




European Medicines Agency review of midostaurin (Rydapt) for the treatment of adult patients with acute myeloid leukaemia and systemic mastocytosis

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ABSTRACT

On 18 September 2017, a marketing authorisation valid through the European Union (EU) was issued for midostaurin in combination with standard daunorubicin and cytarabine induction and high-dose cytarabine consolidation chemotherapy and for patients in complete response followed by midostaurin single agent maintenance therapy, for adult patients with newly diagnosed acute myeloid leukaemia (AML) who are Fms-like tyrosine kinase 3 mutation positive and as monotherapy for the treatment of adult patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated haematological neoplasm (SM-AHN) or mast cell leukaemia (MCL). The recommended dose of midostaurin is 50 mg orally twice daily for AML and 100 mg orally twice daily for ASM, SM-AHN and MCL. Midostaurin was evaluated in two pivotal studies. Study A2301 (RATIFY) included 717 patients with AML. Overall survival (OS) was statistically significantly different between the two groups, and the median OS was 74.7 months in the midostaurin+daunorubicin+cytarabine group and 25.6 months in the placebo+daunorubicin+cytarabine group (HR 0.774; 95% CI 0.629 to 0.953; p=0.0078). Study D2201 included 116 patients with ASM, SM-AHN or MCL. An overall response rate, by IWG-MRT/ECNM (international working group – myelofibrosis research and treatment/European competence network on mastocytosis) criteria of 28.3% was observed in all patients and 60.0%, 20.8% and 33.3% in patients with ASM, SM-AHN and MCL respectively. The most common adverse drug reactions (ADRs) with midostaurin treatment in AML were febrile neutropenia, nausea, exfoliative dermatitis, vomiting, headache, petechiae and fever. In ASM, SM-AHN, MCL the most common ADRs were nausea, vomiting, diarrhoea, peripheral oedema and fatigue. The objective of this paper is to summarise the scientific review of the application leading to regulatory approval in the EU.

INTRODUCTION

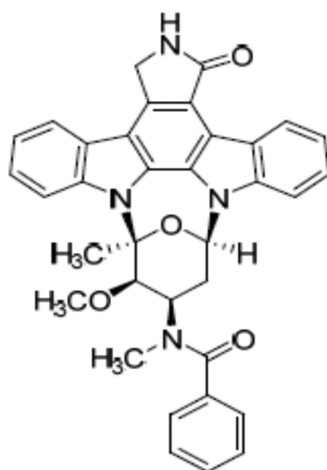
Midostaurin is a multitarget receptor tyrosine kinase inhibitor ([figure 1](#)). Midostaurin inhibits Fms-like tyrosine kinase 3 (FLT3) receptor signalling and induces cell cycle

arrest and apoptosis in leukaemic cells expressing FLT3 internal tandem duplications (ITDs) or tyrosine kinase domain (TKD) mutant receptors or overexpressing FLT3 wild type receptors. In vitro data indicated that midostaurin inhibits D816V mutant KIT receptors at exposure levels achieved in patients (average achieved exposure higher than IC50). Midostaurin interferes with aberrant KIT D816V-mediated signalling and inhibits mast cell proliferation, survival and histamine release.

The objective of this paper is to summarise the scientific review of the application leading to regulatory approval in the EU. The full scientific assessment report and product information, including the Summary of Product Characteristics, are available on the European Medicines Agency (EMA) website (<https://www.ema.europa.eu/en/medicines>).

Background acute myeloid leukaemia (AML)

AML is the most common type of acute leukaemia in adults. AML is a very heterogeneous disease with the presence of acquired mutations as well as cytogenetic and epigenetic alterations that influence disease prognosis. Among the prognostic molecular alterations, one of the most important factors is the presence of FLT3 gene mutations, which occur in approximately 30% of adult patients with AML and have a substantial negative impact on prognosis.¹ In patients with FLT3 mutated AML, the complete remission (CR) rate with standard first-line induction chemotherapy regimens is generally equivalent to that of patients without FLT3 mutations (78% vs 82%). However, the median time to relapse, disease-free survival, event-free survival (EFS) and overall survival (OS) at 5



Molecular formula: C₃₅H₃₀N₄O₄

Relative molecular mass: 570.65 g/mol

The chemical name of midostaurin is: N-[(2S,3R,4R,6R)-3-methoxy-2-methyl-16-oxo-29-oxa-1,7,17-triaza-octacyclo [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

Figure 1 Molecular structure of midostaurin.

years are significantly worse.^{2–5} On average, the median time to relapse for FLT3-mutated AML patients <60 years of age in first remission is estimated at approximately 9 months, compared with approximately 27 months for FLT3 wild type AML patients <60 years of age.^{4,6,7}

In the European Union (EU), recently approved agents for the treatment of AML include decitabine (Dacogen), which is authorised for the treatment of adult patients with newly diagnosed de novo or secondary AML, according to the WHO classification, who are not candidates for standard induction chemotherapy. Azacitidine (Vidaza) is also authorised for the treatment of adult patients who are not eligible for haematopoietic stem cell transplantation (SCT) with: intermediate-2 and high-risk myelodysplastic syndromes according to the International Prognostic Scoring System; chronic myelomonocytic leukaemia with 10%–29% marrow blasts without myeloproliferative disorder; AML with 20%–30% blasts and multilineage dysplasia, according to WHO classification; and AML with >30% marrow blasts according to the WHO classification. Finally, histamine dihydrochloride (Ceplene) is authorised for adult patients with AML in first remission concomitantly treated with interleukin-2 (IL-2). However, at the time of the marketing authorisation of midostaurin in the EU, there were no approved standard therapies specifically for newly diagnosed AML adult patients with FLT3 mutation.

Background mastocytosis

Mastocytosis is a heterogeneous myeloproliferative disorder characterised by the abnormal growth and accumulation of morphologically and immunophenotypically

abnormal mast cells in one or more organs. The disease can be limited to the skin (cutaneous mastocytosis) or involve extracutaneous tissues (systemic mastocytosis). There are different types of systemic mastocytosis including aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated haematological neoplasm (SM-AHN) and mast cell leukaemia (MCL). The incidence of ASM ranges between 0.01 and 0.03 cases per 100 000 person-years, and its prevalence is between 0.1 and 0.3 cases per 100 000. The incidence rate of MCL is 0.01 per 100 000 per year.⁸ ASM is associated with a poor prognosis, with a median OS of 3.5 years in patients with ASM, 2 years in those with an AHN (SM-AHN) and less than 6 months in those with MCL.⁹ Within the subgroup of patients with SM-AHN, prognosis differs depending on the type of associated haematological neoplasm present.¹⁰

Patients with ASM, SM-AHN or MCL have limited treatment options.⁹ At the time of the marketing authorisation of Rydapt, there were no approved standard therapies in the EU for ASM or MCL, but there were different therapies available that were commonly used in clinical practice.^{11,12}

ACUTE MYELOID LEUKAEMIA

Clinical efficacy

The pivotal efficacy study was the RATIFY (study A2301), a phase III, randomised, double-blind study of induction (daunorubicin/cytarabine) and consolidation (high-dose cytarabine) chemotherapy combined with midostaurin or placebo and followed by maintenance therapy (midostaurin or placebo) in newly diagnosed patients <60 years of age with FLT3-mutated AML.¹³

The study included patients younger than 60 years of age with newly diagnosed FLT3-mutation positive AML (ITD or TKD mutation) according to WHO criteria. FLT3 positivity was defined as a 5% or higher percentage of measured mutant FLT3 alleles in a wild type background. Patients who had developed therapy-related AML after prior radiotherapy or chemotherapy for another cancer or disorder were excluded from the study.

The study treatment was 200 mg/m²/day cytarabine (days 1–7) and 60 mg/m²/day daunorubicin (days 1–3) and 50 mg twice daily midostaurin or placebo (days 8–21) during the induction phase. Patients who achieved a CR after up to two cycles of induction therapy received up to four cycles of consolidation therapy with high-dose cytarabine (3 g/m² intravenous every 12 hours on days 1, 3 and 5 of each cycle) followed by midostaurin or placebo (50 mg twice daily on days 8–21). Patients who continued to maintain a CR after consolidation therapy received maintenance therapy with midostaurin 50 mg or placebo twice daily for day 8 to day 21 according to their initial assignment. Patients with continued remission received maintenance therapy with midostaurin or placebo continued until relapse or for 12 cycles (of 28 days each) maximum. A number of studies contributed to the selection of the midostaurin 50 mg twice daily dosing regimen in the RATIFY study.^{14–17}

The primary efficacy endpoint was OS non-censored at SCT. OS was defined as the time from randomisation in the study until death by any cause. The key secondary endpoint was EFS (non-censored at SCT) defined as failure to achieve complete response within 60 days of initiation of protocol therapy, or relapse, or death from any cause whichever occurred first.

OS was statistically significantly different between the two treatment groups, and the median OS was 74.7

months in the midostaurin+daunorubicin +cytarabine group and 25.6 months in the placebo+daunorubicin+cytarabine group (HR 0.774; 95% CI 0.629 to 0.953; p=0.0078) (figure 2). The EFS showed a statistically significant improvement for midostaurin group over placebo group (HR: 0.784; 95% CI 0.662 to 0.930; p=0.0024) and a median EFS of 8.2 months and 3.0 months, respectively (figure 3).

A summary of the key favourable effects observed in the RATIFY study is displayed in table 1.

The efficacy in 60–70 years old patients with AML was evaluated in a supportive study ADE02T, a phase II, single-arm, investigator-initiated study of midostaurin in combination with intensive induction, consolidation including allogeneic SCT and single agent maintenance with midostaurin in patients with FLT3 ITD mutated AML.¹⁸ Based on an interim analysis, the primary endpoint EFS rate at 2 years (primary endpoint) was 27.1% (95% CI 16.6 to 44.1), and the median OS was 15.5 months in patients older than 60 years of age (46 out of 145 patients).

Clinical safety

In the RATIFY study, the overall median duration of exposure to midostaurin and placebo was 42 days (range 2–576 days) and 34 days (range 1–465 days) respectively, over the full treatment period (including induction, consolidation and maintenance). The relative dose intensity was 95.1% in the midostaurin group and 94.8% in the placebo group throughout all treatment phases. Midostaurin did not negatively impact dose intensity of the chemo and the relative dose intensity of daunorubicin and cytarabine was 100% in both groups.

The incidence of grade 3–4 adverse drug reactions (ADRs) over the full treatment period was 94.2% in the

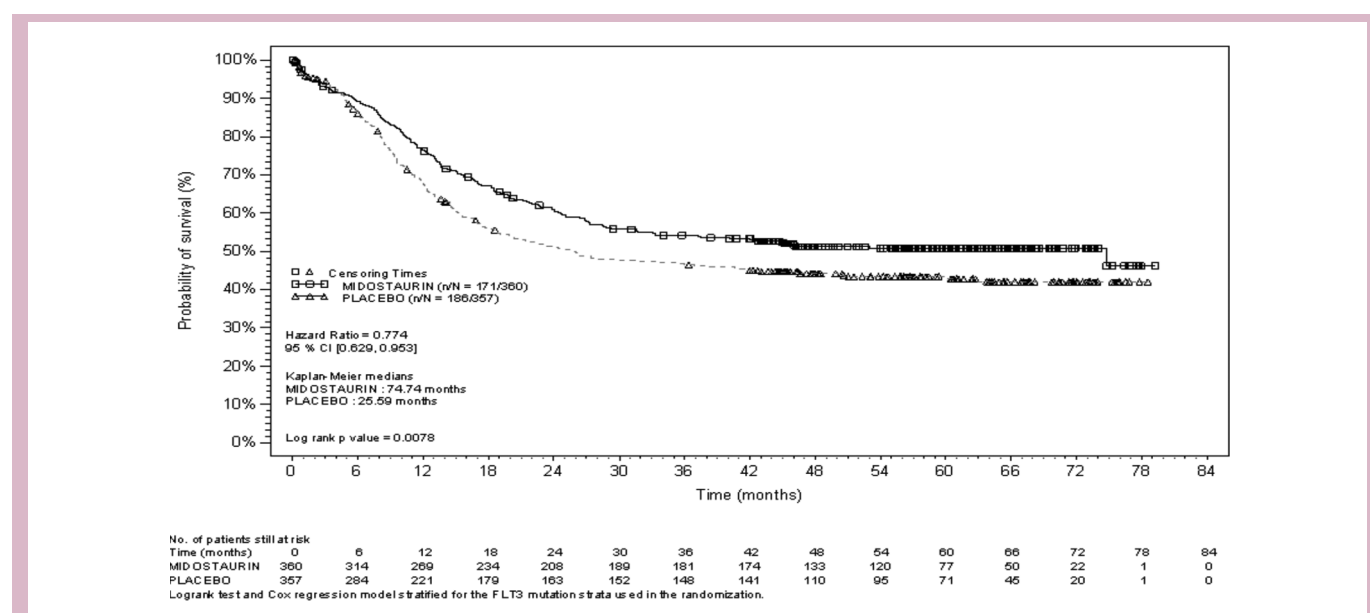


Figure 2 Kaplan-Meier plot of overall survival determined without censoring for SCT (data cut-off date of 1 April 2015, study A2301). FLT3, Fms-like tyrosine kinase 3; SCT, stem cell transplantation.

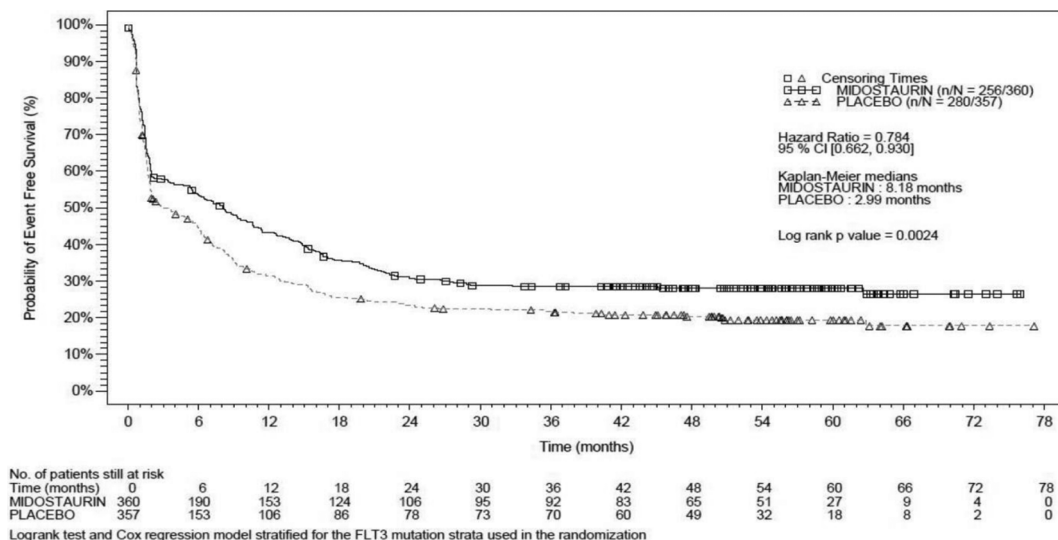


Figure 3 Kaplan-Meier plot of event-free survival (CRs within 60 days of study treatment start), non-censored for SCT, study A2301. CR, complete remission; SCT, stem cell transplantation.

midostaurin group and 91.9% in the placebo group. The most frequent grade 3/4 ADRs were febrile neutropenia (83.5% on midostaurin vs 83.0% on placebo), lymphopenia (20.0% on midostaurin vs 22.7% on placebo), device-related infection (15.7% on midostaurin vs 9.9% on placebo), exfoliative dermatitis (13.6% on midostaurin vs 7.5% on placebo), hyperglycaemia (7.0% on midostaurin vs 5.4% on placebo) and nausea (5.8% on midostaurin vs 10.1% on placebo).

In the RATIFY study, 47.0% and 48.7% of patients experienced at least one serious adverse event in the midostaurin and placebo arms, respectively, with febrile neutropenia being the most frequently observed (15.7% on midostaurin vs 15.8% on placebo). A total of 36 patients died on treatment (on-treatment deaths were defined as all deaths that occurred within 30 days of last dose of study drug); 15 patients (4.3%) in the midostaurin group; and 21 (6.3%) patients in the placebo group. Of these on-treatment deaths, 16 were suspected to be related to study drug: nine patients (2.6%) in the midostaurin group and seven patients (2.1%) in the placebo group. Causes of on-treatment deaths were mostly related to infections.

A dedicated interval between the start of the Q wave and the end of the T wave (QT) study in 192 healthy subjects with a dose of 75 mg twice daily did not reveal clinically significant prolongation of QT by midostaurin and metabolite CGP62221, but the study duration was not long enough to estimate the QTc prolongation effects of the long-acting metabolite CGP52421. Therefore, the change from baseline in QT interval corrected using Fridericia's method (QTcF) with the concentration of midostaurin and both metabolites was further explored in a phase II study in 116 patients with ASM, SM-AHN or MCL. At the median peak C_{min} concentrations attained

at a dose of 100 mg twice daily, neither midostaurin, CGP62221 nor CGP52421 showed a potential to cause clinically significant QTcF prolongation, since the upper bounds of predicted change at these concentration levels were less than 10 ms (5.8, 2.4, and 4.0 ms, respectively). In the ASM, SM-AHN and MCL population, 25.4% of patients had at least one ECG measurement with a QTcF greater than 450 ms and 4.7% greater than 480 ms.

Other important identified risks included leucopenia, severe infections, pulmonary toxicity (including pleural effusion and interstitial lung disease), drug–drug interactions with strong CYP3A4 inhibitors and drug–drug interactions with strong CYP3A4 inducers. Missing information included safety in paediatric population and in patients with severe hepatic impairment.

A summary of the key unfavourable effects observed in the RATIFY study is displayed in [table 1](#).

Benefit–risk assessment

The RATIFY study has provided convincing evidence of clinical efficacy of the addition of midostaurin to standard induction and consolidation chemotherapy, followed by maintenance therapy with midostaurin for 12 cycles in adult patients with newly diagnosed AML who are FLT3 mutation (ITD/TKD) positive. The observed OS benefit (74.7 months in midostaurin arm vs 25.6 months in placebo arm) was considered clinically relevant and robustly demonstrated.

An important remaining uncertainty that was identified during the benefit–risk assessment about the efficacy of midostaurin was the survival benefit in patients ≥ 60 years of age. In the pivotal study, only patients < 60 years of age were enrolled. However, the preliminary findings of the supportive study ADE02T (46 out of 145 patients ≥ 60 years of age) indicated a beneficial effect as suggested by

Table 1 Key favourable and unfavourable effects for midostaurin in combination with standard daunorubicin and cytarabine induction and high dose cytarabine consolidation chemotherapy and for patients in complete response followed by midostaurin single agent maintenance therapy for adult patients with newly diagnosed AML who are FLT3 mutation positive (study A2301; cut-off date: 1 April 2015)

Effect	Short description	Unit	Midostaurin n=360	Placebo n=357	Uncertainties/strength of evidence
Favourable effects					
OS (non-censored for SCT)	Median time from randomisation until death by any cause.	Months	74.7 (31.5, NE)	25.6 (18.6, 42.9)	Benefit in elderly (>60 years) HR: 0.774 (0.629 to 0.953)
EFS	Median time between randomisation and the date of event/censoring	Months	8.2 (5.4, 10.7)	3.0 (1.9, 5.9)	HR=0.784 (0.662 to 0.930)
Unfavourable effects					
ADRs	Grade 3–4	%	94.2	91.9	
Febrile neutropenia	Grade 3–4	%	83.5	83.0	
Lymphopenia	Grade 3–4	%	20.0	22.7	
Device-related infection	Grade 3–4	%	15.7	9.9	
Exfoliative dermatitis	Grade 3–4	%	13.6	7.5	
Hyperglycaemia	Grade 3–4	%	7.0	5.4	
Nausea	Grade 3–4	%	5.8	7.5	Nausea all grades was reported in 83.4% in midostaurin group versus 70.4% in the placebo group.

ADRs, adverse drug reactions; AML, acute myeloid leukaemia; EFS, event free survival; OS, overall survival; SCT, stem cell transplantation.

an EFS rate at 2 years of 27.1% (95% CI 16.6 to 44.1) and median OS of 15.5 months in patients older than 60 years of age. Furthermore, the safety profile of midostaurin appeared similar in patients >60 versus those <60 years of age based on an analysis of the ADE02T study. The biology of AML may differ between young and old AML patients, but this does not seem to affect the response to treatment in the subset of patients with FLT3 mutations eligible to intensive chemotherapy. Therefore, it was considered that there are no reasons to expect that the activity of the product differs between older and younger FLT3-positive AML patients. Age was also not expected to affect the pharmacokinetic (PK) of midostaurin.

The added value of maintenance treatment to the overall treatment effect could not be established, as in the absence of a rerandomisation step following induction and consolidation therapy, the start of maintenance treatment is a postrandomisation event. One may argue that a valuable contribution of a period of maintenance therapy in FLT3-mutated AML following the induction and consolidation phases can be expected as the high relapse rate that can be at least in part be attributed to FLT3 clones.⁴ Importantly, efficacy of midostaurin has been demonstrated with the continuation/maintenance phase as part of the treatment strategy, and the safety profile of midostaurin monotherapy is favourable. For these reasons, the proposed indication that includes a postremission maintenance phase was considered acceptable. While a similar benefit of treatment was evident in most subgroups a remarkable exception was an apparent difference in OS benefit between men and women (HR in men: 0.53, 95% CI 0.39 to 0.72, HR in women of 1.01, 95% CI 0.76 to 1.34). Additional analyses indicated that it is likely that SCT substantially contributed to the apparent gender effect. As censoring for SCT (sensitivity analysis) in the ITT population (HR 0.75, 95% CI 0.54 to 1.03) confirmed the observed OS benefit conferred by midostaurin observed in the primary analysis (HR 0.774; 95% CI 0.629 to 0.953) and as a benefit of treatment for females was seen in the secondary endpoints EFS, CR and cumulative incidences of relapse (CIR), it was considered that there is sufficient evidence of benefit in women.

In conclusion, based on the plausible assumption of similar disease biology between the age subgroups, the results of the supportive study and the safety profile in patients ≥ 60 years of age, the Committee for Human Medicinal Products (CHMP) concluded that the observed survival benefit in the population of the pivotal study (<60 years of age) can be extrapolated to the ≥ 60 years of age population and hence that no age restriction in the therapeutic indication was necessary. The results from the on-going (study ADE02T; final results expected in 2021) and planned studies (studies A2408 and E2301; final results expected in 2022 and 2023, respectively) were requested to further quantify the OS benefit of midostaurin in patients ≥ 60 years of age. However, until further data become available, treating physicians should

be aware of the limitation in the experience in the elderly for their clinical decision making.

The majority of adverse events were reported during the induction and consolidation phases, and the adverse events were less frequently reported during the maintenance phase. The absence of chemotherapy administration is the most likely reason for the lower frequency of AEs in the maintenance phase.

The apparent midostaurin-related increase in QT prolongation events and in a >60 ms shift from baseline QTc values in terms of exposure/dose–effect relationships has not been explained. QT prolongation (mainly) occurred in the presence of other confounding factors (concomitant medication and/or, for example, electrolyte imbalances). While it may be unlikely that midostaurin treatment on its own has the potential to induce QT prolongation, a possible contribution of midostaurin to QT prolongation in patients at risk for this event cannot be excluded. Therefore, caution is warranted in patients at risk of QTc prolongation (eg, due to concomitant medicinal products and/or electrolyte disturbances), and interval assessments of QT by ECG should be considered if midostaurin is taken concurrently with medicinal products that can prolong QT interval.

Overall, the safety profile of midostaurin was considered to be manageable and acceptable in view of the therapeutic context and given the observed benefits.

Based on the review of data on quality, safety and efficacy, the EMA CHMP concluded by consensus that the risk–benefit balance of midostaurin in combination with standard daunorubicin and cytarabine induction and high dose cytarabine consolidation chemotherapy, and for patients in complete response followed by midostaurin single agent maintenance therapy, for adult patients with newly diagnosed AML who are FLT3 mutation (ITD/TKD) positive was favourable and hence recommended the granting of the marketing authorisation.

The most current information on this medicinal product is available on the EMA website (<https://www.ema.europa.eu/en/medicines>).

SYSTEMIC MASTOCYTOSIS

Clinical efficacy

The pivotal efficacy study for midostaurin in the systemic mastocytosis indication was study D2201. Study D2201, a single arm, phase II, open-label study was conducted in 116 patients, of whom 89 were considered eligible for response assessment and constituted the primary efficacy population.¹⁹

Patients were required to have a diagnosis of ASM, SM-AHN or MCL and at least one measurable C-finding as per modified Valent criteria.²⁰ A C-finding was defined as a clinical finding that was considered by the investigator and corroborated by the study steering committee chairperson or designee as attributable to the mast cell disease component and not to an associated haematological clonal non-mast cell lineage disease or any other cause.

Midostaurin was administered orally at 100 mg (four capsules of midostaurin 25 mg) twice daily until disease progression or intolerable toxicity.

The primary efficacy endpoint was ORR defined as the percentage of patients with a confirmed response (major or partial response (PR)) as assessed by the study steering committee based on modified Valent/Cheson criteria^{20–22} and with an initial response occurring in the first six cycles and confirmed at least 56 days later. The 89 patients who were considered eligible for response assessment constituted the primary efficacy population. Of these 89 patients, 16 had ASM, 57 had SM-AHN and 16 had MCL. The ORR based on modified Valent/Cheson criteria after six cycles of treatment was 59.6% (with 45% of the patients achieving a major response and 15% of the patients achieving a PR) and the ORR was 75.0%, 57.9% and 50.0%, respectively, in patients with ASM, SM-AHN and MCL. There were no complete responses.

In an analysis using the IWG-MRT/ECNM criteria²³ conducted in 113 patients, the overall ORR was 28.3%, and 60.0%, 20.8% and 33.3%, respectively, in patients with ASM, SM-AHN and MCL.

Regarding the secondary endpoint duration of response (DOR) as per IWG criteria, this was analysed for patients who had a confirmed response of complete response, PR or clinical improvement, calculated as the time from the first observation of response until disease progression or death due to systemic mastocytosis. The analyses of DOR as per IWG criteria show that responses to midostaurin treatment were durable and that they were even more durable among patients who achieved a CR or PR. The median DOR was not reached in the primary analysis of DOR in either response subgroup (figure 4).

A summary of the key favourable effects in study D2201 is displayed in table 2.

Supporting data for the efficacy of midostaurin in systemic mastocytosis came from a single arm, multi-centre, open-label, phase II study of 26 patients with ASM, SM-AHN or MCL (A2213).²⁴ Midostaurin was administered orally at 100 mg twice daily continuously in cycles of 28 days. Three patients had ASM, 17 patients had SM-AHN and 6 patients had MCL. The primary endpoint was ORR evaluated by the Valent criteria²⁰ during the first two cycles of treatment. Nineteen patients (73.1%; (95% CI 52.2 to 88.4)) achieved a response during the first two cycles of treatment (13 patients achieving a major response and 6 of the patients achieving a partial response).

Clinical safety

The safety of midostaurin as a single agent in patients with ASM, SM-AHN and MCL was evaluated in 142 patients in two open-label, single-arm, multicentre studies (studies DD01 and A2213). In the pooled safety set, the median duration of exposure to midostaurin was 11.4 months (range: 0–81 months).

The mean relative dose intensity was 91.8% in the midostaurin group in study D2201 and 98.0% in study A2213. The incidence of grade 3–4, ADRs was 88.8% in study D2201, 61.5% in study A2213 and 83.8% in the pooled safety set. The most frequent grade 3/4 ADRs were fatigue (8.5%), sepsis (7.7%), pneumonia (7%), febrile neutropenia (7%) and diarrhoea (6.3%). ADRs of any grade leading to treatment discontinuation were observed in 9.2% of patients. Overall, 67 patients (47.2%) had at least one dose interruption.

In the pooled safety set, there were 26 on-treatment deaths reported (ie, deaths occurring on treatment and up to 28 days after the last dose of study drug). Ten deaths were related to study indication and one to the

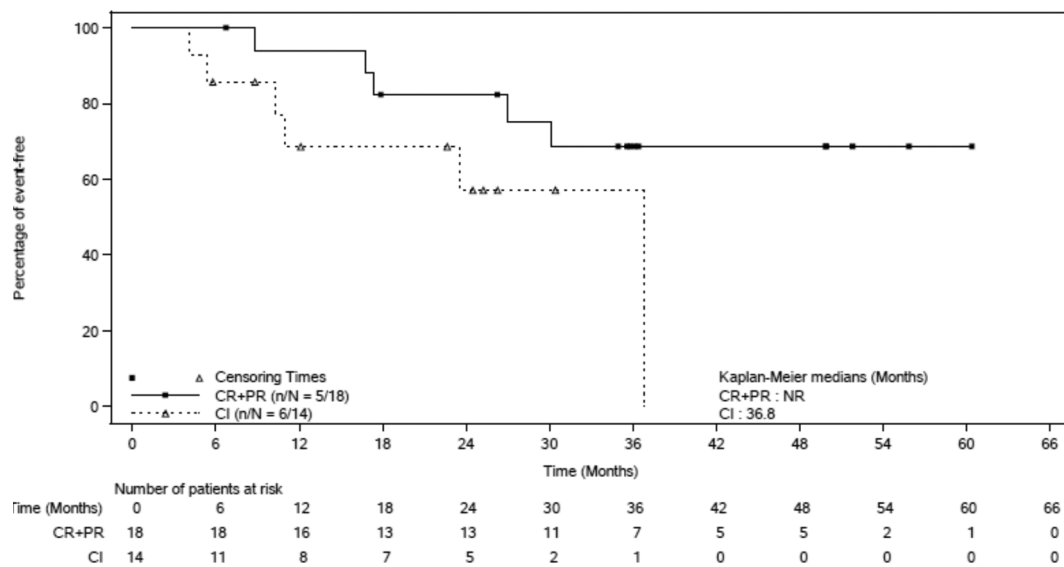


Figure 4 Kaplan-Meier plot of duration of response as per international working group (IWG) response criteria (12-week confirmation) in study D2201. CR, complete remission; NR, not reached.

Table 2 Effects table for midostaurin in adult patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated haematological neoplasm (SM-AHN) or mast cell leukaemia (MCL) (study D2201; cut-off date: 1 December 2014)

Effect	Short description	Unit	Midostaurin	Uncertainties/ strength of evidence
Favourable effects				
ORR (modified Valent/Cheson criteria)	Proportion of patients with a best response of MR or PR.	%	Overall (n=89): 59.6. ASM (n=16): 75.0. SM-AHN (n=57): 57.9. MCL (n=16): 50.0.	
ORR (IWG criteria)	ORR according to IWG criteria.	%	Overall (n=113): 28.3. ASM (n=15): 60.0. SM-AHN (n=72): 20.8. MCL (n=21): 33.3.	
DOR (IWG criteria)	Median time from the first confirmed response until the date of first confirmed PD or death due to ASM or MCL.	Months	Overall (11/32): NE (27.0–NE). ASM (4/9): 36.8 (10.3–36.8). SM-AHN (4/15): NE (17.3–NE). MCL (3/7): NE (4.1–NE).	
Unfavourable effects (pool safety set – studies D2201 and A2213)				
ADRs	Grade 3–4	%	83.8	
Fatigue	Grade 3–4	%	8.5	
Sepsis	Grade 3–4	%	7.7	
Pneumonia	Grade 3–4	%	7.0	
Febrile neutropenia	Grade 3–4	%	7.0	
Diarrhoea	Grade 3–4	%	6.3	

ADRs, adverse drug reactions; CR, complete remission; DOR, duration of response; IWG, international working group; MR, major response; NE, not estimable; ORR, overall response rate; PR, partial response.

progression of the AHNMD to acute myeloid leukaemia. The remaining 15 deaths (10.6%) were most commonly related to cardiac disorders (five patients) and infections (six patients). None of the deaths was considered related to study drug by the investigators.

QT prolongation-related events were reported 16.2% of patients in the pooled safety set; the most commonly reported event was ECG QT prolonged (15 patients; 10.6%) and resulted in discontinuation in three patients.

A summary of the key unfavourable effects of the pooled safety set (studies D2201 and A2213) is displayed in [table 2](#).

Benefit–risk assessment

The initial indication proposed by the applicant-company included the use of midostaurin as monotherapy for the treatment of adult patients with advanced systemic mastocytosis. However, the CHMP considered that the wording of the indication should be amended in order to specifically reflect the enrolled patient population in line with the WHO classification. Based on this, the indication was revised to include ASM, SM-AHN or MCL.

There were also concerns related to the accuracy of the ORR as primary endpoint including the use of Valent and Cheson criteria that were considered to be outdated since the cut-off values for C-findings were not stringent enough (eg, grade 1 thrombocytopenia) and the fact that a too short minimum DOR was used (8 weeks). During the conduct of study D2201, new consensus response criteria for advanced systemic mastocytosis were published by IWG-MRT-ECNM. Using IWG-MRT-ECNM criteria, a laboratory finding requires a CTCAE grade 2 equivalent abnormality for such tests as haemoglobin, neutrophil count, platelets, albumin, transaminases and bilirubin to qualify as a C-finding. Similarly, for a major response, the C-findings must return reproducibly to the normal range. This assures that the C-finding has been corrected. Therefore, based on the post hoc analysis, in which ORR was determined using the most recent response criteria (IWG-MRT and ECNM criteria), the above concerns were relieved.

Based on the ORR analysis according to the more recent and more clinically relevant IWG-MRT-ECNM criteria, the ORR was 28.3% overall and 60.0%, 20.8% and 33.3%, respectively, in patients with ASM, SM-AHN and MCL. Clinically relevant durations of response were observed in patients who achieved response according to IWG criteria. This analysis showed that responses to midostaurin treatment were most durable among patients who achieved a CR or PR (median not reached, 95% CI 27.0 to NE) and less durable in patients with clinical improvement alone. Therefore, the magnitude of response was correlated with DOR, and this was considered a clinical benefit in terms of delaying worsening of the disease.

The absence of comparative efficacy data was also an uncertainty expressed by the CHMP during the assessment. However, the specific circumstances such as the extreme rarity of the diseases and the great unmet

medical need in systemic mastocytosis patients were further considered. Furthermore, it was considered that the provided efficacy data for midostaurin was compelling relative to what is historically known for available (but non-approved) therapies. Midostaurin conferred durable responses, which correlated with survival benefit, and the responses were further corroborated by durable reductions in bone marrow mast cell burden). For other available (but non-approved) therapies such as interferon- α and cladribine, the evidence for efficacy is much weaker and comes mostly from retrospective investigations or small single-arm studies.

The safety profile of midostaurin in ASM/SM-AHN/MCL was acceptable in view of the severity of the disease and the benefits observed.

Based on the review of data on quality, safety and efficacy, the EMA Committee for Human Medicinal Products concluded by consensus that the risk–benefit balance of midostaurin as monotherapy for the treatment of adult patients with ASM, SM-AHN, or MCL was favourable and recommended the granting of the marketing authorisation.

The most current information on this medicinal product is available on the EMA website (<https://www.ema.europa.eu/en/medicines>).

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