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ADISINSIGHT REPORT

Midostaurin: First Global Approval

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Abstract Midostaurin (Rydapt®) is a multikinase inhibitor being developed by Novartis Pharmaceuticals. In April 2017, midostaurin was approved in the USA for the treatment of adult patients with newly diagnosed, FMS-like tyrosine kinase 3 (FLT3) mutation-positive acute myeloid leukaemia (AML) [in combination with standard cytarabine and daunorubicin induction, and cytarabine consolidation], or aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated haematological neoplasm (SM-AHN) or mast cell leukaemia (MCL) [collectively known as advanced SM]. The article summarizes the milestones in the development of midostaurin leading to this first global approval.

1 Introduction

Novartis Pharmaceuticals has developed midostaurin (Rydapt®), an orally administered inhibitor of multiple receptor tyrosine kinases (TKs), for the treatment of newly-diagnosed FMS-like tyrosine kinase 3 (FLT3)-mutated acute myeloid leukaemia (AML) [1]. Approximately 30% of adults with AML have FLT3 mutations [most commonly internal tandem duplication (ITD) and less commonly tyrosine kinase domain (TKD) mutations], which are associated with a poor prognosis [2]. Midostaurin was also developed for the treatment of aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated haematological neoplasm (SM-AHN) and mast cell leukaemia (MCL) [collectively known as advanced SM] [1]. Greater than 80% of patients with SM have a D816 KIT mutation, which is associated with resistance against targeted drugs such as imatinib [3]. Until recently, the management of AML and advanced SM mainly involved chemotherapy or cytoreductive therapy and allogeneic haematopoietic stem cell transplantation (alloHSCT) [4, 5]. The need for better medical therapy for AML patients with FLT3 mutations and advanced SM patients has led to the development of multiple kinase inhibitors such as midostaurin [2–4, 6].

In April 2017, midostaurin was approved in the USA for the treatment of adult patients with newly diagnosed, FLT3 mutation-positive AML (in combination with standard cytarabine and daunorubicin induction, and cytarabine consolidation), or ASM, SM-AHN or MCL (i.e. advanced SM) [1, 7, 8]. Patients with newly-diagnosed AML are to be selected for midostaurin treatment based on the presence of an FLT3 mutation as detected by an FDA-approved test [1], and the LeukoStrat® companion diagnostic test (CDx) FLT3 Mutation Assay (Sect. 2.5) is an FDA-approved diagnostic test for that purpose [9].

The recommended dosage of oral midostaurin in adults with newly-diagnosed FLT3-mutated AML is 50 mg twice daily with food on days 8–21 of each cycle of cytarabine and daunorubicin induction therapy and on days 8–21 of each cycle of high-dose cytarabine consolidation therapy [1]. The recommended dosage in adults with ASM, SM-AHN or MCL is 100 mg twice daily with food until disease progression or unacceptable toxicity. Anti-emetics are recommended prophylactically prior to midostaurin treatment to lower the risk of nausea and vomiting [1].

This profile has been extracted and modified from the *AdisInsight* database. *AdisInsight* tracks drug development worldwide through the entire development process, from discovery, through pre-clinical and clinical studies to market launch and beyond.

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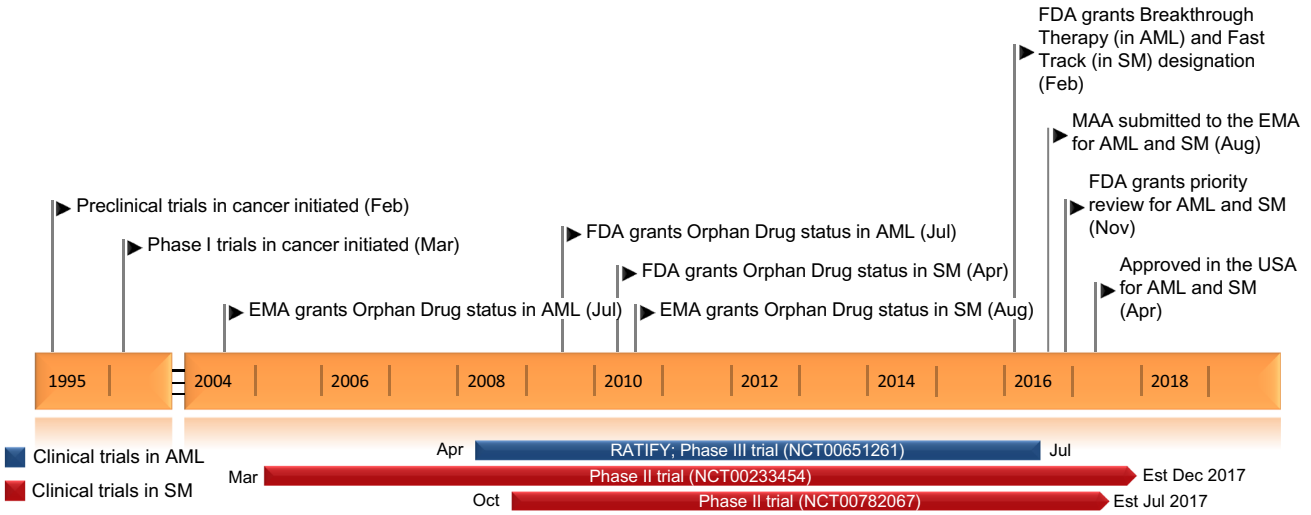


Key development milestones for midostaurin in acute myeloid leukaemia and advanced systemic mastocytosis. *AML* acute myeloid leukaemia, *EMA* European Medicines Agency, *MAA* Marketing Authorisation Application, *SM* systemic mastocytosis

The marketing authorization application for midostaurin is under regulatory review in the EU for AML and advanced SM, under phase 3 development in Australia, Brazil and Canada for AML and under phase 2 development in Australia, Canada and Turkey for SM [10]. Development of midostaurin in acute lymphoblastic leukaemia, colorectal cancer, diabetic macular oedema, gastrointestinal (GI) stromal tumours, multiple myeloma and non-Hodgkin's lymphoma appears to have been discontinued [10].

1.1 Patent Information

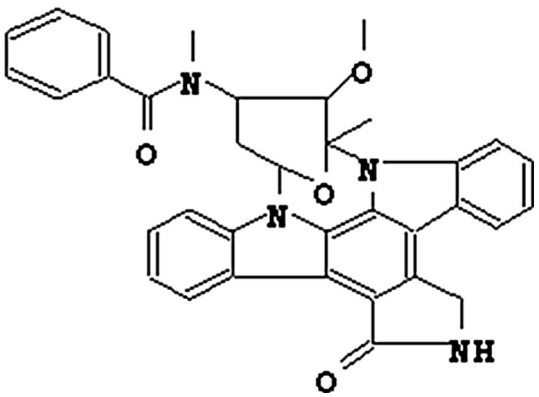
Midostaurin has method of use patents in Europe, Japan and the USA that are valid until 2024, 2024 and 2030, respectively [10]. Formulation patents in the EU and Japan expire in 2020 [10].

2 Scientific Summary

2.1 Pharmacodynamics

Midostaurin is an inhibitor of multiple receptor TKs [1]. In vitro, it has been shown that midostaurin or its major active metabolites (CGP52421 or CGP62221) inhibit the activity of FLT3 (wild type, and ITD and TKD mutants), KIT (wild type and the D816V mutant), PDGFRα/β, VEGFR2 and members of the serine/threonine kinase protein kinase C family [1, 11]. Midostaurin has the ability to inhibit FLT3 receptor signalling as well as cell proliferation, and it can induce apoptosis in leukaemic cells overexpressing wild-type FLT3 and PDGF receptors or expressing ITD and TKD mutant FLT3 receptors [1, 11]. In addition, midostaurin can inhibit KIT signalling, and neoplastic MC proliferation, histamine release and survival [1, 12].

In a study of healthy volunteers, treatment with midostaurin 75 mg twice daily for 3 days was not associated with clinically relevant effects on QT prolongation or changes in QTc dependent on concentrations of midostaurin, CGP52421 or CGP62221 [1, 13]. In a study of patients with AML, a higher percentage of midostaurin recipients than placebo recipients experienced QTc prolongation (10.1% of midostaurin recipients vs. 5.7% of placebo recipients had QTcF >480 ms, 6.2 vs. 2.6% had QTcF >500 ms, and 18.4 vs. 10.7% had QTcF >60 ms) [1]. Pooled data from studies in patients with advanced SM who received midostaurin treatment showed 4.7% of patients with QTcF >480 ms, 0% of patients with QTcF >500 ms and 6.3% of patients with QTcF >60 ms compared with baseline [1]. QT interval assessments are recommended when midostaurin is taken concomitantly with medications that can prolong the QT interval [1].



Chemical structure of midostaurin

2.2 Pharmacokinetics

Midostaurin displays time-dependent pharmacokinetics (PK), with minimum plasma concentrations (C_{min}) highest during the first week and declining after ≈28 days to steady-state [1]. CGP2221 exhibits a similar PK profile, and CGP52421 plasma concentrations continue to increase following 1 month of treatment [1].

Midostaurin is rapidly absorbed, reaching peak plasma concentrations (C_{max}) in 1–3 h following administration in a fasted state [1]. Administering midostaurin with a standard meal or a high-fat meal lowers C_{max} by 20 and 27%, delays time to C_{max} by a median of 2.5–3 h, and increases exposure by 1.2- and 1.6-fold compared with administration in a fasted state. Midostaurin has an estimated volume of distribution of 95.2 L (geometric mean). In vitro, midostaurin, CGP52421 and CGP62221 are distributed mainly in plasma and highly (>99.8%) protein bound. Midostaurin is metabolized primarily by CYP3A4, and CGP52421 and CGP62221 are the major metabolites. The terminal half-lives (geometric means) of midostaurin, CGP52421 and CGP62221 are 21, 482 and 32 h, respectively. Midostaurin is excreted mainly in the faeces (95% of the recovered dose), with urinary excretion accounting for 5% of the recovered dose, and mostly (91% of the recovered dose) as metabolites, with unchanged midostaurin accounting for 4% of the recovered dose [1].

2.3 Therapeutic Trials

2.3.1 Acute Myeloid Leukaemia

Midostaurin plus standard induction and consolidation chemotherapy significantly prolonged overall survival (OS) compared with standard induction and consolidation chemotherapy alone in adults with newly diagnosed FLT3-mutated AML in the randomized, double-blind, placebo-controlled, multinational, phase 3, RATIFY trial (NCT00651261) [14]. After a minimum follow-up of 3.5 years (primary analysis), the median OS was significantly longer with midostaurin treatment than with placebo (74.7 vs. 26.0 months; HR 0.77; 95% CI 0.63–0.95; $p = 0.016$) [1, 14]. In addition, the median duration of event-free survival [defined as not achieving complete remission (CR) within 60 days of starting induction therapy or experiencing a relapse or death] was significantly longer with midostaurin than with placebo (8.2 vs. 3.0 months; HR 0.78; 95% CI 0.66–0.93; $p = 0.005$) [1]. These results were consistent across FLT3 subgroups/stratifications (i.e. TKD, high allelic mutation fraction ITD, low allelic mutation fraction ITD) [14].

The RATIFY trial enrolled adults (median age 47 years; range 18–60 years) with newly diagnosed AML that tested positive for an FLT3 mutation, as determined prospectively using a clinical trial assay and confirmed retrospectively

Features and properties of midostaurin

Alternative names	Rydapt®; PKC412; PKC412A; CGP41251; benzoylstaurosporine; 4-*N*-benzoyl staurosporine; *N*-benzoyl-staurosporine
Class	Antineoplastics; carbazoles; indole alkaloids; small molecules; eye disorder therapies; skin disorder therapies
Mechanism of action	Multikinase inhibitor
Route of administration	Oral
Pharmacodynamics	Activity against FLT3 (wild type, and ITD and TKD mutants), KIT (wild type and the D816V mutant) and several other receptors
Pharmacokinetics	Time-dependent PK; C_{max} 1–3 h; standard or high-fat meal ↓C_{max}, ↑T_{max} and ↑ exposure compared with administration in a fasted state
Adverse events	
Most frequent (AML)	Febrile neutropenia, nausea, vomiting, mucositis, headache, petechiae, musculoskeletal pain, epistaxis, device-related infection, hyperglycaemia, upper respiratory tract infection (URTI)
Most frequent (advanced SM)	Nausea, vomiting, diarrhoea, oedema, musculoskeletal pain, abdominal pain, fatigue, URTI, constipation, pyrexia, headache, dyspnoea
ATC codes	
WHO ATC code	L01X-E39; S01 (ophthalmologicals)
EphMRA ATC code	L1X9 (all other antineoplastics); S1 (ophthalmologicals)
Chemical name	*N*-[(2S,3R,4R,6R)-3-methoxy-2-methyl-16-oxo-29-oxa-1,7,17-triazaoctacyclo[12.12.2.12,6.07,28.08,13.015,19.020,27.021,26]nonacosa-8,10,12,14,19,21,23,25,27-nonaen-4-yl]-*N*-methylbenzamide

using the LeukoStrat® CDx FLT3 mutation assay [1]. Patients were randomized to receive oral midostaurin 50 mg ($n = 360$) or placebo ($n = 357$) twice daily with food on days 8–21 of each cycle of induction therapy (intravenous cytarabine 200 mg/m^2 daily on days 1–7 and intravenous daunorubicin 60 mg/m^2 daily on days 1–3) for up to two cycles, and on days 8–21 of each cycle of consolidation therapy (intravenous cytarabine 3 g/m^2 every 12 h on days 1, 3 and 5) for up to four cycles, followed by maintenance therapy with continued midostaurin or placebo for up to a year (i.e. up to 12 additional 28-day cycles) [1, 14]. Patients were permitted to stop treatment and proceed to haematopoietic stem cell transplantation [1, 14].

A phase 1b trial (NCT00093600) [15] provided the basis for the RATIFY trial. The published analysis of NCT00093600 focused on adults with newly diagnosed, mutated or wild-type FLT3 AML who received oral midostaurin 50 mg twice daily ($n = 40$) either concomitantly with (on days 1–7 and 14–21) or sequentially after (on days 8–21) induction therapy with intravenous cytarabine (200 mg/m^2 on days 1–7) and daunorubicin (60 mg/m^2 on days 1–3) [28-day cycles] [15]. Overall, treatment with midostaurin 50 mg twice daily in combination with standard chemotherapy was associated with a high rate of complete response (80% of patients); this included 92% of patients with mutated FLT3 and 74% of patients with wild-type FLT3. Although there were patients who received oral midostaurin 100 mg twice daily ($n = 29$), the higher dosage was associated with grade 3 or 4 nausea and vomiting as well as a high rate of treatment discontinuation (in 79% of patients), and dose schedules involving midostaurin 100 mg twice daily were discontinued [15].

Of note, the clinical activity of midostaurin in adults with FLT3 mutation-positive AML was initially explored in single agent phase 2 trials [a proof-of-concept phase 2 trial [16] and a randomized, open-label, phase 2b trial (NCT00045942) [17] that expanded on the results of the proof-of-concept trial]. Limited clinical activity in these trials (reduction in peripheral blood or bone marrow blasts but rare complete or partial responses) supported studies of midostaurin in combination with other agents such as chemotherapy [16, 17].

In the proof-of-concept trial, adults with advanced AML (relapsed or refractory, or not eligible for induction chemotherapy) or high-grade myelodysplastic syndrome (MDS) who tested positive for an FLT3 mutation (D835Y activating loop or ITD) [$n = 20$] received oral midostaurin 75 mg three times daily until disease progression or unacceptable toxicity [16]. The majority (70%) of patients achieved a >50% reduction in peripheral blast count from baseline. Among these 14 patients, 7 patients had what was considered a significant clinical benefit (a ≥2-log reduction from baseline in peripheral blast count that lasted for ≥4 weeks). In addition, 6 of 20 patients achieved a >50% reduction from baseline in bone marrow blast counts. No patients achieved a complete response, and one patient achieved a partial response [16].

In NCT00045942, adults with AML (relapsed or refractory, or not eligible for standard chemotherapy) or high-risk MDS, with either mutated ($n = 35$) or wild-type ($n = 60$) FLT3, received oral midostaurin 50 or 100 mg twice daily until disease progression, unacceptable toxicity, or no response at 2 months [17]. Among evaluable patients ($n = 92$), 71% of patients with mutated FLT3 and 42% of patients with wild-type FLT3 had achieved a ≥50% reduction in peripheral blood or bone marrow blasts. Of note, this response was seen in 69% (22 of 32) of previously treated patients and 100% (3 of 3) of previously untreated patients in the mutated FLT3 group, and the response was consistent irrespective of dose or type of FLT3 mutation (ITD or D835Y). No patients achieved a complete response, and one patient in the mutated FLT3 group receiving midostaurin 100 mg achieved a partial response [17].

The clinical activity of midostaurin in reducing the risk of relapse in adults with FLT3-ITD-mutated AML following alloHSCT is being explored in two phase 2 trials [the open-label AMLSG 16-10 trial (NCT01477606) [18] and the randomized, open-label RADIUS trial (NCT01883362) [19]].

In AMLSG 16-10, adults with newly diagnosed FLT3-ITD-mutated AML received oral midostaurin 50 mg twice daily (from day 8 to 48 h prior to the next cycle) in combination with cytarabine and daunorubicin induction therapy (intravenous cytarabine 200 mg/m^2 daily on days 1–7 and intravenous daunorubicin 60 mg/m^2 daily on days 1–3) for up to two cycles, and as maintenance therapy for 1 year following either alloHSCT (first priority) or three cycles of consolidation therapy consisting of midostaurin (from day 6 to 48 h prior to the next cycle) and age-adapted high-dose cytarabine [intravenous cytarabine 1 g/m^2 (patients aged >65 years) or 3 g/m^2 (patients aged 18–65 years) every 12 h on days 1, 3 and 5] [18, 20]. Results are available for patients from the first cohort of the trial ($n = 149$). The incidence of relapse was low regardless of whether the FLT3-ITD-mutant to wild-type ratio was high (≥0.5) or low (<0.5) in patients who underwent alloHSCT (5 and 12% of patients) or midostaurin and high-dose cytarabine consolidation therapy (29 and 28%) [18].

In RADIUS, adults with FLT3-mutated AML who had undergone alloHSCT and achieved first complete remission received midostaurin 50 mg twice daily and standard of care (SOC; dictated by the treating physician) or SOC alone continuously for up to 12 months [19]. Efficacy data from this trial are not yet available (expected sometime this year) [19].

The clinical activity of midostaurin in combination with agents other than cytarabine and daunorubicin in newly diagnosed or previously treated AML is being explored in

several trials (Sect. 2.6), including a phase 1/2 trial looking at the combination of midostaurin and azacitadine (NCT01093573 [21]). Completed trials include another phase 1/2 trial examining the combined use of midostaurin and azacitadine (NCT01202877) [22], and a phase 1 trial examining the combined use of midostaurin and decitabine (NCT01130662) [23].

In NCT01093573 ($n = 17$), elderly patients (aged ≥70 years) with previously untreated AML and patients of any age with relapsed/refractory AML or disease not suitable for standard induction received intravenous azacitadine 75 mg/m^2 on days 1–7 and oral midostaurin twice daily (escalating doses of 25, 50 or 75 mg) on days 8–21 of each 28-day cycle [21]. Of note, no patients had FLT3 mutations. Of 14 evaluable patients, three patients had a CR, and two patients had haematological improvement [21].

In NCT01202877 ($n = 54$), adults with untreated or relapsed AML or MDS regardless of FLT3 mutational status received intravenous or subcutaneous azacitadine 75 mg/m^2 on days 1–7 of each 28-day cycle and oral midostaurin 25 mg (phase 1 for cohort 1) or 50 mg (phase 1 for cohort 2, and phase 2) twice daily on days 8–21 during the first cycle and continuously thereafter [22]. After a median duration of 12 weeks, the overall response rate (ORR) was 26% (CR in 2% of patients, CR with incomplete bone marrow recovery in 11% of patients, morphologic leukaemia-free status in 11% of patients and a partial remission in 2% of patients) [22].

In NCT01130662 ($n = 16$), patients aged ≥60 years with newly diagnosed AML not suitable for standard induction and adults with relapsed/refractory AML received intravenous decitabine 20 mg/m^2 on days 1–5 (all cohorts) and oral midostaurin 25 mg twice daily on days 8–21 (cohort 1), 50 mg twice daily on days 8–21 (cohort 2) or 50 mg twice daily on days 1–28 of each 28-day cycle (cohort 3) [23]. Two patients had FLT3-ITD mutations. The ORR was 25% (CR or CR with incomplete platelet recovery were achieved in two patients in cohort 1 and two patients in cohort 2, three of whom achieved the response after completing one cycle) [23].

2.3.2 *Advanced Systemic Mastocytosis*

The efficacy of midostaurin in the treatment of adults with advanced SM was demonstrated in an open-label, multinational, phase 2 trial (NCT00782067) [24]. At a median duration of follow-up of 26 months (range 12–54 months), the ORR in patients with mastocytosis-related organ damage (i.e. clinical findings associated with organ damage from infiltrating mast cells, referred to as C-findings) [$n = 89$; primary efficacy population] was 60% (95% CI 49–70; $p < 0.001$). The ORR consisted of patients whose best overall response (according to modified Valent criteria) was a major response (45% of patients; complete resolution of at least one C-finding) or a partial response [15% of patients; good partial (>50%) or minor partial (>20 to ≤50%) improvement of at least one C-finding] starting in the first six 4-week treatment cycles and lasting for ≥ 8 weeks [24]. Among patients with a major response, although no patients achieved a CR, 38% of patients with ASM, 16% of patients with SM-AHN and 25% of patients with MCL achieved an incomplete remission by an overall median duration of 0.5 months [1, 24]. The ORR was similar irrespective of advanced SM subtype, KIT D816V mutation status or history of prior therapy [24]. Among patients who had a response, the median duration of response (DOR) was 24.1 months (95% CI 10.8–not estimated) [24].

In NCT00782067, patients in the primary efficacy population had a median OS of 28.7 months (95% CI 18.1–not estimated) and a median progression-free survival of 14.1 months [24]. Patients in this population with MCL, the most fatal variant of advanced SM, had a median OS of 9.4 months. In most patients, serum tryptase levels and bone marrow mast-cell burden decreased by >50% [the median best percentage change was −58% for serum tryptase levels (among patients in the primary efficacy population) and −59% for bone marrow mast-cell burden (among 72 patients who had baseline and ≥1 post-baseline evaluations)]. In addition, midostaurin treatment was associated with reduced splenomegaly (among 39 patients who had splenomegaly at baseline, 77% of patients had a reduction in spleen volume, with 26% of patients having a reduction of ≥35%) and improvements in quality of life (30 of 32 symptoms on the Memorial Symptom Assessment Scale had decreased in frequency at the time of best reported total score) [24].

NCT00782067 enrolled adults with a diagnosis of ASM, SM-AHN or MCL [24]. Patients ($n = 116$) received oral midostaurin 100 mg twice daily in 4-week continuous cycles until disease progression, unacceptable toxicity, withdrawal of consent or death. Concomitant antineoplastic treatment was not allowed. Patients eligible for inclusion in the primary efficacy population had at least one measurable C-finding associated with organ damage from infiltrating mast cells (e.g. cytopenias, hypoalbuminemia, liver-function abnormalities, weight loss). At baseline, in the primary efficacy population, the median age was 64 years (range 25–82 years), the majority of patients did not have prior treatment (58% of patients with none vs. 24% with one, 13% with two and 4% with three or more previous therapies) and patients had a KIT D816 mutation status of positive (87% of patients; 73 patients with D816V, three with D816Y and one with D816L), negative (11%) or unknown (2%) [24].

Key clinical trials of midostaurin

Drug(s)	Indication	Phase	Status	Location(s)	Identifier(s)	Sponsor(s)
In AML						
Midostaurin + decitabine	Newly diagnosed or relapsed/refractory AML	1	Completed	USA	NCT01130662	University of Kansas, Novartis
Midostaurin + LGH447, LGH447	Previously untreated or refractory/relapsed AML	1	Recruiting	Multinational	NCT02078609	Novartis Pharmaceuticals
Midostuarin + RAD001	Relapsed, refractory or poor prognosis AML or MDS	1	Ongoing	USA	NCT00819546	Dana-Farber Cancer Institute, Beth Israel Deaconess Medical Center, Massachusetts General Hospital, Brigham and Women's Hospital, Novartis Pharmaceuticals
Midostaurin, daunorubicin, cytarabine	Newly diagnosed, mutated or wild-type FLT3 AML	1b	Completed	USA, Germany	NCT00093600; CPKC412A2106	Novartis Pharmaceuticals
Midostaurin + azacitadine	Untreated or previously treated AML or high-risk MDS, irrespective of FLT3 mutational status	1/2	Completed	USA	NCT01202877	M. D. Anderson Cancer Center, Novartis Pharmaceuticals, Celgene Corporation
Midostaurin + azacitadine	Untreated or relapsed/refractory AML	1/2	Ongoing	USA	NCT01093573	NCI, Case Comprehensive Cancer Center
Midostaurin	AML or high-grade MDS positive for an FLT3 mutation	2	Completed	USA	NA	Dana-Farber Cancer Institute, Memorial Sloan Kettering Cancer Center, MD Anderson Cancer Center, Novartis Pharmaceuticals
Midostaurin	AML or MDS with either wild type or mutated FLT3	2b	Completed	USA	NCT00045942; CPKC412A2104	Novartis Pharmaceuticals, Dana-Farber Cancer Institute, Memorial Sloan Kettering Cancer Center, Weill Medical College of Cornell University, University of California – Los Angeles
Midostaurin + standard primary therapy	c-KIT or FLT3-ITD mutated t(8;21) AML	2	Recruiting	Germany	MIDOKIT; TUD-MIDOKI-052; NCT01830361	Technische Universität Dresden, Novartis Pharmaceuticals
Midostaurin + cytarabine and daunorubicin	AML and FLT3-ITD after alloHSCT	2	Recruiting	Austria, Germany	AMLSG 16-10; NCT01477606	University of Ulm, Novartis Pharmaceuticals
SOC ± midostaurin	To prevent relapse in FLT3-ITD mutated AML patients following an alloHSCT	2	Recruiting	USA, Canada	RADIUS; NCT01883362; CPKC412AUS23	Novartis Pharmaceuticals
Induction (daunorubicin, cytarabine) and consolidation (high-dose cytarabine) + midostaurin or placebo	Newly diagnosed, FLT3 mutation-positive AML	3	Completed	USA, Canada	RATIFY; NCT00651261; CALGB-10603	Alliance for Clinical Trials in Oncology, NCI, Novartis Pharmaceuticals
In advanced SM						
Midostaurin	Advanced SM	2	Ongoing	USA	NCT00233454	Novartis Pharmaceuticals, Stanford University
Midostaurin	ASM, SM-AHN or MCL	2	Ongoing	Multinational	NCT00782067; CPKC412D2201	Novartis Pharmaceuticals
Midostaurin	Indolent SM	2	Completed	Netherlands	NCT01920204	University Medical Center Groningen

AML acute myeloid leukaemia, *ASM* aggressive systemic mastocytosis, *MCL* mast cell leukaemia, *MDS* myelodysplastic syndrome, *NA* not available, *NCI* National Cancer Institute, *SOC* standard of care, *alloHSCT* allogeneic haematopoietic stem cell transplant, *SM* systemic mastocytosis, *SM-AHN* systemic mastocytosis with associated haematological neoplasm

The efficacy of midostaurin in the treatment of patients with advanced SM was also demonstrated in a smaller ($n = 26$), open-label, multicentre, phase 2 trial (NCT00233454) [1]. The trial enrolled adults (median age 64 years; range 24–79 years) with advanced SM [1, 20, 25]. Patients received oral midostaurin 100 mg twice daily with food in continuous 4-week cycles until progression or unacceptable toxicity [1, 25]. A response (according to Valent criteria) starting by two cycles and lasting for ≥8 weeks was achieved in 10 of 17 patients with SM-AHN (nine major and one partial) and two of six patients with MCL (one major and one partial) [1]. At the time of follow-up, the median DOR had not been reached for the SM-AHN group (at least 3.4–79.2 months) or the MCL group (at least 28.6–32.1 months). Of note, the three remaining patients had unconfirmed SM subtypes [1].

The clinical activity of midostaurin was also examined in patients with indolent SM. In a single-centre, phase 2 trial (NCT01920204), midostaurin treatment reduced symptom severity, decreased tryptase levels and improved disease-related quality of life in patients with indolent SM [26]. The trial enrolled adults ($n = 20$) with KITD816V-positive indolent SM who had severe refractory symptoms and elevated tryptase levels. Patients received oral midostaurin 100 mg twice daily for 24 weeks and had the option to continue treatment after a 2-month wash-out period. At week 12, 80% of patients had a significant median reduction from baseline in symptom severity as measured by the Mastocytosis Symptom Assessment Form sumscore (−35%; $p = 0.002$). Of note, the mean reduction from baseline in symptom severity was 38% at week 24. In addition, disease-related quality of life improved 25% (median) from baseline to week 24 ($p = 0.001$). All patients showed significantly ($p < 0.001$) decreased tryptase levels after 4 weeks (15.5 μg/L) compared with baseline levels (36.0 μg/L), and levels persisted and remained stable throughout the trial in the majority of patients. Among 16 bone marrow biopsies that were histologically assessable at week 24, eight showed a reduction, two showed an increase and six showed no change in mast cell infiltration. Following treatment cessation at week 24, symptoms relapsed rapidly in 16 patients, as demonstrated by increased tryptase levels. The majority (10/16) of these patients strongly favoured restarting midostaurin treatment [26].

2.4 Adverse Events

In patients with newly diagnosed FLT3-mutated AML receiving midostaurin in combination with chemotherapy in RATIFY, the most common adverse events (AEs) [occurring in ≥20% of patients and in ≥2% more midostaurin recipients than placebo recipients] were febrile neutropenia (83% of midostaurin recipients vs. 81% of placebo recipients), nausea (83 vs. 70%), vomiting (61 vs. 53%), mucositis (66 vs. 62%), headache (46 vs. 38%), petechiae (36 vs. 27%), musculoskeletal pain (33 vs. 31%), epistaxis (28 vs. 24%), device-related infection (24 vs. 17%), hyperglycaemia (20 vs. 17%) and upper respiratory tract infection (URTI; 20 vs. 15%) [1]. In midostaurin recipients, the most common grade 3 or 4 AEs (incidence ≥10% of patients) were device-related infection, mucositis and febrile neutropenia, and the most common serious AE was febrile neutropenia (16% of patients) [also occurred in 16% of placebo recipients] [1]. The rates of grade ≥3 haematological and non-haematological AEs were not significantly different between midostaurin recipients and placebo recipients [27]. AEs led to treatment discontinuation in 9% of midostaurin recipients and 6% of placebo recipients, and there were no fatal AEs other than those related to disease progression [1].

In a pooled analysis ($n = 142$) of patients with ASM, SM-AHN or MCL who received midostaurin as a single agent in NCT00782067 and NCT00233454, the most common AEs (incidence ≥20% of patients; excluding laboratory abnormalities) were nausea (82%), vomiting (68%), diarrhoea (54%), oedema (40%), musculoskeletal pain (35%), abdominal pain (34%), fatigue (34%), URTI (30%), constipation (29%), pyrexia (27%), headache (26%) and dyspnoea (23%) [1]. The most common grade ≥3 AEs (incidence >5%; excluding laboratory abnormalities) were abdominal pain, diarrhoea, dyspnoea, fatigue, febrile neutropenia, GI haemorrhage, nausea, oedema, pneumonia, renal insufficiency, sepsis and vomiting, and the most common (incidence ≥20%) serious AEs were due to GI disorders, or infections. There were many (five haematological and 17 non-haematological) new or worsening laboratory abnormalities occurring in ≥20% of patients, among which haematological abnormalities (lymphopenia, anaemia, thrombocytopenia and neutropenia) were the most common (>20%) grade ≥3 events. AEs led to treatment discontinuation in 21% of patients. Deaths unrelated to the underlying disease occurred in 11% of patients while on treatment [1].

2.5 Companion Diagnostic

In February 2011, Novartis and Invivoscribe entered into a collaborative agreement to develop and commercialize a CDx to identify patients with FLT3-positive AML and be used in connection with midostaurin [28]. Under the agreement, Invivoscribe developed the LeukoStrat® CDx FLT3 Mutation Assay, which detects ITD mutations and D835 and I836 TKD mutations in the FLT3 gene in mononuclear cell DNA obtained from bone marrow aspirates or the peripheral blood of patients diagnosed with

AML [9, 29]. Of note, Invivoscribe received an exclusive license from Takara Bio to use and sublicense a patent on Takara's FLT3 gene mutation detection method worldwide, with the exception of Japan [30]. The LeukoStrat CDx FLT3 Mutation Assay was approved by the FDA in April 2017 to be used as an aid in the selection of AML patients for whom treatment with midostaurin is being considered [7, 9].

2.6 Ongoing Clinical Trials

NCT00782067 and NCT00233454 (Sect. 2.3.2), two phase 2 trials on which the approval of midostaurin in advanced SM in the USA is based, have estimated completion dates of July 2017 and December 2017, respectively.

AMLSG 16-10 (NCT01477606) and RADIUS (NCT01883362) [Sect. 2.3.1], two phase 2 trials examining the clinical activity of midostaurin in reducing the risk of relapse in adults with FLT3-ITD-mutated AML following alloHSCT, have estimated completion dates of December 2019 and July 2017, respectively.

Several trials are underway to evaluate midostaurin in combination with agents other than cytarabine and daunorubicin in AML. A phase 1 trial will evaluate midostaurin plus LGH447 in adults with previously untreated or refractory/relapsed AML (NCT02078609; recruiting), a phase 1 trial will evaluate midostaurin plus RAD001 in adults with relapsed, refractory or poor prognosis AML or MDS (NCT00819546; ongoing), a phase 1/2 trial will evaluate midostaurin plus azacitadine in patients with untreated or relapsed/refractory AML (NCT01093573; ongoing), and a phase 1/2 trial (NCT01846624; ongoing) and a phase 2 trial (NCT02634827; recruiting) will evaluate midostaurin plus decitabine in older patients (aged ≥60 years) with newly diagnosed, FLT3-mutated AML. In addition, a phase 2 trial is underway to evaluate the efficacy of midostaurin plus standard primary therapy in patients with newly diagnosed c-KIT or FLT3-mutated t(8;21) AML (NCT01830361; MIDOKIT; recruiting). A phase 2 extension trial (NCT02723435) is planned in patients aged ≥60 years who have completed NCT01846624, and a phase 2/3 trial is planned (NCT03092674) to evaluate midostaurin plus azacitadine in older patients (aged ≥60 years) with previously untreated AML or MDS.

3 Current Status

Midostaurin received its first global approval on 28 April 2017 in the USA for the treatment of adults with newly diagnosed, FLT3 mutation-positive AML, in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation, and ASM, SM-AHN and MCL (collectively known as advanced SM).

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Additional information about this Adis Drug Review can be found at http://www.medengine.com/Redeem/3798F060608AFA9C.

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