A phase 1/2, open-label, dose-escalation study of midostaurin in children with relapsed or refractory acute leukaemia

Acute leukaemias comprise approximately 32% of all childhood cancers (National Cancer Institute, 2018). Up to 20% of paediatric patients with acute myeloid leukaemia (AML) have mutations in *FLT3*, conferring a poor prognosis (Balgobind *et al*, 2011; Zwaan *et al*, 2015). Approximately 80% of infants with acute lymphoblastic leukaemia (ALL) have gene rearrangements in *KMT2A* (*KMT2A*-R ALL), often in combination with overexpression of mutation-negative FLT3 (Stam *et al*, 2007). This combination of *KMT2A*-R ALL and FLT3 overexpression is associated with particularly poor long-term outcomes (Stam *et al*, 2007; Chillon *et al*, 2012). Preclinical and clinical work suggests that targeted inhibition of FLT3 may be a promising strategy for paediatric acute leukaemias (Annesley & Brown, 2014).

Midostaurin (PKC412), a multikinase inhibitor with targets that include FLT3, was approved in adults with newly diagnosed *FLT3*-mutated AML (Stone *et al*, 2017). Midostaurin has demonstrated antileukaemic activity in preclinical models of *FLT3*-mutated AML and FLT3-overexpressing *KMT2A*-R ALL (Weisberg *et al*, 2002; Armstrong *et al*, 2003). This dose-escalation and dose-expansion study evaluated the safety and efficacy of single-agent midostaurin in paediatric patients with relapsed or refractory (R/R) *FLT3*-mutated AML or *KMT2A*-R ALL (NCT00866281). Patients had documented diagnosis of *FLT3*-mutated AML or *KMT2A*-R ALL according to local laboratory assessment. *FLT3* mutations were confirmed at a central laboratory but were not required for inclusion of patients with *KMT2A*-R ALL. The primary objective was to determine the maximum tolerated dose (MTD) or recommended dose for expansion (RDE) of oral midostaurin solution, developed for paediatric use, in each age group using a single 3-parameter Bayesian logistic regression model (Appendix S1). A dose-limiting toxicity (DLT) was defined as a nonhaematological grade 3/4 adverse event (AE), drug-related abnormal laboratory value, or AE leading to study discontinuation within 14 days of starting treatment occurring in the dose-determining set. Midostaurin was administered to children in 2 age groups: younger (≥3 months to ≤2 years) and older (>2 years to ≤18 years) (Figure S1).

From September 2009 to October 2014, 22 patients were enrolled (9 *FLT3*-mutant AML, 13 *KMT2A*-R ALL). The study was terminated early due to slow accrual (Appendix S1). Baseline characteristics are presented in Table I and Table SI. All 9 patients with AML were in the older age group. Of 13 patients with *KMT2A*-R ALL, 11 were younger and 2 older. According to the central laboratory analysis of *FLT3*-mutation status, not all patients with AML had a *FLT3* mutation (6 *FLT3*-internal tandem duplication, 1 *FLT3*-mutation–negative [*FLT3*-mut−], and 2 missing/nonevaluable) and only 1 patient with *KMT2A*-R ALL had a *FLT3* mutation (*FLT3*-tyrosine kinase domain; 11 *FLT3*-mut−; 1 missing/nonevaluable) (Table SII). Potential reasons

Table I. Baseline characteristics and best response rates for the full analysis set.

	AML (n = 9)	*KMT2A*-R ALL (n = 13)	Total (N = 22)
Baseline patient characteristics			
Median age (range), years	15·8 (10·5–17·1)	1·6 (0·5–13·8)	2·0 (0·5–17·1)
Sex, *n* (%)			
Male	2 (22)	5 (38)	7 (32)
Female	7 (78)	8 (62)	15 (68)
Race, *n* (%)			
White	9 (100)	8 (62)	17 (77)
Other	0	5 (38)	5 (23)
Disease status, *n* (%)			
First relapse	1 (11)	6 (46)	7 (32)
Without salvage attempt	0	4 (31)	4 (18)
With salvage attempt	1 (11)	2 (15)	3 (14)
Refractory to second induction therapy	4 (44)*	1 (8)	5 (23)
Second relapse	1 (11)	3 (23)	4 (18)
With salvage attempt	1 (11)	3 (23)	4 (18)
Other	3 (33)	3 (23)	6 (27)
Number of prior therapies, median (range)	4 (3–9)	3 (1–8)	4 (1–9)

AML, acute myeloid leukaemia; *KMT2A*-R ALL, acute lymphoblastic leukaemia with *KMT2A* gene rearrangement.

*Note that one patient with AML, who was considered as refractory to second induction therapy at the time of enrollment due to having received prior antineoplastic therapies, was initially incorrectly identified as previously untreated.

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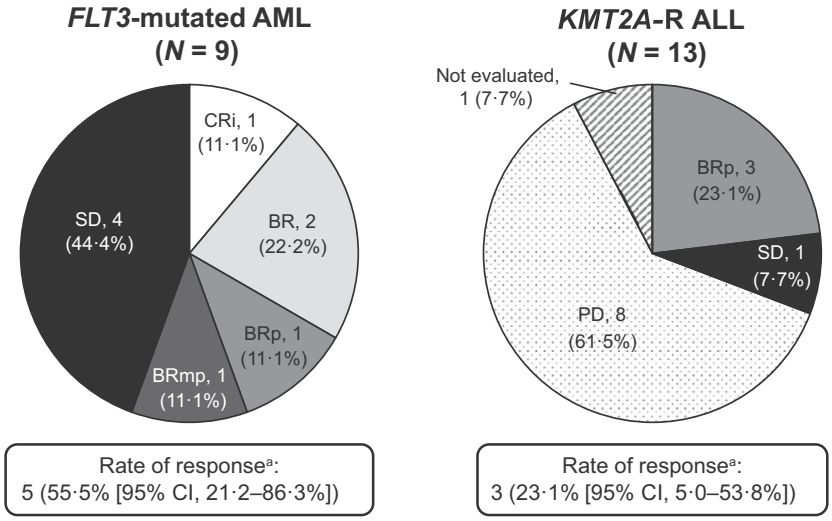

Fig 1. Best clinical response in patients with *FLT3*-mutated AML and *KMT2A*-R ALL. AML, acute myeloid leukaemia; BR, bone marrow blast response; BRm, minor bone marrow blast response; BRmp, minor peripheral blood blast response; BRp, peripheral blood blast response; CI, confidence interval; CR, complete remission; CRi, complete remission with incomplete count recovery; *FLT3*, fms-like tyrosine kinase 3 gene; *KMT2A*-R ALL, acute lymphoblastic leukaemia with *KMT2A* gene rearrangement; PD, progressive disease; SD, stable disease. [a]Best clinical response includes leukaemia-free state, CR, CRi, partial remission, BR, BRm, BRp, and BRmp.

for discrepancy between the local and central laboratory analyses are discussed in the Supplementary Appendix. High levels of phosphorylated FLT3 were not detected in any patient sample (AML or *KMT2A*-R ALL) at baseline (Table SIII).

Of 22 patients, 7 (3 with *FLT3*-mutated AML and 4 with *KMT2A*-R ALL per local assessment) received the starting dose (30 mg/m^2 twice daily [bid]) and 15 (6 with *FLT3*-mutated AML and 9 with *KMT2A*-R ALL per local assessment) received the maximum dose (60 mg/m^2 bid). All patients discontinued treatment (Figure S2). No DLTs or significant safety concerns were observed among the 6 patients who received the 30 mg/m^2 bid dose; therefore, dose escalation proceeded to 60 mg/m^2 bid. Among 11 patients in the dose-determining set who received the 60 mg/m^2 bid dose, a DLT was reported in 1 patient (grade 3 alanine aminotransferase elevation). One patient with *FLT3*-mutated AML in the 60 mg/m^2 bid cohort completed the per-protocol follow-up; the remaining 21 patients died. Median duration of exposure to midostaurin for all patients was 16 days. Because the study design did not allow dosing beyond 60 mg/m^2 bid, a true MTD could not be determined and the 60 mg/m^2 bid dose was chosen as the RDE (Table SIV).

Most patients (95·5%) experienced ≥1 AE on treatment or during the 28-day follow-up period (Table SV). Overall, 77·3% of patients experienced grade 3/4 AEs, with more AEs occurring in the 60 mg/m^2 cohort than in the 30 mg/m^2 cohort. AEs suspected to be study treatment–related were reported in 72·7% of patients.

Efficacy was evaluated in all 22 patients. The rate of best clinical response (assessed per modified Cheson criteria; Appendix S1) to single-agent midostaurin was 55·5% (95% confidence interval [CI], 21·2–86·3%) and 23·1% (95% CI, 5·0–53·8%) in paediatric patients with R/R *FLT3*-mutated AML and *KMT2A*-R ALL, respectively (Fig 1). One patient with *FLT3*-mutated AML achieved a complete remission with incomplete count recovery on day 14; she discontinued midostaurin therapy on day 64 but remained in remission until her last response assessment (day 67), received a haematopoietic stem cell transplant (day 76), and was alive on day 960. In patients with *FLT3*-mutated AML and *KMT2A*-R ALL, median time to response was 14 (range, 8–22) days and 8 (range, 3–8) days, respectively; median overall survival (95% CI) was 3·7 (2·7–8·3) months and 1·4 (1·0–2·9) months, respectively (Figure S3).

This study was the first to evaluate the safety, efficacy, and pharmacokinetics (Appendix S1) of oral midostaurin solution in children. The RDE was set at 60 mg/m^2 bid for the 2 age groups. Single-agent midostaurin showed limited clinical activity in these children with heavily pretreated *FLT3*-mutated AML or *KMT2A*-R ALL. Despite preclinical data suggesting that midostaurin sensitivity in infant *KMT2A*-R ALL overexpressing FLT3 was similar to that in *FLT3*-mutated AML (Stam *et al*, 2007), single-agent midostaurin showed no clinical activity in children with R/R *KMT2A*-R ALL, possibly because overexpression of FLT3 alone is not sufficient to drive the disease or because FLT3 was not inhibited enough at the doses tested to elicit responses. Future studies should aim to understand the kinetics of *FLT3* mutations between diagnosis and relapse, as they present an important prognostic factor for patients with AML. The unmet need in paediatric patients with R/R *FLT3*-mutant AML or *KMT2A*-R ALL is high. Because midostaurin plus chemotherapy demonstrated clinical benefit in adults with

FLT3-mutated AML and single-agent midostaurin was generally well tolerated in paediatric patients, midostaurin will be evaluated in combination with chemotherapy in paediatric patients with *FLT3*-mutated AML.

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Author contributions

This study was designed by the sponsor, Novartis Pharmaceuticals Corporation, and the study steering committee, CMZ, ML, and RP. CMZ, SS, BB, ML, CR, RWS, FF, PAH, C Dufour and RP enrolled patients. EB oversaw the conduct of the study. C Dutreix performed the pharmacokinetic analyses. Data were collected and analysed by the sponsor in conjunction with the authors, who had full access to the data. CMZ and RP wrote the manuscript, with medical writing support from ArticulateScience LLC. All authors contributed to draft revisions and approved the final version of the manuscript.

Disclosure of conflicts of interest

CMZ is a consultant for and has received funding from Novartis Pharmaceuticals Corporation. C Dufour is a consultant for Pfizer and has participated in advisory committees for Novartis Pharmaceuticals Corporation. PAH is a current employee of and has equity ownership in Seattle Genetics. EB and C Dutreix are current or former employees of Novartis Pharmaceuticals Corporation. SS, BB, ML, CR, RWS, FF and RP have no competing interests. Medical editorial assistance with this manuscript was funded by Novartis Pharmaceuticals Corporation.

C. Michel Zwaan[1,2]
Stefan Söderhäll[3,4]
Benoit Brethon[5]
Matteo Luciani[6]
Carmelo Rizzari[7]
Ronald W. Stam[1,8]
Emmanuelle Besse[9]
Catherine Dutreix[9]
Franca Fagioli[10]
Phoenix A. Ho[11]
Carlo Dufour[12]
Rob Pieters[8]

[1]Erasmus MC–Sophia Children's Hospital, Rotterdam, the Netherlands, [2]Innovative Therapies for Children with Cancer European Consortium, Villejuif, France, [3]Karolinska Institutet, [4]Astrid Lindgren Children's Hospital, Stockholm, Sweden, [5]Hôpital Universitaire Robert-Debré, Paris, France, [6]IRCCS Ospedale Pediatrico Bambino Gesù, Rome, [7]Fondazione MBBM, Azienda Ospedaliera San Gerardo, Monza, Italy, [8]Princess Máxima Centre for Paediatric Oncology, Utrecht, the Netherlands, [9]Novartis Pharma AG, Basel, Switzerland, [10]Paediatric Onco-Haematology, Stem Cell Transplantation and Cellular Therapy Division, A.O.U. Città della Salute e della Scienza di Torino, Ospedale Infantile Regina Margherita, Torino, Italy, [11]Seattle Children's Hospital, Seattle, WA, USA and [12]Haematology Unit, IRCCS Istituto Giannina Gaslini, Genova, Italy.
E-mail: c.m.zwaan@erasmusmc.nl

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1. Supplementary Methods; Supplementary Results; Supplementary Discussion

Table SI. Expanded Patient Baseline Characteristics

Table SII. *FLT3* Mutation Status per Central Laboratory Assessment

Table SIII. FLT3 Expression and Phosphorylation Analysis

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

Table SV. Most Common Adverse Events (occurring in ≥10% of patients) With Single-Agent Midostaurin in Paediatric Patients With Relapsed or Refractory Acute Leukaemia

Table SVI. Bioavailability and Safety of Midostaurin Oral Solution and Capsule Formulations in Healthy Volunteers in Study A2108

Table SVII. Modified Cheson Criteria for Response

Fig S1. Trial Design

Fig S2. Patient Disposition
Fig S3. Overall Survival
Fig S4. Pharmacokinetics of Midostaurin and Its Metabolites

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