>
<tr>
<td>100 mg b.i.d.</td>
<td></td>
</tr>
<tr>
<td>(N=29)</td>
<td></td>
</tr>
</tbody>
</table>

A majority of patients presented a clinical response or biologic response, both in the FLT3 mutated group (71.4%) and in the FLT3 wild type group (56.1%). These responses did not appear to be drug dose-dependent across the doses tested. Duration of activity was short, with the median duration of response of 86 days for mutated patients and 113 days for wild type patients.

[Study CPKC412A2104 A4] is a proof-of-concept trial to determine the safety, tolerability, and pharmacokinetics in AML and high risk MDS patients using midostaurin with intra-patient dose escalation or midostaurin in combination with Itraconazole. The most frequent AEs were nausea (62.1%), diarrhea (51.7%), vomiting (44.8%), anemia (41.4%), pyrexia (37.9%), headache (37.9%), fatigue (34.5%), constipation (31%), hypokalaemia (27.6%), thrombocytopenia (17.2%), abdominal pain (27.6%), chills (24.1%), insomnia (24.1%), neutropenia (20.7%), cough (20.7%), dyspnoea (24.1%), febrile neutropenia (17.2%), asthenia (13.8%), hyperglycaemia (17.2%), leucopenia (17.2%), edema peripheral (13.8%), pain (10.3%), hyperuricaemia (10.3%), pain in extremity (13.8%), pleural effusion (13.8%), night sweats (13.8%), and hypotension (13.8%). The most common SAEs, regardless of study drug relationship, were pyrexia (17.2%), blast cell count increased (10.3%), febrile neutropenia (10.3%), leukocytosis (6.9%), splenomegaly (6.9%), chills (6.9%), general physical health deterioration (6.9%), pleural effusion (6.9%), sepsis (6.9%), lung infiltration (6.9%), pericardial effusion (6.9%), angina pectoris (6.9%) and pneumonia (6.9%). Three deaths were recorded as primary causes for study discontinuation. In total 8 deaths occurred within 28 days of last study drug intake. There was one complete response, and no partial responses. Ten out of 29 patients had a blast response including the one complete response.

Study CPKC412A2106

In [Study CPKC412A2106], a total of 69 patients have been enrolled in [Study CPKC412A2106], midostaurin administered sequentially (Arm 1) and concomitantly (Arm 2) with standard induction daunorubicin and cytarabine therapy followed by high-dose consolidation therapy with cytarabine in patients with newly diagnosed, previously untreated AML, both FLT-3 mutated and WT.

The study design consists of one core protocol and 4 amendments to this study, incorporating 3 major design changes for tolerability concerns, which are summarized in Table 1-3 below.
Table 1-3  Overall study design: Study CPKC412A 2106 core and amendments

<table>
<thead>
<tr>
<th></th>
<th># days midostaurin in month 1</th>
<th># days midostaurin in month 2+</th>
<th>midostaurin dose</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Core and Amendment 1</td>
<td>21-28</td>
<td>28</td>
<td>100 mg b.i.d.</td>
<td>14 patients (7 in arm 1, 7 in arm 2), all off study</td>
</tr>
<tr>
<td>Amendment 2</td>
<td>14</td>
<td>14</td>
<td>100 mg b.i.d.</td>
<td>15 patients (7 in arm 1, 8 in arm 2), all off study</td>
</tr>
<tr>
<td>Amendment 3 and 4</td>
<td>14</td>
<td>14</td>
<td>50 mg b.i.d.</td>
<td>40 patients (20 in arm 1, 20 in arm 2), 1 on going</td>
</tr>
</tbody>
</table>

Preliminary results with the original dose of midostaurin of 100mg p.o. b.i.d., demonstrated safety, but poor tolerability due to nausea and vomiting when given in the original schedules: from day 8 continuously (arm 1) or day 1 continuously (arm 2) (n=15) or an amended schedule: day 8-21 (arm 1) or day 1-7, 15-21 (arm 2) (n=15). This study was further amended using the same chemotherapy regimen plus midostaurin at a reduced dose of 50 mg p.o. b.i.d.. Forty patients were enrolled at the dose of 50 mg b.i.d. (median age 49 (20-65): 20 in Arm 1 and 20 in Arm 2. All 40 patients were evaluable for toxicity. No drug-related deaths were observed during induction therapy. The most common drug related toxicities during induction and consolidation cycles were nausea (60%), vomiting (50%), diarrhea (35%), thrombocytopenia (25%), ALT increase (25%), AST increase (23%), anemia (20%), and neutropenia (20%); all were transient and/or reversible. No Grade 3 or 4 nausea and vomiting were recorded. All 40 patients have completed the study per protocol. The last patient on study for maintenance after achieving CR discontinued treatment on 10 September 2008.,

The efficacy results of CR rates by amendments, by arms, and by FLT3 status are summarized in Table 1-4, Table 1-5, and Table 1-6 below.

All patients were eligible for efficacy assessment. When a comparison of CR rate is made across all 69 patients in this study overall, there was a difference between the FLT3 WT CR=28/50 (56%), and FLT3 mutated CR=17/19 (89%). In FLT3 mutated patients the CR rate is consistently excellent across all regimens and all doses.

All 40 patients were evaluable for response at 50 mg b.i.d. dose (Amendment 3/4): 16/20 (80%) achieved CR in Arm 1 and 16/20 (80%) achieved CR in Arm 2.

In the 50 b.i.d. treatment arm there is a trend for a higher CR rate in patients with mutant FLT3 AML (20/27 =74.1% responses) than mutated ones (12/13 = 92.3% responses).
Table 1-4  CPKC412A2106 efficacy: overall study CR rate

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Overall</th>
<th>Arm 1</th>
<th>Arm 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Core + AM1</td>
<td>6/14</td>
<td>42.8%</td>
<td>3/7</td>
</tr>
<tr>
<td>Amendment 2</td>
<td>7/15</td>
<td>46.7%</td>
<td>3/7</td>
</tr>
<tr>
<td>Amendment 3/4</td>
<td>32/40</td>
<td>80%</td>
<td>16/20</td>
</tr>
<tr>
<td>Total CR</td>
<td>45/69</td>
<td>65.2%</td>
<td>22/34</td>
</tr>
</tbody>
</table>

Table 1-5  CPKC412A2106 efficacy: patient responses by FLT3 status - wild type CR rate

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Overall</th>
<th>Arm 1</th>
<th>Arm 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Core + AM1</td>
<td>5/13</td>
<td>38.5%</td>
<td>2/6</td>
</tr>
<tr>
<td>Amendment 2</td>
<td>3/10</td>
<td>30%</td>
<td>1/4</td>
</tr>
<tr>
<td>Amendment 3/4</td>
<td>20/27</td>
<td>74.1%</td>
<td>9/13</td>
</tr>
<tr>
<td>Total CR</td>
<td>28/50</td>
<td>56%</td>
<td>12/23</td>
</tr>
</tbody>
</table>

Table 1-6  CPKC412A2106 efficacy: patient responses by FLT3 status - mutated CR rate

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Overall</th>
<th>Arm 1</th>
<th>Arm 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Core + AM1</td>
<td>1/1</td>
<td>100%</td>
<td>1/1</td>
</tr>
<tr>
<td>Amendment 2</td>
<td>4/5</td>
<td>80%</td>
<td>2/3</td>
</tr>
<tr>
<td>Amendment 3/4</td>
<td>12/13</td>
<td>92.3%</td>
<td>7/7</td>
</tr>
<tr>
<td>Total CR</td>
<td>17/19</td>
<td>89.4%</td>
<td>10/11</td>
</tr>
</tbody>
</table>

Therefore based on these data, midostaurin 50 mg p.o. b.i.d. and standard daunorubicin/cytarabine induction have an acceptable safety and tolerability profile in newly diagnosed <60-year-old AML patients. Additionally, the sequential treatment regimen (Arm2) appears to be as effective as the concomitant regimen (Arm 1) but better tolerated.

1.4 History of Amendments

Amendment #1

Changes to exclusion criteria, additional ECG assessments, allowance of infrequent intrathecal chemotherapy and short courses of corticosteroids, clarification of Schedule of assessments and DLT time period, clarification of PK schedule and population definition, clarification of recruitment minimums for expansion, clarification of response criteria, use of electronic CRF pages and refinement of language for better clarity.
2 Study rationale/purpose

2.1 Study rationale
The survival of children with refractory or relapsed MLL-rearranged ALL or with refractory or second relapse of AML is poor (Pieters 2007, Kaspers 2006). The prognosis remains the same if the patients are treated with intensive chemotherapy protocols, including an allogeneic stem-cell transplantation, if this has not been performed in first or second complete remission. Further intensification of upfront therapy is not possible because it leads to very high toxic-death rates in these children (Slats 2005, Creutzig 2004). Thus, there is need to develop new modalities of treatment for these subtypes of leukemia, which may be added to standard chemotherapy, to further reduce relapse rate without increasing toxicity. As noted above, FLT3 activation plays a role in the development of leukemias and is related to a poor outcome. The addition of a targeted agent against FLT3 may offer the possibility for significant therapeutic advantage as demonstrated in adult AML patients expressing FLT3 (Gilliland 2002). Childhood MLL shows over-expression of FLT3 compared to other types of leukemia (Stam 2005), and AML shows activating FLT3 mutations in a significant percentage of patients (Zwaan 2003). Therefore, FLT3 has the potential to be a promising target for therapy in these subtypes of childhood leukemia. So far, no other FLT3 inhibitors have been developed for use in children.

2.2 Study design rationale
This is a phase I/II pediatric dose-ranging study that will evaluate the safety, tolerability, clinical response, pharmacokinetics and pharmacodynamics of midostaurin in children <18 years and ≥ 3 months of age who have relapsed or refractory leukemias that may benefit from administration of midostaurin, including MLL-rearranged ALL and FLT3 positive AML. Treatment with single agent midostaurin may have potential therapeutic benefit in pediatric AML patients similar to the response seen in adults with the disease, which is summarized in Section 1.3.4.2 from [Study CPKC412A2104]. A similar effect may be seen in MLL-rearranged cases, although there are no adult data to support this, as high FLT3-overexpression in the absence of mutations is a target that is mainly limited to infant ALL. As the main issue in the tolerability of midostaurin is nausea and vomiting, the solution will be administered with standard anti-emetics to improve tolerability and to minimize side-effects. Given midostaurin’s limited potential as a single-agent to induce CRs in adults with AML, it is anticipated that in future protocols, midostaurin will be used mainly in combination with regular chemotherapy. This will be addressed in future phase II trials in MLL and AML. However, before doing so, sufficient background data are needed on its safety and preliminary evidence of activity/efficacy as a single agent, at the same time limiting the number of patients exposed to single-agent midostaurin. Therefore, only a limited number of dose-levels will be assessed, based on availability of adult data, and non-efficacious dose-levels will be avoided.

For this pediatric study a specific oral drinking solution was developed by Novartis, which was tested for bioequivalence in [Study CPKC412A2108] as mentioned in Section 1.3.3.1.

Two age groups will be considered in the current protocol: ≤ 2 years and ≥ 3 months and < 18 and > 2 years old. This reflects similar biological and clinical findings across each age of the
two groups and is also in line with several pediatric oncology protocols grouping patients 2-18 years, to whom the anticancer treatment dose is defined across each age group and delivered proportionally to the patients’ body weight or body surface area in each separate age group. It is expected that 2/3 of the patients enrolled will be AML patients, and 2/3 of the patients will be > 2 years old. Therefore, three patients < 18 and > 2 years old and two patients ≤ 2 years and ≥ 3 months old will be initially treated and evaluated for DLT assessment.

In adults, the maximum tolerated dose of the single agent was 75 mg t.i.d., however this study, [Study CPKC412A2104] performed in relapsed AML, was not a proper phase I dose escalation study. In this study, it was demonstrated that single agent treatment up to 100 mg b.i.d. was most tolerable, with doses above 50 mg b.i.d. still demonstrating presence of blast activity. In [Study CPKC412A2106], the combination dose of 50 mg b.i.d. associated with daunorubicin and cytarabine chemotherapy proved to be the most tolerable, although 100 mg b.i.d. was also tested. Currently the 100 mg b.i.d. dose is only used in Aggressive Systemic Mastocytosis patients where midostaurin is given as single agent therapy. In AML patients midostaurin is given only as 50 mg b.i.d. in sequential combination with chemotherapy and as continuation therapy in patients still in remission at the end of consolidation regimen. The main toxicity in adult studies in terms has been gastro-intestinal, especially nausea and vomiting that generally occurs within a few hours of dosing. In [Study CPKC412A2106], early discontinuation due to gastrointestinal adverse events in the 100 mg b.i.d. group suggest a frequency and peak intensity of these events in the first one to two weeks of treatment with midostaurin.

Based on [Study CPKC412A2106] results, the dose of 50 mg b.i.d. was selected for a phase III combination therapy trial in adult AML, [Study CPKC412A2301]; while 100 mg b.i.d. single agent was selected for a phase II trial in adult Aggressive Systemic Mastocytosis [Study CPKC412D2201].

Therefore, the decision was made to start pediatric dosing at 30 mg/m² b.i.d., the equivalent adult dose of 50 mg b.i.d. Although this dose represents 50% of the single agent dose, we chose this regimen to maximize safety for the starting dose in pediatric patients while still providing a dose with known single agent activity, proven in adults with AML. Additionally, pediatric doses will not exceed 60 mg/m² b.i.d., the equivalent tolerated single agent adult dose of 100 mg b.i.d.

As to not exceed the equivalent treatment doses administered in adults, if a patient has a BSA greater than 1.67, dosing will occur at the equivalent adult dose for that particular dose level. For example, at the first dose level, a patient with a BSA of 2.0 m² will receive 50 mg b.i.d. rather than the calculated 60 mg b.i.d. dose.

Midostaurin will be dosed per m², but in children weighing less than 10 kg, midostaurin will be dosed by body weight. The starting dose in children weighing less than 10 kg will be calculated based on the assumption that 1 m² equals approximately 30 kg, or at the dose of 1 mg/kg b.i.d. At each dose level, the clinical response, pharmacokinetic (PK) and pharmacodynamic response will be determined. The final decision for dose escalation will be determined using the DLT probabilities associated to dose levels obtained from the statistical model after it has been updated with the most recent DLT information across the two strata. There will be no intra-patient dose-escalation. All doses will be rounded off to the nearest 2.5 mg dose.
2.3 Pharmacodynamic evaluations

In addition to clinical response, it is important to look at several other endpoints or parameters that may reflect the response to midostaurin, and correlate these parameters with clinical response. FLT3 activation, measured by phosphorylation of FLT3 protein, has been observed to correlate with activating mutations in FLT3 in AML patients as well as with overexpression of FLT3 message in MLL patients (Stam 2005). In the case of FLT3 message overexpression, the level of overexpression correlated with responsiveness of patient blasts to midostaurin challenge in an ex-vivo setting, using assays to measure FLT3 phosphorylation and cell killing.

The current study will correlate baseline levels of FLT3 activation with clinical outcome. This study also will measure response to midostaurin treatment in vivo, using patient blasts isolated pre and post treatment to measure changes in FLT3 phosphorylation. These changes will be correlated with patient clinical blast response. In addition, for MLL patients, FLT3 phosphorylation changes will be correlated with baseline levels of FLT3 message overexpression, to test the hypothesis that patients with higher FLT3 message levels are more responsive to cell killing by FLT3 inhibitors.

FLT3 mutations will be measured using DNA from bone marrow or peripheral blood following published procedures (Thiede 2002). This methodology has been demonstrated to quantitative and reproducible in multiple laboratories supporting a midostaurin trial in adult FLT3 mutant AML.

FLT3 overexpression will be measured using quantitative PCR on bone marrow or peripheral blood samples. FLT3 levels will be normalized to GAPDH (Stam 2005). This methodology has not yet been validated in a multicenter setting, and as such will be used retrospectively to characterize patient FLT3 overexpression, but will not be used to select or stratify patients for treatment in the current trial.

An additional study of midostaurin effects will be performed on blast cells obtained at baseline, if quantities permit. Blast cells obtained at baseline will be challenged in ex-vivo exposure studies with midostaurin looking at FLT3 dephosphorylation and cell cytotoxicity (in vitro cytotoxicity assay). These responses will be compared to clinical response to see whether these parameters are indicative of a response to midostaurin.

3 Objectives

3.1 Primary objectives

To determine the maximum tolerated dose (MTD) for two age groups (≥ 3 months and ≤ 2 years and >2 years and < 18 years) of pediatric patients with AML or MLL based on the rate of dose-limiting toxicity (DLT) of midostaurin administered orally in dose ranges studied in adults.

3.2 Secondary objectives

- To characterize the safety and tolerability of midostaurin, including acute and chronic toxicities
• To characterize the population PK and trough levels of single and repeated doses of midostaurin and its metabolite(s),
• To determine the response rates, time to relapse and overall survival of patients treated with midostaurin.
• To determine the presence of activating mutations or WT-overexpression of the FLT3 gene in AML and MLL-rearranged ALL samples
• To correlate baseline levels of FLT3 phosphorylation with FLT3 expression levels and clinical outcome in MLL patients
• To correlate baseline levels of FLT3 phosphorylation with activating FLT3 mutations and clinical outcome in AML patients
• To evaluate changes in FLT3 phosphorylation following treatment with midostaurin, and correlate changes with clinical outcome
• To evaluate changes in FLT3 phosphorylation following treatment with midostaurin, and correlate with pharmacokinetic data

3.3 Exploratory objectives
• Depending on sample availability, to perform expression analysis on baseline samples and correlate with response to therapy
• Depending on sample availability, to determine if response to ex-vivo treatment of baseline blast cells with midostaurin (in-vitro cytotoxicity assay) correlates with baseline levels of FLT3 phosphorylation (MLL) or activating FLT3 mutations (AML)
• Depending on sample availability, to determine if response to ex-vivo treatment of baseline blast cells (in-vitro cytotoxicity assay) with midostaurin correlates with clinical outcome
• Model the dose-blast response. to determine the optimal dose based on the maximization of the probability of blast response.

4 Study design
This is a phase I/II, open-label, multi-center trial evaluating the safety, tolerability, clinical, pharmacokinetic and pharmacodynamic responses of twice-daily oral dosing of midostaurin when administered to pediatric patients (≥ 3 months and < 18 years of age) with one of the following relapsed or refractory leukemias:
1. MLL-rearranged ALL patients, who are either refractory to standard induction treatment or who are in first relapse or subsequent relapse, or
2. FLT3 mutated AML patients, either refractory to standard induction treatment (after failure of at least two different induction chemotherapy regimens) or who are in second or greater relapse.

A three-parameter Bayesian logistic regression model (BLRM) (Bailey 2009) employing the escalation with overdose control (EWOC) principle (Babb 1998), will be used during the dose-escalation phase for dose level selection and for determination of the MTD within each stratum.
Patients will be stratified into two age groups, $\geq 3$ months and $\leq 2$ years old or $> 2$ years old but $< 18$ years old. The starting dose level will be twice daily oral midostaurin at 30 mg/m$^2$/dose, based on the 50 mg b.i.d. dose used in adults. As this adult dose does not reflect the MTD in adults, we will start at 100% of the dose used in adults, instead of the usual 80%. Initially 3 patients will be enrolled at the starting dose level for the older patient group and 2 for the younger patient group (see Section 10.7). Once the respective number of patients are assessable for a stratum, the statistical model will be updated and the dose level for the next dose cohort will be determined. The model will be used to guide the decision to escalate, retest or de-escalate the dose level. In the event that a DLT is observed at a dose level it is recommended that at least 3 patients must be observed across the two strata before a decision regarding escalation may occur. Upon completion of a cohort, often in the situation where the probabilities associated to the model are borderline it is always possible to include additional patient(s) in the same cohort according to the discretion of the clinical experts. The model would then be reevaluated after the DLT status for the additional patient(s) has been determined.

Increases in dose may be mandated by the BLRM or by consideration of the totality of the clinical safety data. If needed to better define the dose-toxicity relationship the model may suggest the enrollment of additional patients at the current dose level, to a preceding dose level, or to intermediate dose levels before proceeding with further dose escalation. Patients will be enrolled into dose levels during the dose escalation phase irrespective of indication. Upon determination of the MTD, patient enrollment will be expanded to include approximately 10 or more patients per indication to characterize preliminary clinical activity. A minimum of 6 patients per indication will be enrolled at the MTD.

Pharmacokinetic and pharmacodynamic evaluations will be performed to evaluate the drug levels of midostaurin, and to identify mutations and/or FLT3 message over-expression, as well as FLT3 phosphorylation inhibition after drug exposure.
5 Population

Pediatric patients (≥ 3 months and <18 years old) with relapsed or refractory leukemia’s, including:

- MLL-gene rearranged ALL, who are either refractory to standard induction treatment or who are in first or subsequent relapse
- FLT3 mutated AML, refractory to standard induction (after failure of at least 2 different induction chemotherapy regimens) or refractory to re-induction at 1st relapse (after failure of the first re-induction course), or in second or subsequent relapse

Approximately 22 patients will be enrolled during the study. The actual number of patients enrolled will be determined by results obtained throughout the course of the study, necessity for replacement subjects, and expansion of cohorts.

The investigator or his/her designee must ensure that all patients who meet the following inclusion and exclusion criteria are offered enrollment in the study.

5.1 Inclusion criteria

1. Patients must have a documented diagnosis of one of the following leukemias:
   - MLL-rearranged ALL, refractory to standard induction chemotherapy or in first or subsequent relapse
   - FLT3-mutated AML, refractory to standard induction (after failure of at least 2 different induction chemotherapy regimens) or refractory to re-induction at 1st relapse
(after failure of the first re-induction course), or in second or greater relapse. Please refer to Section 7.10 for further details.

2. Patients must be less than 18 years of age and greater than or equal to 3 months of age.

3. Patients must have a Lansky or Karnofsky performance status ≥ 60. Lansky performance status should be used for patients ≤ 12 years old and Karnofsky performance status should be used for patients > 12 years old.

4. Patients must have the following laboratory values reflecting appropriate organ function:
   - AST and ALT ≤ 5x Upper Limit of Normal (ULN),
   - Serum Bilirubin ≤ 1.5 x ULN
   - Serum Creatinine ≤ 2 x ULN.

5. Patients must have an expected survival of greater than 8 weeks.

6. Parent or legal guardian and/or the patient must give written informed consent, according to local law and regulations.

5.2 Exclusion criteria

1. Patients with symptomatic leukemic CNS involvement.

2. Patients with isolated extramedullary leukemia.

3. Patients must have recovered from prior cytotoxic chemotherapy, with a minimum wash-out time of previous chemotherapy of 72 hours. For intrathecal chemotherapy, the minimum wash-out time is 48 hours (other exceptions for intrathecal chemotherapy are noted in Section 6.6.5).

4. Patients who had prior allogeneic, syngeneic or autologous bone marrow or stem cell transplant less than 2 months from Day 1.

5. Patients who have received any investigational agent within 30 days or 5 half lives, whichever is greater, prior to Day 1. An investigational agent is an agent with no approved medical uses in adults or pediatrics.

6. Patients who have had prior treatment with a FLT3 inhibiting drug or investigational agent.

7. Use of CYP3A4/5 enzyme inducing or inhibiting drugs or herbal supplements while on study drug (e.g., dexamethasone, phenytoin, clarithromycin, telithromycin, carbamazepine, rifampin, rifabutin, phenobarbitol, St. John’s Wort). Please refer to Section 6.6.5 for a list of CYP3A4/5 inhibitors and guidelines.

8. The use of corticosteroids while on study drug (exceptions are noted in Section 6.6.5).

9. Patients who have had any surgical procedure, excluding central venous catheter placement or other minor procedures (e.g. skin or bone marrow biopsy), within 14 days of Day 1.

10. Patients with any other known disease concurrent severe and/or uncontrolled medical condition (e.g. cardiovascular disease including congestive heart failure or active uncontrolled infection) which could compromise participation in the study.

11. Patients with an abnormal chest X-ray and/or any pulmonary infiltrate including those suspected to be of infectious origin. In particular, patients with resolution of clinical
symptoms of pulmonary infection but with residual pulmonary infiltrates on chest x-ray are not eligible until pulmonary infiltrates have completely resolved.

12. Patients with known impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of midostaurin, including active graft-versus-host disease of the liver or the gut.

13. Patients with a known confirmed diagnosis of HIV infection or active viral hepatitis.

14. Patients with a left ventricular shortening fraction < 27% as determined by MUGA scan or echocardiogram

15. Patients with abnormal ECG including:
   - QTcF ≥ 450 ms, PR ≥ 200 msec, QRS complex ≥ 110 msec, at screening or prior to first dosing
   - Any cardiac conduction abnormality
   - Any morphologic abnormality
   - Any ST/T wave abnormality
   - Any atrial or ventricular arrhythmia

16. Female patients who are pregnant or breast feeding, or patients of reproductive potential not employing an effective method of birth control. Barrier contraceptives must be used throughout the trial by both sexes, if applicable. Because oral, implantable, or injectable contraceptives may be affected by cytochrome P450 interactions, an appropriate method of birth control should be used throughout the trial in both sexes, if applicable. Women of childbearing potential must have a negative serum pregnancy test ≤ 48 hours prior to the administration of midostaurin.

17. Males of reproductive potential unwilling to comply with contraceptive requirements

18. Patients/parents unwilling or unable to comply with the protocol

6 Treatment

6.1 Investigational drugs

Study drug refers to any Novartis investigational drug(s) being used for an unapproved indication.

For this study, the term “Study drug” refers to midostaurin (PKC412) 25 mg/mL oral solution, 50mL bottles.

6.1.1 How supplied

The investigational drug, midostaurin, will be prepared by Novartis.

Midostaurin (PKC412) 25mg/mL solution will be provided in bottles of 50mL, labeled and supplied as open-label bulk supply by Novartis Drug Supply Management. The labels will not contain any subject specific information.

Medication labels comply with the legal requirements of each country and are printed in the local language. They will supply no information about the subject. The storage conditions for study drug will be described on the medication label.
6.1.2 Preparation and storage

6.1.2.1 Mode of preparation

Please respect the minimum dose volumes for the dispenser as indicated in the Table 6-1. As such, all doses should be rounded to the nearest 2.5 mg dose.

Tear off the flip-off cap from the midostaurin oral solution bottles, and assemble the dispensing system as described in the separate instructions for use. For example, take out 2.0ml of the midostaurin oral solution for one single dose of 50mg. Midostaurin solution may be diluted with non-sparkling drinking water, orange juice, clear apple juice and Coca Cola “Light”, as described in Post text supplement 2.

For the dosing process, carefully follow the handling/dispensing instructions as described in Post text supplement 2.

<table>
<thead>
<tr>
<th>Dispenser volume</th>
<th>Minimum dose volume deliverable</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 mL</td>
<td>1.0 mL</td>
</tr>
<tr>
<td>1 mL</td>
<td>0.1 mL</td>
</tr>
</tbody>
</table>

If the midostaurin oral solution bottles are being dispensed for out-patient use, proper training must be provided to the patient or care-giver for the appropriate use and storage of the bottles. The site pharmacist must also create a patient card containing such instructions. The patient or caregiver should be instructed to return all unused medication to the site for return to the local Novartis warehouse.

6.1.2.2 Storage

After opening, the 25 mg/mL midostaurin oral solution bottles should be used within a maximum of 2 weeks and stored at 2 - 8°C (36-46°F) between dosing. Close all the bottles with child-resistant screw caps after first opening. The 25 mg/mL midostaurin oral solution bottles that were opened and not used within 2 weeks should be returned to Novartis for destruction.

6.2 Treatment groups

The assignment of a patient to a particular dose level will be coordinated by the sponsor. Patients will be stratified into two groups by age. Initially three patients less than 18 and greater than 2 years old (Stratum 1) will be enrolled and 2 patients less than or equal to 2 years old and greater than or equal to 3 months old (Stratum 2) will be enrolled.

6.3 Patient numbering

Each patient in the study is uniquely identified by a 9 digit patient number which is a combination of his/her 4-digit center number and 5-digit subject number. The center number is assigned by Novartis to the investigative site.

The procedures for subject numbering and cohort coordination between the sites involved will be provided in a separate document prior to study start. Upon signing the informed consent
form, the patient is assigned a subject number by the investigator or his/her designee. Once assigned to a patient, a subject number will not be reused. If the patient fails to be started on treatment for any reason, the reason for not being started on treatment will be entered on the Screening Log eCRF. No other data will be entered into the clinical data base for screen failure patients.

Informed consent must be obtained before any testing to determine a patient’s eligibility.

In addition, the Screening Log should be completed for these patients.

### 6.4 Treatment assignment

Following confirmation of eligibility, the assignment of a patient to a particular dose level will be coordinated by the sponsor.

At screening, patients will be assigned a unique patient number (Section 6.1) by the investigator. Each patient in the study is uniquely identified by a 4-digit center number and 5-digit subject number. The subject number is the lowest available number from the consecutive numbers allocated to the study site. Once assigned to a patient, the subject number will not be reused. If the patient fails to be assigned to treatment for any reason, the center and subject number and the reason for not being assigned to treatment will be entered on the Screening Log eCRF.

### 6.5 Treatment blinding

This will be an open label study.

### 6.6 Treating the patient

Midostaurin will be given as an oral solution twice daily (about every 12 hours). The drug will be used continuously, unless interruption is required to manage toxicity or for progressive disease. Cycles will consist of 14 days, in order to assess safety at an earlier time point. There will be no break between cycles. Following Cycle 1, patients may receive additional cycles of study drug as clinically appropriate (in accordance with Section 7.4.2), according to investigator discretion, and in the absence of safety concerns.

At the beginning of Cycle 2 (day +15) and 3 (day +29) patients will be evaluated for safety and response. Clinical efficacy will be assessed at the beginning of the second and third cycle with a complete blood count, and a bone marrow aspirate. This will be repeated after cycle 3 at the investigators discretion, but at minimum every 3 months. Any patient withdrawing from the study drug prematurely must be followed every 1 month for survival. In the case of progressive disease patients will be discontinued from study drug, as described in Section 7.4.2.

#### 6.6.1 Study drug administration

Midostaurin will be administered by twice-daily oral dosing according to the patients dose cohort assignment. Midostaurin should be administered with water following breakfast and dinner (or a light meal). Doses of midostaurin should be about 12 hours apart. Taking the solution with a light meal may help relieve some of the nausea that may be associated with midostaurin. Do not administer midostaurin with CYP3A4 interacting food such as grapefruit
juice. Patients should take their daily dose at approximately the same time each day. Each daily dose should be given and consumed over as short a time as possible.

It is allowed to give midostaurin solution though a nasogastric tube or a gastrostomy catheter. Please refer to the detailed administration guidance provided in Post text supplement 2.

Dosing should not be repeated if vomiting occurs, however anti-emetic therapy should be optimized.

**6.6.1.1 Ancillary treatments for midostaurin**

At least 30 minutes prior to midostaurin administration, it is required that the patient be given anti-emetic therapy according to local practice. This should be recorded on the Concomitant medications eCRF. Refer to Section 6.6.5 for further information on antiemetics drug interactions.

The investigator should instruct the patient to take the study drug exactly as prescribed (promote compliance). The site pharmacist must also create a patient card containing such instructions for patients who may be treated as an out-patient. All dosages prescribed and dispensed to the patient and any inadvertent dose changes during the study must be recorded on the Dosage Administration Record eCRF.

**6.6.1.2 Starting dose level for cycle 1**

The starting dose will be the approximate dose that was well tolerated in the adult combination chemotherapy [Study CPKC412A2106], 50 mg b.i.d. or approximately 30 mg/m² b.i.d. In patients with BSA ≥ 1.67, midostaurin will be dosed at 50 mg b.i.d. Midostaurin will be dosed per m², but in children weighing less than 10 kg, midostaurin will be dosed by body weight. The starting dose in children weighing less than 10 kg will be calculated based on the assumption that 1 m² equals approximately 30 kg, or at the dose of 1 mg/kg b.i.d.

The weight used for calculation of dosing should be obtained prior to treatment, and thereafter should only be modified for significant (≥10%) changes in body weight (not influenced by weight gain or loss attributed to fluid retention).

**6.6.1.3 Dose escalation levels**

At all dose levels, the adaptive Bayesian logistic model permits alterations in the dose increments based on the observed, clinically relevant, toxicities. The dose escalation level will be selected according to Section 6.6.1.4.1. However it is recommended dose increments adhere to the following rules:

- A maximum of three doses are expected to be studied, in increasing increments of 15 mg/m² (Table 6-2). However, data driven analyses may lead to investigation of intermediate dose levels.
- Patients weighing < 10 kg will be administered a starting dose of 1 mg/kg b.i.d. (2 mg/kg/day). The dose will be escalated under the assumption that 30 kg is approximately equal to 1 m².
- Dose escalation is limited to ≤ 100% increase above the current dose level (e.g. increase from 30 mg/m² to 60 mg/m²). If drug-related adverse event(s) ≥ CTCAE grade 2 are
observed in > 1 patient per cohort, escalation will be limited to ≤ 50% increase from the current dose level (e.g. 30 mg/m² to 45 mg/m²).

- The dose being escalated to must satisfy the overdose criteria, that is, less than 25% chance that the true probability of DLT exceed 0.33
- Patients with BSA ≥ 1.67 will receive the equivalent adult dose; patients will not receive a dose higher than the equivalent adult dose.
- If a DLT is observed within a stratum then at least 3 patients must be evaluable across both strata before a decision to escalate the dose may occur.
- There will be no intra-patient dose escalation

Additional patients may be added to a cohort if the Bayesian model indicates that it is required and if clinical experts consider this necessary.

Table 6-2 demonstrates an example of the intended dose cohorts to be used within each stratum of the study, assuming that the highest dose, 60 mg/m² (~100 mg BID in adults), is safe in this population.

<table>
<thead>
<tr>
<th>Dose Cohort</th>
<th>Twice daily doses</th>
<th>Total daily doses</th>
<th>Equivalent to adult dose / maximum dose per level¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>-1</td>
<td>15 mg/m²</td>
<td>30 mg/m²</td>
<td>25 mg b.i.d.</td>
</tr>
<tr>
<td>1 (starting dose)</td>
<td>30 mg/m²</td>
<td>60 mg/m²</td>
<td>50 mg b.i.d.</td>
</tr>
<tr>
<td>2</td>
<td>45 mg/m²</td>
<td>90 mg/m²</td>
<td>75 mg b.i.d.</td>
</tr>
<tr>
<td>3</td>
<td>60 mg/m²</td>
<td>120 mg/m²</td>
<td>100 mg b.i.d.</td>
</tr>
</tbody>
</table>

¹ In patients with BSA ≥ 1.67, midostaurin will be dosed at the equivalent adult dose.

### 6.6.1.4 Criteria for dose escalation and determination of MTD

At each dose level, the clinical, PK and pharmacodynamic response will be determined. Three patients over the age of two and two patients between 3 months and 2 years old will be initially treated and evaluated for DLT assessment at the starting dose. Based on results from adult studies, detailed in Post text supplement 1, where the primary toxicity has been gastrointestinal, especially nausea and vomiting, the escalation will not exceed the equivalent of the adult dose of 100 mg b.i.d.

#### 6.6.1.4.1 Dose escalation and dose cohort modification

A three-parameter Bayesian logistic regression model (BLRM) (Bailey 2009) employing the escalation with overdose control (EWOC) principle (Babb 1998), will be used during the dose-escalation phase for dose level selection and for determination of the MTD in each stratum.

Cohorts of patients in each stratum will receive escalating doses of midostaurin until either the MTD or 60 mg/m² is reached. Each cohort will consist of newly enrolled patients.

After completion of a given dose cohort within a given stratum, the decision to dose escalate and actual dose chosen will depend on a calculation of risk assessment using the described
BLRM and a medical review of available clinical and laboratory data. Details of the statistical methodology are provided in Section 10 and in the Post text supplement 1. The BLRM estimates the MTDs by updating estimates of probability of observing a DLT for each dose level in both strata of the study as patient information becomes available.

A clinical synthesis of the available toxicity information (including adverse events that are not DLTs), PK, PD, and efficacy information, as well as the recommendations from the BLRM, by the investigators and Novartis study personnel will be used to determine the dose regimen for the next cohort at a dose-escalation teleconference.

### 6.6.1.4.2 Dose escalation minimum safety evaluation

Provisional dose level cohorts are listed in Table 6-2. Possible changes in dose administration according to the BLRM include but are not limited to:

- Expansion of the current dose group to further assess possible adverse events
- Administration of a dose below the starting dose for the study (e.g. 15 mg/m² b.i.d.)
- Administration of an intermediate dose between the current and preceding dose
- Administration of an intermediate dose between the current and the next planned dose
- Termination of any further escalation of study drug

If a decision is made to escalate to a higher dose level, but an additional patient(s) on the lower dose level experiences a DLT, then the statistical model will be updated before any additional patients are enrolled into the higher dose level. Enrollment to the higher dose level may be resumed if the model continues to recommend the higher dose level after updating.

Clinically relevant toxicities will be those assessed as unrelated to disease, disease progression, inter-current illness, or concomitant medications.

If a DLT is observed, then at least three evaluable patients must have been treated before dose escalation can occur.

### 6.6.1.5 Dose-limiting toxicity

Toxicity will be assessed using the NCI Common Terminology Criteria for Adverse Events, version 3.0 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf)

Adverse events will be assessed as related to study treatment if they are not related to any of the following:

- disease,
- disease progression,
- inter-current illness,
- or concomitant medication.

A dose-limiting toxicity (DLT) is defined as a CTCAE grade 3 or 4 non-hematological adverse event or abnormal laboratory value assessed as study treatment-related that occurs within the first 14 days starting from day 1 dosing of midostaurin or that results in treatment discontinuation within the first 14 days from day 1. Safety assessments performed pre-dose on overall study day 15 (Cycle 2, Day 1) are considered as occurring within the first 14 days after...
day 1 and must be considered for DLT assessment. Exceptions to the DLT definition are listed in Table 6-3. Grade 3 and 4 nausea and vomiting that persists despite appropriate anti-emetic treatment will also be considered a DLT.

Hematological toxicities can only be assessed in patients in complete remission, and are therefore not considered in the DLT definition.

### Table 6-3 Exceptions to dose-limiting toxicities

<table>
<thead>
<tr>
<th>Exceptions to the DLT criteria</th>
<th>CTCAE grade 3-4 elevations in alkaline phosphatase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AEs grade 3 or higher related to disease progression</td>
</tr>
<tr>
<td></td>
<td>≥Grade 3 nausea and/or vomiting is only considered a DLT if it persists despite anti-emetic treatment</td>
</tr>
<tr>
<td></td>
<td>Alopecia</td>
</tr>
<tr>
<td></td>
<td>Febrile neutropenia lasting ≤ 3 days</td>
</tr>
</tbody>
</table>

Patients may receive supportive care (e.g. erythropoietin or PRBCs) as per local institutional guidelines. G-CSF may be used to treat patients who have developed dose-limiting neutropenia, as per institutional guidelines.

Decisions regarding dose escalation will mainly rely on events occurring in the first 14 days of study treatment.

Patients must receive a minimum of 75% (≥21 doses) of the planned midostaurin treatment occurring in the first 14 days to be eligible for DLT assessment, or experience a DLT.

All DLTs are considered to be medically significant and therefore must be reported as SAEs as described in Section 8.1. Prior to enrolling patients into a higher dose level, CTCAE grade ≥ 2 adverse events will be reviewed for all patients at the current dose level.

#### 6.6.2 Expansion Phase

Upon determination of MTD, or establishing that there is no DLT at the 60 mg/m² b.i.d. dose level, additional patients may be enrolled to establish a more robust assessment of preliminary clinical response. Enrollment may be expanded to include up to approximately 10 evaluable patients per indication. A minimum of 6 patients per indication will be enrolled at the MTD.

#### 6.6.3 Study drug modifications

Dose modifications will be based on Common Terminology Criteria for Adverse Events v3.0 (CTCAE). Any DLT may be reason to discontinue the affected patient from study treatment. However, following approval by the Investigator and the Sponsor’s medical monitor patients who had a DLT may be retreated, after recovery at fifty-percent of the current dose. If toxicities occur that warrant a dose reduction, the patient will receive a dose reduction to fifty percent of the current dose. No more than one dose reduction will be allowed. Once a dose has been reduced it will not be increased at a later time even if there is no toxicity. Patients who require more than one dose reduction of midostaurin will be permanently discontinued from study drug treatment. If doses of midostaurin are omitted for > 14 consecutive days, the patient will be permanently discontinued from study drug. Guidelines for dose modification are listed in Table 6-4.
### Table 6-4 Specific instructions for interruption and re-initiation of midostaurin following the occurrence of a DLT

<table>
<thead>
<tr>
<th>Worst toxicity CTCAE grade (value)</th>
<th>During a cycle of therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>No toxicity or Grade 1 or 2 toxicity</td>
<td>Maintain dose level</td>
</tr>
</tbody>
</table>

#### Renal

<table>
<thead>
<tr>
<th>Serum Creatinine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3 (&gt;3.0-6.0 x ULN)</td>
</tr>
<tr>
<td>Grade 4 (&gt;6.0 x ULN)</td>
</tr>
</tbody>
</table>

#### Hepatic

<table>
<thead>
<tr>
<th>Bilirubin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3 (&gt;3.0-10 x ULN)</td>
</tr>
<tr>
<td>Grade 4 (&gt;10 x ULN)</td>
</tr>
<tr>
<td>AST or ALT</td>
</tr>
<tr>
<td>Grade 3 (&gt;5.0-20.0 x ULN) &gt; 7 consecutive days</td>
</tr>
<tr>
<td>Grade 4 (&gt;20.0 x ULN)</td>
</tr>
</tbody>
</table>

#### Cardiac

<table>
<thead>
<tr>
<th>Cardiac- prolonged QTcF interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ grade 3 (QTcF &gt;500 msec)</td>
</tr>
<tr>
<td>2. Perform an analysis of serum potassium and magnesium and if &lt; LLN, correct with supplements to WNL</td>
</tr>
<tr>
<td>3. Concomitant medication(s) must be reviewed</td>
</tr>
<tr>
<td>4. Repeat ECG within 1 hour after the first QTcF&gt;500 msec.</td>
</tr>
<tr>
<td>5. If QTcF is still &gt;500 msec, repeat ECG(s) as clinically indicated, but at least once daily until the QTcF returns to within 20 msec of baseline value.</td>
</tr>
<tr>
<td>6. Midostaurin may be restarted at a 50 % reduced dose only after consultation with the sponsor and Principal Investigator, and only if midostaurin can be restarted ≤ 14 days after the last dose</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cardiac general</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ grade 3</td>
</tr>
</tbody>
</table>

#### Allergic/ hypersensitivity or autoimmune

| ≥ grade 3 | No further treatment with midostaurin |
### Worst toxicity CTCAE grade (value) During a cycle of therapy

#### Dermatologic/ skin: rash categories only

<table>
<thead>
<tr>
<th>Grade</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Either no further treatment with midostaurin, or after discussion and agreement with the sponsor and Principal Investigator, omit dose until resolved to ≤ grade 1 or baseline, then decrease dose by 50 %</td>
</tr>
<tr>
<td>4</td>
<td>No further treatment with midostaurin</td>
</tr>
</tbody>
</table>

#### Dermatologic/ skin: all other categories

<table>
<thead>
<tr>
<th>Grade</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Omit dose until resolved to ≤ grade 1 or baseline, then decrease dose by 50 %</td>
</tr>
<tr>
<td>4</td>
<td>No further treatment with midostaurin</td>
</tr>
</tbody>
</table>

#### Neurotoxicity

<table>
<thead>
<tr>
<th>≥ Grade 3</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>No further treatment with midostaurin</td>
</tr>
</tbody>
</table>

#### Pulmonary

<table>
<thead>
<tr>
<th>Grade</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Omit dose until resolved to ≤ grade 1 or baseline, then decrease dose by 50 %</td>
</tr>
<tr>
<td>4</td>
<td>No further treatment with midostaurin</td>
</tr>
</tbody>
</table>

#### Edema

<table>
<thead>
<tr>
<th>Grade</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Omit dose until resolved to ≤ grade 1 or baseline, then decrease dose by 50 %</td>
</tr>
<tr>
<td>4</td>
<td>No further treatment with midostaurin</td>
</tr>
</tbody>
</table>

#### Other adverse event qualifying as a dose limiting toxicity

<table>
<thead>
<tr>
<th>Grade</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Omit dose until resolved to ≤ grade 1 or baseline, then decrease dose by 50 %</td>
</tr>
<tr>
<td>4</td>
<td>No further treatment with midostaurin</td>
</tr>
</tbody>
</table>

All dose modifications should be based on the worst preceding toxicity. Each patient is only allowed one dose reduction to 50 percent of the current dose. In addition, a patient must discontinue treatment with midostaurin if, after treatment is resumed at the reduced dose, the toxicity recurs with the same or worse severity. If a patient requires a dose interruption >14 days from the intended day of the next scheduled dose, then the patient must be discontinued from the study treatment. Patients who discontinue the study for study-related adverse events or an abnormal laboratory value must be followed as described in Section 6.6.4.

Any dose changes or dosing errors must be recorded on the Dosage Administration Record eCRF. Missed doses of midostaurin for any reason during a cycle are not to be recuperated.
6.6.4 Follow up for toxicities

Patients who experience a non-laboratory DLT must be evaluated weekly, at a minimum, until resolution of the adverse event to ≤ Grade 1 and then at least monthly until return to baseline or stabilization of the event, whichever comes first. For abnormal laboratory values that qualify as a DLT, patients will be followed twice weekly until resolution to ≤ Grade 2 and then at least weekly until return to baseline or stabilization, whichever comes first.

If a patient is discontinued from therapy due to treatment-related toxicity, the patient will continue to be followed for toxicity as previously described. All patients will be followed for adverse events and serious adverse events for 28 days following the last dose of midostaurin.

6.6.5 Other concomitant medications

In general, the use of any concomitant medication/therapies deemed necessary for patient supportive care and safety are permitted provided they are documented in the patient records. All medications taken within 30 days of the first dose of study drug and all concomitant medications/therapies must be recorded on the Concomitant/Non-Drug Therapy eCRF.

It is required that all patients receive maximal prophylaxis for the prevention of nausea and vomiting, using antiemetics according to local practice.

Because 5-HT3-receptor antagonist group antiemetics (i.e. Granisetron, Ondansetron, Tropisetron) are metabolized by CYP3/4 (see Table 6-5), there exists the potential for interactions with drugs metabolized by this pathway, but these drugs do not interact with emetogenic cancer therapies so far tested and does not induce or inhibit CYP isoforms. Therefore, the 5-HT3-receptor antagonist class of antiemetics are permitted to be administered while on study drug.

These medications will not be supplied by Novartis. Patients who suffer from severe nausea and/or vomiting despite using anti-emetic therapy, should be withheld from treatment and restarted after recovery of this side-effect, provided that recovery is within 5 days.

Corticosteroid regimens (such as dexamethasone 6 mg/m² or prednisone 40 or 60 mg/m²/day) at doses to control leukemia are not allowed because of their antileukemic effects. However, single doses of corticosteroids are permitted to be administered for the purposes of non-leukemia treatment (i.e. pre-medication, allergic reaction) up to 3 times per cycle. For adrenal insufficiency, substitution dosing of corticosteroids are permitted at dose of ≤ 75 mg/m²/day hydrocortisone equivalent for up to 7 days per cycle.

Other anticancer agents including chemotherapy, radiation therapy, or biologic response modifiers are not permitted during the study with the exception of single doses of intrathecal chemotherapy.

At the investigators discretion, intrathecal chemotherapy may be administered prior to Day 1 to patients with CNS leukemic involvement who do not display clinical symptoms or as prophylaxis. A 72 hour wash out prior to midostaurin treatment is not required for intrathecal chemotherapy, however if administered it must be prior to day 1. The therapy may be repeated once per cycle beginning in cycle 2 at the investigators discretion, at the time of lumbar puncture. The choice of intrathecal medication should be made according to local practice and guidelines. Midostaurin therapy does not need to be stopped for the
administration of intrathecal chemotherapy. Patients requiring a greater frequency of intrathecal chemotherapy should not be enrolled in the study, or if already enrolled, should be discontinued from study treatment.

Children with leukemia may relapse while being on chemotherapy and this relapse can be very aggressive. Thus, if a patient was on chemotherapy while relapsing, such patient can be included on the midostaurin study. In that case, at least 72 hours wash-out time between the last administration of chemotherapy and the start of midostaurin needs to be scheduled, provided that the patient has recovered from the acute toxicities from prior chemotherapy.

Patients must be off growth factors for at least five days in order to declare a neutrophil response.

**Drugs affecting CYP3A P450 function**

Any drug known to inhibit or induce CYP3A4 will likely interact with midostaurin. The extent is normally more profound with CYP3A4 inhibitors than with inducers. A list of inhibitors and inducers is shown in Table 6-5, and cautions should be made for patients taking these drugs. Investigators should not administer concomitant drugs that induce or inhibit CYP3A4/5 in order to maintain midostaurin at therapeutic drug levels. Additionally, patients must not receive any herbal supplements or food products that interact with CYP3A4/5 metabolism pathway. This being the case, meals and drinks should not contain grapefruit (inhibitor of CYP3A4) and intake of St Johns Wort (inducer of CYP3A4) is forbidden.

**Table 6-5** Clinically relevant drug interaction: substrates, inducers and inhibitors of isoenzyme CYP3A.

<table>
<thead>
<tr>
<th>Substrates</th>
<th>Calcium Channel Blockers:</th>
<th>HMG CoA Reductase Inhibitors:</th>
<th>Miscellaneous:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotics:</td>
<td>amlodipine</td>
<td>atorvastatin</td>
<td>buspirone</td>
</tr>
<tr>
<td>clarithromycin</td>
<td>diltiazem</td>
<td>cerivastatin</td>
<td>haloperidol</td>
</tr>
<tr>
<td>erythromycin</td>
<td>felodipine</td>
<td>lovastatin</td>
<td>methadone</td>
</tr>
<tr>
<td>NOT azithromycin</td>
<td>nifedipine</td>
<td>NOT pravastatin</td>
<td>pimozide</td>
</tr>
<tr>
<td>telithromycin</td>
<td>nisoldipine</td>
<td>simvastatin</td>
<td>quinine</td>
</tr>
<tr>
<td>Anti-arrhythmics:</td>
<td>nitrendipine</td>
<td></td>
<td>NOT rosuvastatin</td>
</tr>
<tr>
<td>quinidine</td>
<td>verapamil</td>
<td></td>
<td>sildenafil</td>
</tr>
<tr>
<td>Benzodiazepines:</td>
<td></td>
<td></td>
<td>tamoxifen</td>
</tr>
<tr>
<td>alprazolam</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>diazepam</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>midazolam</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>triazolam</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immune Modulators:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cyclosporine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>tacrolimus (FK506)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV Protease Inhibitors:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>indinavir</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ritonavir</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>saquinavir</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prokinetic:</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Substrates

cisapride

trazodone

Antihistamines:

astemizole

clorpheniramine

vincristine

Inducers

Carbamazepine

Phenobarbital

Phenytoin

Rifabutin

Rifampin

St John’s wort

Troglitazone

Inhibitors

Amiodarone

Cimetidine

Clarithromycin

Delavirdine

Diltiazem

Erythromycin

Fluvoxamine

Grapefruit juice

Indinavir

Itraconazole

Ketoconazole

Mibefradil

Nelfinavir

Troleandomycin

Verapamil

Based on http://medicine.iupui.edu/flockhart/. Please refer to the full prescribing information for details on a specific medication.

Cotrimoxazole at high dose can have an impact on CYP3A4 drugs (e.g. when given with cyclosporin). In general, no drug-drug interactions are observed with cotrimoxazole. This medication is not being prohibited, but caution should be taken if concomitantly administrated with midostaurin.

The investigator should instruct the patient to notify the study site about any new medications he/she takes after the start of the study drug. All medications (other than study drug) and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient starts treatment with study drug must be listed on the Concomitant medications/Significant non-drug therapies after start of study drug eCRF.

6.6.6 Study drug discontinuation

All patients must have evaluations for 28 days after the last dose of study treatment. Patients lost to follow up should be recorded as such on the eCRF. Patients who discontinue study drug before completing the study should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. An End of Treatment form should be completed, giving the date and reason for stopping the study treatment. At a minimum, all patients who discontinue study treatment, including those who refuse to return for a final visit, will be contacted for safety evaluations during the 28 days following the last dose of study drug.

Patients who discontinue study treatment should not be considered withdrawn from the study. If patients refuse to be followed for survival, response and new cancer therapies or are unable
to do so, every effort should be made to contact them or a knowledgeable informant by telephone to determine the patient’s survival status. A Study Evaluation Completion form should be completed.

6.6.7 Premature patient withdrawal

6.6.7.1 End of treatment

Patients may voluntarily withdraw from the study drug or be discontinued from the study drug at the discretion of the investigator at any time. An authorized parent or guardian, where applicable, may also withdraw a patient from the study drug.

If such withdrawal from study drug occurs, the investigator must determine the primary reason for a patient’s premature withdrawal from the study drug and record this information on the End of Treatment eCRF. Patients may be withdrawn from the study drug prematurely for one of the following reasons:

- Adverse event(s)
- Abnormal laboratory value(s)
- Abnormal test procedure result(s)
- Protocol violation
- Subject withdrew consent
- Lost to follow-up
- Administrative problems
- Death
- Disease progression

All cancer medications/therapies given to a patient ≤ 4 weeks after the last dose of study treatment must be recorded in the eCRF.

Patients who discontinue study treatment should be scheduled for an ‘End of Treatment Visit’ as soon as possible (ideally within 7 days) after discontinuing study treatment at which time all of the assessments listed for the End of Treatment Visit (Table 7-1) will be performed. End of Treatment evaluations should include but not be limited to: physical examination, Lansky/Karnofsky performance status, vital signs, concomitant medications and therapies, ECG, blood chemistry, hematology, and adverse events. If possible, please perform: thyroid function test, bone marrow aspirate, blood sampling for biomarkers, and tumor assessments.

All relevant information related to the reason for discontinuation of study treatment, including contributory factors, must be included on the End of Treatment eCRF.

Patients who prematurely withdraw from the study treatment may be replaced at the investigators discretion.

6.6.7.2 Survival

After disease progression, all patients will be followed for survival until death. Any information available on new treatments for the patient’s leukemia and documentation of ongoing response will also be collected. Monitoring may be performed by phone, and should
be conducted every 1 month until death. If applicable, the date of death should be captured on the **Survival eCRF page** if it is not captured on the **End of Treatment eCRF**.

### 6.6.7.3 Study evaluation completion

As a general rule, if a patient discontinues study drug and later is prematurely withdrawn from the study, the reasons for study evaluation completion may include the following:

- Protocol violation
- Subject withdrew consent
- Lost to follow-up
- Administrative problems
- Death

For patients who are lost to follow-up, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.
7 Visit schedule and assessments

Table 7-1 lists all of the assessments and indicates with an “X” the visits when they are performed. All data obtained from these assessments must be supported in the patient’s source documentation. All data are entered into the database. Assessments that generate data for database entry and which are recorded on eCRFs are listed using the eCRF name. Assessments that are transferred to the database electronically (e.g., laboratory data) are listed by test name.

Cycles are defined as 14 days. Unless otherwise specified, all assessments should be performed prior to the morning dose of midostaurin on the scheduled day of assessment.
### Table 7-1  Visit evaluation schedule

<table>
<thead>
<tr>
<th>Visit number</th>
<th>Baseline</th>
<th>Cycle 1</th>
<th>Cycle 2</th>
<th>Cycle 3</th>
<th>End of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit number</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Day</td>
<td>-14 to 0</td>
<td>1 pre-dose</td>
<td>3</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Demography/informed consent</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inclusion/exclusion criteria</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relevant medical history/current medical conditions</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV / Hepatitis screen</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnosis and extent of cancer</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of disease: AML/MLL</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior antineoplastic therapy</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lansky/Karnofsky performance status</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X⁶</td>
</tr>
<tr>
<td>Vital signs / physical exam</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Height and weight</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Bone marrow aspirate/ biopsy</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X⁶</td>
</tr>
<tr>
<td>Bone marrow sample for biomarker analysis¹</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood sample for biomarker analysis²</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lumbar puncture</td>
<td>X</td>
<td></td>
<td>X¹²</td>
<td>X²,¹²</td>
<td>X</td>
</tr>
<tr>
<td>Pregnancy test, if applicable</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest x-ray</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Visit number

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Cycle 1</th>
<th>Cycle 2</th>
<th>Cycle 3</th>
<th>End of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit number</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td>777</td>
</tr>
</tbody>
</table>

### Baseline Cycle 1

<table>
<thead>
<tr>
<th>Test</th>
<th>Baseline</th>
<th>Cycle 1</th>
<th>Cycle 2</th>
<th>Cycle 3</th>
<th>End of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Echocardiogram</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Electrocardiogram (ECG)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematology/chemistry</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thyroid function test</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharmacokinetic- blood draw¹</td>
<td>X</td>
<td>X¹¹</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Pharmacokinetic- urine sample¹⁰</td>
<td>X⁵</td>
<td>X⁵</td>
<td>X⁵</td>
<td>X⁵</td>
<td></td>
</tr>
<tr>
<td>Overall assessment of response</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient medication diary</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose administration record</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior/concomitant medications</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>Continuous</td>
</tr>
<tr>
<td>Adverse events</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study completion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X³</td>
</tr>
<tr>
<td>Follow up/Survival</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X³</td>
</tr>
</tbody>
</table>

¹. A 3 ml heparinized bone marrow sample will be collected at baseline for biomarker analysis. Patient samples will be assayed for FLT3 mRNA expression and mutations of FLT3 gene. FLT3 phosphorylation will be measured by immunoprecipitation and western blotting or other suitable techniques. If sample quantity is sufficient, blast cells will be used for expression profiling and in ex vivo experiments testing effects of midostaurin on FLT3 phosphorylation and cell killing. Please see Section 7.10 for more details.

². 10 ml heparinized peripheral blood for patients >2 y and 5 ml heparinized peripheral blood for patients ≤ 2 y will be collected at baseline, at cycle 1 day 3 and at end of treatment. Blast cells will be isolated and characterized for changes in FLT3 phosphorylation, measured by immunoprecipitation and western blotting or other suitable techniques.

³. Patients will remain on the study after treatment completion. All patients will be followed for survival and response every 1 month until death according to Section 6.6.7.3.

⁴. A patient may continue on therapy for as long as there is clinical benefit (as described in Section 7.4.2). Patients who continue study drug beyond cycle 2, will be evaluated on a reduced schedule.

⁵. All samples should be taken according to Section 7.9. Patients will be randomized to have a Pharmacokinetic sample taken on either day 5 or day 7.
Beginning in cycle 3, the assessments should occur at the beginning of each 14 day cycle.

Beginning in cycle 3, the assessments should occur once every 28 days at the beginning of a cycle.

Beginning in cycle 3, the assessments should occur at the discretion of the investigator order to confirm clinical benefit, but at a minimum of once every three months.

Thyroid function tests will be repeated once every 4 cycles, beginning in cycle 5.

Pharmacokinetic urine samples will be taken only if available, according to Section 7.9

On day 1 of cycle 1 and 2, an ECG should be performed prior to the morning dose and 2 hours post dose. See Section 7.5.7.1 for complete details.

Patients with a lumbar puncture positive for CNS involvement at baseline, but asymptomatic, should have a lumbar puncture performed at the beginning of each cycle until resolution and at end of treatment. Patients with a lumbar puncture negative for CNS involvement at baseline are not required to undergo further lumbar puncture assessments until end of treatment. If intrathecal chemotherapy is to be administered, it should occur at the time of lumbar puncture. If intrathecal chemotherapy is given on Cycle 2 Day 1, it must be held until after all DLT assessments have been performed.
7.1 Information to be collected on screening failures

The patient will be a screen failure if he signs an informed consent, but fails to be started on study treatment for any reason. The reason for not being started on study treatment will be entered on the Screening Log eCRF. No other data will be entered into the clinical data base for screen failure patients.

The reasons for screen failures may include the following:
- Unacceptable medical history/concomitant diagnosis
- Intercurrent medical event
- Unacceptable laboratory value(s)
- Unacceptable test procedure result(s)
- Did not meet diagnostic/severity criteria
- Unacceptable use of excluded medications/therapies
- Subject withdrew consent

7.2 Patient demographics/other baseline characteristics

Baseline patient data pertaining to demographic information and relevant medical history related to study indication should be documented accordingly in the eCRFs to include the following information:
- Date of birth
- Age
- Sex
- Race
- Relevant medical history and if active at start of study
- Date of diagnosis
- Performance status (Lansky/Karnofsky)

A detailed history of all prior antineoplastic therapies, such as medications and transplants, for treatment of leukemia must be recorded on the eCRF including:
- Medication name/ Non-drug therapy
- Dose
- Start/End date
- Best response

Additionally all other medications and significant non-drug therapies taken within 28 days before first dose is administered must be recorded on the eCRF page and updated on a continual basis if there are any new changes to the medication. Medications include physician prescribed, over-the-counter medications, vitamins, and herbal and alternative therapies. Information to be collected on concomitant medications/significant non-drug therapies will include the following:
- Medication/Non-drug therapy trade name
• Reason for medication
• Start/End date and if continuing at time of examination

In addition to the general demographic and relevant medical history information, study specific information will be collected during the screening period as indicated in the assessment schedule (Table 7.1) in order to determine eligibility of the patient. These include but are not limited to a hepatitis and HIV screening.

7.3 Treatments

Study drug treatments and exposure will be documented in the eCRF dosage administration record. Information to be captured at each treatment cycle will include:
• Actual total daily dose administered
• Regimen
• Timing of dosing
• Start/End date
• Dose delay/change and reason for such

Compliance will be assessed by the investigator and/or study personnel at each visit using the medication diary and information provided by the caregiver. This information should be captured in the source document at each visit.

7.4 Efficacy

Every effort should be taken to treat patients for a minimum of 14 days (1 cycle) to allow adequate exposure to study treatment.

7.4.1 Response criteria

Patients should be assessed for response based on the following criteria and must meet all of the criteria listed (adapted from Cheson 2003):
• Morphologic leukemia free state (LFS)
  o < 5 % bone marrow blasts (minimum count 200 with marrow spicules)
  o No Auer rods (in AML patient)
  o No persistent extramedulary disease
  o No circulating blasts in the peripheral blood
  ▪ Note: The presence of a unique phenotype (by flow cytometry) identical to what was found in the pretreatment specimen (e.g., CD34, CD7 coexpression) should be viewed as persistence of leukemia.
• Morphologic complete remission (CR)
  o Meets definition of Morphological leukemia free state
  o Absolute neutrophil count (ANC) ≥ 1000 / µL
  o Platelets ≥ 100,000 / µL
• Morphologic complete remission with incomplete count recovery (CRi)
• Meets definition of CR except for either residual neutropenia (\(<\ 1000 / \mu L\) or thrombocytopenia (\(<\ 100,000 / \mu L\))
  • Platelet transfusion independent

• Partial remission (PR)
  • a decrease in bone marrow blasts of \(\geq 50\%\) to between 5 and 25 %

• Bone marrow blast response (BR)
  • absolute bone marrow blast percentage \(>25\%
  • \(\geq 50\%\) decrease in bone marrow blasts from baseline

• Minor bone marrow blast response (BRm)
  • \(\geq 25\%\) decrease in bone marrow blasts from baseline

• Peripheral blood blast response (BRp)
  • \(\geq 50\%\) decrease in peripheral blood blasts from baseline

• Minor peripheral blood blast response (BRmp)
  • \(\geq 25\%\) decrease in peripheral blood blasts from baseline

• Stable disease (SD)
  • Failure to achieve any response (CR, CRi, LFS, PR, BR, BRm, BRp, BRmp) without meeting the definition of Progressive disease

• Progressive disease (PD)
  • The patient must meet one of the following criteria (Whenever peripheral blood criteria are used to determine PD, blast cells absolute numbers must be confirmed on two consecutive days, and by using morphology plus confirmation with another technique such as flow cytometry):
    ▪ In patients with \(<\ 40\%\) bone marrow blasts at baseline: A \(\geq 100\%\) increase in bone marrow blast percentage from baseline
    ▪ In patients with \(>\ 40\%\) bone marrow blasts at baseline: A \(\geq 50\%\) increase in bone marrow blast percentage from baseline
    ▪ In patients with a leukocyte count \(>\ 20,000x10^6\) at baseline, a peripheral blood blast count increases of \(\geq 50\%\)
    ▪ In patients with a leukocyte count \(<\ 20,000x10^6\) at baseline, an increase in peripheral blood blasts of \(\geq 50\%\) AND an absolute increase of \(\geq 2000\) peripheral blood blasts

• Relapse
  • After meeting the criteria of Morphologic CR, reappearance of leukemic blasts in the peripheral blood, or \(\geq 5\%\) blasts in the bone marrow not attributable to any other cause
  • In the setting of recent treatment, if the marrow contains 5-20 % blasts, a repeat bone marrow performed at least one week later is necessary to distinguish from bone marrow regeneration unless flowcytometric confirmation of leukemia.

7.4.2 Discontinuation based upon response criteria

Patients should be discontinued from midostaurin treatment if:
• The patient meets the criteria of PD, or Relapse
• The patient meets the criteria of SD for > one month
  o Exception: If there are no alternative treatment options available, the patient may continue midostaurin treatment at the investigator’s discretion despite meeting the criteria of SD for > one month

Patients meeting any other response criteria, and in the absence of safety concerns, may continue to receive treatment with midostaurin at the investigator’s discretion, or until relapse. The bone marrow aspirate may be repeated at a decreased frequency beginning in cycle 3 at the investigator’s discretion. The bone marrow aspirate should occur at minimum every 3 months in order to confirm clinical benefit.

7.4.3 Lumbar puncture

A lumbar puncture should be performed on all patients at baseline. Patients with symptomatic CNS involvement are not eligible for the study.

• Asymptomatic patients positive for CNS involvement at baseline must undergo a lumbar puncture on day 1 of each subsequent cycle, in conjunction with each Bone Marrow Aspirate or Biopsy, until resolution.
  o Any abnormal findings should be recorded on the Lumbar Puncture eCRF.
  o As with the bone marrow aspirate/biopsy, the lumbar puncture may be repeated at a decreased frequency beginning after cycle 3 at the investigator’s discretion. The lumbar puncture should be performed any time a bone marrow aspirate/biopsy is performed.

• Patients negative for CNS involvement at baseline are not required to undergo further lumbar punctures while on study. The decision to perform further lumbar punctures is at the investigator discretion.

• All patients should undergo a lumbar puncture at the end of treatment

• Intrathecal chemotherapy may be given at the time of lumbar puncture as described in Section 6.6.5. If intrathecal chemotherapy is given on Cycle 2 Day 1, it must be held until after all DLT assessments have been performed.

7.5 Safety

Protocol specified safety assessments will consist of monitoring and recording all adverse events, including serious adverse events, the regular monitoring of laboratory test, vital signs, and assessment of an individual’s physical condition. Unless otherwise specified, all assessments should be performed prior to the morning dose of midostaurin on that day.

All grade 3 and 4 adverse events occurring after Cycle 2, that are thought to be related to study treatment should be discussed with the PI in order to determine the appropriateness of continued treatment.

7.5.1 Adverse events

An adverse event for the purposes of this protocol is the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) occurring after signing
the informed consent even if the event is not considered to be related to the study drug(s). Please refer to Section 6.1 for the protocol-specific definitions of study drug and study treatment.

Adverse events will be assessed according to the Common Toxicity Criteria for Adverse Events (CTCAE) version 3.0. If CTCAE grading does not exist for an adverse event, the severity of grades 1 - 4, will be used. CTCAE grade 5 (death) will not be used in this study; rather, this information will be collected in the End of Treatment or Survival Information eCRF page. Adverse event monitoring should be continued for at least 4 weeks following the last dose of study treatment.

Adverse events (but not serious adverse events) occurring before starting study treatment but after signing the informed consent form are recorded on the Medical History/Current Medical Conditions Case Report Form. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant or require therapy (e.g., any hematologic abnormality that requires transfusion or cytokine treatment); and should be recorded on the Adverse Events eCRF under the signs, symptoms or diagnosis associated with them. In addition, isolated abnormal laboratory values that are considered clinically significant (e.g., cause study discontinuation or constitutes in and of itself a Serious Adverse Event) should be recorded on the Adverse Events eCRF. SAEs occurring after signing the Informed Consent are recorded on the Adverse Event eCRF.

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. The severity grade (CTCAE grade 1-4)
2. Its relationship to study drug (suspected/not suspected)
3. Its duration (start and end dates or if continuing at final exam)
4. Action taken (no action taken; study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication taken; non-drug therapy given; hospitalization/prolonged hospitalization)
5. Whether it is serious, where a serious adverse event (SAE) is defined as one which:
   - Is fatal or life-threatening
   - Results in persistent or significant disability/incapacity
   - Constitutes a congenital anomaly/birth defect
   - Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
     - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (specify what this includes)
     - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
     - Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
• Social reasons and respite care in the absence of any deterioration in the patient’s general condition
• Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements; see Section 8.1.

All adverse events should be treated appropriately. Such treatment may include changes in study drug treatment including possible interruption or discontinuation, starting or stopping concomitant treatments, changes in the frequency or nature of assessments, hospitalization, or any other medically required intervention. Once an adverse event is detected, it should be followed until its resolution, an assessment should be made at each visit (or more frequently, if necessary) of any changes in its severity, its suspected relationship to the study drug(s), any of the interventions required to treat it, and its outcome.

Information about common side effects already known about the investigational drug can be found in the [Investigator’s Brochure] or will be communicated between IB updates in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

7.5.2 Physical examination, weight, height

Physical examinations must be performed at the following times unless otherwise specified:

- Screening
- Cycle 1 on days 1, 3 and 8
- Cycle 2 on days 1, and 8
- Subsequent cycles, at the beginning of each cycle
- At the end of study treatment

Height and weight:

- Screening
- At least once weekly during Cycle 1 on days 1 and 8.
- Subsequent cycles, at the beginning of each cycle
- At the end of study treatment

Physical examinations and weight will be performed on the scheduled day, even if study medication is being held.

More frequent examinations may be performed at the Investigator’s discretion, if medically indicated.

Information about the physical examination and vital signs must be recorded in the source documentation at the study site. Significant findings present prior to the start of study drug must be included in the Relevant Medical History/Current Medical Conditions eCRF. Significant findings made after the start of study drug which meet the definition of an adverse event must be recorded on the Adverse Event eCRF.
7.5.3 Vital signs

Vital signs must be performed at the following times, unless otherwise specified, as follows:

- Screening
- Cycle 1 on days 1, 3 and 8
- Cycle 2 on days 1, and 8
- Subsequent cycles, at the beginning of each cycle
- At the end of study treatment

Vital signs (temperature, respiratory rate, blood pressure, and pulse) will be assessed prior to the morning dose of midostaurin on that day.

More frequent examinations may be performed at the Investigator’s discretion, if medically indicated.

Information about vital signs must be recorded in the source document at the study site. Significant findings present prior to the start of study drug must be in the Relevant Medical History/Current Medical Conditions eCRF. Significant finding made after the start of study drug which meet the definition of an adverse event must be recorded on the Adverse Event eCRF.

7.5.4 Performance status

Lansky or Karnofsky performance status, described in Table 7-2 and Table 7-3, will be documented at

- Screening
- Scheduled day 1 of Cycle 1 and 2.
- Subsequent cycles, at the beginning of each cycle
- At the end of study treatment

Lansky performance status should be used for patients ≤12 years old at screening and Karnofsky performance status should be used for patients >12 years old at screening. The same performance status measure should be used for an individual patient for all visits.

More frequent assessments may be performed if medically indicated as determined by the Investigator, and these evaluations should be recorded on the Unscheduled Visit eCRF. If the baseline assessment was performed <3 days prior to the first administration of midostaurin, then it does not need to be repeated on day 1 of cycle 1.
### Table 7-2 Lansky performance status

<table>
<thead>
<tr>
<th>Lansky score</th>
<th>Performance status</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>Fully active, normal</td>
</tr>
<tr>
<td>90</td>
<td>Minor restrictions in physically strenuous activity</td>
</tr>
<tr>
<td>80</td>
<td>Active, but tires more quickly</td>
</tr>
<tr>
<td>70</td>
<td>Both greater restriction of and less time spent in play activity</td>
</tr>
<tr>
<td>60</td>
<td>Up and around, but minimal active play; keeps busy with quieter activities</td>
</tr>
<tr>
<td>50</td>
<td>Gets dressed but lies around much of the day, no active play but able to participate in all quiet play and activities</td>
</tr>
<tr>
<td>40</td>
<td>Mostly in bed; participates in quiet activities</td>
</tr>
<tr>
<td>30</td>
<td>In bed; needs assistance even for quiet play</td>
</tr>
<tr>
<td>20</td>
<td>Often sleeping; play entirely limited to very passive activities</td>
</tr>
<tr>
<td>10</td>
<td>No play; does not get out of bed</td>
</tr>
<tr>
<td>0</td>
<td>Unresponsive</td>
</tr>
</tbody>
</table>

Lansky performance status to be used for patients ≤ 12 years old.

### Table 7-3 Karnofsky performance status

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>Normal no complaints; no evidence of disease</td>
</tr>
<tr>
<td>90</td>
<td>Able to carry on normal activity; minor signs of symptoms or disease</td>
</tr>
<tr>
<td>80</td>
<td>Normal activity with effort; some signs or symptoms of disease</td>
</tr>
<tr>
<td>70</td>
<td>Cares for self; unable to carry on normal activity or to do active work</td>
</tr>
<tr>
<td>60</td>
<td>Requires occasional assistance, but is able to care for most of his personal needs</td>
</tr>
<tr>
<td>50</td>
<td>Requires considerable assistance and frequent medical care</td>
</tr>
<tr>
<td>40</td>
<td>Disabled; requires special care and assistance</td>
</tr>
<tr>
<td>30</td>
<td>Severely disabled; hospital admission is indicated although death is not imminent</td>
</tr>
<tr>
<td>20</td>
<td>Very sick; hospital administration necessary; active supportive treatment necessary</td>
</tr>
<tr>
<td>10</td>
<td>Moribund; fatal processes progressing rapidly</td>
</tr>
<tr>
<td>0</td>
<td>Dead</td>
</tr>
</tbody>
</table>

Karnofsky performance status to be used for patients > 12 years old.

### 7.5.5 Laboratory evaluations

The following clinical laboratory analyses will be performed by the institution’s clinical laboratory according to the visit schedule (Table 7.1). Novartis must be provided a copy of the laboratory certification and tabulation of the normal ranges for each parameter required. In addition, if at any time a patient has laboratory parameters obtained from a different outside laboratory, Novartis must be provided with a copy of the certification and a tabulation of the normal ranges for that laboratory.

At any time during the study, abnormal laboratory parameters which are clinically relevant (e.g. require dose modification and/or interruption of study drug, lead to clinical symptoms or signs or require therapeutic intervention), whether specifically requested in the protocol or not, must be recorded on the appropriate laboratory eCRF (and/or, if necessary, as comments) page in addition to the appropriate laboratory eCRF page. When abnormal laboratory values
or test results constitute an adverse event (Section 7.5.1) they must be recorded on the Adverse Events eCRF.

Laboratory tests will be collected on the scheduled day and analyzed, even if study medication is being held. All laboratory assessments should be performed prior to the morning dose of midostaurin on that day.

### 7.5.5.1 Hematology

Hematology includes the following parameters: complete blood count (CBC) consisting of red blood cells (RBCs), a total white blood cell count (WBC) with differential (total neutrophil count including bands, lymphocyte, monocyte, eosinophil, basophil and blast counts); hemoglobin (Hgb); hematocrit and platelet count. Hematology must be performed at:

- [Screening](#)
- [Cycle 1 on days 1, 3 and 8](#)
- [Cycle 2 on days 1 and 8](#)
- Subsequent cycles, at the beginning of each cycle
- At the end of study treatment

All available lab results must be reviewed prior to administration of study drug. More frequent examinations may be performed at the Investigator’s discretion if medically indicated; results should be recorded on the Unscheduled visit eCRF.

In the event of any hematological toxicities that require study drug dose modifications or interruptions, hematological test must be repeated at least twice a week until recovery to the baseline level or grade 1 unless otherwise specified. If a patient is discontinued before the end of cycle 1 and at the time of discontinuation the platelet count is > grade 2, then the CBC must be repeated twice weekly until resolution to either grade 1 or baseline.

### 7.5.5.2 Biochemistry

Biochemistry includes the following parameters: urea or BUN, creatinine, sodium, potassium, glucose, calcium, albumin, total bilirubin (direct and indirect if indicated as detailed below), alkaline phosphatase, AST, ALT, phosphorous, magnesium, and uric acid.

Serum chemistries must be assessed unless otherwise specified at:

- [Screening](#)
- [Cycle 1 on days 1, 3 and 8](#)
- [Cycle 2 on days 1 and 8](#)
- Subsequent cycles, at the beginning of each cycle
- At the end of study treatment

In the event of any non-hematological toxicities that require study drug dose modifications or interruptions, biochemistry tests must be repeated at least twice a week until recovery to the baseline level or grade 1 unless otherwise specified.
7.5.5.3 Thyroid function test
Thyroid Stimulating Hormone (TSH) and free T4 (thyroxine) will be measured at:
- Screening
- Around day 1 every fourth cycle, beginning with cycle 5. This is about every 60 days.
- At the end of study treatment
More frequent examinations may be performed at the Investigator’s discretion if medically indicated; results should be recorded on the Unscheduled Visit eCRFs

7.5.5.4 Pregnancy test
Any female aged 8 years and above is considered a woman of child bearing potential, and must be included among female patients undergoing obligatory pregnancy testing throughout the study. A pregnancy test is to be performed within 48 hours prior to beginning treatment and at the end of treatment. A serum test is mandatory. Urine pregnancy test(s) may be performed in place of serum pregnancy test at the end of study treatment visit. If a patient becomes pregnant they must immediately be discontinued from study drug. All end of treatment assessments should be performed according to Table 7-1, if medically appropriate.

To ensure patient safety, each pregnancy in a patient on study drug must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the local Novartis Integrated Medical Safety Department (IMS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the Novartis study drug of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Pregnancy outcomes must be collected for the female partners of any males who took study drug in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

7.5.5.5 Other laboratory
Pursuant to the work-up of an adverse event, results from coagulation tests, urinalysis or cardiac enzyme tests may be collected, at the discretion of the investigator, and entered into the corresponding unscheduled eCRF page. These are not required assessments.

7.5.6 Chest x-ray
A screening chest x-ray (CXR) must be performed to assess study eligibility.

7.5.7 Cardiac assessments
See Table 7-1 for scheduling of ECGs and Section 7.5.7.2 for baseline assessment of left ventricular shortening fraction.
7.5.7.1 Electrocardiogram (ECG)

A 12-lead ECG will be performed to assess study eligibility and at timepoints described below. All ECG assessments should be performed prior to the morning dose of midostaurin on that day.

- Screening
- Cycle 1, Day 1 pre-dose and 2 hours post dose
- Cycle 1, Day 8 pre-dose
- Cycle 2, Day 1 pre-dose and 2 hours post dose
- Cycle 2, Day 8 pre-dose
- Cycle 3, at the beginning of the cycle
- Every 28 days (every other cycle) thereafter at the beginning of the cycle
- At the end of treatment

Any anomalies should be noted and the risk benefit of continued treatment should be reassessed. Grade 3 and 4 AEs related to ECG occurring after cycle 2 should be discussed with the PI in order to determine the appropriateness of continued therapy.

7.5.7.2 Cardiac imaging -- MUGA (multiple gated acquisition) scan or echocardiogram

A baseline echocardiogram (ECHO) or MUGA to assess left ventricular shortening fractions will be performed ≤ 28 days prior to the first administration of midostaurin. The shortening fraction assessment may be repeated more frequently at the Investigator’s discretion, at least within 3 weeks, if there are signs or symptoms of cardiotoxicity.

7.6 Tolerability

This is not applicable for this study.

7.7 Resource utilization

This is not applicable for this study.

7.8 Patient-reported outcomes

This is not applicable for this study.

7.9 Pharmacokinetics

Blood samples for pharmacokinetic assessment will be collected on all subjects of the study. Patients should take their daily dose at approximately the same time each day. Each daily dose should be given with a glass of water and consumed over as short a time as possible.

If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed before the next scheduled dose. The occurrence and frequency of any vomiting during a treatment cycle must be noted in the adverse event section of the eCRF and the exact time of all episodes of vomiting on the day when blood is taken for PK must also be noted.
7.9.1 Pharmacokinetic blood sample collection and handling

Blood samples (2 mL per sample) will be collected on day 1 at either 1, 2, or 3 hours following an age-based randomization schema. Blood samples collection will also occur at predose on day 5 or day 7, following a randomization schema, and on day 15, immediately prior to the morning dose of midostaurin. In older children, ≥ 10 years old, the other day 1 samples and either the day 5 or 7 sample that the patient was not randomized to are requested to be taken as well. These additional samples are considered optional. For example, if a ten-year-old patient was randomized to day 1, 2 hour sample and day 5 predose sample, the day 1, 1 and 3 hour sample and the day 7 sample are also requested, and are considered optional. The actual dose and dosing time for the last dose administered prior to the PK sampling day and for the dose administered on the PK sampling day should all be recorded in the eCRF.

All blood samples will be taken by an indwelling cannula inserted in a forearm vein or from a central venous catheter.

### Table 7-4 Pharmacokinetic blood collection schedule

<table>
<thead>
<tr>
<th>Cycle Number</th>
<th>PK Collection Number</th>
<th>Day</th>
<th>Time (hours post dose)</th>
<th>Volume (mL)</th>
<th>Sample No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>Day 11, 2</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>Day 11, 2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>Day 11, 2</td>
<td>3</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>Day 1</td>
<td>12h, immediately prior to second dose</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>Day 52, 5</td>
<td>Predose</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>1</td>
<td>3</td>
<td>Day 72, 5</td>
<td>Predose</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>Day 15 (Cycle 2 day 1)</td>
<td>Predose</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>Day 29 (Cycle 3 day 1)</td>
<td>Predose</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>5</td>
<td>6</td>
<td>Day 57 (Cycle 5 day 1)</td>
<td>Predose</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>7</td>
<td>7</td>
<td>Day 85 (Cycle 7 day 1)</td>
<td>Predose</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>9</td>
<td>8</td>
<td>Day 113 (Cycle 9 day 1)</td>
<td>Predose</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>11</td>
<td>9</td>
<td>Day 141 (Cycle 11 day 1)</td>
<td>Predose</td>
<td>2</td>
<td>12</td>
</tr>
</tbody>
</table>

| Total blood collected | Between 6 and 16 ml over 3 months |

1. Patient's PK schedule will be randomized to have either 1, 2 or 3 hour post morning dose PK sample taken. The samples are to be numbered respectively 1, 2 or 3.

2. In children ≥ 10 years old, it is optional to provide samples for the timepoints that the patient was not randomized to.

3. After cycle 3, blood samples will be repeated every other cycle on Day 1 immediately prior to the morning dose until study drug is discontinued (i.e. cycle 5, 7, 9, 11 and so on).

4. A cycle is defined as 14 days.

5. Data from the blood sample will correspond to the last dose administered the night prior to the specimen collection in the analysis.
Blood samples will be collected into pre-cooled (ice bath) lithium heparinized tubes and gently inverted 8-10 times and immediately placed in the ice bath. Plasma will be prepared by centrifugation (ca. 2000 x g, 4°C, 10 min), to be completed within 30 minutes. Following centrifugation, the plasma will be transferred equally by pipette into two polypropylene, cryogenic freezing vials (screw-cap tube, Sarstedt #72.693 or equivalent without a skirted base) and stored frozen at ≤-20°C until shipment to Covance. Covance will provide the sample to SGS Cephac for analysis. Samples needs to be protected from light.

Morning spot urine samples will be collected, if available, prior to dosing on day 1, on day 5 or 7 and on day 15 to explore the potential CYP3A4 induction by midostaurin by measuring urine ratio of 6β-hydroxycortisol to cortisol as an in vivo marker for assessment of CYP3A4 induction activity. The sample should be collected in a urine collection tube stored frozen at ≤-20°C until shipment to Covance. Covance will provide the sample to SGS Cephac for analysis. It is not required to insert a catheter for the purposes of urine collection.

Table 7-5 Urine Collection Schedule

<table>
<thead>
<tr>
<th>Cycle Number²</th>
<th>Day</th>
<th>Time (hours post dose)</th>
<th>Sample No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Day 1</td>
<td>Predose</td>
<td>201</td>
</tr>
<tr>
<td>1</td>
<td>Day 5¹</td>
<td>Predose</td>
<td>202</td>
</tr>
<tr>
<td>1</td>
<td>Day 7¹</td>
<td>Predose</td>
<td>203</td>
</tr>
<tr>
<td>2</td>
<td>Day 15 (Cycle 2, day 1)</td>
<td>Predose</td>
<td>204</td>
</tr>
</tbody>
</table>

¹ Patients will be randomized to have either day 5 or 7 pre morning dose spot urine sample taken. The samples are to be numbered respectively 202 or 203. The assignment will follow the PK blood collection randomization.

² A cycle is defined as 14 days

7.9.2 Sample labeling

The site will complete the label in waterproof ink, attach it to the tube, and cover with clear tape before freezing. Plasma collection tubes for midostaurin should be labeled as in Table 7-6.
### Table 7-6  Labeling of plasma midostaurin samples

<table>
<thead>
<tr>
<th>Study Code</th>
<th>CPKC412A2114</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample</td>
<td>Plasma midostaurin</td>
</tr>
<tr>
<td>Sample Number</td>
<td>1, 2, 3, etc…</td>
</tr>
<tr>
<td>Subject Identifier</td>
<td>0501_05001, 0501_05002, etc…</td>
</tr>
<tr>
<td>Cycle</td>
<td>1, 2, 3 etc….</td>
</tr>
<tr>
<td>Day</td>
<td>1, 5, 7, 15</td>
</tr>
<tr>
<td>Scheduled Time (sampling time)</td>
<td>1h, 2h, 3h, etc</td>
</tr>
</tbody>
</table>

Urine collection for ratio of $6\beta$-hydroxycortisol to cortisol should be labeled as in Table 7-7.

### Table 7-7  Labeling of urine samples

<table>
<thead>
<tr>
<th>Study Code</th>
<th>CPKC412A2114</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample</td>
<td>Urine</td>
</tr>
<tr>
<td>Sample Number</td>
<td>201, 202, 203….</td>
</tr>
<tr>
<td>Subject Identifier</td>
<td>0501_05001, 0501_05002, etc…</td>
</tr>
<tr>
<td>Cycle</td>
<td>1</td>
</tr>
<tr>
<td>Day</td>
<td>1, 5, 7, 15</td>
</tr>
</tbody>
</table>

### 7.9.3  Sample handling

All samples (plasma and urine) must be labeled and frozen upon collection at $\leq -20^\circ C$ and kept frozen thereafter. Every three months, or after each patient completes treatment, all available samples must be carefully packed in suitable packing material containing sufficient dry ice to keep them frozen during shipment.

Include a list of all samples, including the date, subject number, and time of sampling. Clearly indicate if there are any missing samples. Laboratory analyses of specimens collected in this study for determination of midostaurin concentrations will be assigned to a bioanalyst (listed in Notification and Personnel below).

Samples should be sent to Covance Laboratories, as described in the sample procurement kits. Subsequently Covance will forward the samples to:

Christine Bertrand  
SGS  
Life Science Services - Clinical Research  
Client Service Group Contract Specialist  
SGS Cephac Europe SAS  
90 Avenue des Hauts de la Chaume BP. 28  
86281 Saint-Benoît CEDEX - France

Shipments should all be sent on Monday, Tuesday, or Wednesday, using a carrier guaranteeing overnight delivery (i.e. World Courier or Federal Express). The following items should be considered:

- advise the carrier of the type of service desired, need for personalized door-to-door pickup, and delivery guaranteed within 24 hours
• advise the carrier of the nature of the shipment's contents (human biological specimens) and label the package accordingly.

• indicate “Midostaurin Study No. CPKC412A2114” on the face of the parcel to be shipped. The parcel must carry a "dangerous goods" label because of the dry ice (labels supplied by the courier).

• the carrier must be asked to store the parcel(s) in a freezer if shipment is delayed and to replace consumed dry ice before transport continues.

• shipping reservations should be made to allow delivery to Novartis before 15:30 (3:30 pm) local time Monday to Thursday and before 11:00 (11 am) local time on Friday. Shipments should not be sent between Thursday and Sunday, to prevent arrival over the weekend.

7.9.4 Notification and personnel

Laboratory analyses of samples for determination of midostaurin concentrations will be assigned to the respective bioanalyst below (Table 7-8). Samples will be sent to Covance, and then provided to SGS Cephac.

Notify the appropriate bioanalyst or alternate contact person that shipment is scheduled, giving the following information:

• the class of service that will be used (e.g. door-to-door)

• to whom the shipment is addressed, the study number, carrier and the shipping form number (or equivalent air bill number)

• the time and date of shipping and approximate time of arrival

• the total number of cartons and weight of each

• any special handling procedures.

Table 7-8 Samples for midostaurin determination

<table>
<thead>
<tr>
<th>Table</th>
<th>Samples for midostaurin determination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attention to:</td>
<td>Christine Bertrand</td>
</tr>
<tr>
<td>Address:</td>
<td>SGS Cephac Europe SAS</td>
</tr>
<tr>
<td></td>
<td>90 Avenue des Hauts de la Chaume BP. 28</td>
</tr>
<tr>
<td></td>
<td>86281 Saint- Benoît CEDEX- France</td>
</tr>
<tr>
<td>Telephone:</td>
<td>+33 549 57 5006</td>
</tr>
<tr>
<td>Fax:</td>
<td>+33 549 57 2239</td>
</tr>
<tr>
<td>Email:</td>
<td><a href="mailto:Christine.bertrand@sgs.com">Christine.bertrand@sgs.com</a></td>
</tr>
</tbody>
</table>

Samples will be sent to SGS Cephac Europe SAS via the local Covance laboratory.

7.9.5 Analytical method

The plasma concentrations of midostaurin and its two major metabolites, CGP52421 and CGP62221, will be determined by using a validated liquid chromatography/mass spectrometry method with a lower limit of quantitation of 10 ng/mL.

Urinary concentrations of cortisol ad its metabolite 6ß-hydroxycortisol will be determined by an immunoassay or a liquid chromatography/mass spectrometry method as appropriate.
These analyses will be conducted at Cephac.

7.10 Biomarkers

This clinical study includes biomarker components that will be analyzed to support secondary clinical objectives, as well as exploratory objectives. These studies are hypothesis generating (i.e., discovery based research) and will be used to expand the understanding of the disease and protocol treatment.

The sample collection plan required in this study is included in the main consent and is not optional, unless otherwise indicated by local IRB/EC or Health Authority requirements.

A separate signature line in the main informed consent document delineates permission from the patient to allow Novartis long term storage or “retention” (up to 15 yrs) of any leftover biomarker samples (tumor/plasma/serum). These samples may be used to further address scientific questions as new information in regard to the disease or the study drug becomes available.

Biomarker analyses of patient samples in this study will be analyzed to address the following:

- AML Patient FLT3 mutation determination/confirmation of local mutation analysis
- FLT3 activation levels in pretreatment samples
- Changes in FLT3 signaling in response to midostaurin treatment

7.10.1 Midostaurin pharmacodynamic biomarker assessments

Patients with AML must have a documented FLT3 mutation prior to being randomized. FLT3 mutation status can be determined on either bone marrow (preferred) or peripheral blood samples. If the patient cannot wait for the results of the central analysis at the Pediatric Oncology Research Laboratory in Rotterdam (approximately one week), a local FLT3 mutation result is considered acceptable to satisfy the inclusion criteria, as specified below. However, a sample will be collected and centrally analyzed for all patients, regardless of prior local testing. Copies of any local FLT3 mutation results must be kept as source documentation if used for patient inclusion. If central analysis demonstrates a discrepancy in FLT3 mutation status, the patient may remain on the study drug as clinically appropriate, at the discretion of the investigator, as described in Section 7.4.2.

A locally analyzed FLT3 mutation status is acceptable within the following parameters:

- Relapsed AML: the sample must have been taken within 30 days of starting midostaurin treatment (Day 1)
- Refractory AML: the sample must have been taken within 90 days of staring midostaurin treatment (Day 1)

7.10.2 FLT3 activation levels in pretreatment samples

A 3 ml heparinized bone marrow sample will be collected at baseline for biomarker analysis. Patient samples will be assayed for FLT3 mRNA expression and mutations of FLT3 gene (Stam Haematologica 2007). Baseline phosphorylation status of FLT3 will be determined by immunoprecipitation/western blot or other suitable methods. These parameters will be correlated with one another and with clinical response to see if baseline activation of FLT3
correlates with response to midostaurin. If sample quantity is sufficient blast cells will be used for expression profiling and in ex vivo experiments testing effects of midostaurin on FLT3 phosphorylation and cell killing.

### 7.10.3 Midostaurin pharmacodynamic biomarker assessments

Peripheral blood samples will be used to measure changes in cellular protein levels and phosphorylation of FLT3. FLT3 phosphorylation will be compared in baseline samples versus cycle 1 day 3 samples and end of treatment samples to determine whether midostaurin has inhibited FLT3 function in vivo. 10 ml heparinized peripheral blood for patients > 2 years of age and 5 ml heparinized peripheral blood for patients ≤ 2 years of age will be collected at baseline, at cycle 1 day 3 and at end of treatment. Blast cells will be isolated and characterized for changes in FLT3 phosphorylation, measured by immunoprecipitation and western blotting or other suitable techniques.

If sample quantity is sufficient, baseline samples will be used for expression profiling, and also be treated ex-vivo with midostaurin and assayed for changes in FLT3 phosphorylation and cell cytotoxicity. Ex-vivo changes will be compared to baseline measures of FLT3 activation and clinical response. All samples will be analyzed in the Pediatric Oncology Research Laboratory in Rotterdam.

### 8 Safety monitoring

#### 8.1 Serious adverse event reporting

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient or parent/guardian has provided informed consent and until 4 weeks after the patient has stopped study treatment/participation must be reported to Novartis within 24 hours of learning of its occurrence. Any SAEs experienced after this 4-week period should only be reported to Novartis if the investigator suspects a causal relationship to the study drug. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event. All DLTs are considered to be medically significant and therefore must be reported as SAEs.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form. The investigator must assess and record the relationship of each SAE to each specific study drug (if there is more than one study drug), complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours to the local Novartis Integrated Medical Safety Department.

The telephone and telefax number of the contact persons in the local department of Integrated Medical Safety, specific to the site, are listed in the investigator folder provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site.
Follow-up information is sent to the same person to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the [Investigator’s Brochure] and is thought to be related to the Novartis study drug, a Integrated Medical Safety Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

8.2 Pregnancies

To ensure patient safety, each pregnancy in a patient on study drug must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the local Novartis Integrated Medical Safety Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the Novartis study drug of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Pregnancy outcomes must be collected for the female partners of any males who took study drug in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

8.3 Data Monitoring Board

A data safety monitoring board will not be used for this study. Instead, during the dose escalation phase of the trial, Novartis and the site investigators will meet at the end of each treatment cohort to discuss and evaluate all of the gathered safety data including pharmacokinetic data. At these meetings, Novartis and the investigators must reach a consensus on whether to escalate the dose further, or whether to de-escalate and/or expand recruitment into particular cohorts. Novartis will prepare minutes from these meetings and circulate them to each investigator for comment prior to finalization. For further details on this procedure, please refer to Section 6.6.1.4.1.
9 Data review and data management

9.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator’s meeting, a Novartis representative will review the protocol and eCRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the eCRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study drug is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on eCRFs must be traceable to these source documents in the patient's file. Data not requiring a separate written record will be defined before study start and will be recorded directly on the eCRFs, which will be documented as being the source data (see items listed as Category “D” in Table 7-1). The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the eCRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety variables. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients will be disclosed.

9.2 Data collection

Novartis and/or a designated CRO will train designated investigator site staff on the web-based EDC system. Investigator site staff will not be given access to the EDC system until they have been trained. Designated investigator staff will enter the data required by the protocol into the eCRFs using a computer. Automatic validation programs check for data discrepancies in the eCRFs and, by generating appropriate error messages, allow modification or verification of the entered data by the investigator staff in real time. The investigator must certify that the data are complete and accurate, as instructed, after the last transfer of the data prior to analysis. After database lock, the investigator will receive a CD-ROM or paper copies of the patient data for archiving at the investigational site.

Additionally, any severe adverse event of interest (e.g. an adverse event that meets the DLT criteria) should be communicated to Novartis as soon as possible.

9.3 Database management and quality control

Novartis and/or designated CRO staff review the eCRFs entered by investigational staff for completeness and accuracy and instruct the site personnel to address data that appears to be incomplete, inaccurate, and/or inconsistent. Obvious errors are corrected by Novartis and/or
designated CRO personnel. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff are required to respond to the query and make any necessary changes to the data. If the electronic query system is not used, a paper Data Query Form will be faxed to the site. Site personnel will complete and sign the faxed copy and fax it back to the designated CRO and/or Novartis staff who will make the correction to the database. The signed copy of the Data Query Form should be returned to the designated CRO and/or Novartis.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

At the conclusion of the study the occurrence of any protocol violations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be frozen for the data analysis (at the timepoint designated in Section 10). The database will be locked once all patients are no longer on study drug. Changes to the database after the lock can only be made by joint written agreement between the Global Head of Oncology Biostatistics and Data Management and the Global Multi-Program Head.

10 Statistical methods and data analysis

All data will be analyzed by Novartis or a designated CRO. Any data analysis carried out separately by the investigator should be submitted to Novartis in a timely manner before publication or presentation.

It is planned that the data from all centers that participate in this protocol will be combined, so that an adequate number of patients will be available for analysis.

The data will be summarized with respect to demographic and baseline characteristics, occurrence of dose-limiting toxicities (DLTs) efficacy observations and measurements, safety observations and measurements, and pharmacokinetic measurements.

The core safety report will be based on the data from all patients in the dose escalation/expansion part of the study when the last patient has potentially completed at least 1 cycles of treatment, or discontinued treatment. All efficacy data collected up to the data cut off date will be included in the core report. The additional data for any patients continuing to receive study drug past this time, as allowed by the protocol, will be summarized in a separate report once these patients either have completed or discontinued the study.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, 25\textsuperscript{th} and 75\textsuperscript{th} percentiles, minimum, and maximum will be presented.

All data will be listed unless otherwise specified.

10.1 Populations for analysis

The full analysis set (FAS) includes all patients who are enrolled into the trial and received at least one dose of midostaurin. The full analysis set will be the primary population for all analyses unrelated to safety endpoints.
The safety set will consist of all patients who received at least one dose of midostaurin and had at least one post-baseline safety assessment (where the statement that a patient had no adverse event (on the Adverse Events eCRF) constitutes a safety assessment). The safety set will be the primary population for all safety related endpoints except determination of the dose-DLT relationship.

The dose-determining set (DDS) consists of all patients from the safety set who either meet the following minimum exposure criterion and have sufficient safety evaluations, or discontinue earlier due to DLT. This constitutes an evaluable patient for the determination of the MTD. The additional patients in the expansion are not included in this set.

A patient is considered to have met the minimum exposure criterion if they have received $\geq 75\%$ of the planned doses of midostaurin within the first 14 days of dosing. Patients who do not experience DLT during the first 14 days are considered to have sufficient safety evaluations if they have been observed for $\geq 14$ days following the first dose, and have completed all required safety evaluations. Patients who do not meet these minimum safety evaluation requirements will be regarded as ineligible for inclusion into the DDS and will be replaced.

PK set: consists of all FAS patients who have at least one PK timepoint of midostaurin without vomiting within 4 hours of dose administration or significant restricted co-medications.

All statistical tables will be summarized by dose group within each age strata, by dose group and on the overall population. Study indication will also be applied to summarize certain tables. All listings will include age strata, dose group and indication.

### 10.2 Patient demographics/other baseline characteristics

Demographic characteristics and baseline data (including disease characteristics and medical history), will be summarized descriptively on the FAS.

Concomitant relevant medical conditions at study entry will be summarized using MedDRA primary system organ classes and MedDRA preferred terms.

### 10.3 Treatments (study drug, concomitant therapies, compliance)

The study medication administration will be summarized. This will include the number of treated patients, number of patients who had dose reduction and the duration of treatment.

Concomitant medications and significant non-drug therapies prior to and after the start of the study drug will be summarized separately. They will be classified by ATC class and preferred term.

The FAS population will be used.

### 10.4 Primary objective

The primary objectives of the dose-escalation phase of the study is to determine the maximum-tolerated dose (MTD) of midostaurin given orally, twice-a-day, in a 14-day cycle to patients in two age groups ($\geq 3$ months to $\leq 2$ yrs: $> 2$ yrs to $< 18$ yr) of pediatric patients with AML or MLL (Section 3.1).
The corresponding primary analysis method is an adaptive Bayesian logistic regression model guided by the escalation with overdose control (EWOC) (Babb 1998). A prior distribution for the model parameters is derived based on experience with midostaurin in adult patients in clinical [Study CPKC412A2104]. This prior distribution is then updated after each cohort of patients in each stratum with the DLT data from the current study. A detailed description of the used methodology can be found in Section 10.4.2 and Post text supplement 1.

The primary objective of the dose-expansion phase of the study is to be able to have sufficient number of patients to assess the safety and tolerability of midostaurin for pediatric patients with each of the indications AML or MLL, as described in Section 3.1.

### 10.4.1 Variable

Estimation of the MTD at the dose-escalation phase of the study will be based upon the estimation of the probability of DLT for patients in the dose-determining set. This probability is estimated by the model in Section 10.4.2.

Determination of preliminary efficacy will be based on efficacy endpoints determined in Section 7.4. The FAS will be used for the efficacy analyses.

### 10.4.2 Statistical hypothesis, model, and method of analysis

#### Statistical model

The statistical model for the dose-escalation part of the study will be based on a 3-parameter Bayesian logistic regression model (BLRM). Let \( \pi(d) \) be the probability of DLT at dose \( d \), and let \( d^* \) denote a reference dose of midostaurin. Then, the 3-parameter logistic model for these probabilities is of the form

\[
\text{logit}(\pi(d)) = \log(\alpha) + \beta \log(d/d^*) + \gamma I_{\text{age} \leq 2},
\]

where \( \text{logit}(\pi(d)) = \log(\pi(d)/(1-\pi(d))) \), \( \alpha, \beta > 0 \), and \( -\infty < \gamma < \infty \). Doses are rescaled as \( d/d^* \), and as a consequence \( \alpha \) is equal to the odds of the probability of DLT at \( d^* \) for patient greater than 2 years old. If a patient is less than or equal to 2 years old, the indicator \( I_{\text{age} \leq 2} \) takes the value 1, otherwise it takes the value zero. Therefore, \( \gamma \) may be interpreted as the log-odds ratio for the probability of DLT between patients less than or equal to two years old and those greater than two. Note that for a dose equal to zero, the probability of toxicity is zero in both strata.

#### Prior specifications

The Bayesian approach requires the specification of prior distributions for the model parameters. A bivariate normal prior for the model parameters \( \log(\alpha), \log(\beta) \) was elicited based on prior medians and wide confidence intervals for the probabilities of a DLT at each dose, and were obtained as follows:

- Based on clinical data available from study [CPKC412A2104] there were very few DLTs observed in adult patients in a similar disease group (detailed Post text supplement 1).
- In order to be conservative in this new population, the estimated median rate of DLT at the reference dose \( (67.5 \text{ mg/m}^2 \text{ b.i.d.}) \) was set to 15%. The median prior probability of DLT at the starting dose was set to be 0.5%.
• For the remaining doses, the prior medians of probability of DLT were assumed linear in log-dose on the logit-scale.

• Based on the medians for the probability of DLT at each dose and wide prior credible intervals, obtained from minimally informative Beta distributions, (Neuenschwander 2008), the optimal parameters of the individual bivariate normal distributions were obtained.

In addition, a prior was set for the covariate parameter, \( \gamma \), by assuming that the younger population may experience a higher or lower rate of DLT at each dose level compared to the older patients. Therefore, a normal distribution was assumed with prior mean set equal to zero. The 97.5\(^{th}\) percentile was set so under the assumption that a 4-fold increase in the odds of DLT may be seen.

The parameters of the prior distributions of the model parameters are provided in Table 10-1 and Table 10-2.

### Table 10-1  Prior parameters for bivariate normal distribution of model parameters log(alpha) and log(beta)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Means</th>
<th>Standard deviations</th>
<th>Correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td>log((\alpha)), log((\beta))</td>
<td>(-1.746, 0.413)</td>
<td>(2.369, 1.076)</td>
<td>-0.299</td>
</tr>
<tr>
<td>(\gamma)</td>
<td>0</td>
<td>0.707306</td>
<td>NA</td>
</tr>
</tbody>
</table>

### Table 10-2  Prior probabilities of under, targeted and over dosing (derived from prior distribution in Table 10-1)

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>Prior probabilities that Pr(DLT) is in interval:</th>
<th>Mean</th>
<th>SD</th>
<th>Quantile</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-0.16</td>
<td>0.16-0.33</td>
<td>0.33-1.0</td>
<td>2.5%</td>
<td>50%</td>
</tr>
<tr>
<td>Age &gt;2 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>0.793</td>
<td>0.082</td>
<td>0.126</td>
<td>0.113</td>
</tr>
<tr>
<td>30</td>
<td>0.720</td>
<td>0.108</td>
<td>0.172</td>
<td>0.155</td>
</tr>
<tr>
<td>45</td>
<td>0.649</td>
<td>0.123</td>
<td>0.228</td>
<td>0.196</td>
</tr>
<tr>
<td>60(^1)</td>
<td>0.564</td>
<td>0.144</td>
<td>0.292</td>
<td>0.243</td>
</tr>
<tr>
<td>67.5(^1)</td>
<td>0.516</td>
<td>0.156</td>
<td>0.328</td>
<td>0.269</td>
</tr>
<tr>
<td>Age 3 months - 2 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>0.789</td>
<td>0.072</td>
<td>0.139</td>
<td>0.119</td>
</tr>
<tr>
<td>30</td>
<td>0.718</td>
<td>0.094</td>
<td>0.188</td>
<td>0.162</td>
</tr>
<tr>
<td>45</td>
<td>0.644</td>
<td>0.118</td>
<td>0.238</td>
<td>0.204</td>
</tr>
<tr>
<td>60(^1)</td>
<td>0.567</td>
<td>0.134</td>
<td>0.299</td>
<td>0.250</td>
</tr>
<tr>
<td>67.5(^1)</td>
<td>0.523</td>
<td>0.146</td>
<td>0.331</td>
<td>0.276</td>
</tr>
</tbody>
</table>

\(^1\)The data for this dose does not meet overdose (safety) criteria based on prior distribution of DLT rates.

**Dose recommendation**

After each cohort of patients is completed within a stratum, the posterior distribution for the model parameters will be obtained by simulation. The posterior distributions of the model
parameters is used to derive the posterior distributions for \( \pi(d) \). The posterior distributions for \( \pi(d) \) will be summarized by the following three intervals

1. [0,16%) under-dosing
2. [16%,33%) targeted toxicity
3. [33%,100%] excessive toxicity

Following the principle of dose-escalation with overdose control (EWOC) (Babb 1998), (Neuenschwander 2008), after each cohort of patients the recommended dose is the one with the highest posterior probability of DLT in the target interval [16%, 33%) among the doses fulfilling the overdose criteria, namely that there is less than 25% chance that the true rate of DLT falls in the excessive toxicity interval. Note that the dose that maximizes targeted toxicity is the best estimate of the MTD, but it may not be a safe dose according to the overdose criteria if the amount of data is insufficient. Ideally, if enough data is available, the dose recommended for the next cohort and the best estimate of the MTD will coincide.

The dose recommended by the adaptive BLRM for each stratum may be regarded as information to be integrated with a clinical assessment of the toxicity profiles observed thus far in determining the next dose to be investigated (for the exact procedure refer to Section 6.6.1.4.1).

For patients < 18 years old and > 2 years old, cohorts of at least 3 evaluable patients per dose level will be enrolled in the dose-escalation part including at least 6 patients at the MTD level. For patients \( \geq 3 \) months old and \( \leq 2 \) years old, cohorts of at least 2 including at least 6 patients at the MTD level. As an exception, the model will be re-evaluated before enrollment of any additional patients to the cohort if 2 evaluable patients in the cohort experience DLT before the enrollment of the 3rd patient.

**10.4.2.1 Dose-expansion phase**

The dose-expansion phase will continue the enrollment until at least 10 patients in total (including all patients treated at all dose levels) with AML and at least 10 patients in total (including all patients treated at all dose levels) with MLL have been treated in the study. These patients will be treated at the MTD that has been established for the age group that they belong to.

**10.4.2.2 Handling of missing values/censoring/discontinuations**

Patients in the dose-escalation phase who are ineligible for the dose-determining set will be replaced. Patients in the dose-expansion phase who are ineligible for the safety set will be replaced.

Patients continuing to receive study drug at the time of the core or final reports will have time-to-event data (e.g., overall survival, duration of response, etc) censored at the time of last measurement prior to the data cut-off point used in the report. Continuing events (e.g., adverse events, concomitant medication, etc) will be summarized using the data cut-off date as the date of completion, with an indication within listings that the event is continuing.
For patients who discontinue the study with ongoing events, the discontinuation date will be used as the completion date of the event with the appropriate censoring as described in the above paragraph.

The reason for discontinuation from study will be summarized and listed, along with dates of first and last study drug, duration of exposure to study drug and date of discontinuation for each patient, by dose cohort and age stratum.

Other missing data will simply be noted as missing on appropriate tables/listings.

10.4.3 Supportive analyses
Additional exploratory and supportive analyses will be conducted if appropriate.

10.5 Secondary objectives
Although efficacy is not the primary objective of this study it will still be assessed.

The primary analyses for the efficacy secondary endpoints are performed on the FAS. These analyses will be descriptive with 95% two sided CIs provided for the endpoints.

Time to event data will be provided in listings. Kaplan-Meier product-limit estimates and graphs will be produced for the overall population if there is sufficient data.

10.5.1 Response
Best clinical response will be tabulated according to the following categories as described in Section 7.4.1:

- Morphological complete remission (CR)
- Incomplete morphological complete remission (CRi)
- Leukemia free state (LFS)
- Partial remission (PR)
- Bone marrow blast response (BR)
- Bone marrow minor blast response (BRm)
- Peripheral blood blast response (BRp)
- Minor peripheral blood blast response (BRmp)
- Stable disease (SD)
- Progressive disease (PD)
- Not done

Responders are all patients with a best clinical response of CR, CRi, LFS, PR, BR, BRm, BRp or BRmp. SD and PD are considered as non response. Patients with missing tumor assessment or who die or discontinue the study before having their first assessment will be considered non-responders.

Blast response along with the bone marrow and/or peripheral blood status will be summarized using the laboratory data.
10.5.2 Duration of response

The duration of response is defined as the time from the first response until the date of the first documented disease progression or death due to any cause. The Kaplan-Meier product-limit estimates and graphs will be used to describe the response duration (median, 95% confidence intervals, and plots) for the overall population in patients who were responders. Amongst these patients, duration of response will be censored at the date of the last available efficacy evaluation in patients who do not progress.

10.5.3 Time to response

Time to response is defined as the time from date of first study drug intake to date of first response. Time to response will be censored at the date of the last available assessment included in the analysis in patients who are non-responders. Kaplan-Meier product-limit estimates will be used to describe the time to response (median, 95% confidence intervals, and plots) for the overall population.

10.5.4 Overall survival

Overall survival is defined as the time from date of first study drug intake to date of death due to any cause. Survival times for patients not recorded as dead will be censored at the last date they were known to be alive. Kaplan-Meier product-limit estimates will be used to describe the overall survival (median, 95% confidence intervals, and plots) for the overall population. Survival follow up data is used for this analysis.

10.5.5 Other exploratory analyses

In addition to the Bayesian model to estimate the DLT rate an exploratory analysis will also be performed in which we model the dose-blast response. The results for this analysis will be used to determine the optimal dose based on the maximization of the probability of blast response in the absence of a DLT. This model could be used to assist decision making within the dose escalation.

Population and grouping for the analyses

For all safety analyses, the safety population will be used. All listings and tables will be presented by age group, dose cohort and indication.

Safety parameters and analyses

The assessment of safety will be based on the frequency of adverse events and on the number of laboratory values that fall outside of pre-determined ranges. Other safety data will be considered as appropriate.

Adverse events will be summarized by presenting the number and percentage of patients having any adverse event, having an adverse event in each body system and having each individual adverse event. Any other information collected (e.g. severity or relatedness to study medication) will be listed as appropriate.
Laboratory data will be summarized by presenting CTCAE grade shift tables and change from baseline values (means, medians, standard deviations, ranges) and by the flagging of notable values in data listings.

Data from other tests will be listed, notable values will be flagged, and any other information collected will be listed as appropriate.

All analyses are descriptive.

10.5.6 Adverse events (AE)

10.5.6.1 Adverse events (AE)

All adverse events recorded during the study will be summarized. The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by system organ class, severity (based on CTCAE grades), type of adverse event, relation to the study drug by age group, dose cohort and indication. Deaths reportable as SAEs and non-fatal serious adverse events will be listed by patient and tabulated by type of adverse event and age group, dose cohort and indication.

10.5.6.2 Laboratory abnormalities

All laboratory values will be converted into SI units and the severity grade calculated using appropriate common toxicity criteria (CTCAE).

A listing of laboratory values will be provided for each laboratory parameter and a separate listing will display notable laboratory abnormalities (i.e., newly occurring CTCAE grade 3 or 4 laboratory toxicities) Laboratory data will be summarized by presenting CTCAE grade shift tables (baseline to most extreme post-baseline value), by presenting summary statistics of raw data and change from baseline values and by the flagging of CTCAE grades in data listings.

10.5.6.3 Other safety data

Summary statistics for data from other tests will be provided, notable values will be flagged, and any other information collected will be listed as appropriate.

Descriptive summary statistics will be provided for data for:

- Electrocardiograms: changes from baseline to end of study ECG results, new or worsening ECG abnormalities
- Vital signs and weight: summary statistics of raw data and change from baseline values (means, medians, standard deviations) plus newly occurring or worsening abnormalities of vital signs
- Worst post baseline Lansky/Karnofsky performance status.

Listings with flagged notable values and any other information collected will be provided as appropriate.

10.5.7 Tolerability

Not applicable.
10.5.8 Resource utilization
Not applicable.

10.5.9 Patient-reported outcomes
Not applicable.

10.5.10 Pharmacokinetics
The concentration-time data will be tabulated together with descriptive statistics for each dose level. Individual as well as mean, concentration-time plots will be generated.

To quantify the PK profile in pediatrics, particularly with respects to age and body mass, the PK will be compared and integrated with adult PK data from separate studies using an exploratory population PK analysis. The PK profiles will allow estimation of individual daily steady-state exposures, enabling correlations to PD variables.

10.5.11 Biomarkers

10.5.11.1 Midostaurin pharmacodynamic biomarker analyses
These exploratory pharmacodynamic studies are designed to investigate the association between genetic factors, their activation status, and clinical parameters which are collected during the clinical trial. All statistical analysis to be performed will be considered exploratory.

10.6 Interim analysis
No formal interim analyses are planned. However, the dose-escalation design in the dose-escalation phase of the study foresees that decisions based on the current data are taken before the end of the study. More precisely, after each cohort in the dose-escalation phase, the next dose will be chosen depending on the observed data.

10.7 Sample size calculation
Stratum 1 (Age < 18 and > 2 years): Cohorts of at least three MTD-evaluable patients per dose level will be enrolled in the dose-escalation phase including at least six patients at the MTD level.

Stratum 2 (Age ≥ 3 months and ≤ 2 years): Cohorts of at least two MTD-evaluable patients per dose level will be enrolled in the dose-escalation phase including at least six patients at the MTD level. If a DLT is seen for a given dose level at least three patients across both strata are required before dose escalation.

Both strata: Due to the potential for dropouts during the first treatment cycle (e.g. early disease progression), a cohort may be expanded to include additional patient(s) Cohorts may be expanded at any dose level below the MTD for further elaboration of safety and pharmacokinetic parameters as required. Assuming escalation occurs in both strata to 60 mg/m², an expected number of 22 patients will be evaluated in the dose escalation part of the study.
If necessary additional patients will be enrolled in the dose expansion to have at least approximately 10 safety evaluable patients of each disease (AML/MLL) treated across all dose levels.

11 Administrative procedures

Regulatory and ethical compliance

This clinical study was designed and shall be implemented and reported in accordance with the protocol, the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

Responsibilities of the investigator and IRB/IEC/REB

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) before study start. A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC/REB must be given to Novartis before study initiation. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs and regulatory authorities as required.

Informed consent

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC/REB-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient’s representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC/REB, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC/REB approval.
Women of child bearing potential should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

**Amendments to the protocol**

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC/REB. Only amendments that are required for patient safety may be implemented prior to IRB/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC/REB at the study site should be informed within 10 working days.

**Discontinuation of the study**

Novartis reserves the right to discontinue this study under the conditions specified in the clinical trial agreement.

**Study drug supply and resupply, storage, and tracking/drug accountability**

Study drugs must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated assistants have access. Upon receipt, the study drug should be stored according to the instructions specified on the drug labels. Clinical supplies are to be dispensed only in accordance with the protocol.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the drug but no information about the patient.

The investigator must maintain an accurate record of the shipment and dispensing of study drug in a drug accountability ledger. Drug accountability will be noted by the field monitor during site visits and at the completion of the trial. Patients will be asked to return all unused study drug and packaging at the end of the study or at the time of study drug discontinuation.

At the conclusion of the study, and, as appropriate during the course of the study, the investigator will return all used and unused study drug, packaging, drug labels, and a copy of the completed drug accountability ledger to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

**Exploratory Biomarker consent form**

Studies with an optional Exploratory Biomarker component will have a separate consent question covering those studies. If a subject opts not to participate in the optional Exploratory Biomarker assessments, this in no way affects the subject’s ability to participate in the main research Study.
12 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the trial to request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.
13 References (available upon request)


EMEA Guideline on Clinical Trials in Small Populations; EMEA 2006


Hollink IH, Zwaan CM, Zimmermann M, et al (2009) Favorable prognostic impact of NPM1 gene mutations in childhood acute myeloid leukemia, with emphasis on cytogenetically normal AML. Leukemia; (23(2); 262-70


