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APPLICATION NUMBER:

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MEDICAL REVIEW(S)

Clinical Review
 Yvette Kasamon, MD
 NDA 207997, Orig 1
 RYDAPT (Midostaurin)

CLINICAL REVIEW

Application Type	New Molecular Entity
Application Number(s)	NDA 207997, Original 1
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Division/Office	Office of Hematology and Oncology Products / Division of Hematology Products
Reviewer Name(s)	Yvette Kasamon, MD Donna Przepiorka, MD PhD (Team Leader)
Review Completion Date	February 3, 2017
Established Name	Midostaurin, PKC412
(Proposed) Trade Name	RYDAPT
Applicant	Novartis Pharmaceuticals Corporation
Formulation(s)	25 mg capsule
Dosing Regimen	100 mg orally twice daily
Applicant Proposed Indication(s)/Population(s)	Treatment of adult patients with advanced systemic mastocytosis
Recommendation on Regulatory Action	Regular approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of adult patients with aggressive systemic mastocytosis, systemic mastocytosis with associated hematological neoplasm, or mast cell leukemia

Table of Contents

Glossary	8
1 Executive Summary.....	10
1.1. Product Introduction	10
1.2. Conclusions on the Substantial Evidence of Effectiveness.....	10
1.3. Benefit-Risk Assessment.....	10
2 Therapeutic Context.....	14
2.1. Analysis of Condition	14
2.2. Analysis of Current Treatment Options.....	14
3 Regulatory Background.....	16
3.1. U.S. Regulatory Actions and Marketing History.....	16
3.2. Summary of Presubmission/Submission Regulatory Activity.....	16
3.3. Foreign Regulatory Actions and Marketing History.....	16
4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety	17
4.1. Office of Scientific Investigations (OSI).....	17
4.2. Product Quality.....	17
4.3. Clinical Microbiology	17
4.4. Nonclinical Pharmacology/Toxicology.....	17
4.5. Clinical Pharmacology	18
4.5.1. Mechanism of Action.....	18
4.5.2. Pharmacodynamics	18
4.5.3. Pharmacokinetics	18
4.6. Devices and Companion Diagnostic Issues	19
4.7. Consumer Study Reviews	19
5 Sources of Clinical Data and Review Strategy.....	20
5.1. Table of Clinical Studies.....	20
5.2. Review Strategy.....	21
6 Review of Relevant Individual Trials Used to Support Efficacy.....	22

6.1.	Study D2201 (PKC412D2201): A Single Arm, Phase II, Open-Label Study to Determine the Efficacy of 100mg Twice Daily Oral Dosing of Midostaurin Administered to Patients with Aggressive Systemic Mastocytosis or Mast Cell Leukemia +/- an Associated Hematological Clonal Non-Mast Cell Lineage Disease	22
6.1.1.	Study Design	22
6.1.2.	Study Results	25
6.2.	Study A2213 (PKC412A2213): A Single Arm, Phase II, Open-Label Study To Determine The Efficacy Of Twice Daily Oral Dosing Of PKC412 Administered To Patients With Aggressive Systemic Mastocytosis (ASM) and Mast Cell Leukemia (MCL) +/- Hematological Clonal Non-Mast Cell Lineage Disease.....	27
6.2.1.	Study Design	27
6.2.2.	Study Results	30
7	Integrated Review of Effectiveness	31
7.1.	Assessment of Efficacy Across Trials	31
7.1.1.	Primary Endpoints	36
7.1.2.	Secondary and Other Endpoints	42
7.1.3.	Subpopulations.....	48
7.1.4.	Dose and Dose-Response	49
7.1.5.	Onset, Duration, and Durability of Efficacy Effects	49
7.2.	Additional Efficacy Considerations.....	50
7.2.1.	Considerations on Benefit in the Postmarket Setting.....	50
7.2.2.	Other Relevant Benefits.....	50
7.3.	Integrated Assessment of Effectiveness	50
8	Review of Safety	51
8.1.	Safety Review Approach.....	51
8.2.	Review of the Safety Database.....	52
8.2.1.	Overall Exposure.....	52
8.2.2.	Relevant Characteristics of the Safety Population	53
8.2.3.	Adequacy of the Safety Database.....	55
8.3.	Adequacy of Applicant’s Clinical Safety Assessments	55
8.3.1.	Issues Regarding Data Integrity and Submission Quality.....	55
8.3.2.	Categorization of Adverse Events	55
8.3.3.	Routine Clinical Tests	55

8.4.	Safety Results	55
8.4.1.	Deaths	55
8.4.2.	Serious Adverse Events.....	56
8.4.3.	Dropouts and/or Discontinuations Due to Adverse Effects.....	57
8.4.4.	Significant Adverse Events	61
8.4.5.	Treatment-Emergent Adverse Events and Adverse Reactions	64
8.4.6.	Laboratory Findings	69
8.4.7.	Vital Signs.....	71
8.4.8.	Electrocardiograms (ECGs).....	71
8.4.9.	QT	71
8.4.10.	Immunogenicity.....	71
8.5.	Analysis of Submission-Specific Safety Issues	71
8.6.	Safety Analyses by Demographic Subgroups	72
8.7.	Specific Safety Studies/Clinical Trials	72
8.8.	Additional Safety Explorations	72
8.8.1.	Human Carcinogenicity or Tumor Development.....	72
8.8.2.	Human Reproduction and Pregnancy.....	72
8.8.3.	Pediatrics and Assessment of Effects on Growth.....	72
8.8.4.	Overdose, Drug Abuse Potential, Withdrawal, and Rebound.....	72
8.8.5.	Safety in Patients with Hepatic Impairment.....	72
8.8.6.	Day 120 Safety Update	73
8.9.	Safety in the Postmarket Setting.....	74
8.9.1.	Safety Concerns Identified Through Postmarket Experience	74
8.9.2.	Expectations on Safety in the Postmarket Setting	74
8.10.	Additional Safety Issues From Other Disciplines	74
8.11.	Integrated Assessment of Safety	74
9	Advisory Committee Meeting and Other External Consultation	75
10	Labeling Recommendations	75
10.1.	Prescribing Information.....	75
10.2.	Patient Labeling.....	76
11	Risk Evaluation and Mitigation Strategies (REMS).....	76

12	Postmarketing Requirements and Commitments.....	76
13	Appendices.....	77
13.1.	References.....	77
13.2.	Financial Disclosure.....	79
13.3.	Clinical Spectrum of Systemic Mastocytosis	81
13.4.	Classification of Systemic Mastocytosis	82
13.5.	Valent and Modified Valent Response Criteria	83
13.6.	IWG-MRT-ECNM Response Criteria for AdSM	86
13.7.	Toxicity Management Guidelines in Study D2201.....	88
13.8.	Schedule of Study D2201 Assessments	89
13.9.	Trials Included in the Integrated Summary of Safety	91
13.10.	FDA Grouping of Preferred Terms for Safety Analysis	93
13.11.	Cardiac Dysfunction and Pulmonary Toxicity in Patients with AdSM.....	95

Table of Tables

Table 1: Clinical Trials of Midostaurin in Systemic Mastocytosis	20
Table 2: Supportive Safety Studies for AdSM Indication (Midostaurin Monotherapy, 200-225 mg Daily or Pediatric Equivalent).....	21
Table 3: Comparison of Valent and Modified Valent Criteria	24
Table 4: Reported Protocol Deviations – Study D2201	26
Table 5: Efficacy Measures in Study D2201 vs. Study A2213	29
Table 6: Baseline Characteristics of Efficacy Populations (D2201, A2213)	32
Table 7: Prior and On-Study Treatments (D2201, A2213).....	34
Table 8: Disposition of Patients with AdSM (D2201, A2213)	36
Table 9: SSC-Adjudicated Response per Modified Valent Criteria – D2201 PEP	37
Table 10: Response per IWG-MRT-ECNM Criteria – Study D2201	39
Table 11: Response per Valent Criteria – Study A2213	41
Table 12: Response per IWG-MRT-ECNM Criteria – Study A2213	42
Table 13: Progression-Free Survival – Study D2201	45
Table 14: Overall Survival – Study D2201	46
Table 15: Quality of Life Assessments – D2201 PEP	47
Table 16: Subgroup Analysis of Response – Study D2201	49
Table 17: Exposure in Safety Populations (Midostaurin Monotherapy, 200-225 mg Daily or Pediatric Equivalent).....	52
Table 18: Baseline Characteristics of Safety Populations	54
Table 19: On-Treatment Deaths in Patients with AdSM (FDA Analysis).....	56
Table 20: SAEs by SOC in $\geq 2\%$ of Either Safety Population.....	57
Table 21: Treatment Discontinuation Due to AEs in AdSM Safety Population (FDA Analysis)	58
Table 22: AEs Causing Treatment Modification in $\geq 5\%$ of AdSM Patients	59
Table 23: Time Course of Common AEs in AdSM Safety Population.....	60
Table 24: Grade ≥ 4 AEs Reported in $\geq 2\%$ of Either Safety Population, Excluding Laboratory Terms	61
Table 25: Selected Non-Hematologic AESIs in AdSM Safety Population.....	62
Table 26: Most Common ($\geq 20\%$) AEs with Midostaurin Monotherapy (200-225 mg/day), Excluding Laboratory Terms	64
Table 27: Most Common ($\geq 20\%$) AEs in Diabetic Patients, Excluding Laboratory Terms (Study C99PKC412001).....	65
Table 28: Most Common ($\geq 20\%$) AE Categories in AdSM Patients by SOC	65
Table 29: Common ($\geq 10\%$) AEs in AdSM Pool (FDA Grouped Terms)	67
Table 30: Selected Clinically Relevant AEs in $< 10\%$ of AdSM Pool	68
Table 31: Common ($\geq 10\%$) AEs in Other Patients with Hematological Malignancies, Excluding Laboratory Terms.....	69
Table 32: Common ($\geq 10\%$) Treatment-Emergent Laboratory Findings in AdSM Pool	70
Table 33: Grade ≥ 3 AEs in AdSM Patients with Baseline Hepatic Impairment.....	73

Table 34: World Health Organization Variants of Systemic Mastocytosis	82
Table 35: Original Valent Criteria.....	83
Table 36: Response Definitions in Studies D2201 and A2213	84
Table 37: Response Criteria for C-Findings in Studies D2201 and A2213	85
Table 38: IWG-MRT-ECNM Response Criteria	86
Table 39: IWG-MRT-ECNM Criteria for Clinical Improvement	87
Table 40: Dose Modification Guidelines – Study D2201	88
Table 41: Core On-Treatment Evaluations – Study D2201	89
Table 42: Safety Studies in the ISS	91
Table 43: FDA Grouping of Preferred Terms	93
Table 44: Cardiac Dysfunction Reported in the AdSM Safety Population	95
Table 45: Pulmonary Toxicity Reported by Sponsor in the AdSM Safety Population	96

Table of Figures

Figure 1: Exposure in D2201 Primary Efficacy Population (N = 89)	35
Figure 2: DOR (Modified Valent) in D2201 PEP	43
Figure 3: Disease Status in First 6 Cycles per SSC	44
Figure 4: Progression-Free Survival – D2201 PEP (Modified Valent Criteria).....	45
Figure 5: Overall Survival by Diagnosis – D2201 FAS.....	46
Figure 6: Exposure in AdSM Safety Population (N = 142).....	53
Figure 7: Time to First Dose Modification for AE (AdSM Safety Population)	60
Figure 8: Spectrum of Disease in Systemic Mastocytosis	81

Glossary

AESI	adverse event of special interest
AHNMD	associated hematological non-mast cell lineage disorder
AHN	associated hematological neoplasm
AdSM	advanced systemic mastocytosis
AR	adverse reaction
ASM	aggressive systemic mastocytosis
BM	bone marrow
BOR	best overall response
CI	clinical improvement, confidence interval
CRO	contract research organization
CSR	clinical study report
DOR	duration of response
FAS	full analysis set
FLT3	Fms-like tyrosine kinase 3
ECNM	European Competence Network on Mastocytosis
GPR	good partial response
HM	hematological malignancy
IQR	interquartile range
IR	information request
ISS	integrated summary of safety
IWG	International Working Group
MC	mast cell
MCL	mast cell leukemia
minR	minor response
MR	major response
MRT	Myeloproliferative Neoplasms Research and Treatment
MSAS	Memorial Symptom Assessment Scale
NE	not evaluable, not estimable
NR	not reached
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PI	prescribing information
PEP	primary efficacy population
PR	partial response
PRO	patient reported outcome
PT	preferred term

Clinical Review
Yvette Kasamon, MD
NDA 207997, Orig 1
RYDAPT (Midostaurin)

SAE	serious adverse event
SAP	statistical analysis plan
SCE	summary of clinical efficacy
SCS	summary of clinical safety
SD	stable disease
SF-12	Short Form Health Survey-12
SOC	system organ class
SMQ	standardized MedDRA query
SSC	study steering committee
SM	systemic mastocytosis
TD	transfusion dependent
TEAE	treatment-emergent adverse event
TTR	time to response
WHO	World Health Organization

1 Executive Summary

1.1. Product Introduction

Midostaurin (proposed proprietary name, RYDAPT) is an orally bioavailable, small-molecule inhibitor of multiple receptor tyrosine kinases, including c-KIT. The review team recommends regular approval of midostaurin for the treatment of adult patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated hematological neoplasm (SM-AHN), or mast cell leukemia (MCL). The proposed starting dose-schedule is 100 mg orally twice-daily, with a 28-day cycle length and continuation until disease progression or unacceptable toxicity. Midostaurin is a new molecular entity (NME).

1.2. Conclusions on the Substantial Evidence of Effectiveness

The submitted data meet the evidentiary standard of effectiveness for adult patients with previously treated or untreated ASM, SM-AHN, and MCL.

The efficacy evaluation is based primarily on overall response rate (ORR) and duration of response (DOR) in a multicenter phase 2 single-arm study (Study D2201) in the intended population. With 6 cycles of midostaurin at the recommended dose-schedule, the ORR, based on modified Valent criteria, was 60% (45% major response, 15% partial response), with an estimated median response duration of 31 months. According to the more stringent IWG-MNRT-ECNM (International Working Group-Myeloproliferative Neoplasms Research and Treatment-European Competence Network on Mastocytosis) consensus criteria, the ORR was 17%, with the median DOR not reached and response durations ranging from 6.8+ to 60.5+ months. According to either set of response criteria, a treatment effect was demonstrated in all histologic subtypes and across other major subgroups. Efficacy outcomes in a supportive single-arm study in the intended population (Study A2213) were comparable. The overall safety profile was acceptable.

Given the rarity of these fatal diseases and the clinically meaningful activity of midostaurin, the review team recommends regular approval.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Efficacy

The determination of efficacy is based primarily upon ORR and DOR in a multicenter phase 2 study (Study D2201) in the intended population. In the assessment of effectiveness, the review team considered response as determined both by modified Valent or Valent criteria and by the more stringent IWG-MRT-ECNM criteria. In Study D2201, in 89 patients in the primary efficacy population, the ORR with 6 cycles based on modified Valent criteria was 60% (45% MR, 15% PR), with an estimated median DOR of 31 months. In 115 patients evaluated using the more stringent IWG-MRT-ECNM criteria, the ORR with 6 cycles was 17% (2% CR, 15% PR), with response durations ranging from 6.8+ to 60.5+ months. According to either set of response criteria, a treatment effect was demonstrated in all histologic subtypes and across other major subgroups.

The review team recommends that the Prescribing Information present efficacy according to IWG-MRT-ECNM criteria as well as modified Valent or Valent criteria.

Safety

Midostaurin carried an acceptable safety profile in the intended population. The primary safety assessment involved an integrated analysis of 142 adult patients with AdSM who received at least one dose of midostaurin at the recommended dose-schedule (100 mg po BID until disease progression or unacceptable toxicity).

The most common ARs ($\geq 20\%$) were nausea, vomiting, diarrhea, constipation, abdominal pain, edema, fatigue, upper respiratory tract infection, pyrexia, arthralgia, headache, and dyspnea. The most common grade 3-4 hematologic laboratory abnormalities ($\geq 20\%$) included anemia, thrombocytopenia, and neutropenia.

Eleven percent of patients died on-treatment for reasons unrelated to the underlying malignancy, most often from infection. SAEs were reported in two-thirds of patients, most commonly involving infections and gastrointestinal disorders. AEs led to dose interruption or reduction in 56% of patients, with the leading reasons being nausea, vomiting, QT prolongation, and neutropenia. Treatment discontinuation due to AEs occurred in 21% of patients, most often due to infection, nausea or vomiting, QT prolongation, and hemorrhage.

The supportive safety assessment involved an integrated analysis of 85 other patients with hematologic malignancies patients who received midostaurin at a planned dosage that equaled or approximated the proposed dosage for AdSM. The overall AE profiles in the primary and supportive safety analyses were congruent.

Overall benefit-risk assessment for the recommended indication

Advanced SM is rare and fatal. Treatment is generally palliative, there are no approved therapies for SM-AHN or MCL, and imatinib is the only approved therapy for ASM. However, the imatinib indication is applicable to only approximately 10% of patients with ASM, as most cases of SM harbor the D816V c-Kit mutation that confers imatinib resistance.

Based on response rate and response duration, the efficacy results with midostaurin in advanced SM are clinically meaningful, with an overall favorable benefit/risk profile. Given the rarity of this heterogeneous group of diseases and the poor prognosis, the review team recommends regular approval.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Advanced SM is rare and fatal.	Patients with advanced SM (ASM, SM-AHN, and MCL) have unmet medical needs.
Current Treatment Options	- There are no approved therapies for SM-AHN or MCL. - Imatinib is the only approved treatment for ASM. However, the imatinib indication is irrelevant to most patients, because most cases of SM harbor the D816V c-Kit mutation that confers imatinib resistance.	There is an immediate need for effective yet tolerable therapy for patients with all subtypes of advanced SM.
Benefit	- Efficacy was evaluated in two multicenter, phase 2 single-arm studies of midostaurin monotherapy in the intended population. In the primary efficacy study (D2201), among 89 patients assessed by the SSC, ORR with 6 cycles based on modified Valent criteria was 60% (45% MR, 15% PR), with an estimated median DOR of 31 months. - According to IWG-MRT-ECNM criteria, among 115 patients assessed in Study D2201, ORR with 6 cycles was 17% (2% CR, 15% PR), with response durations ranging from 6.8+ to 60.5+ months. - A treatment effect was demonstrated in all histologic subtypes. - Efficacy outcomes in the supportive study (A2213) were congruent.	The treatment effect of midostaurin, based on response rate and response duration, is clinically meaningful in patients with advanced SM.
Risk	- Safety was evaluated in 142 patients with advanced SM from the above phase 2 trials combined. The median exposure was 11 months. 66% of patients had SAEs, and 21% discontinued treatment due to AEs. 56% of patients had dose modifications for AEs, most commonly due to nausea, vomiting, QT prolongation, and neutropenia. - The most common ARs ($\geq 20\%$) were nausea, vomiting, diarrhea, constipation, abdominal pain, edema, fatigue, upper respiratory tract infection, pyrexia, arthralgia, headache, and dyspnea. 11% of patients died on-treatment for reasons other than disease progression, most often	- The overall risk profile of midostaurin at the proposed dose-schedule is acceptable in the intended population. - The benefit-risk profile of midostaurin is favorable in the intended population.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	because of infection.	
Risk Management	• Serious risks were potentially mitigated in protocols by patient selection criteria and toxicity management guidelines. • Gastrointestinal ARs, which were common, were generally manageable with supportive care and dose modifications. • The majority of dose modifications for toxicity occurred in the first several months, with a median time to first dose modification of 1.6 months.	• The PI should describe trial eligibility criteria with respect to end-organ function and performance status. • The PI should recommend prophylactic antiemetics and should contain explicit guidelines for toxicity management. • The PI should recommend particularly close monitoring for actionable toxicities during the first 3 months of treatment. At least weekly monitoring during the first month is recommended.

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2 Therapeutic Context

2.1. Analysis of Condition

SM is a rare, heterogeneous disease caused by the uncontrolled accumulation of neoplastic mast cells, including in the skin, bone marrow, liver, spleen, and gastrointestinal tract. Somatic gain-of-function mutations in *KIT*, particularly the D816V mutation, occur in most adult cases of SM (Garcia-Montero AC et al 2006). The *KIT* D816V mutation, detected in approximately 90% of cases, encodes a constitutively activated receptor tyrosine kinase that drives disease pathogenesis (Garcia-Montero AC et al 2006; Gotlib J et al 2016).

Overviews of the classification and clinical spectrum of SM are presented in the Appendix (Figure 8 and Table 34). Symptoms are caused both by the release of vasoactive mast cell mediators and by organ damage from mast cell infiltration (Gotlib J et al 2016; Pardanani 2015; Tremblay D et al 2015). In aggressive variants, C-findings (clinical manifestations of organ infiltration by mast cells) include cytopenias, skeletal lesions, palpable hepatomegaly with impaired liver function and/or portal hypertension, splenomegaly with hypersplenism, and weight loss due to gastrointestinal involvement (Arber DA et al 2016; Pardanani 2015; Tremblay D et al 2015). Progressive organ infiltration ultimately causes organ failure and death.

The World Health Organization (WHO) subtypes of ASM, SM-AHN, and MCL are regarded as forms of advanced SM (AdSM). In contrast to indolent variants, the prognosis of AdSM is poor, with an estimated median overall survival (OS) of 3.5 years with ASM, 2 years with SM-AHN, and < 6 months with MCL (Lim KH, Tefferi A et al 2009). SM-AHN is itself prognostically heterogeneous, with the prognosis being contingent on the type of AHN (Pardanani et al 2009; Lim KH, Tefferi A et al 2009). The observed risk of leukemic transformation is 5% in ASM, 13% in SM-AHN broadly, and 29% in SM-MDS (Lim KH, Tefferi A et al 2009).

2.2. Analysis of Current Treatment Options

Available Therapy

Treatment of AdSM is generally palliative, with limited and largely unsatisfactory options (Lim KH et al 2009).

There are no approved therapies for SM-AHN or MCL. Imatinib mesylate (Gleevec) received regular FDA approval on 10/19/2006 as a single agent for the treatment of adult ASM without the D816V c-Kit mutation or with c-Kit mutational status unknown. The approval was based on 28 patients with ASM, comprising a mixture of literature and study patients, in whom 8 (29%) achieved a complete hematologic response and 9 (32%) a partial hematologic response with imatinib. Response durations ranged from 1+ to 30+ months. However, the imatinib indication

Clinical Review
Yvette Kasamon, MD
NDA 207997, Orig 1
RYDAPT (Midostaurin)

is applicable to only approximately 10% of ASM patients, as SM that harbors a D816V c-Kit mutation is considered resistant to imatinib (Venga-Ruiz A et al 2009).

Cladribine, interferon- α , and hydroxyurea, the most commonly considered cytoreductive agents for AdSM, have been associated with limited major response rates and response durations in mostly small, retrospective studies (Hauswirth AW et al 2004; Lim KH et al 2009). Allogeneic hematopoietic stem cell transplantation might be considered, although its value in SM is questionable (Ustun C et al 2014).

Response Assessment

Response criteria for SM in the literature vary, which limits the generalizability of findings in such a heterogeneous and rare disease.

In the Valent response criteria for AdSM, published in 2003 and supported in a 2007 consensus statement, the status of C-findings is the fundamental basis for response assessment (Valent P et al 2003; Valent P et al 2007). Major response (MR) requires normalization of at least 1 C-finding, with subcategories of MR based on the degree of reduction in mast cell infiltrates, serum tryptase levels, and SM-associated organomegaly (Appendix 13.5, Table 35). Partial response (PR) requires incomplete regression of at least 1 C-finding.

Numerous limitations to the Valent criteria have, however, been recognized (Gotlib J et al 2013) including:

- Responses in C-findings such as ascites and bone lesions are difficult to quantify. This in turn might increase interobserver variability.
- Patients with baseline laboratory values just outside normal range can achieve MR with modest improvement in disease burden.
- Criteria for baseline transfusion dependence and response are not defined.
- The minimal required DOR is unclear.
- Manifestations of organ damage caused by the SM component vs the AHN can overlap.
- Distinguishing cytopenias from bone marrow infiltration vs from other causes (such as hypersplenism, bone marrow fibrosis, and myelosuppression from prior therapy) can prove difficult.

The more rigorous IWG-MRT-ECNM response criteria for AdSM (Gotlib J et al 2013) overcome some (though not all) of these limitations. These criteria are summarized in Appendix 13.6 (Table 38 and Table 39). A comparison of the performance of the Valent and IWG-MRT-ECNM criteria has not, however, been published.

3 Regulatory Background

3.1 U.S. Regulatory Actions and Marketing History

Midostaurin is an NME.

3.2 Summary of Presubmission/Submission Regulatory Activity

Midostaurin was granted orphan designation for mastocytosis in 4/2010. Based on top-line results from a randomized phase 3 trial (Study A2301), midostaurin was granted Breakthrough Therapy Designation in 1/2016 for treatment of newly diagnosed, FLT3-mutated AML in adults eligible to receive standard induction and consolidation chemotherapy. Rolling review was granted in 4/2016, with a single NDA covering both disease indications. The NDA has been administratively split.

The clinical development program for AdSM was discussed at a Type C end-of-phase 2 meeting in 10/2011 and a Type C meeting in 1/2013. It was agreed that mature data from two single-arm studies (D2201, A2213) with sufficiently durable responses were considered adequate for consideration of regular approval in this rare disease. A Type B pre-NDA meeting for both indications occurred in 9/2015. In a 5/2016 pre-NDA meeting held primarily for the AML indication, the Sponsor agreed to include an integrated summary of safety (ISS) and pooled safety databases from multiple studies.

3.3 Foreign Regulatory Actions and Marketing History

Midostaurin has not been marketed outside of the U.S.

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4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

OSI was consulted to conduct inspections for Study D2201 at clinical sites in the Netherlands (Site 180) and Germany (Site 150). These sites were chosen based on relatively high accrual and outliers in efficacy results. Through site inspection, the data were determined to be acceptable.

OSI inspection of the Sponsor, however, identified instances of failure to ensure that Study D2201 was conducted in accordance with the protocol. This mainly consisted of late conduct of monitoring visits for 5 clinical sites. The issues identified do not affect the interpretability of the results.

4.2. Product Quality

No product quality concerns were identified on preliminary CMC review.

4.3. Clinical Microbiology

Not relevant to this application.

4.4. Nonclinical Pharmacology/Toxicology

In animal toxicology studies, midostaurin was predominantly associated with toxicities on proliferating tissues, especially the gastrointestinal tract (emesis, diarrhea, intestinal mucosal alteration, gastric hemorrhage), reproductive system (e.g., degenerated spermatogonia), bone marrow (hypocellularity, associated with cytopenias), and lymphoid tissues (depletion, atrophy). Reversible increases in liver enzymes and liver weight occurred in several species. Other findings included the heart (prolongation in P-Q interval, decreased heart rate, myocardial degeneration, myocarditis), lung (bronchopneumonia, lung edema), and possibly the neuromuscular system (ataxia, abnormal gait).

In animal studies, midostaurin caused embryo-fetal toxicity, including fetal anomalies and embryo-fetal death, at doses lower than the recommended human dose. Thus, midostaurin could cause fetal harm when administered to pregnant women. Based on animal data, midostaurin could impair male and female fertility, and could pass into the milk of lactating females.

Midostaurin does not appear to be genotoxic. Carcinogenicity studies were not performed.

4.5. Clinical Pharmacology

4.5.1. Mechanism of Action

Midostaurin is an orally bioavailable, small molecule that potently inhibits a range of receptor tyrosine kinases. In vitro, midostaurin or its two major active metabolites (CGP62221 and CGP52421) inhibit the activity of KIT (wild type and D816V mutant), FLT3, PDGFR, CSF-1R, ROS1, members of the protein kinase C family, and several other receptor tyrosine kinases including FGFR and VEGFR2.

In mastocytosis, somatic gain-of-function point mutations in the *KIT* gene (primarily D816V) lead to constitutive activation and autophosphorylation of KIT, with expansion of clonal mast cell populations. Such activating KIT mutations are detected in most patients with SM. In mast cells, midostaurin inhibits KIT signaling, cell proliferation and histamine release and induce apoptosis in vitro. The in vitro activity against KIT, including KIT mutations associated with resistance to other tyrosine kinase inhibitors such as imatinib (Growney JD et al 2005), provides biologic rationale for the development of midostaurin for SM treatment.

4.5.2. Pharmacodynamics

Cardiac electrophysiology: The Sponsor regarded Study CPKC412A2113A as a thorough QT study. This randomized, placebo- and moxifloxacin-controlled trial evaluated the effect of midostaurin 75 mg BID for 3 days on the QTc interval. No clinically significant prolongation of QTc interval was identified, nor was a significant relationship between changes in QTc and concentrations of midostaurin and its two active metabolites. However, the Interdisciplinary Review Team (IRT) reviewer noted that the study's major limitation is insufficient treatment duration to cover steady state therapeutic exposures of the active metabolite, CGP52421.

Per IRT review, in the AdSM safety population (defined in Section 5.1), 4.7% of patients had a post-baseline QTcF > 480 ms, no patients had a QTcF > 500 ms, and 6.3% had a Δ QTcF > 60 ms compared to baseline. In a randomized placebo-controlled study in AML, QTc prolongation was more frequent in patients randomized to midostaurin compared to patients randomized to placebo (QTcF > 480 ms, 10.1% vs 5.7%; QTcF > 500 ms, 6.2% vs 2.6%; and Δ QTcF > 60 ms, 18.4% vs 10.7%, respectively).

4.5.3. Pharmacokinetics

Midostaurin is primarily metabolized by CYP3A4.

Midostaurin exhibits time-dependent pharmacokinetics, with an initial increase in trough concentrations ($C_{\min}$) that reach maximal concentrations during the first week followed by a

Clinical Review
Yvette Kasamon, MD
NDA 207997, Orig 1
RYDAPT (Midostaurin)

decline to a steady-state after approximately 28 days. The pharmacokinetics of the metabolite CGP62221 showed a similar trend, whereas plasma concentrations of the metabolite CGP52421 continued to increase after one month of treatment. Notably, the maximal trough and steady-state concentrations of midostaurin, CGP62221, and CGP52421 were similar with 50 mg twice-daily and 100 mg twice-daily with food.

The mean terminal half-life is 21 hours for midostaurin, 32 hours for CGP62221 and 482 hours for CGP52421. Midostaurin is excreted mainly through the feces, primarily as metabolites.

Co-administration of midostaurin with a standard or high-fat meal is associated with 1.2-fold or 1.6-fold increases, respectively, in midostaurin exposure (area under the curve) as compared to administration in a fasted state. Midostaurin maximum concentration is reduced by 20% with a standard meal and by 27% with a high-fat meal, with delayed time to maximal concentration (1 to 3 hours in a fasted state).

Population PK analysis suggests that midostaurin PK is not significantly influenced by sex, age in adults, mild or moderate hepatic impairment, and mild or moderate renal impairment.

4.6. Devices and Companion Diagnostic Issues

A companion device or diagnostic is not included in this application. In 9/2015, FDA determined that a companion diagnostic for KIT D816V mutation is not required, because midostaurin has clinical activity in SM with or without this mutation.

4.7. Consumer Study Reviews

Not applicable.

Appears this way on original

5 Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

The trials in Table 1 are the primary basis for the efficacy and safety review.

Table 1: Clinical Trials of Midostaurin in Systemic Mastocytosis

Trial	Design	Regimen	Endpoints	Patients enrolled	Centers
Uncontrolled studies to support efficacy and safety					
D2201 (primary)	Phase 2, multicenter, single-arm study in previously treated or untreated advanced SM	Midostaurin 100 mg BID continuously	Primary: ORR (modified Valent) Secondary: DOR, TTR, PFS, OS, PRO	116 (FAS), 89 (PEP)	12 (global)
A2213 (supportive)	Phase 2, multicenter, single-arm study in previously treated or untreated advanced SM	Midostaurin 100 mg BID continuously	Primary: ORR (Valent) Secondary: OS	26	3 (US)

FAS, full analysis set; PEP, primary efficacy population; PRO, patient-reported outcome; TTR, time to response

Appendix 13.9 lists all trials of midostaurin that were included in the ISS. The AdSM safety population consists of the 142 patients in studies D2201 and A2213 combined. Table 2 summarizes other trials of midostaurin monotherapy, at or near the recommended dose for SM, that the reviewer selected for supportive safety data. The rationale for selecting these trials is discussed in Section 8.1.

Clinical Review
Yvette Kasamon, MD
NDA 207997, Orig 1
RYDAPT (Midostaurin)

Table 2: Supportive Safety Studies for AdSM Indication (Midostaurin Monotherapy, 200-225 mg Daily or Pediatric Equivalent)

Study	Title	N	Planned midostaurin dose	Planned dose (n) included in safety analysis
Second safety pool: hematological malignancies other than SM				
A2104	An open-label, phase II (proof of concept) trial of PKC412 mono-therapy in patients with AML and patients with high risk MDS	20	75 mg TID	75 mg TID (20)
A2104E1 ^a	An open label, randomized phase II trial of PKC412 mono-therapy in patients with AML and patients with high risk MDS with either wild-type or mutated <i>FLT3</i>	95	50 mg BID 100 mg BID	100 mg BID (43)
CPKC412-0006	A single center, open, multi-dose, exploratory phase II clinical trial of CGP 41251 in patients with advanced stage, progressive Chronic Lymphocytic Leukemia (CLL) or Non-Hodgkin's Lymphoma (NHL) to monitor tolerability, safety and biological activity	21	25 mg QD 75 mg BID 75 mg TID	75 mg TID (7)
A2114	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	22	30 mg/m ² BID 60 mg/m ² BID ^b	60 mg/m ² BID (15)
Other				
C99-PKC412-001	A phase I, ascending dose, placebo-controlled study of the safety, tolerability, and pharmacokinetics of multiple doses of PKC412 in patients with diabetes mellitus.	86	25 mg BID 50 mg BID 75 mg BID 75 mg TID 100 mg TID	75 mg TID (15)

^a Study A2104E2 in MDS/AML was excluded due to inpatient dose escalation.

^b Pediatric equivalent of 100 mg BID

5.2. Review Strategy

The clinical review was conducted by one primary reviewer. Study D2201 served as the primary basis for the review. Data reviewed included the ISS, summary of clinical safety (SCS), summary of clinical efficacy (SCE), individual clinical study reports (CSRs), patient narratives, and numerous information requests (IRs). JMP 11 was used to reproduce key analyses, based on data analysis datasets, and to conduct additional exploratory analyses.

6 Review of Relevant Individual Trials Used to Support Efficacy

6.1. Study D2201 (PKC412D2201): A Single Arm, Phase II, Open-Label Study to Determine the Efficacy of 100mg Twice Daily Oral Dosing of Midostaurin Administered to Patients with Aggressive Systemic Mastocytosis or Mast Cell Leukemia +/- an Associated Hematological Clonal Non-Mast Cell Lineage Disease

6.1.1. Study Design

Overview and Objectives

This is a single arm, open-label, multicenter phase 2 study of midostaurin 100 mg BID for previously treated or untreated AdSM, with a primary endpoint of ORR by 6 cycles. The study used an adapted Fleming two-stage design followed by an extension phase, with eligibility and response adjudicated by a Study Steering Committee (SSC).

Data submission: all enrolled subjects

Original protocol version: 4/17/2008

Study initiation: 1/6/2009

Status: ongoing; enrollment completed 6/12/2012

Data lock: 12/1/2014

Objectives and Endpoints:

Primary: SSC-assessed ORR in the first 6 cycles, defined as PR or MR per modified Valent criteria and revised IWG MDS criteria for transfusion-dependent cytopenias, with confirmation of response required after ≥ 8 weeks.

Secondary:

- DOR, TTR, PFS, OS
- Safety/tolerability
- Histopathologic response (% BM mast cells, serum tryptase levels)

Exploratory objectives include:

- Change in all C-findings, including non-measurable C-findings, per protocol response criteria
- PROs (per SF-12, MSAS)
- Pathology and PK correlates

Key Eligibility Criteria (Study D2201)

- Disease-related:
 - “ASM or MCL +/- AHN” with relapse to 0 to 2 prior regimens of SM treatment

Clinical Review
Yvette Kasamon, MD
NDA 207997, Orig 1
RYDAPT (Midostaurin)

- Relapse/progression after imatinib, if SM has eosinophilia and known F1P1L1-PDGFR α fusion
- At least 1 of the following:
 - a. ≥ 1 measurable C-finding defined as:
 - ANC $< 1000/\mu\text{L}$, hemoglobin $< 10\text{g/dL}$ or platelets $< 100,000/\mu\text{L}$,
 - Hepatomegaly with impaired liver function (+/- ascites, portal hypertension)
 - Palpable splenomegaly with hypersplenism
 - Malabsorption with hypoalbuminemia and/or significant weight loss
 - b. Transfusion-dependent (TD) anemia (≥ 4 transfused units within 56 days)
- AHN is not life-threatening or acute stage
- > 30 days since chemotherapy – no restriction on steroids
- Age ≥ 18 y
- ECOG PS 0-3
- QTcF ≤ 450 ms
- End-organ function:
 - AST and ALT ≤ 2.5 x ULN unless due to AdSM, then AST/ALT ≤ 5 x ULN
 - Bilirubin ≤ 1.5 x ULN unless due to AdSM, then bilirubin ≤ 3 x ULN
 - Creatinine ≤ 2.0 mg/dL
 - ANC $\geq 1500/\mu\text{L}$, hemoglobin ≤ 10 g/dL, and platelets $\geq 75,000/\mu\text{L}$ unless disease-related
- No cardiovascular disease, including LVEF $< 50\%$, recent MI, and poorly controlled hypertension
- No pulmonary infiltrates, even if clinical symptoms of pulmonary infection are resolved

Treatment Plan

Midostaurin 100 mg po BID after meals, with 28-day cycle length, continued until disease progression or unacceptable toxicity.

Dose modifications for toxicity: Guidelines are summarized in Appendix 13.7 (Table 40).

Supportive care: Inpatient monitoring was required on days 1-3 of cycle 1. A protocol amendment mandated prophylactic antiemetics. Concomitant glucocorticoids were permitted to mitigate symptoms from SM.

Schedule of evaluations: Refer to Appendix 13.8 (Table 41).

Statistical Analysis Plan

This was an adaptive Fleming 2-stage design, with an extension phase if the H_0 was rejected (H_0 : ORR $\leq 30\%$).

Clinical Review
 Yvette Kasamon, MD
 NDA 207997, Orig 1
 RYDAPT (Midostaurin)

Analysis sets

- Full analysis set (FAS): all patients assigned to study treatment.
- Primary efficacy population (PEP): response-evaluable patients (based on modified Valent criteria described below) with ≥ 1 measurable C-finding or TD anemia. The SSC evaluated efficacy in the PEP.

Response Criteria

Study D2201 introduced modifications to the Valent criteria as summarized in Table 3. The criteria are compared further in Appendix 13.5 (Table 36, Table 37). Because Valent criteria cannot accurately assess response in patients with transfusion-dependent anemia or thrombocytopenia, the modifications included use of IWG criteria for MDS (Cheson BD et al 2006), which considered transfusion therapy in the assessment of RBC and platelet response.

Table 3: Comparison of Valent and Modified Valent Criteria

Criterion	Valent criteria	Modified Valent criteria (D2201)
Minimum increase required for good PR, in addition to C-finding reversion	ANC 100/ μ L, hemoglobin 1 g/dL, platelets 10,000/ μ L	ANC 200/ μ L, hemoglobin 1.5 g/dL, platelets 20,000/ μ L
Threshold for minor response	C-finding reversion by $> 0\%$ to $\leq 50\%$	C-finding reversion by $> 20\%$ to $\leq 50\%$
Non-measurable C-findings (e.g. ascites, bone lesions)	Included	Not included, for stringency of response assessment
Transfusion-dependent anemia	Not differentiated from transfusion-independent anemia as a C-finding	Included as an eligible C-finding
Minimum response duration	Not specified	≥ 8 weeks

Source: Adapted from response to 10/18/2016 IR.

In contrast to Study A2213, Study D2201 considered patients on corticosteroids (> 10 mg prednisone daily or equivalent for ≥ 1 cycle) unevaluable for response in the primary analysis.

Protocol Amendments

Of 6 amendments, the following are considered major:

Clinical Review
Yvette Kasamon, MD
NDA 207997, Orig 1
RYDAPT (Midostaurin)

D2201	Key changes:
Amendment 1 (11/2008)	• No longer require imatinib for KIT D816V mutation-negative disease • Extend minimum response duration from 4 weeks to 8 weeks • Expand secondary objectives to include DOR, time to response, safety, OS, and characterization of KIT mutation status
Amendment 2 (11/2010)	• Limit enrollment to patients with measurable C-findings • Add response criteria for patients receiving blood transfusions • Refine definition of PEP • Conduct central pathology review by 2 expert pathologists in SSC • Add histopathologic response as secondary objective • Systematically collect mediator-related symptoms • Mandate prophylactic antiemetics • Implement extension phase to provide more safety and efficacy data
Amendment 6 (5/2014)	• Revise definition of end-of-study to allow extended data collection

Data Quality and Integrity: Sponsor's Assurance

The Sponsor described methods of assuring data quality and integrity, including data verification at all sites and auditing of the data management CRO to monitor consistency between electronic CRFs and source data.

6.1.2. Study Results

Compliance with Good Clinical Practices

The Sponsor stated that study was conducted in compliance with Good Clinical Practice.

Financial Disclosure

See Appendix 13.2. Of the 208 investigators, all provided disclosure information, and 6 of 208 reported disclosable financial interests. The financial disclosure information did not raise concerns about data integrity.

Patient Disposition: See Section 7.1 (Table 8).

Protocol Violations/Deviations

Table 4 summarizes reported protocol deviations. Approximately 25% of patients had at least one major protocol deviation, most commonly the absence of measurable C-findings, resulting in exclusion from the PEP. Also of note were the significant proportions of patients having outdated or missing disease and safety assessments at baseline.

Clinical Review
 Yvette Kasamon, MD
 NDA 207997, Orig 1
 RYDAPT (Midostaurin)

Table 4: Reported Protocol Deviations – Study D2201

	From N of 116:	
	n	(%)
Any protocol deviation	97	(84%)
Major protocol deviation	30	(26%)
AdSM eligibility criteria not met per SSC, with resultant exclusion from PEP	27	(23%)
Other concurrent antineoplastic therapy	3	(3%)
Other prohibited medication	3	(3%)
Minor protocol deviation	94	(81%)
Selected deviations:		
Baseline echo or MUGA > 14 days old or not done	56	(48%)
Baseline abdomen/pelvis CT > 14 days old or not done	42	(36%)
Midostaurin dose below 100 mg/day	30	(26%)
Baseline skeletal survey > 3 months old or not done	19	(16%)
Baseline chest x-ray > 28 days old or not done	15	(13%)
Baseline labs > 7 days old	12	(10%)
No 28-day safety follow-up after last dose	9	(8%)
Dose modification not per protocol	8	(7%)
Response assessment not performed	3	(3%)
Cardiovascular disease at baseline	3	(3%)
Baseline QTcF > 450 ms	2	(2%)

Source: D2201 CSR, Section 10.2 and Table 14.1-2.1

Review comments:

- The multiple missing evaluations raise concern about the quality of study oversight and conduct.
- Because patients not meeting disease eligibility criteria were excluded from the PEP and response was adjudicated by the SSC, the overall interpretability of the primary efficacy analysis is not affected.
- However, the large number of other protocol deviations raises potential safety concerns, including in patients whose baseline labs, chest imaging, and cardiac function were either outdated or not performed, and patients whose 28-day safety follow-up was not performed. Such deviations might have modest impact on the overall assessment of safety and efficacy.

Table of Demographic Characteristics

Section 7.1 (Table 6) presents demographics side-by-side for studies D2201 and A2213, along with other baseline parameters.

Other Baseline Characteristics: Refer to Section 7.1 (Table 6).

Clinical Review
Yvette Kasamon, MD
NDA 207997, Orig 1
RYDAPT (Midostaurin)

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Approximately 25% of patients had a reported total midostaurin dose of < 100 mg/day (Table 4). To what extent this reflects noncompliance versus toxicity is unclear. The majority (66%) of patients had an RDI of $\geq 90\%$, with a mean RDI of 89% (Table 7).

Per FDA analysis, 22% of patients received at least one dose of corticosteroids during study treatment, most commonly to treat symptoms of SM.

Efficacy Results – Primary Endpoint: Refer to Section 7.1.1.

Efficacy Results – Secondary and other relevant endpoints: Refer to Section 7.1.2.

Dose/Dose Response: Refer to Section 7.1.4.

Durability of Response: Refer to Section 7.1.2.

Persistence of Effect: Refer to Section 7.1.2.

Additional Analyses Conducted on the Individual Trial: Refer to Section 7.1

6.2. Study A2213 (PKC412A2213): A Single Arm, Phase II, Open-Label Study To Determine The Efficacy Of Twice Daily Oral Dosing Of PKC412 Administered To Patients With Aggressive Systemic Mastocytosis (ASM) and Mast Cell Leukemia (MCL) +/- Hematological Clonal Non-Mast Cell Lineage Disease

6.2.1. Study Design

Overview and Objectives

This is a single-arm, open-label, multicenter phase 2 trial of midostaurin 100 mg po BID for previously treated or untreated AdSM, with a primary endpoint of ORR by 2 cycles per investigator assessment.

Data submission: all enrolled subjects

Original protocol version: 8/18/2004

Study initiation: 6/27/2005

Status: ongoing; enrollment complete

Data lock: 12/3/2012

Clinical Review
Yvette Kasamon, MD
NDA 207997, Orig 1
RYDAPT (Midostaurin)

Objectives and Endpoints

Primary: investigator-assessed ORR in the first 2 cycles, defined as PR or MR per original Valent criteria (Appendix, Table 35).

Secondary: include safety and PK, 1-year OS

Key Eligibility Criteria (Study A2213)

- Disease-related:
 - Histologically documented “ASM or MCL +/- AHN”
 - Relapse or progression after imatinib, if SM has eosinophilia and known positivity for F1P1L1-PDGFR α fusion
 - > 30 days since chemotherapy; glucocorticoids tapered to off or minimum dose by Day 1
- Age $\geq$ 18 y
- Karnofsky $\geq$ 30% (ECOG PS 0-3)
- End-organ function:
 - Normal AST/ALT, unless due to AdSM, then AST/ALT $\leq$ 4 x ULN and/or bilirubin $\leq$ 4 x ULN
 - Creatinine $\leq$ 2.0 mg/dL
 - ANC $\geq$ 1500/ μ L, hemoglobin $\leq$ 10 g/dL, and platelets $\geq$ 75,000/ μ L unless disease-related
- No active, unrelated pulmonary disease, HIV infection, or active viral hepatitis

Treatment Plan

Midostaurin 100 mg po BID after meals for up to twelve 28-day cycles, with option for continued treatment on an extension protocol if there was continued response without requirement for other chemotherapy. Failure to achieve PR or MR after 2 cycles required treatment discontinuation.

Supportive care: Inpatient monitoring was required on Days 1-3 of Cycle 1. Prophylactic antiemetics were optional. Concomitant glucocorticoids were permitted to mitigate symptoms from SM.

Evaluations: Response assessment occurred after each cycle for Cycles 1-12, with bone marrow biopsy scheduled after Cycles 1, 2, 3, 6, 9 and 12, followed by a reduced evaluation schedule. After treatment discontinuation, patients were followed every 3 months for up to 1 year.

Statistical Analysis Plan

This was a Simon two-stage design based on response rate (Ho: ORR $\leq$ 10%). The same population met criteria for the FAS and PEP.

Response Assessment

Response was evaluated by the investigator using original Valent criteria (Appendix 13.5).

Review comments:

- **Notably, Study A2213 did not specify that response be maintained for a minimum duration in order to be counted as a response. Unconfirmed ORR is likely an overestimate of the treatment effect, because it includes transient improvements in disease burden.**
- **In contrast to Study D2201, Study A2213 considered patients on concurrent corticosteroids to be evaluable for response. Because high-dose corticosteroids potentially confound the response assessment, regarding such patients as evaluable might also overestimate the treatment effect.**
- **For the assessment of efficacy, several other differences between studies D2201 and A2213 are noteworthy and summarized in Table 5.**

Table 5: Efficacy Measures in Study D2201 vs. Study A2213

Key differences in design	Study D2201	Study A2213
Adjudication of eligibility	Yes	No
Response criteria	Modified Valent and Cheson criteria	Published Valent criteria
C-findings used for response assessment	Measurable C-findings only	Measurable and non-measurable C-findings
Use of transfusion data in response assessment	Yes	No
Confirmation of responses	Yes	No*
Adjudication of responses	Yes, by the SSC	No
Timing of responses for primary efficacy analysis	During first 6 cycles (168 days) of treatment	During first 2 cycles (56 days) of treatment
Duration of participation in study	Until disease progression	Until disease progression; non-responders discontinued after 2 cycles
Duration of OS follow-up	Until end of study (5 years after LPFT, or all patients discontinued)	1 year post treatment

Source: SCE Table 3-1

Amendments

The following protocol amendments and extensions to A2213 are considered major:

A2213	Key changes:
Core protocol, Amendment 1 (11/2004)	• Remove secondary objective of evaluating PK effect of itraconazole; remove combined treatment with midostaurin and itraconazole • Revise dose modification guidelines for toxicity
Extended Treatment Protocol (11/2006)	• Allow treatment beyond 12 cycles in patients with continued response

Clinical Review
Yvette Kasamon, MD
NDA 207997, Orig 1
RYDAPT (Midostaurin)

6.2.2. Study Results

Compliance with Good Clinical Practices

The Sponsor stated that study was conducted in compliance with Good Clinical Practice.

Financial Disclosure

See Appendix 13.2. Of the 49 investigators, 4 had missing disclosures and the remainder reported no disclosable financial interests. The disclosure information did not raise concerns about data integrity.

Patient Disposition: Refer to Section 7.1 (Table 8).

Protocol Violations/Deviations

All patients had at least one reported protocol deviation, although none were major (A2213 CSR Table 14.1-2.1). Deviations included missing response assessments after Cycle 2 (23%), and treatment continuation despite lack of documented response after 2 cycles (12%) or despite >14 days of treatment interruption (8%). The deviations do not affect the overall interpretability of the results.

Table of Demographic Characteristics: Refer to Section 7.1 (Table 6).

Other Baseline Characteristics: Refer to Section 7.1 (Table 6).

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment compliance appeared high, based on most patients (85%) having an RDI of >90% (Table 7). Approximately 30% of patients received at least one dose of corticosteroid during the course of study treatment.

Efficacy Results – Primary Endpoint: Refer to Section 7.1.1.

Data Quality and Integrity – Applicant’s Assurance

Study A2213 was investigator-initiated and led. The Sponsor contracted a CRO to verify data quality and accuracy. The CRO produced a new database and new electronic CRFs to meet the Sponsor’s requirements. A major limitation of the CRFs – failure to collect C-findings – is discussed in Section 7.1.1.

Efficacy Results – Secondary and other relevant endpoints: Refer to Section 7.1.2.

Dose/Dose Response: Refer to Section 7.1.4.

Durability of Response: Refer to Section 7.1.2.

Persistence of Effect: Refer to Section 7.1.3.

7 Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

The assessment of efficacy is based primarily on Study D2201, with Study A2213 as supportive. As described in Section 6, both studies evaluated a planned midostaurin dose-schedule of 100 mg po BID (cycle length, 28 days) until disease progression or unacceptable toxicity in patients with treated or untreated advanced SM. The studies had similar eligibility criteria, had a primary endpoint of ORR, and had additional outcome measures that included DOR. Notable differences in efficacy measures are discussed in Section 6.2.1.

To integrate the efficacy analysis, the tables that follow present baseline patient and disease characteristics, treatment, and disposition side-by-side for studies D2201 and A2213.

Review comments:

- **The Sponsor presented efficacy for “ASM with or without AHN” and “MCL,” with MCL also including cases of AHN. This classification is unconventional; per the WHO classification, ASM and MCL by definition exclude AHN.**
- **For evaluations of efficacy to be interpretable and generalizable, analyses must instead be presented according to the established WHO classification of SM subtypes, as determined by central histopathology review. Therefore, FDA required that the Sponsor submit efficacy data according to centrally confirmed histologic subtype.**

Baseline Characteristics

Baseline characteristics of patients in Studies D2201 and A2213 are summarized in Table 6. In both studies, the median age was > 60, and SM-AHN was the common histologic subtype. The majority of patients had a documented D816V mutation at baseline (81% in Study D2201), most had splenomegaly, hepatomegaly, and bone lesions, and approximately half had ascites.

Of the 116 patients treated on Study D2201, an SSC evaluated 89 for response in the primary efficacy analysis because these patients met disease eligibility criteria, including having measurable C-findings. In the PEP, the most common ($\geq 20\%$) measurable C-findings were thrombocytopenia (62%), anemia (31%), transfusion-dependent anemia (22%), hypoalbuminemia (54%), and hyperbilirubinemia (28%)(Source: CSR Table 11-6).

Table 6: Baseline Characteristics of Efficacy Populations (D2201, A2213)

	D2201 PEP (N=89)		D2201 FAS (N=116)		A2213 ^a (N=26)	
Demographics						
Age						
Median (range)	64	(25-82)	63	(25-82)	64	(24-79)
≥ 65	43	(48%)	51	(44%)	13	(50%)
≥ 70	32	(36%)	34	(29%)	5	(19%)
Male sex						
	57	(64%)	76	(66%)	15	(58%)
Race						
Caucasian	86	(97%)	111	(96%)	21	(81%)
Black	1	(1%)	2	(2%)	0	(0%)
Other or unknown	2	(2%)	3	(3%)	5	(19%)
ECOG performance status						
0 or 1	57	(64%)	77	(67%)	12	(46%)
2	25	(28%)	31	(27%)	10	(38%)
3	7	(8%)	8	(7%)	4	(15%)
Disease Parameters						
WHO diagnosis per central review						
ASM	16	(18%)	16	(14%)	0	(0%)
SM with AHN	57	(64%)	73	(63%) ^e	17	(65%)
MCL	16	(18%)	21	(18%)	6	(23%)
SM type unknown	0	(0%)	6	(5%)	3	(12%)
Diagnosis (Sponsor categorization)						
ASM with or without AHN	73	(82%)	95	(82%)	20	(77%)
MCL	16	(18%)	21	(18%)	6	(23%)
KIT D816 mutation status						
Mutated	77	(87%)	98	(84%)	18	(69%)
Documented D816V mutation	73	(82%)	94	(81%)	14	(54%)
Wild type	10	(11%)	13	(11%)	8	(31%)
Unknown	2	(2%)	5	(4%)	0	(0%)
Disease burden						
Hepatomegaly	63	(71%)	73	(63%)	17	(65%)
Splenomegaly	82	(92%)	104	(90%)	22	(85%)
Ascites	51	(57%)	58	(50%)	14	(54%)
Bone lesions	56 ^b	(63%)	73 ^b	(63%)	20	(77%)
Serum tryptase (µg/L), median (IQR)	236	(174-436)	200	(117-410)	347 ^c	(141-662)

Table 6: Baseline Characteristics of Efficacy Populations (D2201, A2213)

	D2201 PEP (N=89)	D2201 FAS (N=116)	A2213 ^a (N=26)
Measurable C-findings			
1	31 (35%)	–	–
2	20 (22%)		
≥ 3	38 (43%)		

Source: FDA analysis, Section 14.1 of individual CSRs, and SCE Tables 3-8 and 3-9

^a In A2213, the same population comprises the FAS and PEP.

^b Missing in 3 patients on D2201 (2 in PEP).

^c Median per FDA analysis; differs slightly from reported value.

^d 3 patients had missing values.

^e The most common AHNs were CMML and MDS/MPN.

In Study D2201, 31 patients overall (27%) , including 25 in the PEP (28%), were not assessable for MCL because of the quality of the bone marrow aspirates. The SSC categorized such cases as ASM because of the presence of one or more C-findings. Twenty-one patients overall (18%) had unconfirmed presence of AHN and were thus categorized as not having AHN (Source: SCE Table 3-7).

Review comments:

- In Study D2201, although central histopathology review confirmed SM in each case, significant uncertainties about the type of SM remain.
- These limitations in data affect the analysis of efficacy according to SM subtype. The limitations should be mentioned in the PI.

Treatment and Exposure

Table 7 summarizes prior treatments for SM and the exposure to midostaurin. Notably, in Study D2201, 59% of patients overall had no prior therapy for SM, 23% had 1 prior therapy, and 17% had 2 or more prior therapies. The distribution in the PEP was similar. Fifteen percent overall had a tyrosine kinase inhibitor (mainly imatinib), with other treatments including cladribine and interferon.

Table 7: Prior and On-Study Treatments (D2201, A2213)

	D2201 PEP (N = 89)		D2201 FAS (N = 116)		A2213 FAS (N = 26)	
PRIOR TREATMENT ^a						
Prior SM regimens (excluding AHN regimens)						
No	57	(64%)	69	(59%)	8	(31%)
Yes	32	(36%)	47	(41%)	18	(69%)
1	19	(21%)	27	(23%)	10	(38%)
2	11	(12%)	14	(12%)	2	(8%)
≥ 3	2	(2%)	6	(5%)	6	(23%)
Selected SM regimens						
Tyrosine kinase inhibitor	15	(17%)	17 ^b	(15%)	13	(50%)
Imatinib	10		11		10	
Dasatinib	5		6		4	
Nilotinib	1		1		0	
Cladribine	12	(13%)	16 ^b	(14%)	5	(19%)
Interferon	7	(8%)	11 ^b	(9%)	3	(12%)
Relapses to prior SM therapy, after response						
0	27	(30%)	37	(32%)	26	(100%)
1-2	9	(10%)	14	(12%)	0	(0%)
≥ 3	0	(0%)	0	(0%)	0	(0%)
Missing	53	(60%)	65	(56%)	0	(0%)
MIDOSTAURIN ^b						
Exposure time, months						
Median (range)	11	(< 1-68)	11	(< 1-68)	10	(< 1-81)
IQR	4 - 28		4 - 30		2 - 35	
Minimum exposure						
< 3 months	19	(21%)	25	(22%)	7	(27%)
≥ 3 months	70	(79%)	91	(78%)	19	(73%)
≥ 6 months	59	(66%)	76	(66%)	15	(58%)
≥ 12 months	42	(47%)	57	(49%)	12	(46%)
≥ 24 months	28	(31%)	39	(34%)	9	(35%)
≥ 36 months	15	(17%)	21	(18%)	6	(23%)
RDI						
Mean, %	91		89		98	
90-100%, n	–		77	(66%)	22	(85%)
80-89%, n			15	(13%)	2	(8%)

Clinical Review
 Yvette Kasamon, MD
 NDA 207997, Orig 1
 RYDAPT (Midostaurin)

< 80%, n	24	(21%)	0	(0%)
Unknown, n	0	(0%)	2	(8%)

^a Source: Individual CSRs Section 14.1 and response to 12/2/2016 IR.

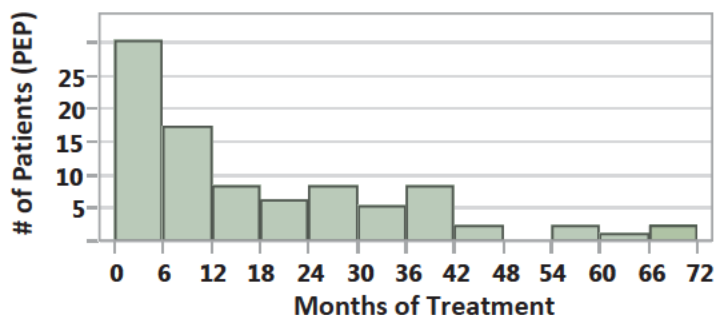
^b Source: FDA analysis.

Review comments

- The efficacy data on patients previously treated for SM is limited, particular for patients having 2 or more prior therapies.
- Missing data in Study D2201 preclude characterization of the number of prior treatment failures.

Table 7 summarizes the exposure to midostaurin. The median exposure was similar in studies D2201 and A2213, ranging from 10 to 11 months. In Study D2201 overall, approximately 80% of patients received at least 3 months of midostaurin, approximately half received at least 12 months, and approximately 30% received at least 24 months. Figure 1 displays the distribution of midostaurin exposure in the D2201 PEP, which was similar to that of the FAS.

Figure 1: Exposure in D2201 Primary Efficacy Population (N = 89)



Source: FDA analysis

Disposition

Table 8 summarizes the disposition of patients in both studies. The leading causes of treatment discontinuation were disease progression and AEs.

Table 8: Disposition of Patients with AdSM (D2201, A2213)

	D2201 PEP (N = 89)	D2201 FAS (N = 116)	A2213 (N = 26)
Treatment ongoing	15 (17%)	21 (18%)	7 (27%)
Primary reason for ending treatment			
AE ^a	–	28 / 95 (29%)	4 / 19 (21%)
Withdrawal of consent	–	10 (11%)	3 (16%)
Death	–	8 (8%)	1 (5%)
Disease Progression	–	44 (46%)	6 (32%)
Unsatisfactory treatment effect	–	0 (0%)	5 (26%)
Other	–	5 (5%)	0 (0%)

Source: D2201 CSR (Section 10.1 and 14) and A2213 CSR (Section 14), except as noted.

^a May include AEs attributable to underlying malignancy.

^b Source: FDA analysis

7.1.1. Primary Endpoints

Although both studies evaluated response based on modified Valent or Valent criteria, the reviewer also considered response according to IWG-MRT-ECNM consensus criteria in the evaluation of efficacy.

Review comments:

- Although “AdSM” is not a WHO category, the term (comprising ASM, SM-AHN, and MCL) is used throughout the literature, including in IWG-MRT-ECNM consensus criteria. Therefore, this review presents efficacy for each SM subtype, as well as for “AdSM” overall.
- Although not prespecified, response evaluation according to IWG-MRT-ECNM criteria is key. The criteria are more rigorous, were designed to address limitations of the Valent criteria, and are expected to be the standard for future studies.

Study D2201 - Response

a. Modified Valent Criteria

The study met its primary efficacy endpoint, rejecting the null hypothesis of an ORR $\leq$ 30% among the 40 patients enrolled in Stage 1.

Of the 116 patients treated, the SSC evaluated 89 for response according to modified Valent

criteria. The median age in this subgroup was 64 years (range: 25 to 82), 36% had prior therapy for SM, and 82% had the KIT D816V mutation detected at baseline (Table 6) . Their median duration of treatment was 11 months (range: < 1 to 68 months), with treatment ongoing in 17%.

Table 9 summarizes response in the PEP according to modified Valent criteria, which required a minimum response duration of 8 weeks. The ORR (major + partial response) in 6 cycles was 60% (95% CI, 49-70) in all AdSM subtypes combined (45% MR), with a median time to response of 9 days. The ORR was 75% in ASM, 58% in SM-AHN, and 50% in MCL, with the lower bounds of the 95% CI ranging from 25 to 48%. Because of the small sample size, the CIs for efficacy measures are wide.

Table 9: SSC-Adjudicated Response per Modified Valent Criteria – D2201 PEP

	PEP, any SM ^h (N = 89)		ASM (N = 16)		SM-AHN (N = 57)		MCL (N = 16)	
Best response with 6 cycles (SSC)^a								
Major response	40	(45%)	10	(63%)	23	(40%)	7	(44%)
Complete remission	0		0		0		0	
Incomplete remission	19		6		9		4	
Pure clinical response	15		4		9		2	
Unspecified	6		0		5		1	
Partial response	13	(15%)	2	(13%)	10	(18%)	1	(6%)
Good partial response	11		1		10		0	
Minor response	2		1		0		1	
No response (SD or PD)	21	(24%)	2		13	(23%)	6	(38%)
Not evaluable	15	(17%)	2		11	(19%)	2	(13%)
ORR with 6 cycles (MR + PR)	53	(60%)	12	(75%)	33	(58%)	8	(50%)
95% CI for ORR ^b	(49, 70)		(48, 93)		(44, 71)		(25, 75)	
DOR, months^c								
Estimated median (95% CI) ^d	31.4	(10.8, –)	NR	–	12.7	(7.4, 31.4)	NR	–
25 th , 75 th percentile	9.0, –		–		7.4, –		10.8, –	
Median of actual values	12.7		29.4		9.1		22.2	
Range ^e	1.9+, 66.9+		2.3+, 66.9+		1.9+, 52.1+		3.6, 65.8+	
Number censored for DOR	22/53	(42%)	2/12	(17%)	18/33	(55%)	2/8	(25%)
Median follow-up for DOR, months^{c, f}	30.5		–		–		–	
Time to response, days^g								
Median (range)	9	(3-113)	9	(3-58)	15	(3-113)	8	(3-91)

Table 9: SSC-Adjudicated Response per Modified Valent Criteria – D2201 PEP

	PEP, any SM ^h (N = 89)	ASM (N = 16)	SM-AHN (N = 57)	MCL (N = 16)

Source: FDA analysis except as noted.

^a Categories of MR and PR are from D2201 CSR Section 14.2.

^b Exact binomial CI.

^c In responders, measured from date of first objective response until date of last assessment.

^d Kaplan-Meier method.

^e + sign indicates censored value.

^f Reverse Kaplan-Meier method.

^g Time from treatment initiation to first confirmed response per SSC.

^h 25 patients were not assessable for the presence of MCL on central histopathology review. Patients with unconfirmed presence of AHN were regarded as not having AHN.

In the PEP, 5 additional patients had confirmed responses (all MR) that began after 6 cycles, for an ORR of 64% (95% CI, 54-75): 2 with ASM, 2 with SM-AHN, and 1 with MCL (Source: D2201 CSR and IR).

Investigator and SSC assessments of ORR were similar. By investigator assessment, the ORR in the PEP in the first 6 cycles, per modified Valent criteria, was 53% (95% CI, 42-64), with 37% MR and 16% PR (Source: D2201 CSR, Table 14.2-1.5).

b. IWG-MRT-ECNM criteria

Per FDA request, the Sponsor also submitted data on response using IWG-MRT-ECNM criteria, which could be applied to 115 of the 116 patients in FAS. Table 10 summarizes response per IWG-MRT-ECNM criteria, which require 12-week confirmation. Midostaurin had activity in all types of AdSM. Notably, however, the observed ORR (defined as CR + PR) and depth of response were lower with these newer criteria. In all patients combined, the ORR was 17% (95% CI, 10-25%), with only 2% CR. Among SM subtypes, ORR ranged from 19 to 31%, with the lower bound of the 95% CI ranging from 5 to 11%.

Table 10: Response per IWG-MRT-ECNM Criteria – Study D2201

D2201 FAS					
	All subtypes (N = 115) ^{b, c, d}	ASM (N = 16)	SM-AHN (N = 72) ^b	MCL (N = 21)	Type unknown (N = 6)
ORR (CR + PR) in 6 cycles, n^a (95% CI)	19 (17%) (10, 25)	5 (31%) (11, 59)	8 (11%) (5, 21)	4 (19%) (5, 42)	2 (33%) (4, 78)
Best response in 6 cycles					
Complete remission	2 (2%)	1 (6%)	0 (0%)	1 (5%)	0 (0%)
Partial remission	17 (15%)	4 (25%)	8 (11%)	3 (14%)	2 (33%)
Clinical improvement	20 (17%)	3 (19%)	13 (18%)	3 (14%)	1 (17%)
SD or PD	63 (55%)	7 (44%)	42 (58%)	12 (57%)	2 (33%)
Not evaluable	13 (11%)	1 (6%)	9 (13%)	2 (10%)	1 (17%)
DOR, months^e					
Range	6.8+, 60.5+	10.2+, 36.4+	6.8+, 51.8+	8.6+, 55.9+	27.3+, 60.5+
Median follow-up for DOR	35.0	–	–	–	–
D2201 PEP					
	All subtypes (N = 89)	ASM (N = 16)	SM-AHN (N = 57)	MCL (N = 16)	
ORR (CR + PR) in 6 cycles, n^a 95% CI for ORR	15 (17%) (10, 26)	5 (31%) (11, 59)	7 (12%) (5, 24)	3 (19%) (4, 46)	
Best response in 6 cycles					
Complete remission	1 (1%)	1 (6%)	0 (0%)	0 (0%)	
Partial remission	14 (16%)	4 (25%)	7 (12%)	3 (19%)	
Clinical improvement	17 (19%)	3 (19%)	12 (21%)	2 (13%)	
SD or PD	49 (55%)	7 (44%)	25 (44%)	10 (63%)	
Not evaluable	9 (10%)	1 (6%)	7 (12%)	1 (6%)	

Source: FDA analysis.

^a Per Sponsor, with 12 week confirmation. The use of high-dose corticosteroid was not taken into account in determining response according to these criteria.

^b Response criteria not applied to 1 patient with SM-AHN.

^c 31 patients were not assessable for MCL on central review. Patients with unconfirmed AHN were classified as not having AHN.

^d Median exposure, 11.2 months.

^e Estimated median DOR was not reached in any subtype. A + sign indicates a censored value.

Review comments:

- Compared to modified Valent criteria, the response rate is lower according to IWG-

MRT-ECNM criteria, if defined as CR + PR. The depth of response is also less, with most responses being partial. Nevertheless, the responses are durable (minimum response duration > 6 months) and are therefore clinically meaningful.

- **The IMG-MRT-ECNM consensus criteria are, in the reviewer’s opinion, unclear as to what minimum level of improvement – in particular, at least PR vs at least clinical improvement (CI) – should constitute a formal response for the purposes of a clinical trial. The paper’s references to response include CI. However, whether and to what degree CI vs PR vs CR constitute potential measures of clinical benefit in AdSM are undefined.**
- **(b) (4) Although CI must be maintained for ≥ 12 weeks, it requires resolution of only one CI measure (Table 39). The CI criteria vary in stringency. For example, transfusion-dependent anemia becoming transfusion-independent for ≥ 12 weeks potentially fulfills criteria for CI, but so does normalization of only 1 liver function test. Thus, while CI might be a surrogate measure of clinical benefit and is reasonably considered “response,” the reviewer recommends that only PR and CR be included in the ORR for the purposes of evaluating this application.**

Study A2213 - Response

In Study A2213, 31% of patients had no prior therapy for SM, 38% had 1 prior therapy, and 31% had 2 or more prior therapies. Approximately half had a documented D816V mutation at baseline, and half had received a tyrosine kinase inhibitor (Table 6, Table 7).

a. Valent criteria

Table 11 summarizes investigator-assessed response according to Valent criteria. The study met its primary efficacy endpoint, rejecting the null hypothesis of an (unconfirmed) ORR of $\leq 10\%$.

Because response lasting less than 2 months suggests chemoresistant disease, and because Study D2201 required confirmation of response after ≥ 8 weeks, Table 11 presents both unconfirmed and confirmed responses.

Table 11: Response per Valent Criteria – Study A2213

	All confirmed subtypes (N = 23)	MCL (N = 6)	SM-AHN (N = 17)	Type unknown (N = 3)
Without response confirmation:				
BOR by 2 cycles, per investigator				
Major response (0 complete)	12 (52%)	1 (17%)	11 (65%)	1
Partial response	5 (22%)	3 (50%)	2 (12%)	1
SD or PD	6 (26%)	2 (35%)	4 (24%)	1
Unconfirmed ORR (MR + PR)	17 ^a (74%)	4 (67%)	13 (76%)	–
95% CI for ORR	(52, 90)	(22, 96)	(50, 93)	
With 8 week confirmation:				
BOR by 2 cycles, per investigator				
Major response	10 (44%)	1 (17%)	9 (53%)	0
Partial response	2 (9%)	1 (17%)	1 (6%)	1
Confirmed ORR (MR + PR)	12 (52%)	2 (33%)	10 (59%)	1
95% CI for ORR	(31, 73)	(4, 78)	(33, 82)	
DOR, months				
Estimated median	NR	NR	NR	–
Median from actual values	29.3	–	24.9	–
Range of DOR	3.4+, 79.2+	28.6+, 32.1+	3.4+, 79.2+	

Source: FDA analysis

^a 1 additional patient responded after 2 cycles (source: SCE Section 3.3.1).

According to Valent criteria, of 17 patients with SM-AHN, 10 achieved a response (1 partial, 9 major) by 2 cycles that was confirmed after 8 weeks. Of 6 patients with MCL, 2 responded. Median DOR for either group had not been reached, with DOR ranging from 3+ to 79+ months in patients with SM-AHN and 29+ to 32+ months in patients with MCL. In the 3 other patients, the subtype of SM was not centrally confirmed.

Review comments:

- In Study A2213, the CRFs failed to collect C-findings, yet C-findings are the fundamental basis of response assessment. Investigator-based responses were furthermore not formally adjudicated. In response to a 9/20/2016 IR (SDN 14), the Sponsor stated that post-hoc review at each time point in the first 2 months did

not identify inconsistencies in response determination, but that “there was no effort to formally corroborate the best overall response analysis.” No submitted datasets contained structured information on Sponsor-assessed baseline and post-treatment C-findings at each response time point.

- Without such structured data, response cannot be verified, and the contribution of this study to informing efficacy is limited.

b. IWG-MRT-ECNM criteria

Per FDA request, the Sponsor submitted data on response in Study A2213 by IWG-MRT-ECNM criteria, which could be applied to 23 of 26 patients (Table 12). Of 16 patients with SM-AHN, 2 achieved response (CR or PR) by 2 cycles. Of the 6 patients with MCL, 1 responded. As in Study D2201, the ORR was lower with these criteria as compared to Valent criteria.

Table 12: Response per IWG-MRT-ECNM Criteria – Study A2213

	All assessable subtypes (N = 22) ^b		MCL (N = 6)		SM-AHN (N = 16) ^b		Type unknown (N = 1)	
BOR by 2 cycles^a								
Complete remission	1	(5%)	0	(0%)	1	(6%)	0	–
Partial remission	2	(9%)	1	(17%)	1	(6%)	0	
Clinical improvement	5	(23%)	1	(17%)	4	(25%)	0	
SD or PD	12	(55%)	3	(50%)	8	(50%)	1	
Not evaluable	3	(14%)	1	(17%)	2	(13%)	0	
ORR (CR + PR) by 2 cycles	3	(14%)	1	(17%)	2	(13%)	–	
95% CI for ORR	(3, 35)		(0, 64)		(2, 38)			

Source: FDA analysis

^a Per Sponsor, with 12 week confirmation.

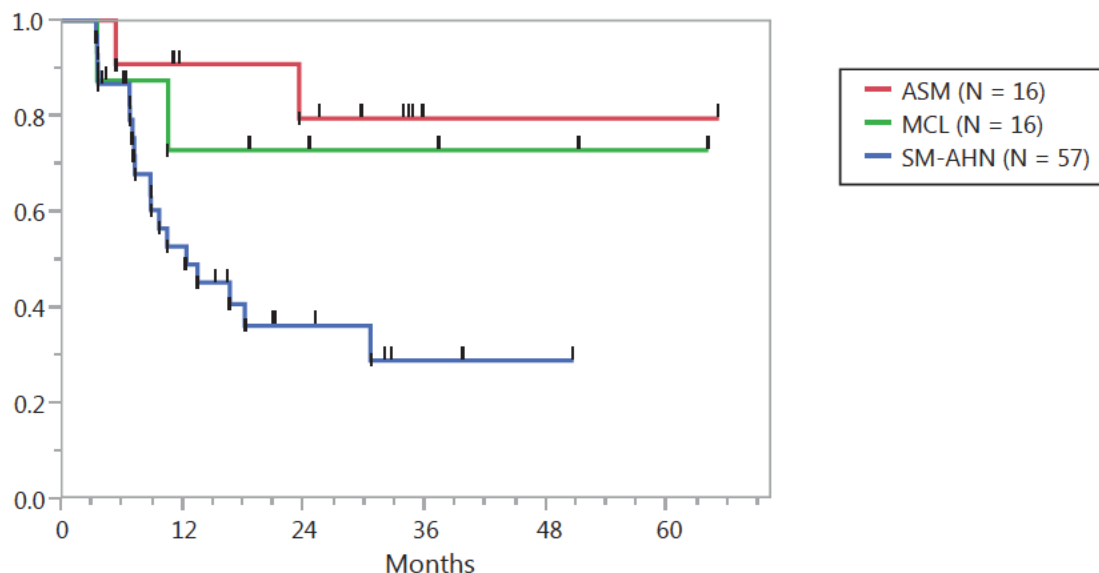
^b Response criteria not applied to 3 patients: 1 with SM-AHN, 2 with unknown subtype.

7.1.2. Secondary and Other Endpoints

Duration of Response

In Study D2201, the primary analysis defined DOR as the time from first response to PD, death, or last adequate assessment. In the PEP, DOR per modified Valent criteria, which require that a response be sustained for at least 8 weeks, is shown in Table 11 and Figure 2. With 30-month median follow-up for response duration, the estimated median DOR was 12.7 months (95% CI, 7.4-31.4 months) in patients with SM-AHN and was not reached in patients with ASM or MCL.

Figure 2: DOR (Modified Valent) in D2201 PEP



Source: FDA analysis

Table 10 summarizes DOR based on IWG-MRT-ECNM criteria, which require that a response be sustained for at least 12 weeks. In the FAS, with 35-month median follow-up for response duration, the estimated median DOR was not reached in any subtype. In ASM, SM-AHN, and MCL, the minimum response duration (censored in each case) was 10.2+ months, 6.8+ months, and 8.6+ months, respectively.

Review comment:

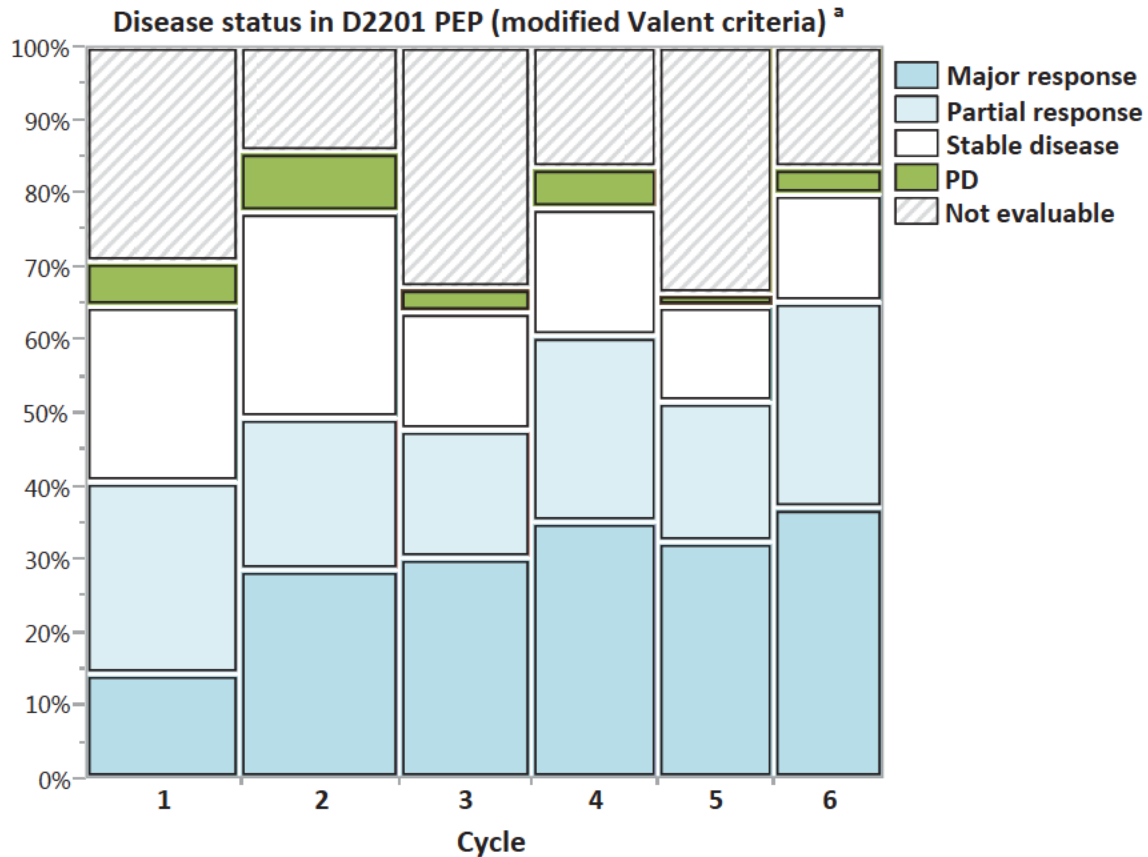
- Summary statistics for response rate and response duration are limited by the small numbers of patients, particularly when using IWG-MRT-ECNM criteria. However, using either set of response criteria, responses to midostaurin are generally durable and thus are clinically meaningful.

DOR in Study A2213 is reviewed in Section 7.1.1.

Time to Response

For the D2201 PEP, time to confirmed overall response (median 9 days per modified Valent criteria) is shown in Table 9. Figure 3 displays response over time in Cycles 1 through 6. Of note, the responses at each time point are unconfirmed, and thus do not necessarily inform the primary endpoint of confirmed response with 6 cycles. The rates of unconfirmed MR tended to increase during the first several cycles, then stabilize.

Figure 3: Disease Status in First 6 Cycles per SSC



Source: FDA analysis

^a Responses are unconfirmed.

Progression-Free Survival and Leukemic Transformation

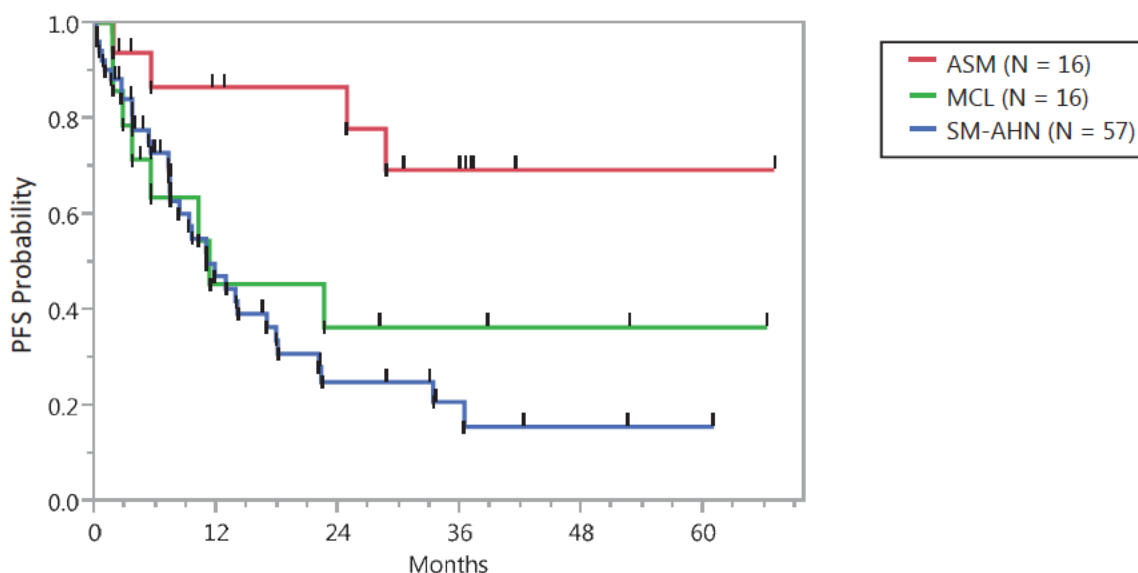
PFS is defined as the time from treatment initiation to PD, death, or last adequate assessment, with censoring upon initiation of other treatment in the absence of PD. PFS estimates are shown in Table 13 and Figure 4. As with response rate, CIs are wide due to the small number of patients. Approximately 50% to 60% of the observations were censored.

Table 13: Progression-Free Survival – Study D2201

PFS according to modified Valent criteria, per SSC	PEP				FAS
	All subtypes (N = 89)	ASM (N=16)	SM-AHN (N = 57)	MCL (N = 16)	All subtypes (N = 116)
Number censored	44 (49%)	12 (75%)	24 (42%)	8 (50%)	71 (61%)
Median (95% CI), months	17 (10.2, 24.9)	NR (24.8, –)	11.0 (7.4, 17.9)	11.3 (2.8, –)	17 (10.2, 24.8)
Point estimates					
1 year (95% CI)	53 (41, 64)	87 (56, 97)	47 (31, 61)	45 (18, 70)	55 (43, 66)
2 year (95% CI)	37 (26, 48)	87 (56, 97)	25 (13, 39)	36 (12, 62)	40 (28, 51)

Source: D2201 CSR Section 14.2.1

Figure 4: Progression-Free Survival – D2201 PEP (Modified Valent Criteria)



Source: FDA analysis

Review comment:

- Interpretation of time-to-event endpoints including PFS and OS is challenging in single-arm clinical trials. It is unclear to what extent the outcomes can be attributed to the treatment effect of the drug.

Leukemic transformation was reported in 15 patients (13%) in Study D2201 and no patients in A2213 (Source: ISS Section 7.3.1 and IR). The criteria for PD did not distinguish between leukemic transformation and non-leukemic progression of SM. Of the patients with leukemic transformation, 14 originally had SM-AHN, and 1 had intervening therapy between midostaurin and the diagnosis of acute leukemia.

Review comment:

- The observed incidence of leukemic transformation is similar to that reported in the literature (Lim KH, Tefferi A et al 2009).

Overall Survival

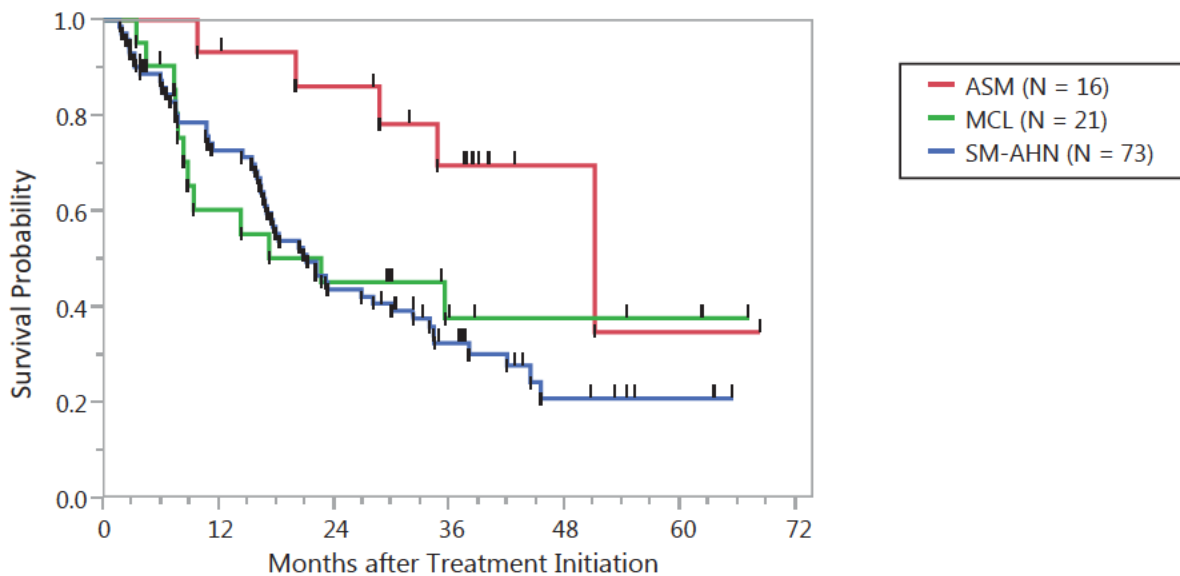
FDA defined OS as the time from treatment initiation to death or last patient contact. Table 14 and Figure 5 provide OS estimates in Study D2201, which had an estimated 40-month median follow-up for vital status. Per FDA analysis, the probability of OS in the PEP was 70% (95% CI, 59-79) at 1 year and 51% (95% CI, 39-61) at 2 years.

Table 14: Overall Survival – Study D2201

OS	PEP	FAS				
	All (N = 89)	All (N = 116) ^b	ASM (N=16)	SM-AHN (N = 73)	MCL (N = 21)	Type unknown (N=9)
Number alive	35 (39%)	54 (55%)	11 (69%)	32 (41%)	13 (62%)	8 (89%)
Median OS, months						
Estimate median (95% CI)	26.8 (17.6, 34.7)	28.7 (20.3, 38.0)	51.1 (28.7, –)	21.1 (16.8, 32.2)	22.6 (8.3, –)	NR –

Source: FDA analysis

Figure 5: Overall Survival by Diagnosis – D2201 FAS



Source: FDA analysis

The Sponsor also compared OS data from studies D2201 and A2213 combined to historical OS data in a registry. The Sponsor concluded that OS, measured from the date of diagnosis, was meaningfully improved in recipients of midostaurin (Source: SCE Section 3.1.13).

Review comment:

- **The analysis of OS relative to historical outcomes is discounted because of its multiple flaws, which include but are not limited to selection bias, the heterogeneity and small number of patients, the single-arm study data, and lack of matching for key patient and disease characteristics.**

Patient Reported Outcomes

As an exploratory efficacy endpoint, the Sponsor evaluated PROs in the D2201 PEP and concluded that quality of life, as assessed by the Memorial Symptom Assessment Scale (MSAS; Portenoy RK et al 1994) and Short Form -12 (Ware JE et al 1996), improved during study treatment (Table 15). (b) (4)

Table 15: Quality of Life Assessments – D2201 PEP

Patients with MSAS scores improved for ≥ 168 days:

Categories	N =89 n (%)
≥ 50% decrease in TMSAS score relative to baseline	20 (22.5)
In evaluable patients	20/52 (38.5)
≥ 50% decrease in MSAS GDI score relative to baseline	25 (28.1)
In evaluable patients	25/49 (51.0)
≥ 50% decrease in PHYS score relative to baseline	19 (21.3)
In evaluable patients	19/51 (37.3)
≥ 50% decrease in PSYCH score relative to baseline	21 (23.6)
In evaluable patients	21/47 (44.7)

80 patients had baseline scores recorded.

Patients with SF-12 scores improved for ≥ 168 days:

Categories	n (%)
≥ 50% increase in PCS score relative to baseline	10 (11.2)
In evaluable patients	10/53 (18.9)
≥ 50% increase in MCS score relative to baseline	3 (3.4)
In evaluable patients	3/53 (5.7)

Source: D2201 CSR Section 11.4.1.3.2

Clinical Review
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NDA 207997, Orig 1
RYDAPT (Midostaurin)

However, of the approximately 80 patients with baseline scores, 47 to 52 were evaluable for MSAS scores at ≥ 168 days, and 53 were evaluable for SF-12 scores at ≥ 168 days. In addition to the large amount of incomplete MSAS data at baseline ($> 40\%$) and throughout the study ($> 30\%$ excluding early drop-outs), limitations noted by the Clinical Outcomes Assessment reviewer included

- the questionable appropriateness of the MSAS, which was developed for solid tumors and combines disease-related and treatment-related symptoms.
- the study sample not being enriched to detect symptom improvement
- the PRO hypothesis not being tested within the main statistical hierarchy (b) (4)

Review comments:

- (b) (4)
- **Because approximately 40% of patients with baseline scores were not evaluable at the post-treatment time point, the degree of improvement in PROs is questionable and subject to overestimation due to selection bias. It would be more conservative to treat the missing data as failures (lack of improvement).**
- **Interpretation of PROs is challenging in uncontrolled and open-label clinical trials. It is unclear to what extent the outcomes can be attributed to the treatment effect of the drug.**

7.1.3. Subpopulations

The small number of patients limits, if not precludes, meaningful subgroup analysis. However, a treatment effect (confirmed overall response) was observed consistently across key subgroups, including patients having prior treatment for SM and patients having a documented D816V c-kit mutation at baseline (Table 16).

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Table 16: Subgroup Analysis of Response – Study D2201

Response Criteria	Variable (# of Patients)	Response (≥ PR) by 6 cycles		
		n	%	95% CI
D2201 PEP (N = 89): Modified Valent criteria	D816V c-kit mutation status			
	Positive (n = 73)	46	(63%)	(51, 74)
	Negative or unknown (n = 16)	7	(44%)	(20, 70)
	Prior therapies for SM +/- AHN			
	No (n = 57)	32	(56%)	(42, 69)
Yes (n = 32)	21	(66%)	(47, 81)	
Age	< 65 (n = 46)	27	(59%)	(43, 73)
	≥ 65 (n = 43)	26	(61%)	(44, 75)
Sex	Male (n = 57)	31	(54%)	(41, 68)
	Female (n = 32)	22	(69%)	(50, 84)
D2201 FAS (N = 115): IWG-MRT-ECNM criteria	D816V c-kit mutation status			
	Positive (n = 93)	16 ^a	(17%)	(10, 26)
	Negative or unknown (n = 22)	3	(14%)	(3, 35)
	Prior therapies for SM +/- AHN			
No (n = 68)	11	(16%)	(8, 27)	
Yes (n = 47)	8	(17%)	(8, 31)	

Source: FDA analysis

7.1.4. Dose and Dose-Response

Data to inform the adequacy of a shorter course of midostaurin or a lower starting dose are not available. The data do not permit an informative analysis of dose-response, since the only efficacy data in AdSM are in patients with a planned midostaurin dose of 100 mg BID, the majority of patients had dose modifications due to toxicity, and the studies are single-arm.

Review comment:

- **The appropriateness of the 100 mg BID starting dose is questionable. By 28 days of midostaurin dosed at 100 mg BID or at 50 mg BID, steady-state levels are quite similar (attributable to autoinduction). Given the similar steady-state levels, the high rate (>50%) of dose modification due to toxicity, and the > 480 hour T1/2β of the active metabolite CPG6525421, the proposed starting dose of 100 mg BID might not be optimal.**

7.1.5. Onset, Duration, and Durability of Efficacy Effects

See Sections 7.1.1 and 7.1.2.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

The patients in studies D2201 and A2213 are not necessarily representative of patients with AdSM in the general population, in part given the protocol eligibility requirements. For example, efficacy data in patients with multiply relapsed or progressive AdSM are limited. Efficacy might also be compromised by noncompliance, particularly since the regimen involves a chronic, twice-daily, oral medication that is commonly associated with gastrointestinal ARs.

7.2.2. Other Relevant Benefits

Patients and providers may consider the oral route of administration to be a relevant benefit. The route of administration does not, however, influence this efficacy assessment.

7.3. Integrated Assessment of Effectiveness

Based on single-arm clinical trial outcomes, the submitted data meet the evidentiary standard of effectiveness for adult patients with previously treated or untreated ASM, SM-AHN, and MCL. In the assessment of effectiveness, the reviewer considered confirmed response rate and response duration as determined both by modified Valent or Valent criteria and by the more stringent IWG-MRT-ECNM criteria. In Study D2201, in 89 patients in the PEP, the confirmed ORR with 6 cycles, based on modified Valent criteria, was 60% (45% MR, 15% PR), with an estimated median DOR of 31 months. In 115 patients in the FAS, the confirmed ORR with 6 cycles, based on IWG-MRT-ECNM criteria, was 17% (2% CR, 15% PR), with response durations ranging from 6.8+ to 60.5+ months. According to either set of response criteria, a treatment effect was demonstrated in all histologic subtypes and across other major subgroups.

For recommendations on the presentation of efficacy data in labeling, refer to Section 10.1.

8 Review of Safety

8.1. Safety Review Approach

Safety Populations

The primary safety evaluation consists of an integrated analysis of all 142 patients with AdSM who received at least one dose of midostaurin on Study D2201 or Study A2213. All patients had a planned dose-schedule of 100 mg po BID, dosed continuously until PD or unacceptable toxicity. The safety analysis considered all-causality AEs reported during treatment and up to 28 days after the last midostaurin dose, with the exception of preferred terms (PTs) that directly described the underlying malignancy (e.g. disease progression, mastocytosis, AML).

For supportive safety data, the reviewer pooled 85 patients with other hematologic malignancies treated with midostaurin monotherapy, with a planned dose that equaled or approximated the recommended starting dose for AdSM. These trials, listed in Section 5.1 (Table 2), evaluated a planned dose-schedule of 100 mg BID, its pediatric equivalent (60 mg/m² BID), or 75 mg TID. Including the latter dose-schedule is justified because of the similar steady-state midostaurin exposures with 75 mg TID and 100 mg BID dosing (Source: SCS Section 1.3.2). Due to significant differences in exposure, safety analyses in AdSM and in other hematologic malignancies are presented separately.

Approach to AE Analysis

The safety analysis considered all-causality AEs reported during treatment and up to 28 days after the last midostaurin dose. The analysis did not consider reported attributions because the studies were single-arm and midostaurin is an NME. Patients were censored for AE reporting at the time of PD. With the exception of on-treatment deaths, the primary safety analysis is based on originally submitted databases, supplemented by responses to IRs.

With the exception of laboratory values, the Sponsor did not collect baseline grade. Therefore, all non-laboratory events, as well as post-treatment laboratory abnormalities having an unknown baseline grade, are assumed to be treatment-emergent. Notably, the Sponsor also did not collect grade 5 events, such that fatal AEs had a designated maximum grade of 4 and in some cases a grade of 3 (see Section 8.2.3). Accordingly, AEs reported as “grade 3-4” are here termed “grade ≥ 3”.

Because laboratory abnormalities were consistently underrepresented in the AE datasets, as compared to the laboratory datasets, the AE tables exclude laboratory terms. Treatment-emergent laboratory abnormalities are instead presented using the dedicated laboratory datasets.

In the main safety analyses, the Sponsor reported AEs using single MedDRA PTs. For increased

sensitivity, FDA instead used a combination of ungrouped and grouped PTs. Except where noted, all analyses presented use the FDA grouping, which is defined in Appendix 13.10 (Table 43).

8.2. Review of the Safety Database

8.2.1. Overall Exposure

Table 17 summarizes exposure in the primary safety population (median exposure, 11.4 months) and in patients with other hematological malignancies (median exposure, 1.2 months). Figure 6 displays the distribution of midostaurin exposure in the AdSM safety population, wherein approximately half of the patients had ≥ 12 months of treatment and approximately one-third had ≥ 24 months of treatment.

Table 17: Exposure in Safety Populations (Midostaurin Monotherapy, 200-225 mg Daily or Pediatric Equivalent)

Variable	AdSM pool (N = 142)		Other heme malignancies (N = 85)	
Planned midostaurin regimen				
100 mg BID or equivalent ^a	142	(100%)	58	(68%)
75 mg TID	0	(0%)	27	(32%)
Treatment ongoing	28	(20%)	0	(0%)
Exposure time, months				
Median (range)	11.4	(0.3-81)	1.2	(0-10.4)
IQR	4.0-31.5		0.6-2.1	
Exposure category				
< 3 months	32	(23%)	71	(84%)
≥ 3 months	110	(77%)	14	(16%)
≥ 6 months	91	(64%)	4	(5%)
≥ 12 months	69	(49%)	0	(0%)
≥ 24 months	48	(34%)	0	(0%)
≥ 36 months	27	(19%)	0	(0%)
RDI ^b				
Mean (range), %	91	(33-100)	–	
IQR	86-100			
> 90%	97	(68%)		
70-90%	26	(18%)		
< 70%	17	(12%)		

Table 17: Exposure in Safety Populations (Midostaurin Monotherapy, 200-225 mg Daily or Pediatric Equivalent)

Variable	AdSM pool (N = 142)		Other heme malignancies (N = 85)
Treatment change due to AE ^c			
≥1 dose interrupted or reduced	80	(56%)	–
Permanent stop ^d	31	(22%)	

Source: FDA analysis

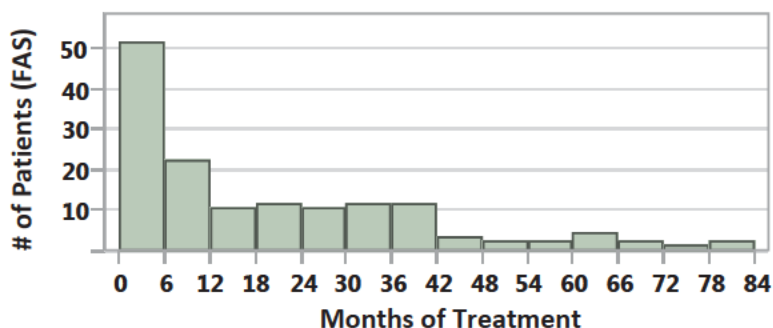
^a Pediatric equivalent, 60 mg/m² BID

^b Missing in all patients without SM (N= 85) and 2 patients from A2213.

^c Excluding AEs describing underlying malignancy.

^d Differs from Sponsor’s reported 35 patients (24%).

Figure 6: Exposure in AdSM Safety Population (N = 142)



Source: FDA analysis

8.2.2. Relevant Characteristics of the Safety Population

Baseline characteristics of both safety populations are summarized in Table 18.

In the AdSM safety population, the median age was 63, 63% had an ECOG performance status of 0 or 1, and 75% had no hepatic impairment at baseline (bilirubin and AST ≤ ULN).

Clinical Review
Yvette Kasamon, MD
NDA 207997, Orig 1
RYDAPT (Midostaurin)

Table 18: Baseline Characteristics of Safety Populations

Parameter	AdSM pool (N = 142)		Other heme malignancies (N = 85)	
Study and indication				
D2201 (SM)	116	(82%)	0	(0%)
A2213 (SM)	26	(18%)	0	(0%)
CPKC412006 (CLL, NHL)	0	(0%)	7	(8%)
A2104, A2104E1 (AML, MDS)	0	(0%)	63	(74%)
A2114 (pediatric leukemia)	0	(0%)	15	(18%)
U.S. site	58	(41%)	49	(58%)
Diagnosis				
SM	142	(100%)	0	(0%)
AML	0	(0%)	63	(74%)
MDS	0	(0%)	6	(7%)
ALL	0	(0%)	9	(11%)
CLL or NHL	0	(0%)	7	(8%)
Age, y				
Median (range)	63	(24 - 82)	63	(< 1 - 82)
≥ 65	64	(45%)	38	(45%)
≥ 70	39	(27%)	29	(34%)
Male sex	91	(64%)	42	(49%)
Race				
Caucasian	132	(93%)	73	(86%)
Black	2	(1%)	1	(1%)
Other or unknown	8	(6%)	11	(13%)
ECOG performance status				
0 or 1	89	(63%)	–	
2	41	(29%)		
3	12	(8%)		
Baseline hepatic impairment category				
None (bili and AST ≤ ULN)	106	(75%)	–	
Mild (bili > ULN but ≤ 1.5 x ULN)	23	(16%)		
Moderate (bili > 1.5 ULN but ≤ 3 x ULN)	8	(6%)		
Severe (bili > 3 x ULN but ≤ 10 x ULN)	2	(1%)		
Missing	3	(2%)		

Source: FDA analysis

Clinical Review
Yvette Kasamon, MD
NDA 207997, Orig 1
RYDAPT (Midostaurin)

8.2.3. Adequacy of the Safety Database

The database is adequate to inform safety in the intended population.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

No issues arose regarding data integrity. Inadequacies in submission quality were addressed through IRs. The Sponsor responded appropriately to requests for additional information, which included submission of revised and additional datasets.

8.3.2. Categorization of Adverse Events

AEs were graded using NCI CTCAE version 3.0 and were classified using MedDRA terminology. AE analysis datasets contained the full MedDRA hierarchy (LLT, PT, HLT, HLGT, and SOC). The Sponsor performed MedDRA 18.0 harmonization for the purposes of integrated safety analyses. Mapping of verbatim terms ("AEVNAM1A") to MedDRA preferred terms ("PT_TXT") was acceptable, based on review of the AE file (AAEV.xpt) for the AdSM safety pool.

8.3.3. Routine Clinical Tests

In studies D2201 and A2213, the schedule of routine clinical evaluations was adequate for safety analysis. Refer to Appendix 13.8 for the schedule of Study D2201 assessments. This monitoring schedule in the protocol included testing on day 3 and weekly in cycle 1, every other week in cycle 2, then after each cycle.

8.4. Safety Results

8.4.1. Deaths

In the AdSM safety population, on-treatment deaths unrelated to the underlying malignancy occurred in 16 patients (11%), most commonly from infection (sepsis or pneumonia), followed by cardiac events (Table 19). Based on review of the death narratives, FDA determined and in some cases revised the cause of death based on available data. Of the on-treatment deaths attributable to disease progression, 4 were also attributable to infection (Table 19). No on-treatment deaths were reported in the other pool of hematological malignancies patients treated with midostaurin monotherapy (planned total daily dose, 200-225 mg).

Table 19: On-Treatment Deaths in Patients with AdSM (FDA Analysis)

AdSM safety population	N, from 142
On-treatment deaths without PD	16
Cardiac^a	5
Cardiac failure, right-sided, with history of pulmonary disease; LVEF 50%	1
Cardiac failure in setting of severe valvular disease, pneumonia, and CAD	1
Cardiac arrest (grade 5) and grade 4 lung disorder, unspecified	1
Myocardial infarction	2
Infection	9
Pneumonia and acute renal failure, complicated by fatal cardiac arrest	1
Pneumonia	1
Sepsis with or without multiorgan failure ^b	7
Other	2
Splenic infarct	1
Multiorgan failure and DIC, precipitant unknown	1
On-treatment deaths in context of PD	14
PD alone ^c	10
Untreated PD accompanied by infection	4

Source: FDA analysis.

Includes deaths occurring up to 28 days after midostaurin completion, reported as of the Day 120 safety update.

^a 1 other fatal cardiac arrest is classified under pneumonia.

^b Includes a case of duodenal ulcer perforation, with fatal post-operative sepsis and multiorgan failure

^c Includes a death from leukemic transformation (AML from CMML)

Review comment:

- A notable limitation of the safety databases is the failure to capture grade 5 events, which instead had a maximum designated grade of 4. With the exception of one study (A2301), the Sponsor did not capture or present grade 5 AEs in any of their studies included in the ISS. In response to an IR, the Sponsor stated that the AdSM AE datasets included all reported, on-treatment fatal events, but that the events had a designated grade of < 5.

8.4.2. Serious Adverse Events

SAEs were reported in 66% of patients (94/142) in the AdSM safety population and 54% of patients (46/85) in the other hematological malignancies pool. Table 20 summarizes SAEs according to the involved system organ class (SOC). In patients with AdSM, SAEs involving

infections and gastrointestinal disorders were most common. SOCs involved in $\geq 20\%$ of either safety population were infections and infestations; gastrointestinal disorders; respiratory, thoracic, and mediastinal disorders; investigations; blood and lymphatic system disorders; and general disorders and administration site conditions.

Table 20: SAEs by SOC in $\geq 2\%$ of Either Safety Population

System Organ Class ^a	AdSM (N = 142)		Other heme malignancies (N = 85)	
	n	%	n	%
Infections, infestations	38	27%	34	40%
Gastrointestinal disorders	34	24%	11	13%
Blood and lymphatic system disorders	23	16%	27	32%
General disorders, administration site conditions	20	14%	17	20%
Respiratory, thoracic, mediastinal disorders	17	12%	29	34%
Cardiac disorders	14	10%	10	12%
Renal and urinary disorders	10	7%	3	4%
Vascular disorders	8	6%	7	8%
Metabolism and nutrition disorders	8	6%	16	19%
Nervous system disorders	7	5%	11	13%
Skin and subcutaneous tissue disorders	7	5%	4	5%
Musculoskeletal and connective tissue disorders	7	5%	5	6%
Investigations	6	4%	19	22%
Injury, poisoning, procedural complications	6	4%	1	1%
Hepatobiliary disorders	5	4%	6	7%
Psychiatric disorders	3	2%	5	6%
Eye disorders	1	1%	2	2%

Source: FDA analysis

^a SOCs are listed in order of decreasing frequency in the AdSM pool. SAEs that directly describe the underlying malignancy are excluded.

SAEs are additionally reviewed in Section 8.4.4.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Because of the significantly longer exposure in the AdSM safety population compared to the other hematological malignancies safety population, the analysis of treatment discontinuation or modification is restricted to AdSM.

Treatment Discontinuation

Per FDA analysis, 21% of patients in the AdSM safety population discontinued treatment permanently due to AEs (Table 21). Commonly reported reasons ($\geq 10\%$) included infection

(20%), nausea or vomiting (13%), QT prolongation (10%), hemorrhage (10%). Worsening ascites, although also a commonly reported, is more likely a manifestation of SM than of toxicity.

Table 21: Treatment Discontinuation Due to AEs in AdSM Safety Population (FDA Analysis)

Cause of discontinuation (1 per patient)	Of 30/142 patients who stopped due to AE:	
	n	%
Infection without other causes ^a	5	17%
Nausea +/- vomiting ^b	4	13%
Bleeding ^c	3	10%
Ascites +/- pleural effusion	3	10%
QT prolongation ^d	3	10%
Cardiac events other than QT prolongation ^e	2	7%
Amylase and/or lipase increased	2	7%
Thrombocytopenia ^f	2	7%
Neutropenia + aggravated DM	1	3%
Fatigue without other causes	1	3%
Spleen infarct	1	3%
Decompensated hepatic cirrhosis	1	3%
Memory impairment	1	3%
General deterioration	1	3%

Source: FDA analysis

Terms related to persistent or progressive disease were excluded.

^a 1 other patient also stopped from GI bleed.

^b 1 patient had a second reason of fatigue.

^c 1 from subdural bleed, 2 from GI bleeds. One patient with GI bleed also stopped from neutropenic fever.

^d Days 57, 57, and 337

^e 1 cardiac arrest, 1 ventricular tachycardia

^f 1 patient had a second reason of grade 3 dyspnea.

Dose Modification and Time Course of AEs

In the AdSM safety population, 80 patients (56%) had dose modification (interruption or reduction) for an AE, as summarized in Table 22. The most common reasons for dose modifications ($\geq 10\%$) were nausea, vomiting, QT prolongation, and neutropenia.

Table 22: AEs Causing Treatment Modification in $\geq$ 5% of AdSM Patients

Reasons for dose interruption or delay (grouped PT) ^a	Patients with dose modification (N = 80, from 142):	
	n	%
Nausea	17	21%
Vomiting	13	16%
QT prolongation	10	13%
Neutropenia	9	11%
Diarrhea	7	9%
Pyrexia	6	8%
Thrombocytopenia	6	8%
Gastrointestinal hemorrhage	5	6%
Lipase increased	5	6%
Fatigue	5	6%
Anemia	4	5%
Rash	4	5%

Source: FDA analysis

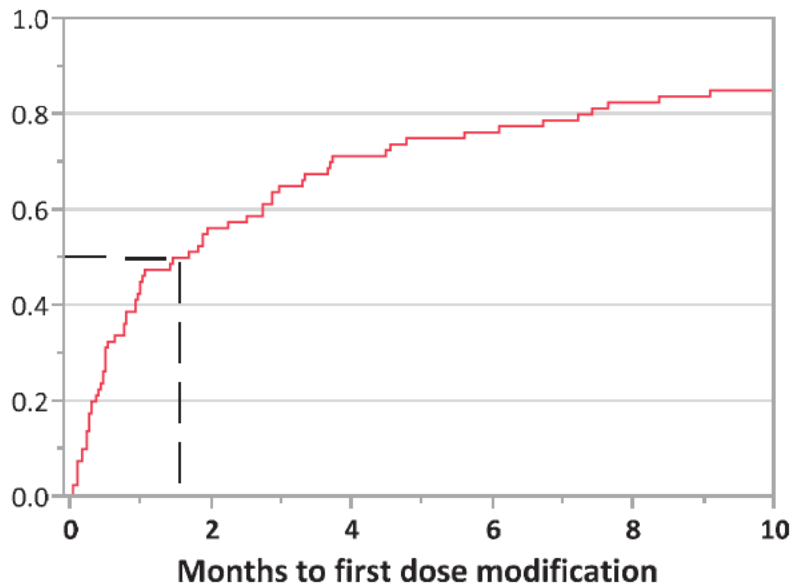
^a More than one AE can cause the dose modification.

Dose modifications for toxicity occurred most commonly in the first 5 months. Figure 7 displays the time course to first dose modification for AE. Per FDA analysis, the median time to first dose modification was 1.6 months (IQR: 0.5 to 5.2 months).

Review comment:

- In the AE datasets, the action taken of “dose modification” included patients who had either temporary interruption of midostaurin or a reduction in midostaurin dosage. These datasets did not permit these actions to be distinguished.

Figure 7: Time to First Dose Modification for AE (AdSM Safety Population)



Source: FDA analysis
 From 80 of the 142 patients with AdSM having dose interruption or reduction due to AE.

To inform safety, FDA requested that the Sponsor evaluate the time to first onset of selected common AEs, as summarized in Table 23. The median time to onset of nausea and vomiting were < 10 days and 1 month, respectively, whereas diarrhea and infections tended to occur later.

Table 23: Time Course of Common AEs in AdSM Safety Population

	From AdSM pool (N = 142):			
	Nausea	Vomiting	Diarrhea	G ≥ 3 Infection
At least 1 event, n	117 (82%)	96 (68%)	73 (51%)	41 (29%)
Time to first onset (months)				
Median	0.3	1.0	7.8	18.4
25 th percentile	0	0.1	0.9	47.8
75 th percentile	2.9	NA	NA	NA

Source: Response to 12/14/2016 IR

Review comments:

- Because the majority of dose modifications or first dose modifications occurred in the first 3 months, close monitoring for actionable toxicities is recommended particularly during this time period.

- Although a QT study did not identify a significant impact of midostaurin on QTc, QT prolongation was a commonly reported AE (>10%), and was a leading reason for treatment modification and discontinuation. The question arises as to whether concomitant QT-prolonging medications (potentially including antiemetics and antifungal azoles) contributed to the QT prolongation. However, the submitted data do not permit an analysis of this potential interaction. EKG monitoring should be considered in patients on concurrent medications with QT-prolonging potential.
- The appropriateness of the dose modification guidelines for toxicity is questionable, as they do not appear to be supported by the pharmacokinetic data.

8.4.4. Significant Adverse Events

SAEs are reviewed in Section 8.4.2, grade ≥ 3 AEs in Section 8.4.5, and grade 4 laboratory abnormalities in Section 8.4.6.

Grade ≥ 4 Adverse Events

Table 24 summarizes grade ≥ 4 AEs reported in $\geq 2\%$ of either safety population. In both populations, sepsis was the most commonly reported cause of life-threatening or fatal AEs.

Table 24: Grade ≥ 4 AEs Reported in $\geq 2\%$ of Either Safety Population, Excluding Laboratory Terms

Grouped PT	AdSM pool (N = 142)		Other heme malignancies (N = 85) ^a	
	n, Grade ≥ 4 *	%	n, Grade ≥ 4	%
Sepsis	9	6%	5	6%
Myocardial infarction	4	3%	0	0%
Cardiac arrest	3	2%	1	1%
Fatigue	3	2%	0	0%
Respiratory failure	2	1%	2	2%
Pneumonia ^b	0 ^b	0%	2	2%
Hypotension	0	0%	2	2%

Source: FDA analysis.

Note: All patients received midostaurin monotherapy with a planned total daily dose of 200-225 mg or pediatric equivalent.

^a In Study A2104, a case of cardiac arrest had no grade and was arbitrarily designated grade 4.

^b Cases of fatal pneumonia occurred; refer to Section 8.4.1.

Adverse Events of Special Interest

In the ISS pool (Appendix 13.9), including patients with AdSM, the Sponsor conducted evaluations of AEs using grouped MedDRA search terms. Table 25 summarizes selected AEs in patients with AdSM.

Table 25: Selected Non-Hematologic AEs in AdSM Safety Population

AE category	AdSM pool (N = 142)							
	Grade ≥ 3		SAEs		Dose modification		Drug discontinuation	
	n	%	n	%	n	%	n	%
Infections	47	(33%)	38	(27%)	14	(10%)	3	(2%)
GI toxicity	21	(15%)	16	(11%)	26	(18%)	4	(3%)
Bleeding	20	(14%)	22	(15%)	7	(5%)	3	(2%)
Hepatic-related events	18	(13%)	10	(7%)	7	(5%)	4	(3%)
QT prolongation	9	(6%)	6	(4%)	10	(7%)	5	(4%)
Cardiac dysfunction	6	(4%)	3	(2%)	0	(0%)	0	(0%)
Pulmonary toxicity	0	(0%)	1	(< 1%)	0	(0%)	0	(0%)

Source: Sponsor analysis (ISS Section 10 and response to 10/18/2016 IR).

Infection: For the AdSM safety population, FDA requested data on ANCs associated with the Sponsor summarized the ANCs associated with all grade ≥ 3 AEs captured under the “infections and infestations” SOC (Source: response to 12/14/2016 IR). Most of these infections occurred in the absence of documented grade 4 neutropenia.

Review comment:

- (b) (4)
Because the AdSM studies were single-arm, one cannot discern an increased infection risk from midostaurin from the overall increased infection risk seen in immunosuppressed patients. Most infections occurred without grade 4 neutropenia. In Study A2301, among patients randomized to the midostaurin arm (planned dose-schedule, 50 mg BID), increased risks of infection (apart from device-related infections), grade ≥ 3 neutropenia, and grade ≥ 3 lymphopenia were not observed as compared to patients randomized to the placebo arm. Animal data did not suggest an excess infection risk with midostaurin, based on Pharmacology/Toxicology review. (b) (4)

Cardiac dysfunction: (b) (4)
(b) (4) Reports of cardiac dysfunction in Study D2201 are summarized in Appendix 13.11 (Table 44). In Study D2201, echo or MUGA was required at baseline, after

Clinical Review
Yvette Kasamon, MD
NDA 207997, Orig 1
RYDAPT (Midostaurin)

Cycles 3, 6 and 12, then yearly and at end of treatment. As summarized in Appendix 13.11 and Section 8.4.1, two deaths occurred from CHF: one from severe valvular disease, and one from right-sided CHF in setting of COPD and a preserved LVEF. The Sponsor described 3 other cases of notably reduced LVEF in patients with a normal baseline (Table 44). Limitations of this analysis, however, include a) the lack of central review of echocardiograms, and b) the amount of missing data.

In Study A2301, no differences in the risk of cardiac dysfunction were identified in the midostaurin arm as compared to the placebo arm. However, the study was not specifically designed to evaluate changes in cardiac function.

Review comment:

- **Based on the Pharmacology/Toxicology review, cardiac dysfunction from midostaurin is plausible.**

(b) (4)

Pulmonary toxicity: The Sponsor proposed a Warning and Precaution of pulmonary toxicity / interstitial lung disease. Per FDA request, the Sponsor submitted additional data on pulmonary complications in the ISS pool (response to 12/29/2016 IR, SDN 61). Based on a MedDRA SMQ of interstitial lung disease, the Sponsor reported 5 cases of pulmonary toxicity, each grade <3, in patients with AdSM. However, as summarized in Appendix 13.11 (Table 45), at least two of these cases were from infection. For a description of additional cases of pulmonary toxicity, please refer to the Clinical Review of the AML indication (NDA 207997 Original 2, Ward and Przepiorka 2017). Based on the narratives submitted for the ISS pool, the majority of cases were of pulmonary infection rather than pulmonary toxicity.

Review comment:

- **In the ISS pool, multiple cases categorized as pulmonary toxicity were instead infectious. However, midostaurin might have contributed to some cases of interstitial lung disease or pneumonitis, and studies D2201 and A2213 excluded patients with pulmonary infiltrates in order to mitigate the risk. Pulmonary toxicity from midostaurin is possible, based on Pharmacology/Toxicology review. Although clinical data are limited, this reviewer supports the Warning and Precaution on pulmonary toxicity.**

Other AEsIs: The Sponsor also evaluated hematologic toxicity (anemia, leukopenia, and thrombocytopenia) using grouped AE terms. However, the reviewer found that incidences of hematologic toxicities were underrepresented in this analysis, as compared to the analysis of treatment-emergent hematologic abnormalities using the laboratory datasets (Table 32).

8.4.5. Treatment-Emergent Adverse Events and Adverse Reactions

Most Common AEs in Either Safety Population

Table 26 summarizes all-grade AEs that were reported in $\geq 20\%$ of either safety population. Although midostaurin exposure differed significantly between the two safety pools, the pattern of most common AEs was consistent.

Table 26: Most Common ($\geq 20\%$) AEs with Midostaurin Monotherapy (200-225 mg/day), Excluding Laboratory Terms

SOC ^a	Grouped PT	ANY GRADE (%)	
		AdSM (N = 142) ^b	Other HM (N = 85) ^b
Gastrointestinal disorders	Nausea	82%	64%
	Vomiting	68%	58%
	Diarrhea	51%	47%
	Abdominal pain	34%	(18%)
	Constipation	29%	21%
General disorders and administration site conditions	Fatigue	34%	39%
	Pyrexia	27%	35%
	Edema	39%	28%
Infections and infestations	URTI	30%	(8%)
Blood and lymphatic system disorders	Febrile neutropenia	(8%)	20%
Respiratory, thoracic, and mediastinal disorders	Cough	(18%)	24%
	Dyspnea	21%	20%
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	37%	21%
Skin and subcutaneous tissue disorders	Pruritus	20%	(2%)
Nervous system disorders	Headache	26%	24%
Metabolism and nutrition disorders	Decreased appetite	(8%)	22%

Source: FDA analysis.

HM, hematologic malignancies.

^a Grouped by most commonly involved SOC in AdSM patients.

^b Median exposure: AdSM 11.4 months, other HM 1.2 months

For supportive safety data, the reviewer additionally evaluated the most common AEs reported in a trial of midostaurin for diabetes mellitus (Table 27). Among the 15 patients who received a planned dose-schedule of 75 mg TID for 28 days, the overall pattern of AEs was consistent with that observed in the two other safety populations.

Clinical Review
 Yvette Kasamon, MD
 NDA 207997, Orig 1
 RYDAPT (Midostaurin)

Table 27: Most Common (≥ 20%) AEs in Diabetic Patients, Excluding Laboratory Terms (Study C99PKC412001)

Diabetes Mellitus (N = 15) ^a			
SOC	PT	Any grade ^b	
		n	%
Gastrointestinal disorders	Diarrhea	13	87%
	Nausea	10	67%
	Vomiting	4	27%
Musculoskeletal and connective tissue disorders	Arthralgia	4	27%
	Back pain	3	20%
Nervous system disorders	Headache	8	53%
General disorders and administration site conditions	Fatigue or asthenia	7	47%

Source: FDA analysis

^a Patients without malignancy; planned midostaurin dose, 75 mg TID for 28 days.

^b No SAEs or grade 4 AEs were reported.

Common AEs in the AdSM Safety Population

For the AdSM safety population, Table 28 displays the SOCs under which AEs were most commonly reported. Almost all patients had at least one reported gastrointestinal AE, > 70% had AEs under the “general disorders and administration site conditions” category, and > 60% had AEs under the “infections and infestations” category.

Table 28: Most Common (≥ 20%) AE Categories in AdSM Patients by SOC

AdSM pool (N = 142)		
System Organ Class	n	(%)
Gastrointestinal disorders	137	96%
General disorders and administration site conditions	102	72%
Infections and infestations	90	63%
Blood and lymphatic system disorders	83	58%
Respiratory, thoracic, and mediastinal disorders	81	57%
Musculoskeletal and connective tissue disorders	78	55%
Investigations	77	54%
Skin and subcutaneous tissue disorders	71	50%
Nervous system disorders	70	49%
Metabolism and nutrition disorders	62	44%
Psychiatric disorders	49	35%
Vascular disorders	38	27%
Cardiac disorders	36	25%
Injury, poisoning, and procedural complications	34	24%

Source: FDA analysis

Clinical Review
Yvette Kasamon, MD
NDA 207997, Orig 1
RYDAPT (Midostaurin)

Table 29 summarizes common all-grade and grade ≥ 3 AEs in patients with AdSM. The most frequent AEs (reported in $\geq 20\%$) were nausea, vomiting, diarrhea, constipation, abdominal pain, edema, fatigue, upper respiratory tract infection, pyrexia, arthralgia, headache, and dyspnea. Grade ≥ 3 AEs reported in $\geq 5\%$ of patients, excluding laboratory terms, were fatigue, sepsis, pneumonia, febrile neutropenia, gastrointestinal hemorrhage, diarrhea, edema, nausea, vomiting, abdominal pain, and dyspnea.

The time course of selected common AEs is reviewed in Section 8.4.3. Grade 4 events are described further in Section 8.4.4.

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Table 29: Common (≥ 10%) AEs in AdSM Pool (FDA Grouped Terms)

AdSM pool (N = 142)					
System Organ Class ^a	Grouped Preferred Term	All Grades		Grade ≥ 3	
		n	%	n	%
Gastrointestinal disorders	Nausea	117	82%	8	6%
	Vomiting	96	68%	8	6%
	Diarrhea	73	51%	9	6%
	Abdominal pain	48	34%	8	6%
	Constipation	41	29%	1	< 1%
	GI hemorrhage ^b	16	11%	11	8%
	Ascites	14	10%	4	3%
General disorders and administration site conditions	Edema	56	39%	9	6%
	Fatigue	48	34%	13	9%
	Pyrexia	38	27%	6	4%
Infection and infestations	Upper resp. tract infection	42	30%	2	1%
	Urinary tract infection	22	15%	4	3%
	Pneumonia	14	10%	10	7%
Respiratory, thoracic, and mediastinal disorders	Dyspnea	30	21%	8	6%
	Cough	26	18%	1	< 1%
	Pleural effusion	18	13%	6	4%
	Epistaxis	17	12%	4	3%
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	52	37%	5	4%
	Arthralgia	27	19%	3	2%
Investigations	EKG QT prolonged	15	11%	1	< 1%
Skin and subcutaneous tissue disorders	Pruritus	29	20%	4	3%
	Rash	16	11%	4	3%
Nervous system disorders	Headache	37	26%	2	1%
	Dizziness	19	13%	0	0%
Psychiatric disorders	Insomnia	15	11%	0	0%
	Depression	16	11%	0	0%

Source: FDA analysis

^a SOCs are listed in order of decreasing frequency of involvement.

^b In a case of acute hemorrhagic gastritis, the reviewer assigned two PTs: gastritis, as in the submitted database, and gastrointestinal hemorrhage.

Review comments:

- A limitation of the AE database is that the Sponsor did not collect baseline grade. Multiple common AEs are also common manifestations of SM; these include abdominal pain, ascites, pleural effusion, pyrexia, fatigue, musculoskeletal pain, pruritus, and depression. As such, identifying true ARs is

- challenging.
- [Redacted] (b) (4)
 - The reviewer recommends that [Redacted] (b) (4) be omitted from the table of common ARs. In making this determination, the reviewer also considered the AEs reported in other safety studies and in the randomized phase 3 trial in AML (Study A2301).

Selected relevant AEs reported in < 10% of patients are summarized in Table 30. Because of their clinical relevance, the reviewer recommends that they be included in the PI.

Table 30: Selected Clinically Relevant AEs in < 10% of AdSM Pool

AdSM pool (N = 142) Grouped PT	All grades		Grade ≥ 3	
	n	%	n	%
Sepsis	13	9%	13	9%
Hypotension	13	9%	3	2%
Febrile neutropenia	11	8%	10	7%
Renal failure	8	6%	4	3%
Cardiac failure	7	5%	4	3%
MI or troponin increase	6	4%	5	4%
Angioedema or anaphylactic shock	3	2%	2	1%
Enteritis	10	7%	1	< 1%
Interstitial lung disease or pneumonitis	3	2%	0	0%
Pulmonary hypertension	1	< 1%	1	< 1%

Source: FDA analysis

Appears this way on original

Common AEs in the Supportive Safety Population

As summarized in Table 31, the overall pattern of common AEs was similar between the AdSM safety population and the supportive safety population (patients with hematological malignancies other than SM).

Table 31: Common (≥ 10%) AEs in Other Patients with Hematological Malignancies, Excluding Laboratory Terms

SOC	Grouped PT	From N of 85: Any grade	
		n	%
Gastrointestinal disorders	Nausea	54	64%
	Vomiting	49	58%
	Diarrhea	40	47%
	Constipation	18	21%
	Abdominal pain	15	18%
General disorders and administration site conditions	Fatigue	33	39%
	Pyrexia	30	35%
	Edema	24	28%
Respiratory, thoracic, and mediastinal disorders	Cough	20	24%
	Dyspnea	20	20%
	Hypoxia	11	13%
Nervous system disorders	Headache	20	24%
	Dizziness	12	14%
Blood and lymphatic system disorders	Febrile neutropenia	17	20%
Infections and infestations	Pneumonia	13	15%
	Sepsis	9	11%
Metabolism and nutrition disorders	Decreased appetite	19	22%
	Dehydration	9	11%
Psychiatric disorders	Anxiety	13	15%
	Insomnia	9	11%
Skin and subcutaneous tissue disorders	Rash	12	14%
Vascular disorders	Hypotension	9	11%

Source: FDA analysis

Note: The planned midostaurin dose was 200-225 mg daily or pediatric equivalent.

8.4.6. Laboratory Findings

Table 32 summarizes new or worsening laboratory abnormalities identified in patients with AdSM. The common (≥ 10%) grade 3-4 non-hematologic laboratory abnormalities were hyperglycemia, lipase increase, and hyperuricemia. The most common grade 3-4 hematologic laboratory abnormalities (≥ 20%) included anemia, thrombocytopenia, and neutropenia. Grade

Clinical Review
Yvette Kasamon, MD
NDA 207997, Orig 1
RYDAPT (Midostaurin)

4 hematologic abnormalities occurring in $\geq 5\%$ were thrombocytopenia (17%), neutropenia (11%), lymphopenia (7%), and anemia (6%).

Table 32: Common ($\geq 10\%$) Treatment-Emergent Laboratory Findings in AdSM Pool

From AdSM pool (N = 142)	Grade 1-4	Grade 3-4	Grade 3		Grade 4	
	%	%	n	%	n	%
Hematology^a						
Lymphopenia	73%	46%	55	39%	10	7%
Anemia	97%	44%	53	37%	9	6%
Thrombocytopenia	84%	37%	29	20%	24	17%
Neutropenia	58%	27%	22	15%	16	11%
Chemistries						
Hyperglycemia ^b	80%	18%	25	18%	1	< 1%
Lipase increase	37%	18%	21	15%	4	3%
Hyperuricemia	37%	11%	0	0%	15	11%
Alk phos increase	39%	9%	13	9%	0	0%
GGT increase	28%	7%	6	4%	4	3%
Amylase increase	20%	7%	6	4%	4	3%
Hyponatremia	45%	6%	8	6%	1	< 1%
Hypokalemia	29%	6%	6	4%	2	1%
Hyperkalemia	23%	4%	5	4%	1	< 1%
Hyperbilirubinemia	29%	4%	5	4%	0	0%
AST increase	31%	4%	5	4%	0	0%
ALT increase	32%	3%	3	2%	1	< 1%
Hypocalcemia	65%	2%	1	< 1%	2	1%
Hypoalbuminemia	61%	1%	2	1%	0	0%
Hypophosphatemia	22%	1%	2	1%	0	0%
Hypercalcemia	10%	1%	2	1%	0	0%
Bicarbonate decrease	26%	< 1%	1	< 1%	0	0%
Creatinine increase	25%	< 1%	1	< 1%	0	0%
Hypomagnesemia	30%	0%	0	0%	0	0%
Hypermagnesemia	13%	0%	0	0%	0	0%

Source: FDA analysis

Represents maximum grade post-treatment, if worsened from baseline or if worsening from baseline unknown, ordered by decreasing frequency of Grade 3-4 events.

^a Also meeting criteria: PTT/APTT prolongation

^b Not fasting

Hy's Law screen: Two patients with AdSM experienced concurrent elevations in ALT or AST $> 3 \times$ ULN and total bilirubin $> 2 \times$ ULN, with alkaline phosphatase $\leq 2 \times$ ULN (Source: ISS Section 10.7.1). The reviewer considers neither to be a Hy's law case, although a contribution of midostaurin cannot be excluded.

Review comment:

•

(b) (4)

The reviewer recommends that the PI present treatment-emergent laboratory abnormalities, particularly because cytopenias and hepatic dysfunction are frequent manifestations of the underlying malignancy.

8.4.7. Vital Signs

The Sponsor did not identify safety concerns regarding vital signs. Although hypertension is a potential off-target effects of VEGF inhibition, a safety signal in this regard did not arise.

8.4.8. Electrocardiograms (ECGs)

Refer to Section 4.5.2.

8.4.9. QT

Refer to Section 4.5.2.

8.4.10. Immunogenicity

Assessments for immunogenicity are generally not needed for small-molecule drugs.

8.5. Analysis of Submission-Specific Safety Issues

Submission-specific safety issues are covered in Sections 8.4.1 through 8.4.6, including adverse events of special interest (Section 8.4.4) and the time course of common AEs (Section 8.4.5).

8.6. Safety Analyses by Demographic Subgroups

In patients with AdSM, the Sponsor reported that the median RDI and median duration of midostaurin exposure were similar in those aged < 65 years (N= 78) and those aged ≥ 65 years (N = 64)(Source: ISS Section 2.1.2). SAEs and grade 3-4 AEs were reported more frequently in patients aged ≥ 65 years, whereas the overall incidence of AEs was generally similar (Source: SCS Section 2.5.1).

Overall, reporting of AEs was balanced between genders (Source: ISS Section 4.5.2.1). Because most of the patients were Caucasian, no meaningful conclusions can be drawn from subgroup analysis by race.

8.7. Specific Safety Studies/Clinical Trials

Section 4.5.2 describes a dedicated QT study (A2213). For results of a dedicated study in patients with no, mild, or moderate hepatic impairment (A2116), please refer to the Clinical Pharmacology review. A dedicated renal impairment study was not conducted for midostaurin.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

See Section 4.4.

8.8.2. Human Reproduction and Pregnancy

See Section 4.4. There are no human data on fertility or fetal effects.

8.8.3. Pediatrics and Assessment of Effects on Growth

Not applicable for the proposed indication.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Doses above or below 100 mg BID (apart from dose reductions for toxicity) have not been examined in patients with AdSM. No studies have been conducted that assess overdose, withdrawal, and rebound effects of midostaurin.

8.8.5. Safety in Patients with Hepatic Impairment

Given the few patients with AdSM having moderate (n = 8) or severe (n = 2) hepatic impairment at baseline (Table 18), no meaningful conclusions regarding safety can be made for these subgroups. On FDA analysis, of the 33 patients with at least mild hepatic impairment at

baseline, 25 (76%) had SAEs, excluding SAEs related directly to the underlying malignancy. Grade 3-4 AEs in patients with baseline hepatic impairment are summarized in Table 33.

Table 33: Grade $\geq$ 3 AEs in AdSM Patients with Baseline Hepatic Impairment

Grouped PT ^a	From N of 33: Grade $\geq$ 3 AEs reported in $\geq$ 2 patients	
	n	%
Gastrointestinal hemorrhage	4	12%
Edema	3	9%
Diarrhea	3	9%
Dyspnea	3	9%
Sepsis	3	9%
Febrile neutropenia	2	6%
Pneumonia	2	6%
Cholecystitis	2	6%
Cholelithiasis	2	6%
Nausea	2	6%
Acute kidney injury	2	6%
Renal failure	2	6%
Tumor lysis syndrome	2	6%
Nausea	2	6%
Ascites	2	6%

Source: FDA analysis

^a Excluding laboratory parameters

^b 23 patients had mild hepatic insufficiency, 8 moderate, 2 severe.

Review comment:

- **Hepatic impairment is a common manifestation of ASM and is a potential C-finding. The pharmacokinetic profile, safety and tolerability of midostaurin in patients with severe hepatic dysfunction are unknown.**

8.8.6. Day 120 Safety Update

The safety update, submitted 12/23/2016 with a database lock of 7/1/2016 and Novartis safety database listings from 7/2/2016 to 10/30/2016, mainly consisted of updated Study D2201 data (300 patient-months) and additional follow-up on the 7 patients on Study A2213 whose treatment was previously ongoing. The updated information did not reveal new safety concerns. Information on new deaths or updated causes of deaths is incorporated into Section 8.4.1.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

Not applicable, as midostaurin is not marketed in any country.

8.9.2. Expectations on Safety in the Postmarket Setting

Because recipients of marketed drug might not have met eligibility criteria for the studies supporting marketing approval, AEs may occur with higher incidence and severity in the postmarket setting. For example,

- Safety in patients with significant comorbidities has not been defined, including in the setting of cardiac dysfunction, pulmonary dysfunction or infiltrates, and moderate and severe hepatic impairment.
- Safety in patients with multiply relapsed or progressive AdSM is not well defined.

New safety signals might also emerge with larger numbers of patients exposed to midostaurin.

8.10. Additional Safety Issues From Other Disciplines

Strong CYP3A Modulators: Strong CYP3A inhibitors might adversely affect the tolerability of midostaurin. The safety and tolerability of midostaurin in patients taking strong CYP3A4 inhibitors are, however, incompletely characterized. Per the Clinical Pharmacology review, caution and consideration of alternative agents are recommended, as concomitant use of strong CYP3A4 inhibitors may increase exposure to midostaurin. In the presence of strong CYP3A inhibitor, midostaurin exposure was found to increase by up to 10-fold following a single midostaurin dose and by approximately 2-fold around steady state.

8.11. Integrated Assessment of Safety

Midostaurin carries an acceptable safety profile in the intended population. The primary safety assessment involved an integrated analysis of 142 adult patients with AdSM who received at least one dose of midostaurin on Studies D2201 or A2213 (planned regimen, 100 mg po BID until disease progression or unacceptable toxicity). The median exposure to midostaurin was 11 months.

The most common ARs ($\geq 20\%$) were nausea, vomiting, diarrhea, constipation, abdominal pain, edema, fatigue, upper respiratory tract infection, pyrexia, arthralgia, headache, and dyspnea. The most common grade 3-4 hematologic laboratory abnormalities ($\geq 20\%$) included anemia, thrombocytopenia, and neutropenia.

Eleven percent of patients died on-treatment for reasons unrelated to the underlying malignancy, most often from infection (sepsis or pneumonia), followed by cardiac events. SAEs were reported in two-thirds of patients, most commonly involving infections and

Clinical Review
Yvette Kasamon, MD
NDA 207997, Orig 1
RYDAPT (Midostaurin)

gastrointestinal disorders. AEs led to dose interruption or reduction in 56% of patients, usually in the first 5 months. The leading reasons for dose modifications ($\geq 10\%$) were nausea, vomiting, QT prolongation, and neutropenia. Treatment discontinuation due to AEs occurred in 21% of patients, most often due to infection, nausea or vomiting, QT prolongation, and hemorrhage.

Supportive safety data were obtained from 85 patients with other hematological malignancies who received midostaurin monotherapy at a planned dosage that equaled or approximated that in AdSM (median exposure, 1 month). The overall AE profile was congruent with that described in the primary safety analysis.

9 Advisory Committee Meeting and Other External Consultation

Midostaurin was not presented to the Oncologic Drug Advisory Committee or other external consultants.

10 Labeling Recommendations

10.1 Prescribing Information

The following are recommendations for the RYDAPT PI based on this review:

Indication: Regular approval of midostaurin for the treatment of adult patients with aggressive systemic mastocytosis, systemic mastocytosis with associated hematological neoplasm, or mast cell leukemia (100 mg po BID with food, until disease progression or unacceptable toxicity)

Dosing and administration:

- Recommend prophylactic antiemetics.
- (b) (4) toxicity management guidelines to match protocol D2201.
- Recommend particularly close monitoring for actionable toxicities, such as gastrointestinal toxicities, during the first 3 months of treatment. The minimum suggested monitoring schedule is once weekly during cycle 1, every other week during cycles 2 and 3, and monthly thereafter.
- Recommend EKG monitoring in patients taking concomitant medications that can prolong the QT interval.

Efficacy:

- Present efficacy according to IWG-MRT-ECNM response criteria, in addition to modified Valent or Valent criteria, with response defined as $\geq$ PR.

Clinical Review
Yvette Kasamon, MD
NDA 207997, Orig 1
RYDAPT (Midostaurin)

- Present ≥ 8 week confirmed, (b) (4) response rates for Study A2213.
- Present efficacy outcomes according to the WHO classification of SM, (b) (4)
- (b) (4)

Safety:

- Include pulmonary toxicity as a Warning and Precaution.
- Present ARs using selected grouped preferred terms, (b) (4) for more sensitive and informative labeling.
- In the table of common ARs in the AdSM safety population,
 - Add the following preferred terms or grouped preferred terms: gastrointestinal hemorrhage, rash, QT prolongation, musculoskeletal pain, arthralgia, abdominal pain, and insomnia.
 - Categorize (b) (4) ARs as “grade 3 to 5,” (b) (4)
- Add myocardial infarction, renal failure, enteritis, pneumonitis or interstitial lung disease, and respiratory failure as clinically significant, uncommon ARs.
- Include all of the most common laboratory abnormalities and all grades in Section 6, (b) (4)
- Present treatment-emergent laboratory abnormalities (b) (4)

10.2. Patient Labeling

Review of patient labeling by the Division of Medical Policy Programs was ongoing at the time of this review.

11 Risk Evaluation and Mitigation Strategies (REMS)

This reviewer and the Division of Risk Management reviewer do not recommend a REMS. Based on the risk/benefit profile of midostaurin, safety issues can be adequately managed through appropriate labeling and routine post-marketing surveillance.

12 Postmarketing Requirements and Commitments

For the AdSM indication, no postmarketing requirements or postmarketing commitments are recommended from a clinical standpoint. The reviewer considered a PMC to evaluate a lower starting dose of midostaurin for AdSM. However, given the rarity and prognostic heterogeneity

Clinical Review
Yvette Kasamon, MD
NDA 207997, Orig 1
RYDAPT (Midostaurin)

of AdSM, as well as the anticipated approval of the midostaurin 100 mg BID dose-schedule, an informative trial would be challenging to conduct. In order to mitigate serious toxicities, the PI will include instructions for frequent monitoring. The PI will also include more detailed guidelines on toxicity management (b) (4)

13 Appendices

13.1. References

Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood* 2016; 127: 2391-2405.

Cheson BD, Greenberg PL, Bennett JM, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. *Blood* 2006; 108: 419-425.

Garcia-Montero AC, Jara-Acevedo M, Teodosio C, et al. KIT mutation in mast cells and other bone marrow hematopoietic cell lineages in systemic mast cell disorders: a prospective study of the Spanish Network on Mastocytosis (REMA) in a series of 113 patients. *Blood* 2006; 108: 2366-2372.

Gotlib J, Kluin-Nelemans HC, George TI, et al. Efficacy and safety of midostaurin in advanced systemic mastocytosis. *NEJM* 2016; 374: 2530-2541.

Gotlib J, Pardanani A, Akin C, et al. International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) & European Competence Network on Mastocytosis (ECNM) consensus response criteria in advanced systemic mastocytosis. *Blood* 2013; 121: 2393-2401.

Growney JD, Clark JJ, Adelsperger J, et al. Activation mutations of human c-KIT resistant to imatinib mesylate are sensitive to the tyrosine kinase inhibitor PKC412. *Blood* 2005; 106: 721-724

Hauswirth AW, Simonitsch-Klupp I, Uffmann M, et al. Response to therapy with interferon alpha-2b and prednisolone in aggressive systemic mastocytosis: report of five cases and review of the literature. *Leuk Res* 2004; 28: 249-257.

Lim KH, Pardanani A, Butterfield JH, et al. Cytoreductive therapy in 108 adults with systemic mastocytosis: outcome analysis and response prediction during treatment with interferon-alpha, hydroxyurea, imatinib mesylate or 2-chlorodeoxyadenosine. *Am J Hematol* 2009; 84:

Clinical Review
Yvette Kasamon, MD
NDA 207997, Orig 1
RYDAPT (Midostaurin)

790-794.

Lim KH, Tefferi A, Lasho TL, et al. Systemic mastocytosis in 342 consecutive adults: survival studies and prognostic factors. *Blood* 2009; 113: 5727-5736.

Pardanani A. Systemic mastocytosis in adults: 2015 update on diagnosis, risk-stratification, and management. *Am J Hematol* 2015; 90: 251-262.

Pardanani A, Lim KH, Lasho TL, Finke C, et al. Prognostically relevant breakdown of 123 patients with systemic mastocytosis associated with other myeloid malignancies. *Blood* 2009; 114: 3769-3772.

Portenoy RK, Thaler HT, Kornblith AB, et al. The Memorial Symptom Assessment Scale: an instrument for the evaluation of symptom prevalence, characteristics and distress. *Eur J Cancer* 1994; 30A: 1326-1336.

Tremblay D, Carreau N, Kremyanskaya M, Mascarenhas J. Systemic mastocytosis: Clinical update and future directions. *Clin Lymphoma, Myeloma & Leukemia* 2015; 15: 728-738.

Ustun C, Reiter A, Scott BL, et al. Hematopoietic stem-cell transplantation for advanced systemic mastocytosis. *JCO* 2014; 32: 3264-3274.

Valent P, Akin C, Escribano L, et al. Standards and standardization in mastocytosis: consensus statements on diagnostics, treatment recommendations and response criteria. *Eur J Clin Invest* 2007; 37: 435-453.

Valent P, Akin C, Sperr WR, et al. Aggressive systemic mastocytosis and related mast cell disorders: current treatment options and proposed response criteria. *Leuk Res* 2003; 27: 635-641.

Vega-Ruiz A, Cortes JE, Sever M, et al. Phase II study of imatinib mesylate as therapy for patients with systemic mastocytosis. *Leuk Res* 2009; 33: 1481-1484.

Ware JE Jr, Kosinski M, Keller SD. A 12-item Short-Form health survey: construction of scales and preliminary tests of reliability and validity. *Med Care* 1996; 34: 220-233.

13.2. Financial Disclosure

Covered Clinical Study: D2201		
Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>208</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>6</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u> Significant payments of other sorts: <u>6</u> Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator in sponsor of covered study: <u>0</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Clinical Review
 Yvette Kasamon, MD
 NDA 207997, Orig 1
 RYDAPT (Midostaurin)

Covered Clinical Study: A2213		
Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>49</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u> Significant payments of other sorts: <u>0</u> Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator in sponsor of covered study: <u>0</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>4</u>		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

13.3. Clinical Spectrum of Systemic Mastocytosis

Figure 8: Spectrum of Disease in Systemic Mastocytosis

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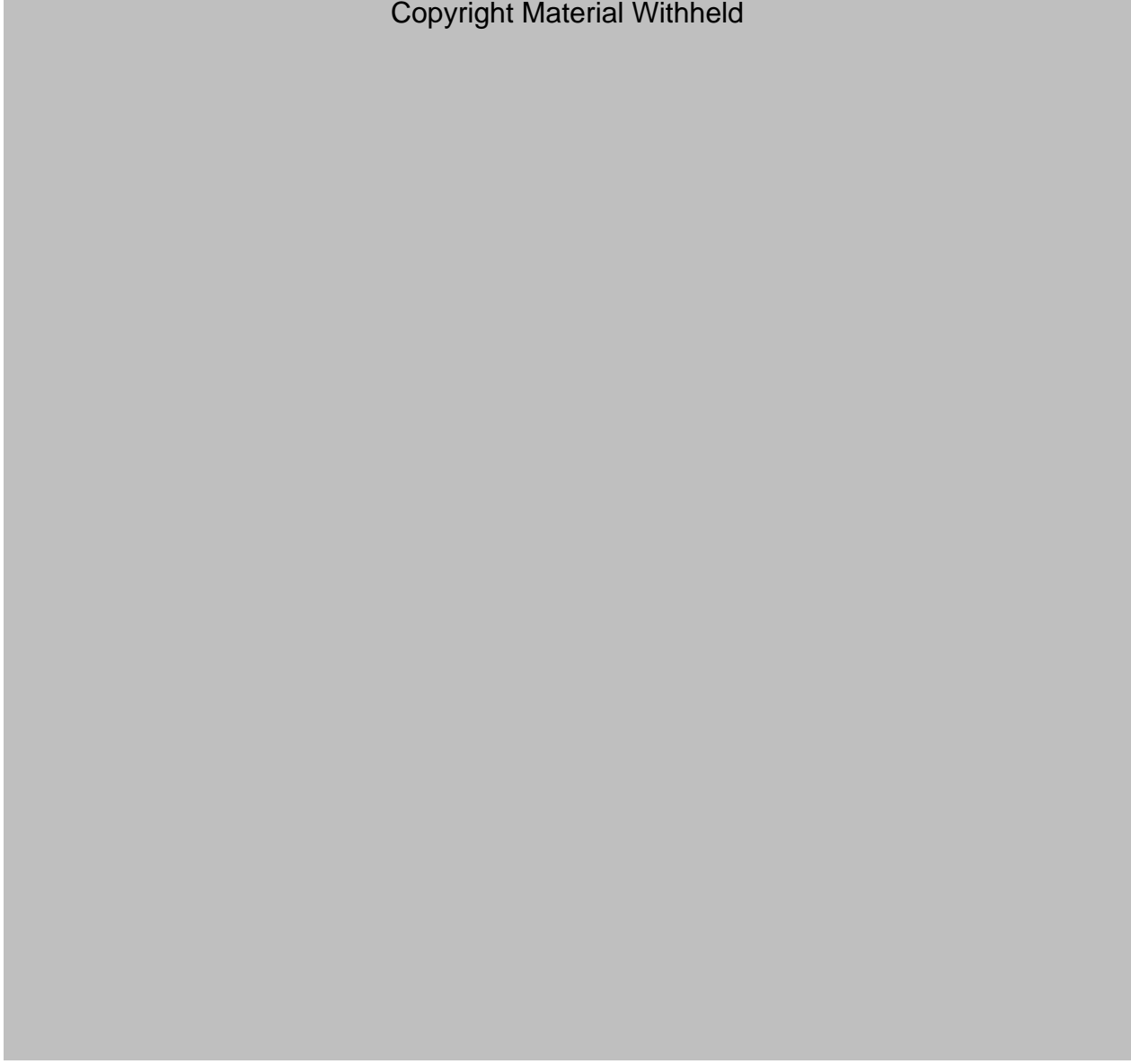


Source: Arber DA et al 2016 and Figure 1 from Tremblay D et al 2015

13.4. Classification of Systemic Mastocytosis

Table 34: World Health Organization Variants of Systemic Mastocytosis

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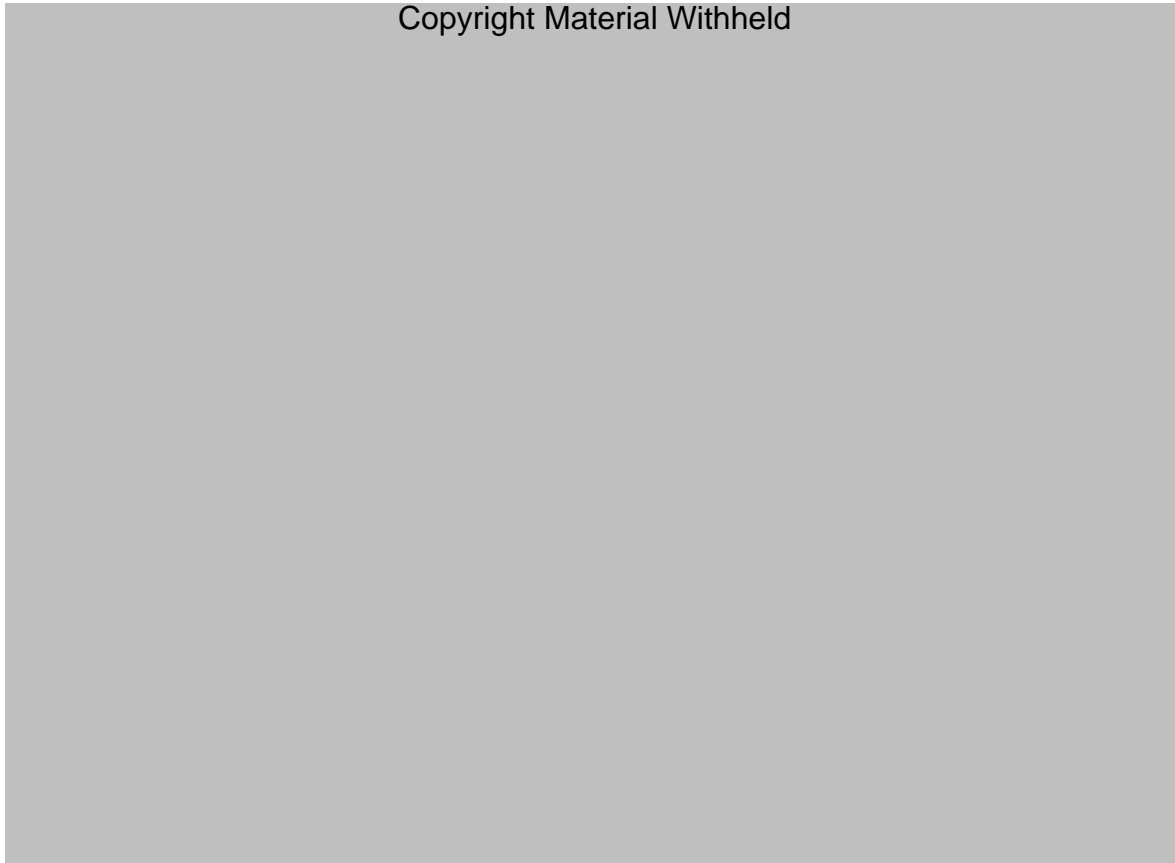
Source: Gotlib J et al 2016, supplementary table S1.

Note: Advanced SM is not a WHO classification.

13.5. **Valent and Modified Valent Response Criteria**

Table 35: Original Valent Criteria

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Source: Gotlib J et al 2013 synopsis of Valent P et al 2003

Table 36: Response Definitions in Studies D2201 and A2213

D2201:	Response category	Definition
Modified Valent criteria	Major response (MR)	Complete resolution of at least one C-finding, and no confirmed progression in other C-findings.
	Complete remission (CR)	Disappearance of all mast cell infiltrates in affected organs, decrease of serum tryptase level to <20 ng/mL, and disappearance of SM-associated organomegaly.
	Incomplete remission (IR)	Decrease in mast cell infiltrates in affected organs and/or substantial decrease (>50%) of serum tryptase level from baseline and/or visible regression of organomegaly
	Pure clinical response (PCR)	No significant response in mast cell infiltrates, tryptase levels, organomegaly that could reach the score of CR or IR.
	Partial response (PR)	Measurable improvement in one or more C-finding(s) without confirmed progression in other C-findings.
	Good partial response (GPR)*	>50% regression of one or more C-findings and no progression in other C-findings.
	Minor response (MinR)*	>20% to ≤ 50% regression of one or more C-findings and no progression in other C-findings.
	No response (NR)	
	Stable disease (SD)	C-findings show constant range, not meeting the criteria for a response or progressive disease
	Progressive disease (PD)	At least one C-finding show progression, defined as >20% worsening compared to the last value before the start of study drug
* GPR and MinR are not defined for C-findings of TD anemia and TD thrombocytopenia.		
A2213:	Response category	Definition
Original Valent criteria	Major response (MR)	Complete resolution of at least one C-finding and no progression of other C-findings.
	Complete remission (CR)	Complete disappearance of mast cell infiltrates in affected organs, decrease serum tryptase levels to <20 ng/mL, and disappearance of SM-associated organomegaly
	Incomplete remission (IR)	>50% decrease in mast cell infiltrates in affected organs and/or >50% decrease of serum tryptase level, and/or >50% visible regression of organomegaly.
	Pure clinical response (PCR)	Without decrease in mast cell infiltrates, without decrease in tryptase levels, and without regression of organomegaly.
	Partial response (PR)	Incomplete regression of one or more C-findings without complete regression and without progression in other C-findings
	Good partial response (GPR)	>50% regression of one or more C-findings and no progression in other C-findings
	Minor response (MinR)	≤ 50% regression of one or more C-findings and no progression in other C-findings.
	No response (NR)	C-findings persistent or progressive*
	Stable disease (SD)	C-findings show constant range
	Progressive disease (PD)	At least one C-finding show progression
*In the case of progressive C-findings and a documented response in other C-findings, the summary response designation was progressive disease		

Source: SCE Table 3-3 (Study D2201) and Table 3-4 (Study A2213)

Table 37: Response Criteria for C-Findings in Studies D2201 and A2213

C-finding	MR	PR (subcategory GPR)*
Bone marrow/blood		
Neutropenia (ANC <1000/ μ L)	ANC >1000/ μ L	Decrease below 1000/ μ L reverted by >50%, and a minimum increase of 200/ μ L (Study D2201) / 100/ μ L (Study A2213)
Anemia (Hemoglobin <10 g/dL)	Hemoglobin >10 g/dL	Decrease below 10g/dL reverted by >50%, and a minimum increase of 1.5 g/dL (Study D2201) / 1 g/dL (Study A2213)
Thrombocytopenia (Platelet count <100,000/ μ L)	Platelet count >100,000/ μ L	Decrease to <100,000/ μ L reverted by >50%, and a minimum increase of 20,000/ μ L (Study D2201) / 10,000/ μ L (Study A2213)
Study D2201 only: TD anemia	No RBC transfusions during 2 consecutive cycles (56 days)	$\geq$ 50% decrease in units transfused during a period of 56 days, compared to the 56 day period prior to start of study drug
Anemia (Hemoglobin <10 g/dL), with 1-3 RBC transfusions within a period of 56 days prior to treatment start	As above, and hemoglobin >10 g/dL during 2 consecutive cycles (56 days)	As above, and/or Hgb decrease below 10g/dL reverted by >50%
Study D2201 only: TD thrombocytopenia	No platelet transfusions during 2 consecutive cycles (56 days), and platelet count >30,000/ μ L	$\geq$ 50% decrease in units transfused during a period of 56 days, compared to the 56 day period prior to start of study drug
Thrombocytopenia (Platelet count <100,000/ μ L), with 1-3 platelet transfusions within a period of 56 days prior to treatment start	As above	As above
Liver		
Elevated ALT, AST Study D2201 only: total bilirubin	Decrease to normal	Increase reverted by >50%
Hypoalbuminemia	Increase to normal	Decrease reverted by >50%
Study A2213 only: Hepatomegaly with ascites	No ascites	Decrease of frequency of paracenteses by 50%
Spleen		
Palpable splenomegaly with hypersplenism-thrombocytopenia	No signs of hypersplenism, platelet count >100,000/ μ L	Parameters indicating hypersplenism (platelet count) improved by >50% Study D2201 only: minimum increase in platelet count of 20,000 / μ L
GI tract		
Malabsorption with hypoalbuminemia and/or weight loss	Normal albumin Study D2201 only: Pre-study weight (within 6 months + 3 weeks) Study A2213 only: Normal weight	Decrease in albumin improved by >50%, weight loss reverted by >50%, or (Study D2201 only) regaining >5% weight
Study A2213 only: Bones		
Huge osteolyses or/and severe osteoporosis with pathologic fractures	No osteolyses	Partial resolution of osteolyses

Source: SCS in AdSM, Table 3-2. TD = transfusion dependent.

* PR subcategory of MinR requires improvement of > 20%.

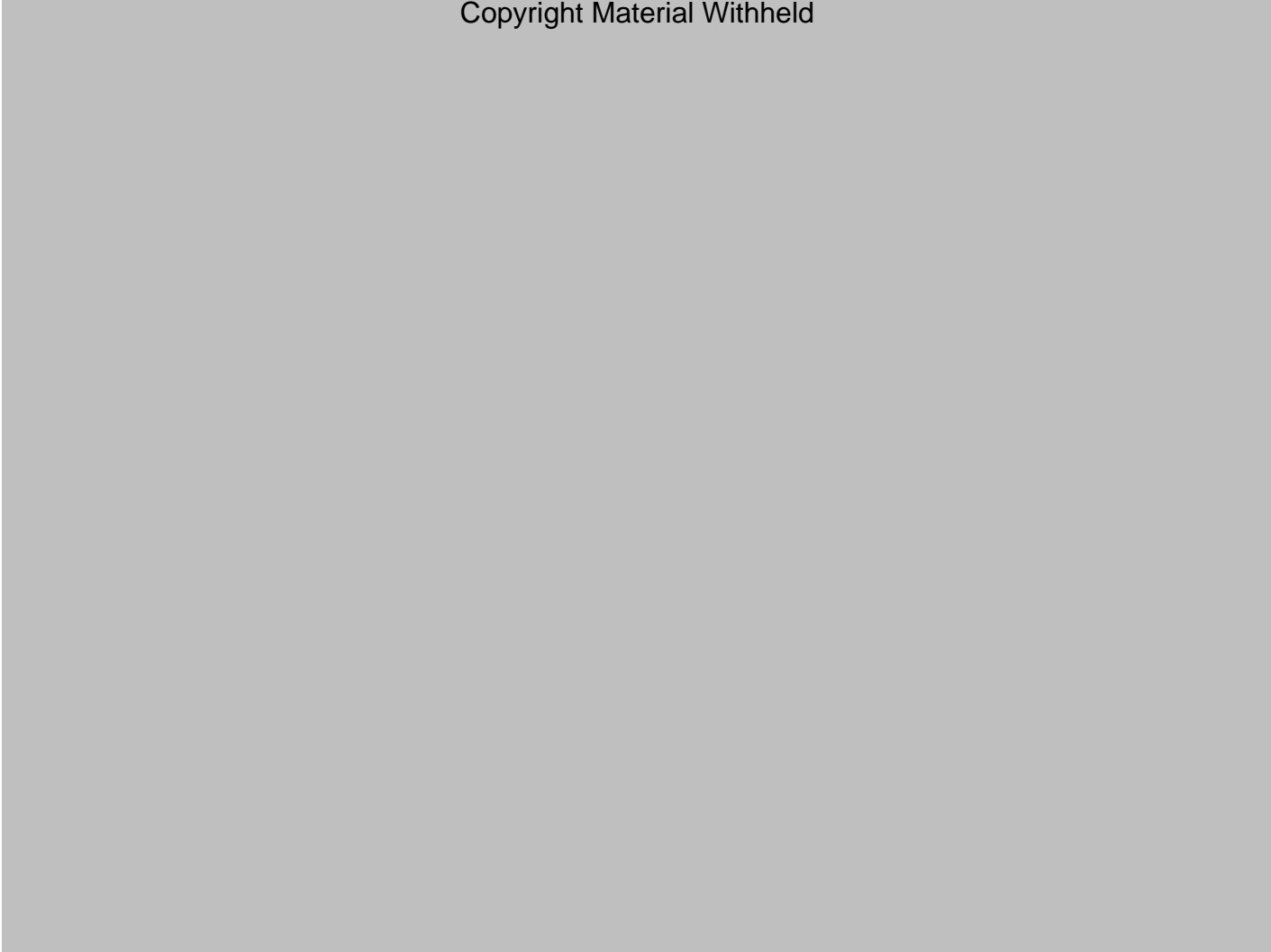
For C-findings of TD anemia and TD thrombocytopenia, PR is not subdivided into GPR or MinR.

13.6. IWG-MRT-ECNM Response Criteria for AdSM

The following response criteria apply to ASM, SM-AHN, and MCL.

Table 38: IWG-MRT-ECNM Response Criteria

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Source: Adapted from Gotlib J et al 2013, Table 4

* Response that is not maintained or confirmed for a period of ≥ 12 weeks does not fulfill criteria for CR, PR, or CI.

† Only applies if pretreatment tryptase level is ≥ 40 ng/mL

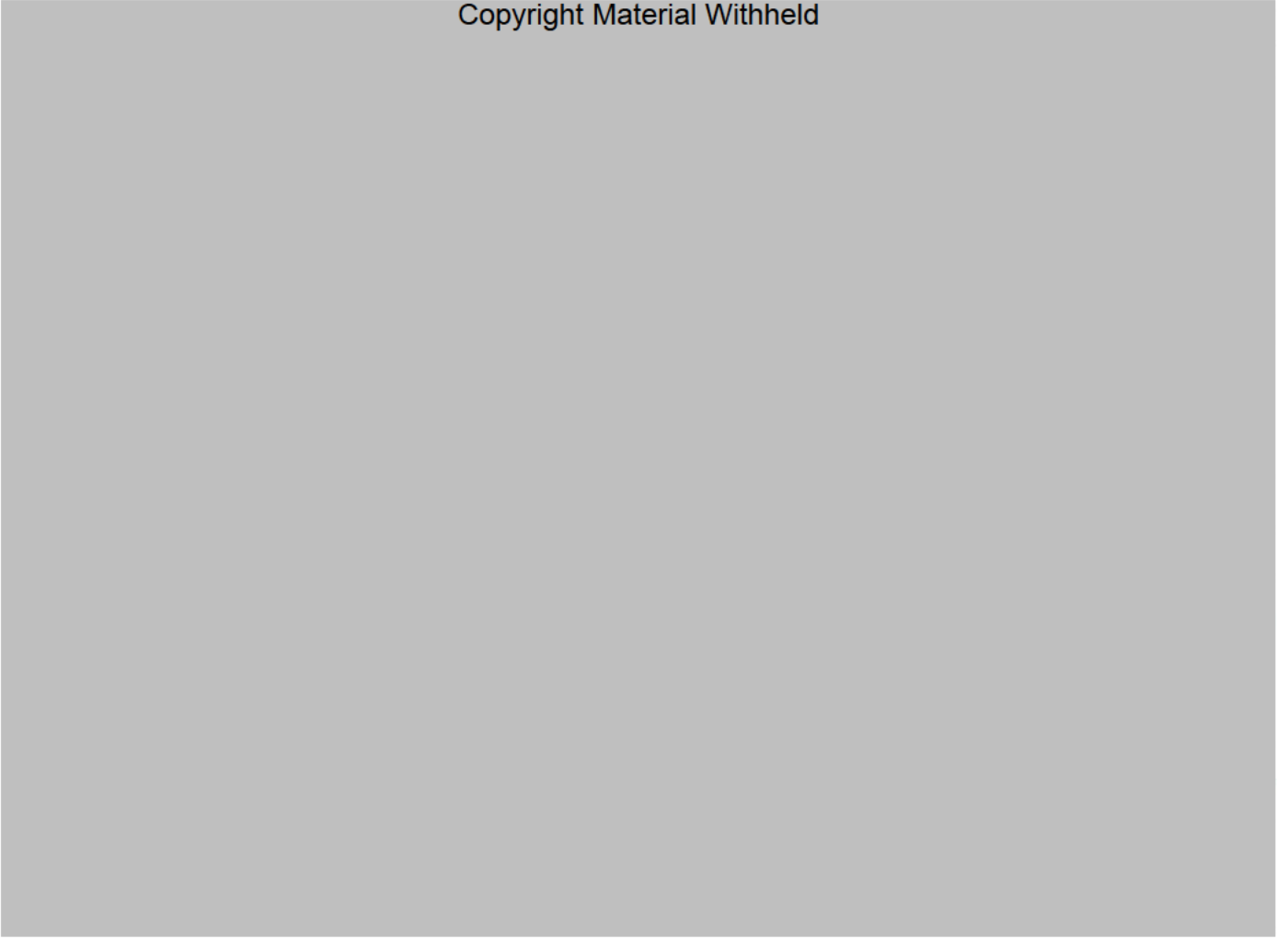
‡ Organ biopsy in addition to BM biopsy may be considered

¶ Progression of underlying AHN to AML is also considered PD in clinical trials.

§ For clinical trials using 3D CT or MRI, progressive splenomegaly defined as $\geq 25\%$ increase in spleen volume.

Table 39: IWG-MRT-ECNM Criteria for Clinical Improvement

Copyright Material Withheld



Source: Gotlib J et al 2013, Table 3
CI: clinical improvement

13.7. Toxicity Management Guidelines in Study D2201

Table 40: Dose Modification Guidelines – Study D2201

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Source: Gotlib J et al 2016, supplementary table S3

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13.8. Schedule of Study D2201 Assessments

Table 41: Core On-Treatment Evaluations – Study D2201

		Screening ^A							Cycle 1							Cycle 2		Cycle 3-11	Cycle 12	Subsequent cycles ^V
		1	2	3	4	5	6	7	8	9	10-18	19	20+							
Visit no.		1	2	3	4	5	6	7	8	9	10-18	19	20+							
Day of cycle		-28 to 0 ^A	1 ⁺	3 ⁺	8	15	22	28	15	28	28	28	at end of 3 rd cycle							
Physical examination	S	X	X			X		X		X	X	X	X							
Height	D	X																		
Weight	D	X	X					X		X	X	X	X							
Vital signs	D	X	X	X	X	X	X	X	X	X	X	X	X							
Performance Status (ECOG)	D	X	X	X	X	X	X	X	X	X	X	X	X							
12-lead ECG ³	D	X		X				X		X	X	X	X ¹⁸							
Echocardiogram or MUGA scan	D	X ^U									X ^U	X ^U	X ^U							
Chest x-ray ⁴	D	X									X ^A	X	X ¹⁷							
Spiral CT (MRI) abdomen/pelvis ⁵	D	X									X ^A	X	X ¹⁷							
Skeletal bone survey ⁵	D	X									X ^A	X	X ¹⁷							
Hematology ⁷	D	X	X ₁₂	X	X	X	X	X	X	X	X	X	X							
Coagulation test ⁷	D	X				X		X		X	X	X	X ¹⁸							
Serum chemistries ⁷	D	X	X ¹²	X	X	X	X	X	X	X	X	X	X							
Urinalysis ⁷	D	X						X		X	X	X	X ¹⁷							
Serum pregnancy test ⁷	D	X																		
Thyroid function test (T4, TSH) ^{7, 8}	D	X						X			X ^A	X	X ¹⁷							
Serum tryptase ⁹	D	X	X ¹²	X	X	X		X	X	X	X	X	X							

(continued)

Table 41: Core On-Treatment Evaluations – Study D2201

		Screening ⁴	Cycle 1							Cycle 2		Cycle 3-11	Cycle 12	Subsequent cycles ⁵			
Visit no.		1	2	3	4	5	6	7	8	9	10-18	19	20+				
Day of cycle		-28 to 0 ^A	1 [*]	3 [*]	8	15	22	28	15	28	28	28	at end of 3 rd cycle				
BM/ blood samples for histopathology, immunochemistry ¹⁰	D	X									X ^A	X	X ¹⁷				
BM sample for KIT mutation status ¹⁰	D	X									X ^A						
Pharmacokinetic blood/urine samples	D		X ¹³	X ¹⁴	X ¹⁴	X ¹⁴	X ¹⁴	X ¹⁴	X ¹⁴	X ¹⁴	X ¹⁴	X					
Overall assessment of response	D							X		X	X	X	X				
Transfusion log (RBC, whole blood and platelets) ¹¹	D		Continuous during the study and up to 28 days after the last study drug														
Mediator-related symptoms	D		X					X		X	X	X	X ¹⁸				
PRO, QL: SF-12 + MSAS	D		X					X		X	X	X	X ¹⁸				
Midostaurin dosing	D		←	←	←	←	←	←	←	←	Continuous	→	→	→	→	-	
Adverse Events	D		←	←	←	←	←	←	←	←	Continuous	→	→	→	→	-	
Prior/ concomitant medications/ Significant non-drug therapies	D	X		←	←	←	←	←	←	←	←	←	Continuous	→	→	→	→
Prior/ concomitant SM- or antineoplastic therapies	D	X		←	←	←	←	←	←	←	←	←	Continuous	→	→	→	→

Source: Adapted from Table 7-1 of Protocol D2201, version 6
D = database entry, S = source documents only.

13.9. Trials Included in the Integrated Summary of Safety

Table 42: Safety Studies in the ISS

Study	Study design	Population/Number of patients	Midostaurin dose (mg)
Advanced SM			
D2201	Phase II, open-label, single arm	Patients with ASM/MCL +/- AHNMD Safety set; N=116	100 mg bid
A2213	Phase II, open-label, single arm	Patients with ASM/MCL +/- AHNMD Safety set: N=26	100 mg bid
AML			
A2301*	Phase III, double blind, randomized	Patients with newly-diagnosed FLT3-mutated AML / randomized N=717 Safety set: N=680 midostaurin N=345 placebo N=335	50 mg bid (N=359) or placebo (N=358), sequentially with chemotherapy, then continuously x 12 months
Studies in hematological indications. dose finding studies – Combination treatment			
A2106	Phase IB, open-label,	Patients with newly-diagnosed WT/FLT3-mutated AML Safety set: N=69 (n=40 treated at 50 mg bid) Note: safety set for the re-run outputs N=68	100 mg bid, 50 mg bid either sequentially or concomitantly with chemotherapy; following consolidation therapy patients could continue to receive single agent midostaurin
Studies in hematological indications. dose finding studies – Single agent treatment			
A2104	Phase II, open-label, single arm	Patients with relapsed/refractory FLT3-mutated AML or high risk MDS / Safety set: N=20	75 mg tid
A2104E1	Phase II, open label, randomized	Patients with relapsed/refractory WT/FLT3-mutated AML or high risk MDS / Safety set: N=95	50 mg bid, 100 mg bid
A2104E2	Phase I/II, open label, dose escalation	Patients with relapsed/refractory WT/FLT3-mutated AML or high risk MDS / Safety set: N=29 ^f	PKC412 dose escalation up to 300 mg bid Itraconazole + PKC412 100mg bid for 2 days followed by 50 mg bid
A2114 ^g	Phase I	Pediatric patients with relapsed or refractory MLL-rearranged ALL or FLT3 mutated AML / Safety set: N=22	30 mg/m ² bid, 60 mg/m ² bid
0006**	Phase II, open label, multi dose	Patients with chronic lymphocytic leukemia or non-Hodgkin's lymphoma/ Safety set: N=21	25mg qd, 75 mg bid, 75 mg tid.

(continued)

Table 42: Safety Studies in the ISS

Study	Study design	Population/Number of patients	Midostaurin dose (mg)
Studies in solid tumors and diabetes - Single agent treatment			
0002	Phase Ib, open label, dose escalation	Patients with advanced solid tumors / Safety set: N=32	12.5 mg qd 12.5 mg bid, 25 mg bid, 50 mg bid, 75 mg bid, 75 mg tid, 100 mg tid.
C99-A001	Phase I, ascending dose, placebo controlled	Patients with diabetes / Safety set: N=86	25 mg bid, 50 mg bid, 75 mg bid, 75 mg tid, 100 mg tid.
0003 [§]	Phase II, double blind, randomized, dose finding, Placebo controlled	Patients with diabetic macular edema / Safety set: N=141	25 mg bid, 50 mg bid, 75 mg bid.
Special safety studies			
A2113	QT study, double-blind, randomized, placebo and active control	Healthy subjects Safety set: N=191 Midostaurin: 79 Moxifloxacin: 44 Placebo: 68	Midostaurin: 75 mg tid on Days 1 and 2 Placebo: 75 mg qd on Day 3 Moxifloxacin: 400 mg
A2116	PK, safety and tolerability of midostaurin in subjects with hepatic impairment, compared to healthy control subjects	Healthy subjects patients Safety set: N=30 hepatic impairment mild: 10 moderate: 7 normal: 13	50 mg bid from day 1 to Day 6, 50 mg single dose on Day 7
Other Clinical pharmacology studies – healthy subjects			
7 clinical pharmacology studies	Various	N=261	From 1 mg qd to 75 mg qd

Source: ISS Table 1-1

Note: Other Sponsor-supported clinical trials of midostaurin have been conducted.

13.10. FDA Grouping of Preferred Terms for Safety Analysis

Table 43: FDA Grouping of Preferred Terms

Grouped term	PTs included
Abdominal pain	abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness, abdominal discomfort
Anxiety	anxiety, anxiety disorder
Ascites	ascites, abdominal ascites
Cardiac failure	cardiac failure, cardiac failure chronic, cardiac failure congestive
Cough	cough, productive cough
Depression	depression, depressed mood
Dyspnea	dyspnea, dyspnea exertional
Edema	edema, edema peripheral, peripheral swelling, generalized edema, fluid retention
Enteritis	enteritis, enterocolitis, gastroenteritis, gastroenteritis viral, gastroduodenitis
Fatigue	fatigue, asthenia
Gastritis	gastritis, gastritis erosive, gastritis hemorrhagic
Gastrointestinal hemorrhage	lower GI hemorrhage, upper GI hemorrhage, esophageal hemorrhage, esophageal varices hemorrhage, gastric hemorrhage, gastrointestinal hemorrhage, intestinal hemorrhage, duodenal ulcer hemorrhage, rectal hemorrhage, melena
Headache	headache, sinus headache
Hypertension	hypertension, hypertensive crisis
Musculoskeletal pain	musculoskeletal pain, musculoskeletal chest pain, bone pain, back pain, myalgia, musculoskeletal discomfort, neck pain
Myocardial infarction	myocardial infarction, acute myocardial infarction, troponin increase, troponin ^a
Neuropathy peripheral	neuropathy peripheral, peripheral sensory neuropathy
Pulmonary hemorrhage	pulmonary hemorrhage, pulmonary alveolar hemorrhage
Pneumonia	pneumonia, bronchopneumonia, specific pneumonia types, lung infiltration, ^b lung infection ^b
Rash	rash, rash erythematous/macular/maculo-papular/papular/pustular, toxic skin eruption
Sepsis	sepsis, bacterial sepsis (includes specific types), bacteremia
Skin infection	skin infection, skin bacterial infection
Upper respiratory tract infection	URTI, viral URTI, nasopharyngitis, pharyngitis, pharyngitis streptococcal, rhinitis, sinusitis, acute sinusitis, chronic sinusitis
Urinary tract infection	UTI + specific types of UTI + cystitis
Laboratory parameters:	
Anemia	anemia, hemoglobin decreased
Lymphopenia	lymphopenia, lymphocyte count decreased
Leukopenia	leukopenia, wbc count decrease

Clinical Review
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NDA 207997, Orig 1
RYDAPT (Midostaurin)

Table 43: FDA Grouping of Preferred Terms

Grouped term	PTs included
Neutropenia	neutropenia, neutrophil count decreased, granulocytopenia
Thrombocytopenia	thrombocytopenia, platelet count decreased
Hyponatremia	hyponatremia, blood sodium decrease
Blood creatinine increase	Blood creatinine increase, acute kidney injury
Lipase increase	Lipase increase, hyperlipasemia
Eosinophilia	Eosinophilia, eosinophil count increased
Hypoalbuminemia	Blood albumin decreased, hypoalbuminemia
^a 1 case (grade 4)	
^b Selected cases, based on verbatim term	

13.11. Cardiac Dysfunction and Pulmonary Toxicity in Patients with AdSM

Table 44: Cardiac Dysfunction Reported in the AdSM Safety Population

Patient ID	Age	Description
Cases included as narratives ^a		
D2201-0101-00003	73	Death on Day 80 from right-sided CHF, in context of COPD history. LVEF 64% on Day 60, 50% at baseline. Symptoms of RV failure noted on Day 34.
D2201-0150-00023 ^b	72	Death on Day 672 from cardiac failure secondary to aortic valve stenosis. Patient had aortic valve disease at baseline.
D2201-0150-00014	72	Normal baseline echo. EF after 6 cycles was 70%. In context of grade 4 “chronic cardiac failure,” echo on Day 339 showed mitral and tricuspid valve insufficiency and endomyocardial fibrosis (EF unknown), with resultant valve remodeling procedures.
D2201-0150-00024	72	History of active COPD. Several episodes of dyspnea at an unspecified time point were attributed to cardiac insufficiency (EF unknown) and led to midostaurin dose reduction. Death on Day 235 from endocarditis and sepsis.
D2201-0140-00005	64	Death on Day 1157 from refractory sepsis associated with cardiac decompensation, after transformation to AML.
D2201-0150-00019	69	Decompensated heart failure occurred in the context of acute renal failure and aggravated diarrhea, with resultant drug interruption on Day 169. Recovered on Day 187 shortly after resolution of renal failure.
D2201-0300-00002 ^b	68	Cardiac failure on Day 835 in context of transfusion-requiring anemia and disease exacerbation
Cases described as having notable post-baseline LVEF changes ^{c, d}		
D2201-0142-00005	58	Baseline EF 50%; after Cycle 6, EF 41% (-9)
D2201-0150-00022	68	Baseline EF 65%; after Cycle 3, EF 49% (-16)
D2201-0150-00023 ^b	72	Baseline EF 60%; after Cycle 3, EF 45% (-15)
D2201-0300-00002 ^b	68	Baseline EF 56%; at end of treatment, EF 45% (-11)

^a Source: Response to 12/29/2016 IR (SDN 61) and echo dataset (AECH.xpt)

^b Described in both sections of this table

^c Source: Response to 1/27/2017 IR (SDN 71) and D2201 CSR Table 14.3-4.3.1

^d Patients were excluded from this analysis if they had decreased baseline LVEF, or if the LVEF was coded in character but not numeric format.

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Table 45: Pulmonary Toxicity Reported by Sponsor in the AdSM Safety Population

Patient ID	Age	Ungrouped PT ^a	Start day	Grade reported	SAE	Description
Lung infection absent or unknown						
D2201-0140-00016	64	Interstitial lung disease	822	1	No	Attributed by investigator to concomitant medications other than midostaurin, with rheumatoid arthritis as contributory
D2201-0140-00022	58	Interstitial lung disease	94	2	No	Diagnosed 10 days after midostaurin stopped due to PD. No details.
D2201-0300-00002	68	Lung infiltration	875	2	No	No details. Treatment discontinued on Day 874 due to PD.
Lung infection present						
D2201-0142-00004	76	Pneumonitis	9	2	Yes	Recovered with 4 days of antibiotic.
A2213-0002-00002	69	Lung infiltration	560	2	No	Occurred in context of pneumonia complicated by critical illness.

Source: Response to 12/29/2016 IR (SDN 61).

^a Sponsor selected cases based on SMQ of interstitial lung disease.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

YVETTE L KASAMON

02/03/2017

DONNA PRZEPIORKA

02/03/2017

I concur with the primary reviewer's recommendation for regular approval of midostaurin for the treatment of adult patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated hematological neoplasm (SM AHN), or mast cell leukemia (MCL).

Clinical Review

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NDA 207997

Rydapt® (midostaurin)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	207997 (Original-2)
Priority or Standard	Priority
Submit Date(s)	August 29, 2016
Received Date(s)	August 29, 2016
PDUFA Goal Date	April 28, 2017
Division/Office	Division of Hematology Products / Office of Hematology and Oncology Products
Reviewer Name(s)	Ashley Ward, MD
Review Completion Date	February 4, 2017
Established Name	Midostaurin
(Proposed) Trade Name	Rydapt®
Applicant	Novartis
Formulation(s)	Soft capsule 25 mg
Dosing Regimen	50 mg twice daily on days 8 to 21 of each cycle of induction and consolidation chemotherapy
Applicant Proposed Indication(s)/Population(s)	Rydapt is indicated in combination with standard induction and consolidation chemotherapy (b) (4) for adult patients with newly diagnosed acute myeloid leukemia (AML) who are FLT3 mutation-positive, as detected by an FDA approved test.
Recommendation on Regulatory Action	Full approval for revised indication
Recommended Indication(s)/Population(s) (if applicable)	Rydapt is indicated, in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation chemotherapy, for the treatment of adult patients with newly diagnosed acute myeloid leukemia (AML) who are FLT3 mutation-positive, as detected by an FDA approved test.

Clinical Review

Ashley Ward, MD
NDA 207997
Rydapt® (midostaurin)

Table of Contents

Glossary 8

1 Executive Summary 10

 1.1. Product Introduction.....10

 1.2. Conclusions on the Substantial Evidence of Effectiveness.....10

 1.3. Benefit-Risk Assessment 10

2 Therapeutic Context.....14

 2.1. Analysis of Condition.....14

 2.2. Analysis of Current Treatment Options 14

Source: FDA analysis.....15

3 Regulatory Background 15

 3.1. U.S. Regulatory Actions and Marketing History.....15

 3.2. Summary of Presubmission/Submission Regulatory Activity 15

 3.3. Foreign Regulatory Actions and Marketing History 16

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety 16

 4.1. Office of Scientific Investigations (OSI) 16

 4.2. Product Quality 17

 4.3. Nonclinical Pharmacology/Toxicology 17

 4.4. Clinical Pharmacology 18

 4.4.1. Mechanism of Action 18

 4.4.2. Pharmacokinetics.....19

 4.5. Devices and Companion Diagnostic Issues 20

 4.6. Consumer Study Reviews.....21

5 Sources of Clinical Data and Review Strategy 21

 5.1. Table of Clinical Studies 21

 5.2. Review Strategy 26

6 Review of Relevant Individual Trials Used to Support Efficacy 26

Clinical Review

Ashley Ward, MD

NDA 207997

Rydapt® (midostaurin)

6.1.	Study A2301	26
6.1.1.	Study Design	26
6.1.2.	Study Results	37
6.2.	Study A2106	52
6.2.1.	Study Design	52
6.2.2.	Study Results	53
6.3.	Study ADE02T	56
6.3.1.	Study Design	56
6.3.2.	Study Results	58
6.4.	Studies A2104, A2104E1, and A2014E2	61
6.4.1.	Study Design	61
6.4.2.	Study Results	63
7	Integrated Review of Effectiveness	64
7.1.	Assessment of Efficacy Across Trials	64
7.1.1.	Primary Endpoints	64
7.1.2.	Secondary and Other Endpoints	64
7.1.3.	Dose and Dose-Response	65
7.1.4.	Onset, Duration, and Durability of Efficacy Effects	65
7.2.	Additional Efficacy Considerations	65
7.2.1.	Considerations on Benefit in the Postmarket Setting	65
7.3.	Integrated Assessment of Effectiveness	65
8	Review of Safety	66
8.1.	Safety Review Approach	66
8.2.	Review of the Safety Database	66
8.2.1.	Overall Exposure	66
8.2.2.	Relevant characteristics of the safety population:	68
8.2.3.	Adequacy of the safety database:	69
8.3.	Adequacy of Applicant’s Clinical Safety Assessments	70
8.3.1.	Issues Regarding Data Integrity and Submission Quality	70
8.3.2.	Categorization of Adverse Events	70

Clinical Review

Ashley Ward, MD

NDA 207997

Rydapt® (midostaurin)

- 8.3.3. Routine Clinical Tests 71
- 8.4. Safety Results 71
 - 8.4.1. Deaths 71
 - 8.4.2. Serious Adverse Events 73
 - 8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects 74
 - 8.4.4. Treatment Emergent Adverse Events and Adverse Reactions 75
 - 8.4.5. Laboratory Findings 79
 - 8.4.6. Vital Signs 79
 - Source: FDA analysis 80
 - 8.4.7. Electrocardiograms (ECGs) 80
 - 8.4.8. QT 80
- 8.5. Analysis of Submission-Specific Safety Issues 81
 - 8.5.1. Embryo-fetal toxicity 81
 - 8.5.2. Nausea and vomiting 82
- 8.6. Safety Analyses by Demographic Subgroups 82
- 8.7. Specific Safety Studies/Clinical Trials 83
- 8.8. Additional Safety Explorations 83
 - 8.8.1. Human Carcinogenicity or Tumor Development 83
 - 8.8.2. Human Reproduction and Pregnancy 83
 - 8.8.3. Pediatrics and Assessment of Effects on Growth 84
 - 8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound 84
- 8.9. Safety in the Postmarket Setting 84
 - 8.9.1. Safety Concerns Identified Through Postmarket Experience 84
 - 8.9.2. Expectations on Safety in the Postmarket Setting 84
- 8.10. Additional Safety Issues From Other Disciplines 85
- 8.11. Integrated Assessment of Safety 85
- 9 Advisory Committee Meeting and Other External Consultations 86
- 10 Labeling Recommendations 86
 - 10.1. Prescribing Information 86
 - 10.2. Patient Labeling 87

Clinical Review

Ashley Ward, MD

NDA 207997

Rydapt® (midostaurin)

11 Risk Evaluation and Mitigation Strategies (REMS) 87

12 Postmarketing Requirements and Commitments 87

13 Appendices 87

 13.1. References 87

 13.2. Financial Disclosure 90

 13.3. Grouped Preferred Terms 93

Clinical Review

Ashley Ward, MD

NDA 207997

Rydapt® (midostaurin)

Table of Tables

Table 1: Currently Available Treatments for Acute Myelogenous Leukemia	15
Table 2: Listing of Clinical Trials Relevant to this NDA.....	22
Table 3: Study A2301 – Disposition of Patients	38
Table 4: Study A2301 – Major Protocol Deviations	39
Table 5: Study A2301 – Patient Demographics.....	40
Table 6: Study A2301 – Baseline Disease Characteristics	41
Table 7: Study A2301 – Restricted Mean Survival Time	44
Table 8: Study A2301 - Stem Cell Transplantation Rates.....	46
Table 9: Study A2301 - Impact of HSCT on Overall Survival Analyses	47
Table 10: Study A2301 – EFS Events and Reasons for Censoring	48
Table 11: Study A2301 – Results of Additional Efficacy Endpoints.....	50
Table 12: Study A2301 - Efficacy Results by Gender	51
Table 13: Study A2106 – Disposition of Patients	54
Table 14: Study A2106 – Complete Responses.....	55
Table 15: Study ADE01T – Disposition of Patients.....	59
Table 16: Study ADE02T – EFS Events.....	60
Table 17: Study ADE02T – Other Endpoints	60
Table 18: Studies A2104, A2104E1 and A2104E2 – Complete and Partial Responses	64
Table 19: Pooled Safety Database – Safety Population, Size and Denominators	67
Table 20: Duration of Exposure ¹ to Midostaurin in the Safety Population	68
Table 21: Planned Total Daily Dose of Midostaurin in the Safety Population	68
Table 22: Demographics of the Safety Population	69
Table 23: Deaths in the Safety Pool.....	71
Table 24: Study A2301 – Deaths by Treatment Phase.....	72
Table 25: Study A2301 – Causes of Deaths Occurring Within 30 Days of Treatment.....	72
Table 26: Study A2301 - Adverse Events Leading to Discontinuation in ≥ 2 Patients.....	75
Table 27: Study A2301 – TEAE Occurring in ≥ 10% of Patients by System Organ Class ¹	76
Table 28: Study A2301 – TEAE in ≥ 10% of Patients and ≥ 2% More Frequently on the Midostaurin Arm by Preferred Term	77
Table 29: Study A2301 - TEAE in ≥ 10% of Patients and ≥ 2% More Frequently on the Midostaurin Arm During Maintenance Therapy.....	77
Table 30: Safety Pool – Adverse Events Occurring in ≥ 10% of Patients.....	78
Table 31: Study A2301 – Newly Occurring Liver Function Abnormalities	80
Table 32: Pooled Safety Database – Vital Signs.....	80
Table 33: Study A2301 – TEAEs Occurring ≥ 5% More Frequently in One Gender on the Midostaurin Arm	83

Clinical Review

Ashley Ward, MD

NDA 207997

Rydapt® (midostaurin)

Table of Figures

Figure 1: Study A2301 – Study Design Schema.....27
Figure 2: Study A2301 – Overall Survival 44
Figure 3: Study A2301 – Subpopulation Analysis of the Primary Endpoint 45
Figure 4: Study A2301 – Overall Survival From Start of Maintenance Therapy 47
Figure 5: Study A2301 – Event-Free Survival 49
Figure 6: Study ADE02T – Trial Schema 57

Clinical Review

Ashley Ward, MD

NDA 207997

Rydapt® (midostaurin)

Glossary

AE	adverse event
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
APL	acute promyelocytic leukemia
AST	aspartate aminotransferase
AUCinf	area under the curve (infinity)
AUC0-T	area under the curve (time)
BID	twice daily
BPM	beats per minute
CALBG	Cancer and Leukemia Group B
CBC	complete blood count
CDRH	Center for Devices and Radiological Health
CLCr	creatinine clearance
Cmax	concentration (maximum)
Cmin	concentration (minimum)
CMC	chemistry, manufacturing, and controls
CNS	central nervous system
COD	cause of death
CR	complete response/remission
CRF	case report form
CRO	contract research organization
CRp	complete response with incomplete platelet recovery
CSR	clinical study report
DBP	diastolic blood pressure
DFS	disease-free survival
DMEPA	Division of Medication Error Prevention and Analysis
DMPH	Division of Maternal and Pediatric Health
DSMB	data safety monitoring board
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EFS	event-free survival
FAB	French-American-British
FAS	full analysis set
FDA	Food and Drug Administration
FLT	FMS-like tyrosine kinase

Clinical Review

Ashley Ward, MD

NDA 207997

Rydapt® (midostaurin)

GCP	good clinical practice
hERG	human ether-a-go-go
HR	hazard ratio
HSCT	hematopoietic stem cell transplantation
IND	Investigational New Drug
IRT	interdisciplinary review team
ITD	internal tandem duplication
IWG	international working group
MAED	MedDRA Adverse Events Diagnostic
MedDRA	Medical Dictionary for Regulatory Activities
MDS	myelodysplastic syndrome
MTD	maximum tolerated dose
NA	North America
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
NNA	non-North America
NPM1	nucleophosmin
OS	overall survival
OSI	Office of Scientific Investigation
PK	pharmacokinetics
PMA	pre-marketing application
PMC	postmarketing commitment
PMR	postmarketing requirement
PPS	per protocol set
PR	partial response
PREA	Pediatric Research Equity Act
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SBP	systolic blood pressure
SDN	study document number
SEER	Surveillance, Epidemiology, and End Results
SMQ	standard MedDRA query
SOC	system organ class
TBili	total bilirubin
TEAE	treatment emergent adverse event
TKD	tyrosine kinase domain
Tmax	Time (maximum)
ULN	upper limit of normal
WHO	World Health Organization

Clinical Review

Ashley Ward, MD

NDA 207997

Rydapt® (midostaurin)

1 Executive Summary

1.1. Product Introduction

Novartis submitted NDA 207997 for midostaurin (Rydapt®), also known as PKC412 or CGP41251, a new molecular entity (NME) for use in combination with chemotherapy for the treatment of previously untreated acute myeloid leukemia (AML) with *fms*-like tyrosine kinase-3 (FLT3) kinase domain mutations or internal tandem duplications. Midostaurin inhibits oncogenic mutant and wild-type forms of FLT3, KIT kinase, vascular endothelial growth factor receptor 2 (VEGFR2), fibroblast growth factor receptor (FGFR), members of the serine/threonine kinase family protein kinase C (PKC) and other receptor tyrosine kinases.

The applicant's proposed indication is "in combination with standard induction and consolidation chemotherapy [REDACTED] (b) (4) for adult patients with newly diagnosed AML who are FLT3 mutation-positive, as detected by an FDA approved test". The proposed dosing schedule for patients with acute myeloid leukemia is 50 mg administered orally twice daily on days 8-21 of each cycle of induction and consolidation chemotherapy, [REDACTED] (b) (4).

1.2. Conclusions on the Substantial Evidence of Effectiveness

I conclude that the information submitted by the applicant has provided substantial evidence for the effectiveness of midostaurin, in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation chemotherapy, for the treatment of adult patients with newly diagnosed AML who are FLT3 mutation-positive, as detected by an FDA approved test, and supports full approval in this indication. This conclusion is based on the results of a single randomized, double-blind, placebo-controlled study in previously untreated patients age ≤ 60 years that demonstrated an overall survival advantage in patients who received midostaurin in addition to standard chemotherapy compared with those who did not (HR 0.77, P=0.016). The study included a maintenance phase in which patients continued either midostaurin or placebo as a single agent after completion of standard chemotherapy. However, the study was not re-randomized at the start of maintenance, and as a result, the applicant provided insufficient evidence to support the effectiveness of midostaurin maintenance. The applicant provided a summary of safety and efficacy data from an investigator-sponsored trial of midostaurin in combination with intensive chemotherapy for untreated AML that included adults age > 60, supporting an indication unrestricted by age. The applicant provided data from several studies of midostaurin monotherapy in patients with previously untreated and relapsed/refractory AML that showed no evidence of clinical benefit of monotherapy in these indications, supporting a limitation of use.

1.3. Benefit-Risk Assessment

Clinical Review

Ashley Ward, MD

NDA 207997

Rydapt® (midostaurin)

Benefit-Risk Summary and Assessment

Midostaurin is a small molecule that inhibits multiple receptor tyrosine kinases. In vitro biochemical or cellular assays have shown that midostaurin or its major human active metabolites CGP62221 and CGP52421 inhibits the activity of FMS-like tyrosine kinase 3 FLT3 (wild type and D835Y mutant) and many other kinases. Approximately 35% of patients with AML harbor mutations of the *FLT3* gene on chromosome 13q12 which result in constitutive activation of FLT3 kinase. These mutations can be internal tandem duplications (ITD) or point mutations in the tyrosine kinase domain (TKD). FLT3-ITD mutations are associated with an increased likelihood of relapse and decreased overall survival (OS) in AML, while the prognostic effect of FLT3-TKD mutations is still under debate. The applicant's proposed indication evaluated in this review is "in combination with standard induction and consolidation chemotherapy (b) (4) for adult patients with newly diagnosed AML who are FLT3 mutation-positive, as detected by an FDA approved test". The benefit-risk assessment supports full approval of midostaurin, in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation for the treatment of adults with FLT3+ AML. (b) (4)

The efficacy of midostaurin is primarily based on the results of a single large randomized, double-blinded, placebo-controlled phase 3 study that compared midostaurin, administered at 50 mg by mouth twice daily on days 8-21 of each cycle of induction and consolidation chemotherapy, followed by continuous daily therapy at the same dose for up to 12 months of maintenance, to placebo in patients with previously untreated FLT3+ AML. The study was jointly sponsored by a cooperative group (CALGB, now Alliance) and the commercial sponsor. A total of 717 patients (360 on the midostaurin arm and 357 on the placebo arm) were evaluated on this study, which found that midostaurin yielded a statistically significant OS advantage (HR=0.77, p=0.016). Due to plateauing of the OS curves, estimates of median OS are not reliable, but the restricted mean survival advantage ranges from 2.6 - 5.4 months depending on time of follow-up. The median event-free survival (EFS) was 8.2 months on the midostaurin arm and 3.6 months on the placebo arm. Rates of complete response (CR) by day 60 were also higher on the midostaurin arm (59% vs 54%). Although the pivotal study was conducted in patients age < 60, data from an investigator-sponsored trial of midostaurin in combination with intensive chemotherapy in older adults with AML lend support for a broad indication without age restriction. Data from several studies of midostaurin monotherapy in patients with newly-diagnosed or relapsed/refractory AML show toxicity without substantial clinical activity, and resulted in a limitation of use statement in the product label.

The safety database for midostaurin consists of 1,298 patients exposed to midostaurin across 24 studies in patients with AML, patients with other malignancies, patients without malignancy and healthy volunteers. In general, midostaurin appears well-tolerated. Most fatal adverse

Clinical Review

Ashley Ward, MD

NDA 207997

Rydapt® (midostaurin)

events (AEs) occurred on studies of patients with AML receiving intensive chemotherapy, and were less frequent in the midostaurin arm than the placebo arm on the pivotal study. These events primarily consisted of infections, which are common causes of treatment-related mortality in this patient population. The most frequent serious adverse reaction was febrile neutropenia. Common adverse reactions (>20%) included anemia, nausea, rash, vomiting, mucositis, headache, elevated transaminases, musculoskeletal pain, petechiae, hyperglycemia, device-related infections and epistaxis. The high frequency of mild-moderate nausea and vomiting observed with midostaurin use warrants a recommendation to administer concomitant anti-emetics. As nonclinical reproductive studies noted fetal anomalies and fetal loss secondary to midostaurin, and the chemotherapy regimen midostaurin will be indicated for use with is frequently used in pregnant women with AML, I recommend a boxed warning against use in pregnancy.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• There were 19,950 new cases of AML and 10,430 deaths from AML in the United States in 2016. AML occurs in all age groups, but is primarily a disease of older adults, with a median age at diagnosis of 67 years. • AML is universally fatal without treatment, with a median survival of approximately two months.	AML is a fatal disease.
Current Treatment Options	• Intensive chemotherapy regimens, with or without HSCT, yield CR rates of 60-70% and 2-year OS of approximately 50% in patients < 60 years of age. • Older patients (age ≥ 60) fare less well, with CR rates of approximately 50% and 2-year overall survival of approximately 20%.	Current standard of care regimens are insufficient, and more effective therapies are needed.
Benefit	• Study A2301 was a randomized, double-blind, placebo-controlled study of midostaurin in combination with up to 6 cycles of intensive chemotherapy, followed by 12 months of maintenance with monotherapy, in patients with previously untreated FLT3+ AML. • The midostaurin arm had a statistically significant improvement in overall survival (HR 0.77, p=0.016).	Midostaurin 50 mg bid on days 8-21 in combination with daunorubicin / cytarabine for up to 2 cycles of induction and high dose cytarabine for up to 4 cycles of consolidation improves survival in patients with FLT3+ AML compared to standard therapy.

Clinical Review

Ashley Ward, MD

NDA 207997

Rydapt® (midostaurin)

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<u>Risk</u>	• Life-threatening toxicities are rare. • The most frequent serious adverse reaction was febrile neutropenia. • Common adverse reactions (>20%) include anemia, nausea, rash, vomiting, mucositis, headache, elevated transaminases, musculoskeletal pain, petechiae, hyperglycemia, device-related infections and epistaxis.	The overall safety profile of midostaurin is acceptable for patients with AML.
<u>Risk Management</u>	• Midostaurin causes fetal anomalies and fetal loss in nonclinical reproductive studies; the chemotherapy regimen labeled for use with midostaurin is frequently used in pregnant women. • Midostaurin is toxic and fails to produce clinical responses when administered as monotherapy to patients with AML.	The prescribing information will include a boxed warning with information about risk to pregnant women. There will be a limitation of use statement that midostaurin should not be used as monotherapy in AML.

Appears this way on original

2 Therapeutic Context

2.1. Analysis of Condition

Acute myeloid leukemia (AML) is a heterogeneous group of hematopoietic neoplasms characterized by a clonal proliferation of myeloid precursors with limited ability to differentiate into more mature myeloid cells. These blasts replace normal hematopoietic tissue in the bone marrow, resulting in pancytopenia. According to the National Cancer Institute's SEER database, it is estimated that there were 19,950 new cases of AML and 10,430 deaths from AML in the United States in 2016. AML occurs in children and adults of all ages, but is primarily a disease of older adults, with a median age at diagnosis of 67 years. AML is more common in men than women (5.0 vs 3.4 new cases per 100,000 persons per year) and does not have a strong racial or ethnic predilection. AML is universally fatal without treatment, with a median survival of approximately two months (Oran and Weisdorf, *Haematologica* 2012).

Approximately 35% of patients with AML harbor mutations of the FMS-like tyrosine kinase 3 (*FLT3*) gene on chromosome 13q12. These mutations typically result in either an internal tandem duplication (ITD) of amino acids in the juxtamembrane region of the FLT3 protein or, less frequently, a point mutation in the activation loop of the tyrosine kinase domain (TKD). Both ITD and TKD mutations result in constitutive activation of FLT3 kinase. FLT3-ITD mutations of any length are associated with an increased likelihood of relapse (Schnittger et al, *Blood* 2002), and FLT3-ITD mutations with a high mutant/wild type ratio are associated with decreased overall survival (Thiede et al, *Blood* 2002). The prognostic effect of FLT3-TKD mutations is still under debate, and may be dependent on additional mutations in individual patients (Bacher et al, *Blood* 2008).

2.2. Analysis of Current Treatment Options

With the exception of a rare subtype of AML called acute promyelocytic leukemia (APL), which is frequently curable with retinoic acid and arsenic trioxide and will be excluded from further discussion in this review, combination chemotherapy regimens with or without hematopoietic stem cell transplantation (HSCT) are a mainstay of therapy for patients with AML. A list of chemotherapy agents with FDA approval for the treatment of AML is provided in Table 1. In patients who can tolerate intensive therapy, which may be limited by factors such as age and comorbid conditions, cytarabine and daunorubicin induction followed by high-dose cytarabine consolidation (the so-called "7+3" regimen) is frequently used. This regimen typically results in CR rates of 60-70% and 2-year OS of approximately 50% in patients < 60 years of age (Fernandez et al, *NEJM* 2009). However, older patients (age ≥ 60) fare less well, with CR rates of approximately 50% and 2-year overall survival of approximately 20% (Estey, *JCO* 2006). While

Clinical Review

Ashley Ward, MD

NDA 207997

Rydapt® (midostaurin)

improved HSCT and supportive care regimens have reduced early death rates, no new therapies that confer a survival advantage in AML have been developed since the “7+3” regimen was shown to be effective in the early 1970s (Yates et al, Cancer Chemotherapy Reports 1973). There remains a clear need for new treatments for patients with AML.

Table 1: Currently Available Treatments for Acute Myelogenous Leukemia

Agent	Excerpted Indication
Cyclophosphamide	Indicated for the treatment of acute myelogenous and monocytic leukemia. Although effective alone in susceptible malignancies, is more frequently used concurrently or sequentially with other antineoplastic drugs.
Cytarabine	Indicated, in combination with other approved anticancer drugs, for remission induction in acute non-lymphocytic leukemia of adults and children.
Daunorubicin	Indicated, in combination with other approved anticancer drugs, for remission induction in acute non-lymphocytic leukemia of adults.
Doxorubicin	Has been used successfully to produce regression in disseminated neoplastic conditions including acute myeloblastic leukemia.
Idarubicin	Indicated, in combination with other approved anti-leukemic drugs, for the treatment of acute myeloid leukemia in adults. This includes FAB classifications M1 through M7.
Mitoxantrone	Indicated, in combination with other approved drugs, in the initial therapy of acute nonlymphocytic leukemia in adults. This category includes myelogenous, promyelocytic, monocytic and erythroid acute leukemias.
Thioguanine	Indicated for remission induction and remission consolidation treatment of acute nonlymphocytic leukemias. Is not recommended for use during maintenance therapy or similar long-term continuous treatments due to the high risk of liver toxicity. Reliance upon thioguanine alone is seldom justified for initial remission induction of acute non-lymphocytic leukemias because combination chemotherapy including thioguanine results in more frequent remission induction and longer duration of remission than thioguanine alone.
Vincristine	Indicated in acute leukemia.

Source: FDA analysis

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Midostaurin is not currently marketed in the United States.

3.2. Summary of Presubmission/Submission Regulatory Activity

Clinical Review

Ashley Ward, MD
NDA 207997
Rydapt® (midostaurin)

The trials included in this application were conducted under IND 057120, which was opened in the United States in November of 1998. The IND has never been placed on clinical hold.

The FDA granted orphan designation (#09-2859) to midostaurin for the treatment of acute myeloid leukemia on July 7, 2009.

At the end of phase 2 meeting held on July 12, 2006, the FDA generally agreed with dose, regimen, and patient population proposed for Study A2301. However, there was disagreement about (b) (4) and the Agency encouraged the Sponsor to submit the study for Special Protocol Assessment (SPA). A request for SPA was received by the FDA on January 12, 2007. After this more detailed review of the protocol, there was continued disagreement between the FDA and the Sponsor about (b) (4)

As a result of these and other potential deficiencies, the FDA determined that the design and planned analysis of the study did not address the objectives necessary to support a regulatory submission and there was no SPA agreement.

The FDA granted breakthrough therapy designation for the treatment of adult patients with newly diagnosed AML who are FLT3 mutation positive as detected by an FDA-approved test and who are eligible to receive standard induction and consolidation chemotherapy on January 29, 2016.

This NDA was submitted under a rolling submission, for which it qualified after receiving breakthrough therapy designation. Part 1 included the complete nonclinical module, and was submitted April 5, 2016. Part 2 included the complete quality module, and was submitted May 26, 2016. Part 3 included the summary of clinical efficacy, and was submitted July 25, 2016. Part 4 (the final part) included the clinical module and the summary of clinical safety, and was submitted August 29, 2016. The Applicant requested priority review with the submission of the final portion of the NDA, and the FDA granted priority review on October 28, 2016.

3.3. Foreign Regulatory Actions and Marketing History

Midostaurin is not currently available in any foreign markets.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Clinical Review

Ashley Ward, MD

NDA 207997

Rydapt® (midostaurin)

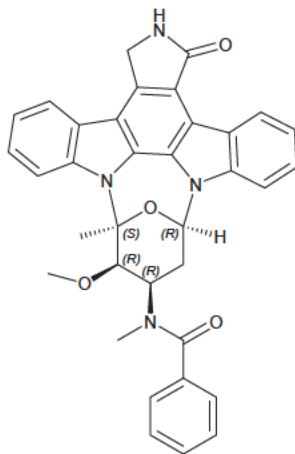
The Office of Scientific Investigations conducted inspections for Study A2301 at clinical sites in Ulm, Germany (Universitätsklinikum Ulm), Hanover, Germany (Kliniken der Med. Hochschule Hannover) and Lake Success, New York (North Shore-Long Island Jewish Health System/Monter Cancer). These sites had the highest accrual, highest number of protocol violations per patient, and/or greatest impact on the primary endpoint. The inspection of these sites is still pending.

The applicant (Novartis) was also audited. Inspection review identified a number of regulatory deficiencies related to: (b) (5)

A Form 483 was issued to Novartis describing these deficiencies. Given that the pivotal study was conducted at hundreds of trial sites, these findings, while serious, are not likely to significantly impact the results of the clinical trial. A final regulatory determination is pending.

4.2. Product Quality

Midostaurin is supplied as a soft capsule containing 25 mg of midostaurin. It is intended for oral administration. The capsule contains polyoxyl 40 hydrogenated castor oil, gelatin, polyethylene glycol 400, glycerin 85%, dehydrated alcohol, corn oil mono-di-triglycerides, titanium dioxide, vitamin E, ferric oxide yellow, ferric oxide red, carmine, hypromellose 2910, propylene glycol, and purified water. The molecular formula for midostaurin is $C_{35}H_{30}N_4O_4$. The molecular weight is 570.65 g/mole. The chemical structure of midostaurin is shown below:



No product quality concerns were identified on preliminary CMC review, and approval is recommended.

4.3. Nonclinical Pharmacology/Toxicology

In mouse, rats and dogs, PKC412 administered orally caused end-organ toxicities in multiple organ/systems. The organs/systems involved were gastrointestinal tract (gastric hemorrhage,

Clinical Review

Ashley Ward, MD

NDA 207997

Rydapt® (midostaurin)

diarrhea, emesis and loose feces), liver (↑ organ weight, ↑AST, ALT), immune system (thymic atrophy, lymphoid depletion in lymph nodes), hematopoietic system (low red blood cell parameters, bone marrow hypocellularity and hemorrhage), lungs (bronchopneumonia, alveolar hemorrhage), heart (prolongation in P-Q interval), reproductive system (reduced spermatogenesis and organ weight of prostate and seminal vesicle, uterine atrophy, and follicular distension of ovaries), and possibly the neuromuscular system (ataxia, abnormal gait).

Carcinogenicity studies have not been performed with midostaurin. Midostaurin was not mutagenic in vitro in the bacterial reverse mutation assay (Ames test) or in Chinese hamster V97 cells. Midostaurin increased the frequency of polyploidy cells in an in vitro chromosomal aberrations assay in Chinese hamster ovary cells, but was not clastogenic in an in vivo rat bone marrow micronucleus assay when tested to the maximum tolerated dose (MTD) of 200 mg/kg (1200 mg/m²). This dose was approximately 20-fold the recommended human dose, based on body surface area.

Based on nonclinical findings, male and female fertility may be compromised by treatment with midostaurin. Reproductive toxicity was observed in a fertility study, in which treated female rats were mated with treated males at oral doses of 10, 30 and 60 mg/kg/day of midostaurin (approximately 0.02, 0.11, and 0.13 times, respectively, the AUC in patients with cancer at the recommended human dose of 50 mg BID). In males, testicular degeneration and atrophy was observed at doses greater than or equal to 10 mg/kg/day and reduced and reduced sperm count and motility, and a decrease in reproductive organ weights were observed at 60 mg/kg/day. In females, increased resorptions (including total resorption of litter), decreased pregnancy rate, number of implants and live embryos were observed at 60 mg/kg/day. When F1 generation males were mated with F1 females from dams treated with 30 mg/kg/day midostaurin in an oral pre- and postnatal development study in the rat, the number of implantation sites and live fetuses/litter were reduced. In a 3-month toxicology study in dogs, there was inhibition of spermatogenesis was seen in dogs at doses greater than or equal to 3 mg/kg/day (approximately 0.012 times the exposure measured by AUC in patients with cancer at the recommended human dose).

The preclinical pharmacology/toxicology reviewer recommended approval.

4.4. Clinical Pharmacology

Clinical pharmacology reviewers determined that the evidence of effectiveness and the proposed dose and regimen were sufficiently supported by the application and recommended approval.

4.4.1. Mechanism of Action

Midostaurin is a small molecule that inhibits multiple receptor tyrosine kinases. In vitro

Clinical Review

Ashley Ward, MD

NDA 207997

Rydapt® (midostaurin)

biochemical or cellular assays have shown that midostaurin or its major human active metabolites CGP62221 and CGP52421 inhibit the activity of FLT3 (wild type and D835Y mutant), KIT D816V mutant, SYK, CSF-1R, PDGFR α , PDGFR β , and ROS1, as well as members of the serine/threonine kinase PKC family. In addition, midostaurin inhibits several other receptor tyrosine kinases like FGFR and VEGFR2.

Midostaurin demonstrated the ability to inhibit FLT3 receptor signaling and cell proliferation and induce apoptosis in leukemic cells expressing ITD and TKD mutant FLT3 receptors or overexpressing wild type FLT3 and PDGF receptors. Midostaurin also demonstrated the ability to inhibit KIT signaling, cell proliferation and histamine release, and induce apoptosis in mast cells.

4.4.2. Pharmacokinetics

Midostaurin exhibits time-dependent pharmacokinetics with an initial increase in trough concentrations (C_{min}) that reach maximal concentrations during the first week followed by a decline to a steady-state after approximately 28 days. The pharmacokinetics of the CGP62221 showed a similar trend. The plasma concentrations of CGP52421 continued to increase after one month of treatment. The maximal trough concentrations and steady-state concentrations of midostaurin, CGP62221, and CGP52421 were similar when RYDAPT was administered at a dose of 50 mg twice daily or 100 mg twice daily with food.

Absorption: The time to maximal concentrations (T_{max}) occurred between 1 to 3 hours post dose in the fasted state. Midostaurin exposure, represented by area under the curve over time to infinity (AUC_{inf}), increased 1.2-fold when midostaurin was co-administered with a standard meal (457 calories, 50 g fat, 21 g proteins, and 18 g carbohydrates) and 1.6-fold when co-administered with a high-fat meal (1007 calories, 66 g fat, 32 g proteins, and 64 g carbohydrates) compared to when midostaurin was administered in a fasted state. Midostaurin maximum concentrations (C_{max}) were reduced by 20% with a standard meal and by 27% with a high-fat meal compared to a fasted state. T_{max} was delayed when midostaurin was administered with a standard meal or a high-fat meal (median T_{max} = 2.5 hrs to 3 hrs).

Distribution: Midostaurin has an estimated mean volume of distribution of 95.2 L. Midostaurin and its metabolites are distributed mainly in plasma in vitro. Midostaurin, CGP62221, and CGP52421 are greater than 99.8% bound to plasma protein in vitro. Midostaurin is mainly bound to α 1-acid glycoprotein in vitro.

Elimination: The geometric mean terminal half-life (% coefficient of variation) is 21 hours (19%) for midostaurin, 32 hours (31%) for CGP62221 and 482 hours (25%) for CGP52421. Midostaurin is primarily metabolized by CYP3A4. CGP62221 and CGP52421 account for $28 \pm 2.7\%$ and $39 \pm 6.6\%$ (mean $\pm$ standard deviation) respectively of the total circulating radioactivity. Fecal excretion accounted for 95% of the recovered dose with 91% of the recovered dose excreted as

Clinical Review

Ashley Ward, MD

NDA 207997

Rydapt® (midostaurin)

metabolites and 4% of the recovered dose as unchanged midostaurin. Only 5% of the recovered dose was found in urine.

Specific Populations: Age (20-94 years), sex, race, and mild (total bilirubin > 1.0 to 1.5 times the upper limit of normal (ULN) or aspartate aminotransferase (AST) greater than the ULN) or moderate (total bilirubin 1.5 to 3.0 times the ULN and any value for AST) hepatic impairment or renal impairment (creatinine clearance (CLcr) > 30 mL/min) did not have clinically meaningful effects on the pharmacokinetics of midostaurin, CGP62221, or CGP52421. The pharmacokinetics of midostaurin in patients with baseline severe hepatic impairment (total bilirubin greater than 3.0 times the ULN and any value for AST) or severe renal impairment (CLcr 15 to 29 mL/min) is unknown.

Effect of Strong CYP3A4 Inhibitors on Midostaurin: Coadministration of ketoconazole (400 mg daily for 10 days) with a single dose of midostaurin (50 mg) on Day 6 increased the AUC_{inf} of midostaurin by 10.4-fold and CGP62221 by 3.5-fold and area under the curve over time to last measurable concentrations (AUC_{0-t}) of CGP52421 by 1.2-fold compared to a single RYDAPT dose coadministered with placebo. Coadministration of itraconazole (100 mg twice daily on Days 22-28 for 13 doses) with multiple doses of midostaurin (100 mg twice daily on Days 1 to 2 and 50 mg twice daily on Days 3 to 28) increased Day 28 trough concentrations of midostaurin by 2.1-fold, CGP62221 by 1.2-fold, and CGP52421 by 1.3-fold compared to the respective Day 21 trough concentrations with midostaurin alone.

Effect of Strong CYP3A4 Inducers on Midostaurin: Coadministration of rifampicin (600 mg daily on Days 1 to 14) with a single dose of midostaurin (50 mg) on Day 9 decreased the AUC_{inf} of midostaurin by 96%, the AUC_{inf} of CGP62221 by 92%, and the AUC_{0-t} of CGP52421 by 59%.

Effect of Midostaurin on Sensitive CYP3A substrates: Midazolam (sensitive CYP3A substrate) AUC_{inf} was not affected following 4 days of midostaurin administration. The clinical relevance of this interaction is unknown as the midostaurin was administered for only 4 days.

Effects of Midostaurin: Midostaurin, CGP52421 and CGP62221 inhibit CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP2E1, and induce CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A in vitro. Midostaurin inhibits organic anion transporter polypeptide 1A1 and induces multidrug resistance protein 2 in vitro.

4.5. Devices and Companion Diagnostic Issues

The applicant is seeking an indication for patients with AML who have a FLT3-TKD or FLT3-ITD mutation. Invivoscribe Technologies, Inc. has developed a companion diagnostic for the purposes of selecting candidates for midostaurin. The applicant claims that this companion diagnostic is intended to provide information that is essential for the safe and effective use of

Clinical Review

Ashley Ward, MD

NDA 207997

Rydapt® (midostaurin)

midostaurin by identifying patients who are most likely to benefit. Invivoscribe submitted a Pre-Marketing Application (PMA) P160040 for review by the Center for Devices and Radiologic Healthy (CDRH). This review is ongoing, and a major deficiency letter is still awaiting response.

4.6. Consumer Study Reviews

The Division of Medication Error Prevention and Analysis (DMEPA) reviewed the proposed Prescribing Information and the proposed carton and vial labels. This review is ongoing, but DMEPA has not identified any significant issues that would interfere with product approval.

5 Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

The Applicant submitted clinical study reports from 24 clinical trials of midostaurin (Table 2). Of these, 3 were studies of midostaurin in combination with intensive chemotherapy for treatment-naïve AML, 3 were studies of midostaurin monotherapy in previously untreated or relapsed or refractory AML or myelodysplastic syndrome (MDS), 5 were studies of midostaurin monotherapy in other types of cancer, and 13 were studies performed in healthy volunteers or patients without cancer. Raw datasets for clinical review were submitted for 5 of the 6 studies conducted in patients with AML; datasets were not available for the investigator-sponsored trial ADE02T. Raw datasets for clinical review were submitted for most of the 18 remaining studies; the exceptions were a old study for which datasets were not available (001) and Study A2120, which was terminated after enrollment of a single patient. See Table 2 for further details.

Clinical Review

Ashley Ward, MD

NDA 207997

Rydapt® (midostaurin)

Table 2: Listing of Clinical Trials Relevant to this NDA

Trial Identity	Trial Design (Primary Endpoint)	Regimen, Schedule, Route	Treatment Duration	No. of Patients Enrolled	Study Population	Countries and No. of Centers
<i>Pivotal Study</i>						
A2301*	Phase III, randomized, double-blind, placebo-controlled study of induction (daunorubicin/ cytarabine) and consolidation (high-dose cytarabine) ± midostaurin (OS)	“7+3” induction followed by HDAC consolidation Midostaurin 50 mg PO BID Days 8-21 of each cycle of induction and consolidation, or placebo 50 mg PO BID as maintenance, or placebo	Up to one year	717	Untreated FLT3+ AML, age ≤ 60 years	Australia: 1 Austria: 5 Belgium: 4 Canada: 5 Czech Rep: 4 France: 1 Germany: 64 Hungary: 1 Italy: 24 Netherlands: 1 Slovakia: 1 Spain: 8 US: 58
<i>Studies to Support Efficacy and Safety</i>						
A2106*	Phase Ib, open-label study of midostaurin with standard chemotherapy for AML (Safety)	50 mg or 100 mg PO BID with “7+3” induction then HDAC consolidation	Until PD or unacceptable toxicity	69	Untreated AML	Germany: 2 US: 4
ADE02T	Phase II investigator-sponsored trial of midostaurin with standard chemotherapy for AML (EFS)	50 mg PO BID days 8-21 of each cycle of “7+3” induction and HDAC consolidation, with continuation after HSCT	Until PD or unacceptable toxicity	153	Untreated FLT3+ AML	Austria: 5 Germany: 50
A2104*	Phase II, open-label (ORR)	75 mg PO TID	Until PD or unacceptable toxicity	20	Relapsed/refractory FLT3+ AML or MDS	US: 3

Clinical Review

Ashley Ward, MD

NDA 207997

Rydapt® (midostaurin)

Trial Identity	Trial Design (Primary Endpoint)	Regimen, Schedule, Route	Treatment Duration	No. of Patients Enrolled	Study Population	Countries and No. of Centers
A2104E1*	Phase II, randomized open-label study to compare two doses (ORR)	50 mg or 100 mg PO BID	Until PD or unacceptable toxicity	95	Relapsed/refractory AML/MDS	Germany: 2 US: 4
A2104E2*	Phase II, open-label study of inpatient dose escalation and to assess the effect of itraconazole (Safety)	100 to 300 mg PO BID	Until PD or unacceptable toxicity	29	Relapsed/refractory AML/ MDS	Germany: 2 US: 3
<i>Studies to Support Safety in Patients With Cancer</i>						
D2201*	Phase II, open-label, single arm (ORR)	100 mg PO BID	Until PD or unacceptable toxicity	116	Aggressive systemic mastocytosis or mast cell leukemia	Australia: 2 Austria: 1 Belgium: 1 Canada: 2 France: 2 Germany: 5 Netherlands: 1 Norway: 1 Poland: 1 Turkey: 1 UK: 3 US: 9
A2213*	Phase II, open-label, single arm (ORR)	100 mg PO BID	Until PD or unacceptable toxicity	26	Aggressive systemic mastocytosis or mast cell leukemia	US: 3
A0002*	Phase I, open-label, dose escalation (Safety)	2.5 to 300 mg PO total daily dose on a 4 weeks on, 1 week off schedule	Until PD or unacceptable toxicity	32	Advanced cancer	UK: 2
A0006*	Phase II, open-label, multi-dose (Biologic activity)	25 to 225 mg PO total daily dose	14 days	21	Relapsed/refractory CLL/NHL	UK: 1

Clinical Review

Ashley Ward, MD

NDA 207997

Rydapt® (midostaurin)

Trial Identity	Trial Design (Primary Endpoint)	Regimen, Schedule, Route	Treatment Duration	No. of Patients Enrolled	Study Population	Countries and No. of Centers
A2114*	Phase I/II, open-label, dose escalation (Safety)	30 or 60 mg/m ² BID	Until PD or unacceptable toxicity	22	Relapsed/ refractory leukemia, age ≥3m and < 18y	France: 1 Italy: 4 Netherlands: 1 Sweden: 1 US: 1
<i>Studies to Support Safety in Healthy Volunteers and Patients Without Cancer</i>						
001	Open-label, single ascending dose study of two formulations (PK)	1 to 25 mg PO	Single dose	20	Healthy volunteers	Switzerland: 1
A1101*	Randomized, double-blind, placebo-controlled single ascending dose (PK)	25 to 100 mg PO, or placebo	Single dose	40	Healthy volunteers	Japan: 1
A2107*	Open-label ADME study (PK)	50 mg PO	Single dose	6	Healthy volunteers	US: 1
A2108*	Open-label, randomized, crossover study to compare bioavailability of 3 formulations	50 mg PO	3 doses (1 of each formulation)	54	Healthy volunteers	US: 1
A2109*	Open-label, randomized, placebo-controlled study to assess the effect of ketoconazole (PK)	50 mg PO on Day 6 Ketoconazole 400 mg PO daily, days 1-10	Single dose	47	Healthy volunteers	Germany: 1
A2110*	Open-label, randomized, placebo-controlled study to assess the effect of rifampicin (PK)	50 mg PO on Day 9 Rifampicin 600 mg PO daily, Days 1-14	Single dose	47	Healthy volunteers	Germany: 1
A2111*	Open-label, randomized, parallel group study to assess food effect on 2 formulations (PK)	50 mg PO	Single dose	50	Healthy volunteers	Germany: 1

Clinical Review

Ashley Ward, MD

NDA 207997

Rydapt® (midostaurin)

Trial Identity	Trial Design (Primary Endpoint)	Regimen, Schedule, Route	Treatment Duration	No. of Patients Enrolled	Study Population	Countries and No. of Centers
A2112*	Open-label, single arm study to assess the effect of midazolam (PK)	100 mg PO Day 3 and 50 mg PO BID Days 4-6 Midazolam 4 mg PO Days 1, 3 and 8	4 days	20	Healthy volunteers	Germany: 1
A2113*	Randomized, double-blind, placebo- and active-controlled study of effect on cardiac intervals	75 mg PO BID Days 1 & 2 and once on Day 3 Moxiflox 400 mg PO Day 3	3 days	192	Healthy volunteers	US: 1
A2120	Open-label, randomized, crossover study to compare bioavailability of oral and IV formulation (PK)	50 mg PO or 25 mg IV	2 doses (1 of each formulation)	1	Healthy volunteers	Germany: 1
A2116*	Open-label, parallel dose study to assess PK and safety in subjects with normal or impaired hepatic function (Safety)	50 mg PO BID	11 days	30	Healthy volunteers and patients with hepatic dysfunction	Belgium: 1 Bulgaria: 1 Germany: 2 Romania: 1
C99-001*	Phase I, placebo-controlled dose escalation (PK)	25, 50 or 75 mg PO BID, or 75 mg PO TID	28 days	86	Diabetes mellitus	US: 2
A0003*	Phase II, randomized, double-blind, placebo-controlled, dose finding	25, 50 or 75 mg PO BID	3 months	142	Diabetic macular edema	Germany: 2 Portugal: 1 US: 9

Source: FDA synopses of individual studies provided by the Applicant in Module 2.7.6.

Abbreviations: ADME, absorption, distribution, metabolism and excretion; BID, twice daily; CLL, chronic lymphocytic leukemia; HDAC, high dose cytarabine; HSCT, hematopoietic stem cell transplantation; IV, intravenously; NHL, non-Hodgkin lymphoma; ORR, overall response rate; PD, progressive disease; PK, pharmacokinetics; PO, by mouth; TID, three times daily

* Raw datasets for clinical review provided by Applicant

Clinical Review

Ashley Ward, MD

NDA 207997

Rydapt® (midostaurin)

5.2. Review Strategy

The key materials used for the review of efficacy and safety include:

- NDA 207997
- Relevant published literature
- Relevant information in the public domain

The review of efficacy was primarily based on analysis of Study A2301 and supported as follows:

- Efficacy data from Study A2106 was used to support the analysis of dose selection
- Summarized efficacy data from investigator-sponsored Study ADE02T was used to support the analysis of the patient population covered by the proposed indication
- Efficacy data from Studies A2104, A2104E1 and A2104E2 were used to justify a limitation of use

Results from all 24 trials listed in Table 2 were used to support the analysis of safety. Review emphasis was placed on safety data from Study A2301, but this was supported as follows:

- Summarized safety data from Study A2106 and from investigator-sponsored Study ADE02T were used to support the analysis of the patient population covered by the proposed indication, and to support the analysis of dose selection in the indicated patient population
- Pooled safety data from all trials of midostaurin monotherapy in patients with cancer was used to analyze the impact of dose on safety, and to look for potential safety signals
- Pooled safety data from all trials of midostaurin monotherapy in healthy volunteers and patients without cancer was used look for potential safety signals

All major efficacy and safety analyses were reproduced or audited. Summaries of data and statistical analyses by the reviewer were performed using JMP 12.0 (SAS Institute, Inc., Cary, NC), and Excel 2010 (Microsoft, Redmond, WA). MedDRA Adverse Events Diagnostic 1.3 (MAED) (FDA, Silver Spring, MD) was used to look for safety signals. All hazard ratios and p-values included in the time-to-event analyses in this review were calculated using an unstratified Cox proportional hazards method except where indicated. P-values were not adjusted for multiplicity except where indicated. See the statistician's review for additional analyses of efficacy endpoints.

6 Review of Relevant Individual Trials Used to Support Efficacy

6.1. Study A2301

6.1.1. Study Design

Clinical Review

Ashley Ward, MD

NDA 207997

Rydapt® (midostaurin)

Overview and Objective

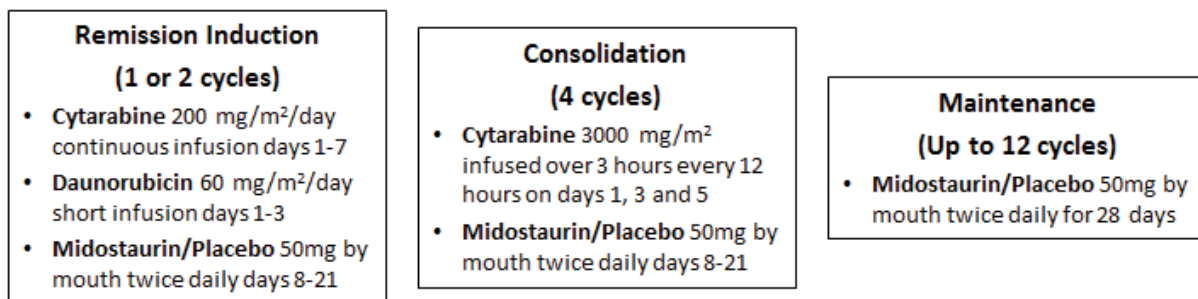
Study A2301 is a phase 3, randomized, double-blinded, placebo-controlled trial of midostaurin in combination with standard chemotherapy for the treatment of patients < 60 years of age with newly diagnosed AML harboring an internal tandem duplication (ITD) or tyrosine kinase domain mutation (TKD) of FLT3. The primary objective of the study was to determine if the addition of midostaurin to daunorubicin/cytarabine induction, high-dose cytarabine consolidation, and continuation therapy improves OS in FLT3-ITD and FLT3-TKD patients with AML.

The key secondary objective was to compare the EFS between the two treatment groups. Other secondary efficacy objectives were to compare the OS when patients who receive a hematopoietic stem cell transplant (HCST) are censored at the time of transplantation, the CR rate, the disease-free survival (DFS), the DFS rate at one year after completion of continuation therapy, and the HSCT rate between the two groups. Other secondary objectives were to assess the interaction between treatment outcome and pretreatment patient or disease characteristics, the toxicity of the experimental combination and the population pharmacokinetics of midostaurin and its two major metabolites.

Trial Design

Patients age 18 to 59 with an unequivocal diagnosis of AML (>20% blasts in the bone marrow) and documented FLT3 mutation as determined by central laboratory testing who had not received prior therapy were randomized 1:1 to receive up to six 28-day cycles of standard chemotherapy in combination with either placebo or midostaurin (Figure 1) followed by up to twelve 28-day cycles of single agent maintenance therapy. Randomization was stratified by FLT3 mutation status (ITD allelic ratio < 0.7, ITD allelic ratio $\geq$ 0.7, or TKD). Patients with M3 AML (APL), therapy-related AML, or central nervous system (CNS) leukemia were not eligible for the study.

Figure 1: Study A2301 – Study Design Schema



Reviewer comment: Lack of re-randomization prior to maintenance makes it difficult to make inferences about the effectiveness of maintenance therapy.

Clinical Review

Ashley Ward, MD

NDA 207997

Rydapt® (midostaurin)

A bone marrow aspiration was performed on day 21 of the first cycle of induction therapy. Patients without a CR were administered a second cycle of induction therapy beginning on or shortly after day 24, and patients with residual AML by bone marrow aspirate after completion of a second remission induction were removed from protocol therapy. Patients who achieved a CR after 1 or 2 cycles of induction therapy proceeded to receive 4 cycles of consolidation therapy, with each cycle beginning after recovery of absolute neutrophil count (ANC) to $\geq 1000/\mu\text{L}$ and platelets $\geq 100,000/\mu\text{L}$. Patients who remained in CR by bone marrow aspirate after completion of consolidation therapy proceeded to maintenance therapy. Patients who were unable to complete four cycles of consolidation therapy due to toxicity but who remained in CR were allowed to proceed to maintenance therapy with approval from the study chair. Bone marrow aspirates to assess disease status were performed every four months during maintenance therapy. Patients whose AML relapsed at any time were removed from study therapy. All patients who enrolled on the study were followed for the primary endpoint of overall survival. There was no re-randomization prior to maintenance therapy, and cross-over was not allowed. Patients were allowed to proceed to HSCT at any time; these patients came off protocol-directed therapy but were followed for OS.

Eligibility criteria (summarized):

1. Unequivocal diagnosis of AML ($>20\%$ blasts in the bone marrow based on the WHO classification), excluding M3 (acute promyelocytic leukemia). Patients with neurologic symptoms suggestive of CNS leukemia were recommended to have a lumbar puncture. Patients whose cerebrospinal fluid is positive for AML blasts were not eligible.
2. Documented FLT3 mutation (ITD or point mutation) determined by analysis in a protocol-designated FLT3 screening laboratory.
3. Age ≥ 18 and < 60 years.
4. No prior chemotherapy for leukemia or MDS except: emergency leukapheresis, emergency treatment for hyperleukocytosis with hydroxyurea for ≤ 5 days, cranial radiotherapy for CNS leukostasis (one dose only) and growth factor / cytokine support.
5. AML patients with a history of antecedent MDS were eligible, but must not have had prior cytotoxic therapy (e.g. azacitidine or decitabine).
6. Patients who have developed therapy related AML after prior radiation therapy or chemotherapy for another cancer or disorder were not eligible.
7. Patients with symptomatic congestive heart failure were not eligible.
8. Bilirubin $< 2.5x$ the upper limit of normal.
9. Not pregnant and not nursing, and willing to use highly effective method of birth control.

Study assessments:

Bone marrow and peripheral blood samples for FLT3 mutation screening were obtained during the screening period and, in consenting patients, also at the time of relapse. Samples were

Clinical Review

Ashley Ward, MD

NDA 207997

Rydapt® (midostaurin)

shipped via overnight carrier on the day of collection to a central laboratory site for analysis.

Bone marrow aspirate smears and biopsy specimens for central morphology review were obtained during screening, on day 21 of remission induction therapy and at additional time points as described above. Samples were shipped within one week of collection to a central laboratory site for analysis. Local biopsy and immunophenotyping reports, including differential cell counts, cytochemistry results and French-American-British (FAB) classification were collected along with the samples. If the day 21 bone marrow aspirate revealed < 5% blasts in a cellular marrow (>20%), then a second bone marrow aspiration was performed one week after recovery of ANC $\geq$ 1000/ μ L and platelets $\geq$ 100,000/ μ L to document complete response. The bone marrow examination to document complete response must be performed on or before day 60, regardless of whether the patient received 1 or 2 cycles of induction therapy.

History and physical exam, including height, weight, body surface area, performance status, and drug toxicity assessment were collected at the time of screening (within 16 days prior to randomization). Screening laboratory assessments consisted of complete blood counts with differential (CBC), a comprehensive metabolic panel, coagulation studies, urinalysis, thyroid function tests and urine or serum pregnancy test in women of childbearing potential. Other screening assessments were an assessment of left ventricular ejection fraction by multigated (MUGA) scan or echocardiogram, a chest x-ray, and a lumbar puncture for patients with neurologic symptoms suggestive of CNS leukemia.

History, physical exam, and drug toxicity assessment were repeated at least twice weekly during induction therapy, once weekly during consolidation therapy, and monthly during maintenance therapy. A CBC, basic metabolic panel, and tests of liver function were repeated at least weekly during induction and consolidation therapy, and monthly during maintenance therapy. Thyroid function tests were repeated at 1, 6 and 12 months after registration, and 30 days after discontinuation of study therapy. Electrocardiograms (ECGs) were collected for assessment of the QTc interval prior to midostaurin/placebo dose on days 8, 10, and 21 during each cycle of induction and consolidation, and on day 1 of each cycle of maintenance therapy.

Peripheral blood was collected for pharmacokinetic (PK) assessments in consenting patients at the following time points:

- Cycle 1 of remission induction therapy (days 8 and 21)
- Cycle 1 of consolidation therapy (days 8 and 21)
- Cycle 4 of consolidation therapy (days 8 and 21)
- Cycle 8 of maintenance therapy (day 1)
- Cycle 12 of maintenance therapy (day 1)

All samples were to be collected prior to the morning midostaurin/placebo dose. Midostaurin and its major metabolites (CGP52421 and CGP62221) were analyzed at Novartis Pharma SAS, Bioanalytics, in France.

Clinical Review

Ashley Ward, MD

NDA 207997

Rydapt® (midostaurin)

Dose modifications and management of toxicity:

Midostaurin/placebo was taken at approximately the same time each day with approximately 12 hours between the morning and evening doses. Each daily dose was taken with food and a glass of water (~240 mL). Patients were instructed to swallow capsules whole without chewing, and to not re-dose in the event of vomiting. Missed doses of midostaurin/placebo were not made up. Modifications of the dose and schedule of midostaurin/placebo were not allowed except in the following circumstances:

- For QTc interval > 470 ms and ≤ 500 ms, midostaurin/placebo dose was decreased to 50 mg once daily for the remainder of the cycle, then resumed at the initial dose in the next cycle if the QTc is ≤ 470 ms. Otherwise, midostaurin/placebo was continued at 50 mg once daily.
- For QTc interval > 500 ms, midostaurin/placebo was held for the remainder of the cycle and resumed at the initial dose in the next cycle in which the QTc is ≤ 470 ms.
- Dose modifications for grade 1-2 non-hematologic toxicities were not allowed during induction and consolidation therapy. Drug holidays of up to 28 consecutive days for persistent grade 1-2 non-hematologic toxicities were allowed during maintenance.
- For grade 3-4 non-hematologic toxicities considered to be at least possibly related to midostaurin/placebo, midostaurin/placebo was interrupted and then resumed at the same dose upon resolution of the toxicity to grade ≤ 1 (in induction and consolidation) or ≤ grade 2 (in maintenance). If midostaurin/placebo was held for >28 days for toxicity during maintenance therapy, patients were required to discontinue study therapy.
- For grade ≥ 3 pulmonary infiltrates, midostaurin/placebo was held for the remainder of the cycle and resumed (in a subsequent cycle) at the same dose when infiltrate resolved to grade ≤ 1.
- (Added in a protocol amendment) For grade 4 neutropenia during maintenance, midostaurin/placebo was held until ANC ≥ 100/μL, then resumed at previous dose. If neutropenia persisted longer than 2 weeks, patients were required to discontinue midostaurin/placebo.

Initial and subsequent doses of daunorubicin were modified for hepatotoxicity as follows:

- Total bilirubin ≤ 2 mg/dL: give 100% of daunorubicin dose
- Total bilirubin > 2 to ≤ 3 mg/dL: give 75% of daunorubicin dose
- Total bilirubin > 3 mg/dL: give 50% of daunorubicin dose

For neurotoxicity grade ≥ 2 due to high dose cytarabine during consolidation therapy, cytarabine was discontinued for the remainder of the cycle. If the neurotoxicity resolved to grade ≤ 1, cytarabine could be resumed for the next consolidation therapy cycle with a dose modification from 3 g/m² to 2 g/m².

All drug doses were based on actual body weight, with no modifications for obesity. Doses of

Clinical Review

Ashley Ward, MD

NDA 207997

Rydapt® (midostaurin)

chemotherapy were not adjusted for body weight changes in subsequent cycles unless the body weight change was at least 10%. Total administered dose of chemotherapy could be rounded up or down within a range of 5% of the actual calculated dose.

Concomitant medications:

Supportive care medications were allowed, including transfusions of blood and blood products, antibiotics, antiemetics and allopurinol. However, the use of aprepitant was not permitted. Treatment with hormones or other chemotherapeutic agents was not permitted except for steroids given for adrenal failure and hormones given for non-disease-related conditions (e.g. insulin for diabetes). Steroids were permitted for the treatment or prevention of hypersensitivity reactions or transfusion reactions. Brief use of corticosteroids as anti-emetics was permitted but not recommended. Myeloid growth factors were permitted only for neutropenic patients with prognostic factors predictive of clinical deterioration (e.g., pneumonia, hypotension, sepsis, fungal infection) as per American Society of Clinical Oncology (ASCO) guidelines.

Physicians were advised that midostaurin is a competitive inhibitor of CYP3A4/5 and thus co-administration of drugs which are potent inducers (e.g., phenytoin) or, especially, potent inhibitors (e.g., itraconazole) of this isoenzyme could decrease or increase midostaurin concentrations, and, potentially, decrease the effectiveness or increase toxicity, respectively. However, such agents were not prohibited on this study.

Response criteria:

Responses must have been maintained with no evidence of AML for more than 4 weeks. Response assessments required a bone marrow aspirate, or, in the event of a dry tap, a bone marrow biopsy. Central histologic review was required for documentation of complete response following induction therapy. Response criteria were defined in the protocol and were based on the revised recommendations of the International Working Group in AML (Cheson et al, JCO 2003)

Complete response / remission (CR) was defined as all of the following:

- Peripheral blood: ANC $\geq$ 1,000/ μ L, platelet count $\geq$ 100,000/ μ L, no leukemic blasts in the peripheral blood and adequate erythroid recovery so that RBC transfusions are not necessary [time frame not defined]
- Bone marrow: adequate cellularity [not further defined], no Auer rods, and < 5% blasts
- No extramedullary leukemia

Complete response with incomplete platelet recovery (CRp) was defined as: all CR criteria are met except that platelets are < 100,000/ μ L.

Partial remission (PR) was defined as: all CR criteria are met except that the bone marrow may

Clinical Review

Ashley Ward, MD
NDA 207997
Rydapt® (midostaurin)

contain 5-24% blasts.

Treatment failure was defined as: failure to achieve a CR by 60 days after the start of initial induction therapy. Patients who were treated appropriately, survived for > 30 days after the start of study therapy, and failed to achieve remission due to persistent AML as determined by peripheral blood and bone marrow aspirate and biopsy were deemed to have treatment failure due to resistant disease. Patients who died within 30 days of starting protocol therapy were deemed to have treatment failure due to death of the patient.

Reviewer comment: It is unusual to require that a CR occur within 60 days after the first dose of therapy. The more widely accepted definition of primary refractory AML is failure to achieve a CR after two cycles of induction therapy, regardless of the timing of count recovery (Ravandi, Br J Haematol 2011).

Relapse was defined as any of the following, occurring after either CR, CRp, or PR:

- The reappearance of circulating blast cells not attributable to “overshoot” following recovery from myelosuppressive therapy
- > 5% blasts in the marrow, not attributable to another cause (e.g., CSF, bone marrow regeneration)
- Development of extramedullary leukemia

Study Endpoints

The primary endpoint was overall survival, defined as the period from the date of randomization until death by any cause. Patients alive at the end of the study period were censored for this endpoint.

The key secondary endpoint (made key in Amendment 4) was EFS, defined as the time from randomization until an EFS event was observed. EFS events were defined as a failure to obtain a CR within 60 days after the first dose of protocol therapy (i.e., treatment failure), or relapse, or death from any cause. Patients who were alive and event-free at the end of the study period were censored for this endpoint.

Other secondary endpoints were:

- OS, where patients who received a HSCT are censored at the time of transplantation (added in Amendment 4)
- CR rate in the remission induction stage of the study
- DFS
- DFS rate one year after completing the planned continuation phase
- Rate of HSCT (added in Amendment 10)

DFS was defined only for patients who achieved a CR within 60 days after the first dose of study

Clinical Review

Ashley Ward, MD

NDA 207997

Rydapt® (midostaurin)

therapy, and was defined as the time from the date of first CR to relapse or death from any cause, whichever occurs first. Patients who were alive and disease-free at the end of the study period were censored for this endpoint.

Statistical Analysis Plan

The baseline assumptions were as follows:

- The study would accrue 300 FLT3 mutation-positive patients per year
- 1 in 7 accrued patients would have FLT3-TKD and the other 6 would have FLT3-ITD
- Median OS is 15 months in the placebo arm and 21 months in the midostaurin arm
- CR rate is 75% in the placebo arm and 83% in the midostaurin arm
- DFS is 11 months in the placebo arm and 15.4 months in the midostaurin arm
- Early death rate (before CR is determined) is 7%
- Stem cell transplantation rate is 15%

Based on these assumptions, accrual of 514 patients over 1.7 years with a 2-year follow up would, in all cases with a Type I error of 0.025 (one-sided):

- Yield 374 OS events and provide 90% power to detect an OS hazard ratio of 0.714
- Provide 56% power to detect an 8% difference in CR rates between the two regimens
- Yield 433 EFS events and provide 95% power to detect a difference in median EFS
- Yield 335 DFS events and provide 87% power to detect a difference in median DFS

One interim analysis for the overall survival endpoint was planned, after 50% of expected events (187), with an alpha spend of 0.005. A conditional probability of rejecting the null hypothesis of < 0.10 was planned to be grounds for stopping for early futility. This interim analysis occurred in June 2012 and the Data Safety Monitoring Board (DSMB) concluded that the study should proceed without changes.

The original statistical analysis plan was finalized in June of 2011 based on protocol amendment 4, which increased the sample size to 714 patients and number of required OS events to 509 due to revised assumptions about the frequency of HSCT and FLT3-TKD on the study (see below). A revised statistical analysis plan was generated in 2015 due to slow accrual of OS events (see below), and was finalized prior to the primary analysis of the primary endpoint in July of 2015. The data cut-off date used for preparation of this marketing application was April 1, 2015.

The final analysis of the primary endpoint of OS was not event-driven, and was performed prior to reaching the planned 509 OS events. All deaths up to and including April 1, 2015, were included as OS events. Information regarding OS events obtained during a data sweep after the April 1, 2015 were used to “back-track” and determine the vital status on April 1, 2015. Patients with no post-baseline data were censored on the date of randomization. Patients known to be

Clinical Review

Ashley Ward, MD

NDA 207997

Rydapt® (midostaurin)

alive at their last contact were censored at their date of last contact before April 1, 2015. If date of last contact was missing from the follow-up case report form (CRF), it was imputed as the end date of the corresponding reporting period. All others were considered alive on April 1, 2015 and were censored for OS analysis on this date. If a death was reported without a corresponding death date, the missing date was imputed as the start date of the reporting period in the CRF in which the death was reported.

Reviewer comment: Imputation of the date of last contact as the end date of the corresponding reporting period may artificially increase estimates of OS on both arms.

For assessments of response/relapse, only data from CRFs collected prior to April 1, 2015, were used. CRFs collected after April 1, 2015, were not used to “back track” and determine clinical status on April 1, 2015. All responses were investigator-determined. A CR was only considered if it occurred within 60 days after the first administration of any study treatment. Treatment failure was defined as a failure to achieve a CR within 60 days after the first administration of any study treatment, and was an event considered for the calculation of EFS. The date of treatment failure was calculated by Novartis from the dates reported by the investigator as follows:

- For patients with a clinical assessment but who did not achieve a CR within 60 days after first administration of study drug, treatment failure date was the date of the last clinical assessment within the 60 day window
- For patients who had no clinical assessment and died within the 60 day window, treatment failure date was the date of death
- For patients who had no clinical assessment, did not die, and discontinued treatment within the 60 day window, treatment failure date was the date of last treatment administration
- For patients who had no clinical assessment, did not die, and did not discontinue treatment within the time window, treatment failure date was the randomization date

Relapses were events considered for the time-to-event endpoints EFS, DFS and remission duration. A relapse was only considered for patients who achieved a CR within 60 days after the first administration of any study treatment, and was calculated from the dates reported by the investigator as the earliest known date of relapse, even if observed after missing assessments.

The date of the last clinical assessment in response up to and including April 1, 2015, was used as the censoring date for the time-to-event endpoints EFS, DFS and remission duration. It was taken for patients who achieved CR and had no relapse up to and including the last clinical assessment.

The final analysis of the key secondary endpoint of EFS was not event-driven. A total of 717 patients accrued uniformly to the trial over 40 months. Based on an assumed median EFS of 8.5

Clinical Review

Ashley Ward, MD

NDA 207997

Rydapt® (midostaurin)

months for the placebo patients and 14 months for the midostaurin patients, 507 EFS events could have been observed with a minimum follow-up of 3.5 years for all patients. Under these assumptions, the trial would have a power of approximately 89% using a one-sided alpha of 2.5% to detect a hazard ratio of 1.34 using a Cox regression model.

For all time-to-event endpoints, a stratified log-rank test, adjusting for the FLT3 mutation strata used in the randomization, was used to test the null hypotheses and calculate the one-sided p-value. Stratified Cox regression models were used to provide estimates of the hazard ratios and associated 95% confidence intervals. Kaplan-Meier plots were used to depict events over time in each treatment arm.

The patient sets considered for the evaluation of the study were as follows:

- Full Analysis Set (FAS) was defined according to intent-to-treat (ITT) principles and included all randomized patients with a signed informed consent. Patients were analyzed according to treatment arm and stratum assigned at randomization. The FAS was used for the analyses of efficacy endpoints and baseline characteristics.
- The Per Protocol Set (PPS) was the subset of the FAS who received at least one dose of midostaurin/placebo and had no major protocol deviations that could affect response to treatment. The PPS was used for additional analyses of OS and EFS.
- The Safety Set included all patients with a signed informed consent that received at least one dose of midostaurin/placebo. Patients who were randomized to one arm but only received the study drug (midostaurin/placebo) of the other arm during the study were analyzed in the arm of the study drug they received. All patients who received at least one dose of the study drug they were randomized to were analyzed in their randomized treatment arm. The Safety Set was used for the analyses of safety endpoints, concomitant medications and treatment exposure.
- The Pharmacokinetic Set (PK Set) included all patients with a signed informed consent who received at least one dose of midostaurin and who provided at least one evaluable PK concentration. The PK Set was used for the analyses of PK endpoints.

Protocol Amendments

The study was activated on April 1, 2008, and the first patient was randomized to the study on July 3, 2008. Enrollment was completed in October of 2011, with 719 patients randomized. The study was revised a total of 10 times between activation and finalization in June of 2015. Key protocol revisions are summarized as follows:

- Amendment 2 (effective April 1, 2009, 101 patients enrolled) changed the dosing of midostaurin/placebo in maintenance from 14 days out of every 28 to continuous daily dosing in order to maintain midostaurin drug concentrations above the IC₅₀.
- Amendment 3 (effective December 1, 2009, 279 patients enrolled) added the collection

Clinical Review

Ashley Ward, MD

NDA 207997

Rydapt® (midostaurin)

of concomitant medications to study procedures. Concomitant medications were collected retrospectively in Non-North-American sites, but not for the 68 North American patients that enrolled prior to the amendment.

- Amendment 4 (effective December 15, 2010, 549 patients enrolled) increased the sample size and the number of required OS events for the final analysis to restore study power. The revised study design required 714 patients, and the final analysis was planned when 509 OS events occurred, with 84% power to detect a hazard ratio of 0.78 with a Type I error of 0.025 (one-sided). These revisions were made due to interim review of blinded data that revealed that the rates of HSCT (25%) and FLT3-TKD mutations (26%) were higher than originally predicted. The study also added OS with censoring at the time of HSCT as a new secondary objective.
- Amendment 10 (effective June 15, 2015, 719 patients enrolled) changed the study design to perform the final analysis with a data cut-off of April 1, 2015, without waiting to achieve the required 509 events. At the same time, the secondary endpoint EFS was promoted to a key secondary endpoint to be tested in a hierarchical manner if the OS endpoint was significant, and HSCT rate was added as a secondary endpoint. These revisions were made due to slow accrual of OS events.

No major changes were made to the eligibility criteria or response criteria over the course of the study.

Data Quality and Integrity: Sponsor's Assurance

Alliance is the owner of [REDACTED] ^{(b) (4)} the protocol, the study database, and the data for this study. The study used study-specific paper case report forms (CRFs). All completed CRFs and corresponding source documents required by the protocol (i.e. pathology reports) were submitted by the sites to the Alliance Statistics and Data Center where the data was reviewed, entered into a database, and queried. In North American (NA) trial sites, where the study was sponsored by Alliance, Novartis and/or a designated contract research organization (CRO) appointed by Novartis performed quality control visits approximately twice yearly. Alliance performed off-site monitoring by checking sources sent by sites to confirm response and relapse. In NA sites, only portions of data were source-verified, and in only 224 of the 236 (94%) of the patients. Non-North American (NNA) trial sites were monitored by Novartis at frequencies varying from every 4 weeks to yearly, which included 100% source data verification of key data and 10% for non-key data for all subjects (n=481).

Data management followed Alliance Legacy Policies and Procedures. Novartis collaborated with the Alliance Statistical Data Center in the review of the blinded safety data via periodic transfers provided by Alliance to Novartis. All efficacy data were cleaned by Novartis and the primary efficacy analyses were prepared by Alliance statisticians for the DSMB meeting held in July 2015. Following DSMB review, the data was further cleaned, validated and transferred to

Clinical Review

Ashley Ward, MD

NDA 207997

Rydapt® (midostaurin)

Novartis in preparation for regulatory submission. After Novartis locked the database, the treatment codes were transferred from Alliance to Novartis to allow the analysis to begin.

As the Applicant for the midostaurin marketing authorization, Novartis stated that they have performed due diligence to ensure the quality and integrity of the data from this collaborative group study. Novartis also states that the database for Study A2301 is complete and accurate for the benefit-risk assessment of midostaurin in this study.

6.1.2. Study Results

Compliance with Good Clinical Practices

The applicant provided attestation that this study was conducted in accordance with U.S. regulations governing the protection of human subjects, institutional review boards, and the obligations of clinical investigators in accordance with good clinical practice (GCP).

Financial Disclosure

A summary of financial disclosures for Study A2301 is provided in the appendix (Section 13.2). The applicant submitted financial disclosure information from 95.3% of investigators at sites in the United States and 99.9% of investigators at all other sites. All missing financial disclosure information was from sub-investigators. Two primary investigators and 3 sub-investigators had financial disclosures. Four of the disclosures, which included both primary investigators, were for grants in excess of \$25,000 from the study sponsor to the investigator to fund ongoing research. These sites enrolled a total of (b) (6) patients. The fifth disclosure was for a proprietary or financial interest in the product tested in the clinical study of undisclosed amount. This site enrolled (b) (6) patients, but analysis of the OS data from the subset of patients enrolled at this site revealed a treatment effect favoring the placebo arm. Removal of all (b) (6) patients enrolled at these sites from the primary analysis did not substantially affect the result. Thus, enrollment of patients by these investigators does not appear to have biased the outcome of the study.

Patient Disposition

Of 3279 patients screened, 719 patients were randomized in Study A2301. Two patients were excluded due to problems with their informed consent, resulting in 717 patients included in the FAS. Of these, 360 were randomized to the midostaurin arm and 357 to the placebo arm. The number of patients that received any portion of study therapy in each treatment phase and the reasons for treatment discontinuation are shown in Table 3. Patients were designated as having received treatment in a study cycle if they received at least one dose of protocol-designated therapy in that cycle. Patients were determined to have completed all 12 cycles of maintenance if at least 12 cycles of maintenance therapy were reported and the investigator checked the box “completed treatment per protocol criteria” in the CRF.

Clinical Review

Ashley Ward, MD

NDA 207997

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Table 3: Study A2301 – Disposition of Patients

	Midostaurin (n=360)	Placebo (n=357)	Total (n=717)
Did not receive any treatment	5 (1%)	3 (1%)	8 (1%)
Received treatment in			
Induction 1	355 (99%)	354 (99%)	709 (99%)
Induction 2	81 (23%)	101 (28%)	182 (25%)
Consolidation 1	231 (64%)	210 (59%)	441 (62%)
Consolidation 2	175 (49%)	158 (44%)	333 (46%)
Consolidation 3	150 (42%)	128 (36%)	278 (39%)
Consolidation 4	129 (36%)	103 (29%)	232 (32%)
Maintenance	120 (33%)	85 (24%)	205 (29%)
Completed 12 cycles of maintenance	69 (19%)	51 (14%)	120 (17%)
Reason for treatment discontinuation¹			
Pursue alternative therapy	110 (31%)	109 (31%)	219 (31%)
Refractory or relapsed AML	88 (24%)	102 (29%)	190 (26%)
Completed study therapy	69 (19%)	52 (15%)	121 (17%)
Withdrawal	24 (7%)	41 (11%)	65 (9%)
Adverse event	35 (10%)	22 (6%)	57 (8%)
Death	18 (5%)	18 (5%)	36 (5%)
Other	13 (4%)	11 (3%)	24 (3%)
Other complicating disease	3 (1%)	2 (1%)	5 (1%)

Source: FDA analysis

¹ 78 events originally coded as “other” were recoded based on additional information recorded by the investigator in the CRF

Only 17% of all study participants completed all protocol-designated therapy, including 12 cycles of maintenance therapy. Nearly one third of the subjects on both arms discontinued study treatment to pursue alternative therapy, most frequently HSCT. More patients in the placebo arm required a second induction (28% vs 23%). Discontinuations for relapsed or refractory disease occurred more frequently on the placebo arm (29% vs 24%), while discontinuations for adverse events occurred more frequently on the midostaurin arm (10% vs 6%).

Protocol Violations/Deviations

A total of 1,743 protocol deviations were reported for 493 patients on Study A2301. The majority (1,626 deviations, 93%) were considered by the applicant to be minor deviations. As deviations were reported in narrow categories (e.g., missing bone marrow assessment during continuation), the FDA summarized the minor deviations into broader categories (e.g., missing bone marrow assessment) for analysis. Summarized, the most frequent minor deviations were

Clinical Review

Ashley Ward, MD

NDA 207997

Rydapt® (midostaurin)

treatment errors (580 deviations affecting 262 patients), missing bone marrow assessments (453 deviations affecting 229 patients), and missing laboratory assessments (400 deviations affecting 36 patients).

Major protocol deviations occurred in 15% of the study patients, with similar frequency on both treatment arms (Table 4). A total of 43 patients (6%) failed to meet one or more eligibility criteria that had the potential to influence evaluation of the primary endpoint; the majority because they received prior treatment for leukemia or MDS. However, of the 34 patients who received prohibited prior treatment for leukemia or MDS, 32 of them had received hydroxyurea in excess of 5 days as their only prohibited prior therapy, which is unlikely to have substantially influenced the results of the study. Seventy patients (10%) had one or more major dosing violations involving the study drug; the majority because they did not receive any midostaurin/placebo. As none of the major deviations were likely to bias the study in favor of the midostaurin arm, all patients, including those with major protocol deviations were included in the FDA's analysis of efficacy endpoints.

Table 4: Study A2301 – Major Protocol Deviations

	Midostaurin (n=360)	Placebo (n=357)	Total (n=717)
Major protocol deviation	53 (15%)	53 (15%)	106 (15%)
Failure to meet eligibility criteria	22 (6%)	21 (6%)	43 (6%)
Had prior treatment for leukemia or MDS	19 (5%)	15 (4%)	34 (5%)
CNS leukemia at baseline	1 (<1%)	3 (<1%)	4 (<1%)
FLT3-ITD < 0.05 threshold at baseline ¹	2 (<1%)	0	2 (<1%)
Age ≥ 60 years at baseline	0	1 (<1%)	1 (<1%)
Histologic diagnosis other than AML	1 (<1%)	0	1 (<1%)
Diagnosis of APL at baseline	0	1 (<1%)	1 (<1%)
Had therapy-related AML at baseline	0	2 (<1%)	2 (<1%)
Major dosing violations	34 (9%)	36 (10%)	70 (10%)
Did not receive any midostaurin/placebo	17 (5%)	20 (6%)	37 (5%)
Treatment arm switched at least once	9 (3%)	7 (2%)	16 (2%)
Midostaurin/placebo interrupted > 28 days but not d/c	4 (1%)	4 (1%)	8 (1%)
Continued dosing after completing protocol therapy	4 (1%)	4 (1%)	8 (1%)
Randomized to placebo, received midostaurin	0	2 (<1%)	2 (<1%)

Source: FDA analysis

¹ Three additional patients (2 on the midostaurin arm and 1 on the placebo arm) were identified after the database lock to have FLT3-ITD below the 0.05 threshold at baseline.

Demographic Characteristics

Demographic information from the patients on Study A2301 is summarized in Table 5. Women and men were both well-represented on this study. However, the treatment arms were somewhat imbalanced with respect to gender, with more female patients on the placebo arm

Clinical Review

Ashley Ward, MD

NDA 207997

Rydapt® (midostaurin)

(59% vs 52%). The treatment arms were otherwise well-balanced with respect to demographic characteristics. The median age of the patients enrolled on this study (47 years) is lower than the median age of patients with previously untreated AML in the United States (69 years, Oran and Weisdorf, Haematologica 2012) because the eligibility criteria specified that patients must be < 60 years at study entry. Although information on race and ethnicity is limited due to the high number of sites that did not collect this information because of local regulations, the study appears to have limited representation of non-white and Hispanic or Latino patients.

Table 5: Study A2301 – Patient Demographics

	Midostaurin (n=360)	Placebo (n=357)	Total (n=717)
Sex			
Female	186 (52%)	212 (59%)	398 (56%)
Male	174 (48%)	145 (41%)	319 (44%)
Age (years)			
Mean	45	46	45
Median	47	48	47
Min, Max	19, 59	18, 60	18, 60
ECOG Performance Status			
0	164 (46%)	142 (40%)	306 (43%)
1	159 (44%)	168 (47%)	327 (46%)
2	29 (8%)	36 (10%)	65 (9%)
3	6 (2%)	9 (3%)	15 (2%)
4	2 (1%)	2 (1%)	4 (1%)
Race			
Unknown or not reported ¹	195 (54%)	213 (60%)	408 (57%)
White	147 (41%)	128 (36%)	275 (38%)
Black or African-American	8 (2%)	9 (2%)	17 (2%)
Asian	8 (2%)	5 (2%)	13 (2%)
Other or more than one race	2 (<1%)	2 (<1%)	4 (<1%)
Ethnicity			
Unknown or not reported ¹	248 (69%)	243 (68%)	491 (68%)
Hispanic or Latino	9 (3%)	7 (2%)	16 (2%)
Not Hispanic or Latino	103 (29%)	107 (30%)	210 (29%)
Region			
North America	121 (34%)	115 (32%)	236 (33%)
United States	117 (32%)	106 (30%)	223 (31%)
Canada	4 (1%)	9 (3%)	13 (2%)
Non-North America	239 (66%)	242 (68%)	481 (67%)

Source: FDA analysis

¹ Data on race and/or ethnicity were not collected in some countries due to local regulations

Other Baseline Characteristics

Clinical Review

Ashley Ward, MD

NDA 207997

Rydapt® (midostaurin)

Characteristics of the AML at baseline, including FAB classification and incidence of selected chromosomal abnormalities were similar across treatment groups (Table 6).

Table 6: Study A2301 – Baseline Disease Characteristics

	Midostaurin (n=360)	Placebo (n=357)	Total (n=717)
Clinical onset of AML			
De novo	343 (94%)	338 (95%)	681 (95%)
MDS-related	14 (4%)	16 (5%)	30 (4%)
Missing	3 (1%)	1 (<1%)	4 (1%)
Treatment-related	0	2 (<1%)	2 (<1%)
FLT3 mutation result			
TKD	83 (23%)	80 (22%)	163 (23%)
ITD (includes patients with both TKD and ITD)	276 (77%)	274 (77%)	550 (77%)
ITD allelic ratio < 0.7	164 (46%)	165 (46%)	329 (46%)
ITD allelic ratio ≥ 0.7	112 (31%)	109 (31%)	221 (31%)
ITD allelic ratio < 0.5	107 (30%)	99 (29%)	206 (29%)
ITD allelic ratio ≥ 0.5	167 (46%)	174 (49%)	341 (48%)
No FLT3 gene mutation or ITD < 0.05 threshold	3 (1%)	4 (1%)	7 (1%)
NPM1 mutation result¹			
Number with results available	294 (82%)	269 (75%)	563 (79%)
NPM1 mutated (% of results available)	162 (55%)	162 (60%)	324 (58%)
NPM1 wild type (% of results available)	132 (45%)	107 (40%)	239 (42%)
Selected chromosomal abnormalities			
AML with inv(16) or t(16;16)	11 (3%)	14 (4%)	25 (3%)
AML with t(8;21) ²	15 (4%)	7 (2%)	22 (3%)
AML with 11q23 (MLL) abnormalities ³	7 (2%)	8 (2%)	15 (2%)
Leukemia classification (FAB subtype)			
M0 – Undifferentiated AML	15 (4%)	11 (3%)	26 (4%)
M1 – AML without maturation	80 (22%)	85 (24%)	165 (23%)
M2 – AML with maturation	73 (20%)	65 (18%)	138 (19%)
M4 – Acute myelomonocytic leukemia	101 (28%)	86 (24%)	187 (26%)
M5 – Acute monocytic leukemia	67 (19%)	79 (22%)	146 (20%)
M6 – Acute erythroid leukemia	1 (<1%)	3 (1%)	4 (<1%)
M7 – Acute megakaryoblastic leukemia	1 (<1%)	0	1 (<1%)
Other	17 (5%)	21 (6%)	38 (5%)
Missing	5 (1%)	7 (2%)	12 (2%)

Source: FDA analysis

¹ Data from a subset of patients on Study A2301 who enrolled on a separate companion protocol

² Includes patients with WHO classification recorded as “t(8;21)” as well as one patient with WHO classification recorded as “other” with specification indicating presence of t(8;21).

³ Includes patients with WHO classification recorded as “AML with 11q23 abnormalities” as well as 4 patients with WHO classification recorded as “Other” with specification indicating presence of t(9;11)(p22,q23) or t(9;11).

Clinical Review

Ashley Ward, MD

NDA 207997

Rydapt® (midostaurin)

FLT3 status was confirmed by a central laboratory. However, there are multiple central laboratory FLT3 results provided for 49 of the 717 patients (7%). The study database provided by the applicant contains the date the sample was received by the central lab, but not the collection date, and therefore provides insufficient information to determine which of the samples were obtained at baseline. In a response (dated January 31, 2017, SDN 73) to an information request by the FDA, the applicant stated that they assumed that the sample with the earliest receipt date was the baseline sample. For patients with more than one result provided with the same receipt date (in all such cases, one result indicates FLT3-TKD and a second indicates FLT3-ITD), the applicant classified the patient as FLT3-ITD. For the purposes of this review, the FDA took the same approach, although the results must be interpreted with caution.

Although 20 patients (7 on the midostaurin arm and 13 on the placebo arm) were incorrectly stratified for randomization based on their FLT3 mutation status, FLT3 mutation status was balanced across treatment arms. The incidence of FLT3-TKD mutations in the general untreated AML population is approximately 5% (Bacher et al, Blood 2008), while the incidence of FLT3-ITD mutations in the same population is 23-27% depending on age (Levis, Hematology ASH Educ Program, 2013). The observed ratio of patients with FLT3-TKD to those with FLT3-ITD observed on Study A2301 was thus somewhat higher than has been observed in the general population. Otherwise, the disease characteristics at baseline observed on Study A2301 generally reflect the general population of patients with previously untreated AML.

Nucleophosmin (NPM1) mutation analysis was performed on a subset of patients enrolled on Study A2301 (n=563) as part of a separate companion protocol. This data was requested by the FDA during review of the application and is summarized in Table 6. NPM1 mutation results were available from 79% of the patients enrolled on Study A2301. NPM1 mutations were slightly more frequent on the placebo arm (60% vs 55%).

A limited amount of cytogenetic information was captured in the CRF by the investigator in the WHO classification and is summarized in Table 6; the majority of patients had a WHO classification of "Other". The protocol specified central review of cytogenetics, but in their response (dated January 31, 2017) to an FDA information request, the applicant stated that this data was never entered into the Alliance database. Therefore, there is insufficient information available to analyze the cytogenetic/molecular prognostic category of patients enrolled on Study A2301.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The applicant did not do an analysis of treatment compliance, and the datasets provided by the applicant were not sufficient to allow the FDA to independently analyze treatment compliance, as reasons for missed doses were not captured in early versions of the CRFs and reasons for

Clinical Review

Ashley Ward, MD

NDA 207997

Rydapt® (midostaurin)

missed doses other than for toxicity were not consistently captured by later versions of the CRFs. However, the median dose intensity of midostaurin/placebo was high (>94%) on both treatment groups. Please see Section 8.2.1 for an analysis of exposure to the study drugs.

Concomitant medications were collected throughout the treatment period for all Non-North American (NNA) patients, but only after Amendment 4 for patients in North America (NA). The analysis of concomitant medications was thus performed only on the subset of patients (n=649, 91%) for whom medications were recorded from the time of randomization. Only the following were required to be reported per protocol: antibiotics, antivirals, antifungals, proton pump inhibitors, H2 antagonists, NSAIDs, opioids, antiemetics, antihistamines, corticosteroids, growth factors, diuretics, antihypertensives, and other CYP3A4 inhibitors or inducers.

The most frequently used (in >40% of patients) concomitant medications in the induction phase were vancomycin, furosemide, acyclovir, ondansetron, acetaminophen and pantoprazole. The most frequently used (in >40% of patients) concomitant medications in the consolidation phase were ondansetron, dexamethasone, levofloxacin, acetaminophen, pantoprazole, acyclovir, furosemide and vancomycin. The most frequently used (in >10% of all patients) concomitant medications in the maintenance phase were pantoprazole, acyclovir and ibuprofen.

The use of concomitant CYP3A4 inhibitors and inducers was of particular interest due to the pharmacokinetics of midostaurin (see Section 4.5 of this review for further details). Moderate or strong CYP3A4 inhibitors were used in 61%, 46% and 11% of patients in the induction, consolidation, and maintenance phases, respectively, and were balanced across treatment groups. The most frequently used moderate or strong CYP3A4 inhibitors were fluconazole, ciprofloxacin, posaconazole and voriconazole. Only 6 patients used a moderate or strong CYP3A4 inducer (nafcillin, phenytoin or carbamazepine) while on Study A2301.

Hematopoietic growth factor use during induction and consolidation therapy was generally balanced across both treatment arms. No growth factor use was reported for any patient during the maintenance phase of therapy. Filgrastim was used in 17% of patients on the midostaurin arm and 13% of patients on the placebo arm, while peg-filgrastim was used in 4% of patients on the midostaurin arm and 7% of patients on the placebo arm. Erythropoietin was used by only one patient, in the placebo group.

Efficacy Results – Primary Endpoint

The primary endpoint of Study A2301 was overall survival. The median time from the date of randomization to data cut-off date (April 1, 2015) was 60.2 months in both groups, with a minimum of 42 months in both groups. The FDA identified 357 death events, 171 (48%) on the midostaurin arm and 186 (52%) on the placebo arm. The remaining patients (n=360) were censored. The majority of the censored patients (292, 81%) had a date of last contact after the

Clinical Review

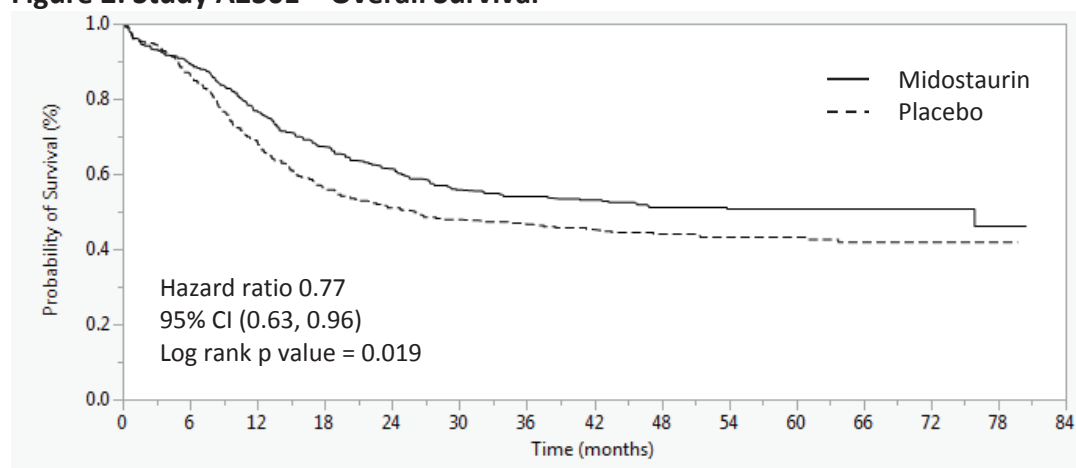
Ashley Ward, MD

NDA 207997

Rydapt® (midostaurin)

data cut-off date, and were thus censored on the data cut-off date. The other 68 patients (19%) had a date of last contact prior to the data cut-off date, and were thus censored on the date of last contact. Imputation of the date of last contact was required for only one patient (Subject ID 115957), and is thus unlikely to have influenced the outcome. Due to the interim analysis, the alpha available for the final analysis of the primary endpoint was 0.0478. There was a statistically significant difference ($p=0.019$) in OS that favored midostaurin treatment, with a hazard ratio of 0.77 (95% CI: 0.63, 0.96) (Figure 2).

Figure 2: Study A2301 – Overall Survival



Source: FDA analysis

Estimates of median OS are not informative since the curves for both treatment arms plateau after approximately 36 months. To get a more reliable estimate of the magnitude of the treatment benefit of midostaurin, when added to standard of care, the FDA analyzed restricted mean survival time, or the average survival up to the follow-up time, for both arms (Table 7).

Table 7: Study A2301 – Restricted Mean Survival Time

Follow-up (years)	Restricted Mean Survival Time (average survival up to follow-up time)		
	Midostaurin (months)	Placebo (months)	Difference (months)
3.0 ¹	25.5	22.9	2.6
3.5	28.7	25.6	3.1
4.0	31.8	28.3	3.5
4.5	34.9	30.9	4.0
5.0	37.9	33.5	4.4
5.5	41.0	36.1	4.9
6.0 ²	44.0	38.6	5.4

Source: FDA statistical reviewer

¹ Minimum follow-up at time of data cut-off

² Maximum follow-up at time of data cut-off

Clinical Review

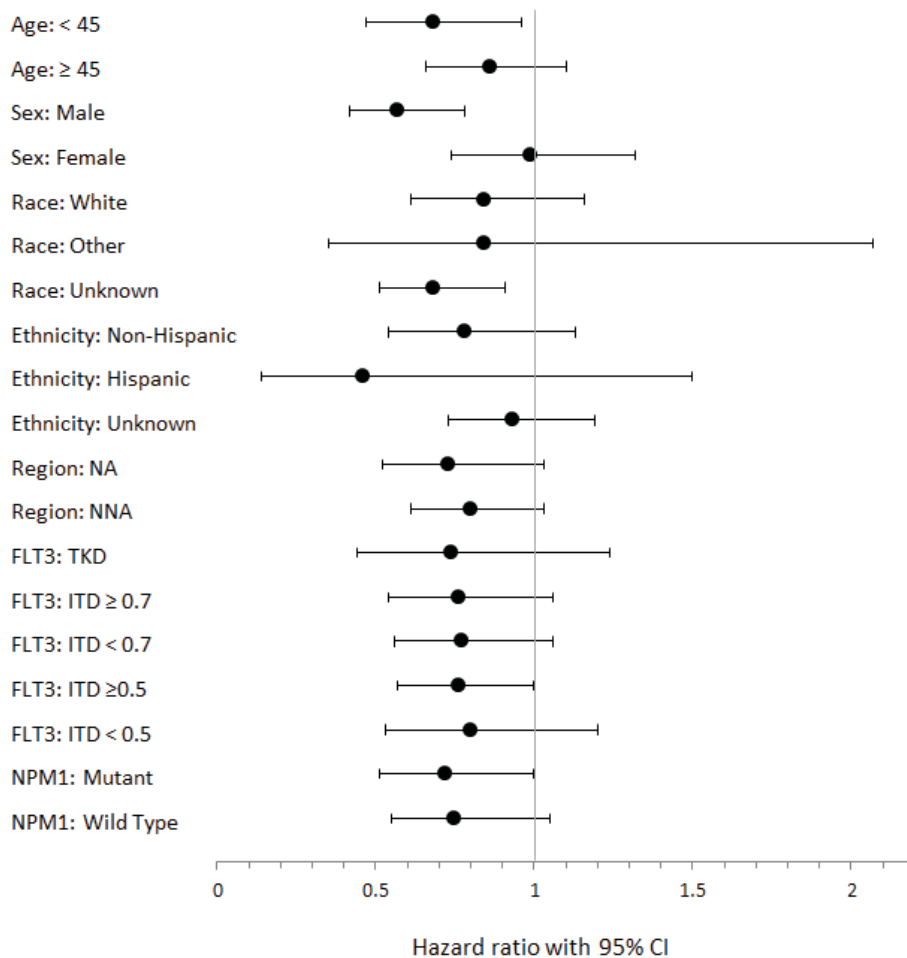
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NDA 207997

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The applicant reported that the primary endpoint was consistent across all subpopulations except for females (n=398; HR 1.01) vs. males (n=319; HR 0.53) and certain subgroups where the population size was small with large variability (A2301 Clinical Study Report Section 11.3.1.2.2). Figure 3 shows the subpopulation analysis of the primary endpoint performed by the FDA, which generally confirmed the applicant's findings.

Figure 3: Study A2301 – Subpopulation Analysis of the Primary Endpoint



Source: FDA analysis

Neither type of baseline FLT3 mutation nor presence of baseline NPM1 mutation appeared to substantially influence the treatment effect of midostaurin on OS. An analysis of OS by age group (arbitrarily selected as age above and below the median) suggests a trend for improved treatment benefit in younger patients. This reviewer believes that the observation that midostaurin did not appear to confer a survival advantage to females compared to placebo on Study A2301 is believed to be at least in part related to the high frequency of NPM1 mutations

Clinical Review

Ashley Ward, MD

NDA 207997

Rydapt® (midostaurin)

in women enrolled on the placebo arm of the trial, and should not be interpreted to be an indicator of lack of efficacy of midostaurin in women. See Additional Analyses Conducted on the Clinical Trial, below, for complete discussion.

At the time of study design and sample size determination, the applicant estimated that approximately 15% of patients would undergo HSCT. The actual number of patients who enrolled on Study A2301 and underwent HSCT was much higher (n=411, 57%). The number of patients enrolled on Study A2301 who underwent HSCT, by type of transplant and disease status, as calculated by the Applicant, is shown in Table 8.

Table 8: Study A2301 – Stem Cell Transplantation Rates

	Midostaurin (n=360)	Placebo (n=357)	Total (n=717)
Type of HSCT – Any	214 (59%)	197 (55%)	411 (57%)
Allogeneic related	95 (26%)	67 (19%)	162 (23%)
Allogeneic unrelated	89 (25%)	108 (30%)	197 (27%)
Autologous	2 (1%)	1 (<1%)	3 (<1%)
Cord blood	12 (3%)	9 (3%)	21 (3%)
Other	16 (4%)	12 (3%)	28 (4%)
Timing of HSCT			
Occurred in patients without CR ¹	86 (24%)	89 (25%)	175 (24%)
Occurred during first CR ²	80 (22%)	69 (19%)	149 (21%)
Occurred after relapse ³	48 (13%)	39 (11%)	87 (12%)

Source: From A2301 Clinical Study Report Table 11-14 dated 05-Jul-2016

¹ No CR within 60 days after starting study therapy

² Achieved CR within 60 days after starting study therapy

³ Achieved CR within 60 days after starting study therapy and then relapsed

The timing of HSCT with respect to disease status was similar in both treatment groups, with 79% of transplantations occurring as part of first line therapy (either during first CR or in patients who did not achieve a CR). However, despite the high frequency of HSCT on the study, the estimation of OS benefit in favor of midostaurin appears consistent whether OS is censored at the time of HSCT, evaluated from the start of HSCT in first CR, or evaluated with HSCT as a time-dependent covariate (Table 9).

Clinical Review

Ashley Ward, MD

NDA 207997

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Table 9: Study A2301 – Impact of HSCT on Overall Survival Analyses

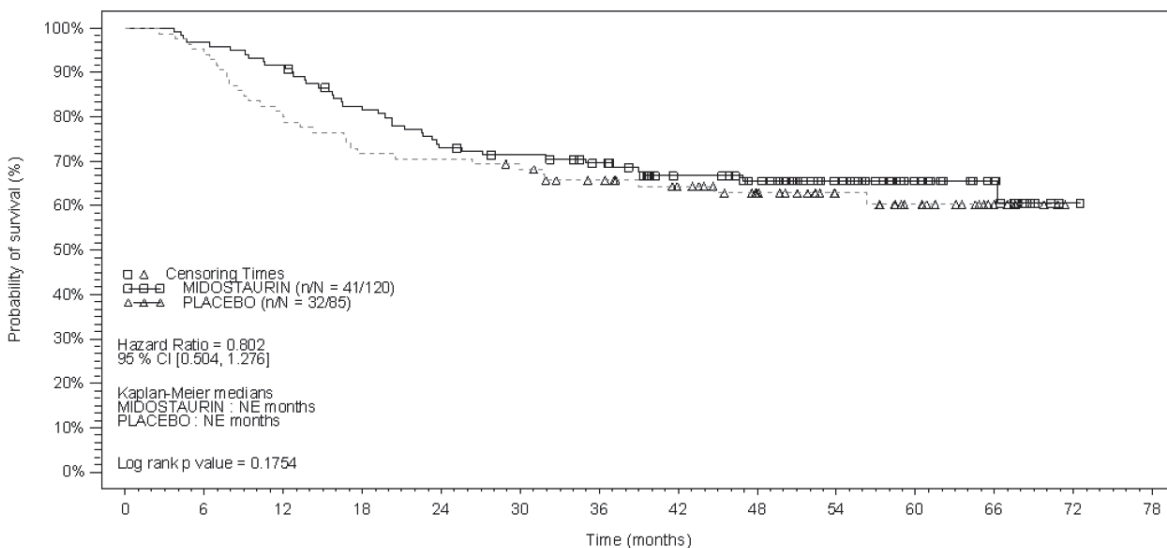
	Midostaurin (n=360)	Placebo (n=357)
OS not censored for HSCT (primary analysis)		
Number of events/N (%)	171/360 (48%)	186/357 (52%)
Hazard ratio, midostaurin/placebo [95% CI]	0.77 [0.63, 0.95]	
OS censored at time of HSCT		
Number of events/N (%)	71/360 (20%)	81/357(23%)
Hazard ratio, midostaurin/placebo [95% CI]	0.75 [0.54, 1.03]	
OS with HSCT as a time-dependent covariate		
Number of events/N (%)	171/360 (48%)	186/357(52%)
Hazard ratio, midostaurin/placebo [95% CI]	0.79 [0.61, 0.98]	
OS from start of HSCT in first CR		
Number of events/N (%)	28/92 (30%)	32/75 (43%)
Hazard ratio, midostaurin/placebo [95% CI]	0.63 [0.38, 1.05]	

Source: FDA statistical reviewer

(b) (4)

the applicant did not re-randomize patients at the start of maintenance, which means that analyses of clinical benefit from maintenance therapy are exploratory only. This problem with the study design was clearly expressed to the applicant by the FDA at the End-Of-Phase 2 meeting held on July 12, 2006. The applicant provided an exploratory analysis of OS from the start of maintenance therapy, in subjects who entered maintenance therapy (Figure 4).

Figure 4: Study A2301 – Overall Survival From Start of Maintenance Therapy



Source: Applicant’s Summary of Clinical Efficacy, Figure 5-11, dated October 14, 2016

Clinical Review

Ashley Ward, MD

NDA 207997

Rydapt® (midostaurin)

Reviewer comment: Although a comparison between treatment arms in OS after start of maintenance therapy is in favor of midostaurin (HR 0.80, 95% CI [0.50, 1.28]) and may justify further study of midostaurin as maintenance therapy, (b) (4)

Data Quality and Integrity – Reviewers’ Assessment

The quality of the original data submission was insufficient to evaluate and review the submission due to missing required information and poor organization. The applicant addressed the most significant of these issues prior to the filing date and thus the application was filed. However, residual issues with missing information limited some of the analyses, as described in this review. The FDA issued multiple requests for information throughout the review period, including a request for NPM1 mutation data from patients on Study A2301, which aided in the evaluation of efficacy. The clinical reviewer audited a sample of case report forms from Study A2301 for consistency with datasets and patient narratives; the quality and integrity of the data required to evaluate the primary endpoint was acceptable.

Efficacy Results – Secondary and other relevant endpoints

The key secondary endpoint was EFS, defined as the time from randomization until an EFS event was observed. EFS events were defined as a failure to obtain a CR within 60 days after the first dose of protocol therapy, or relapse, or death from any cause. Patients who were alive and event-free at the end of the study period were censored at the date of last clinical assessment prior to the data cut-off date. See Table 10 for a summary of the FDA’s analysis of EFS.

Table 10: Study A2301 – EFS Events and Reasons for Censoring

	Midostaurin (n=360)	Placebo (n=357)	Total (n=717)
EFS Event	256 (71%)	280 (78%)	536 (75%)
Treatment failure ¹	147 (41%)	166 (46%)	313 (44%)
Relapse	91 (25%)	90 (25%)	181 (25%)
Death	18 (1%)	24 (1%)	42 (1%)
EFS Censored	104 (29%)	77 (22%)	181 (25%)
No post-baseline data	1 (<1%)	0	1 (<1%)
In remission	103 (29%)	77 (22%)	180 (25%)

Source: FDA analysis

¹ Defined by the applicant as failure to achieve a CR within 60 days after starting study treatment

Of the 181 patients censored for EFS in remission, the median time elapsed between most recent disease evaluation and data cut-off date was 78 days (range 2 to 2059 days) for patients on the midostaurin arm and 138 days (range 1 to 2186 days) for patients on the placebo arm.

Clinical Review

Ashley Ward, MD

NDA 207997

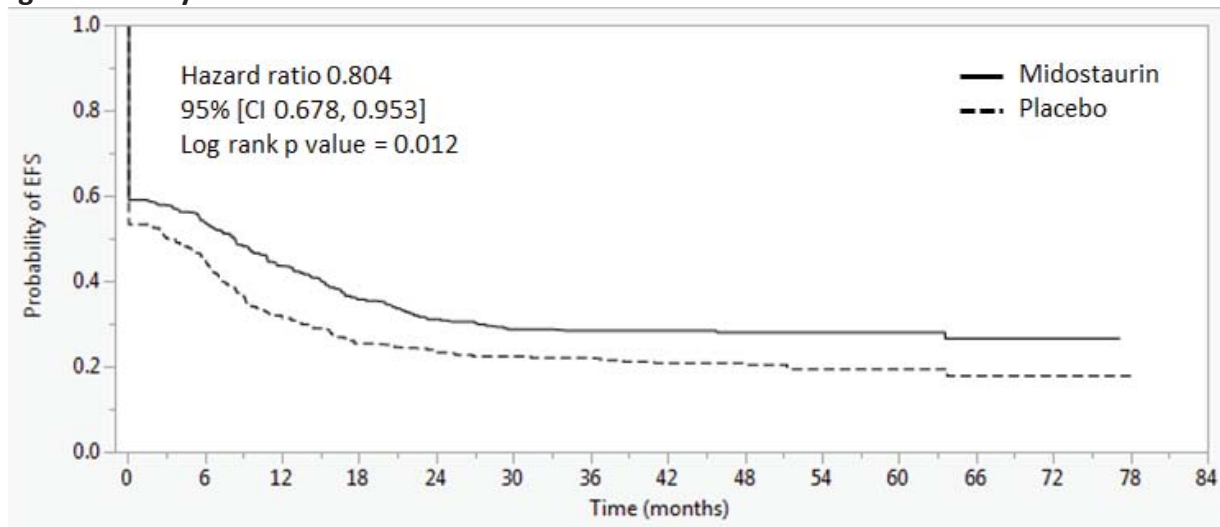
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Reviewer comment: More patients censored for being in remission on the midostaurin arm (75, 73%) had a disease evaluation within 6 months of the study cut-off date than patients on the placebo arm (44, 57%). As patients without frequent disease evaluations could have early relapses that had not yet brought them to clinical attention, the higher number of patients in the placebo group without recent disease assessment could have biased the estimation of EFS effect size in favor of the placebo group.

The Applicant reported a total of 536 EFS events (256 on the midostaurin arm, 280 on the placebo arm), with a median EFS of 8.2 months for patients on the midostaurin arm versus 3.0 months for patients on the placebo arm (HR 0.78, one-sided $p=0.002$) (A2301 Clinical Study Report Section 11.3.1.3). However, the FDA observed that for patients who had no assessment or who did not achieve CR by day 60, the applicant assigned the EFS date as the date of last adequate response assessment prior to day 60. This method of assigning event dates allows for differences in EFS to result from event date assignment rather than from a treatment effect, which is undesirable.

The FDA analyzed EFS by instead assigning the date of treatment failure as day +1 for patients that did not have a CR documented by day +60 (Figure 5). This yields a median EFS of 8.3 months on the midostaurin arm versus 3.6 months on the placebo arm (HR 0.80, one-sided $p=0.012$). Of note, the hazard does not appear to be proportional over time, and most of the difference in the EFS curves between the two treatment arms appears to come from excess treatment failures on the placebo arm during induction therapy.

Figure 5: Study A2301 – Event-Free Survival



Source: FDA analysis

Clinical Review

Ashley Ward, MD

NDA 207997

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Although the protocol defined CR as occurring within 60 days after starting study treatment, this definition is not standard. The FDA thus performed a sensitivity analysis on EFS, defining CR as occurring after 1 or 2 cycles of induction therapy. Sixty-one subjects (34 on the midostaurin arm and 27 on the placebo arm) who were considered treatment failures per protocol but who achieved CR after a median of 72 days (range 61 to 108 days) were recoded for this analysis. The analysis showed a continued benefit of midostaurin on EFS, with a hazard ratio of 0.74 (95% CI: 0.62, 0.87).

A summary of other secondary endpoints is provided in Table 11. Estimates of DFS and CR by day 60 were consistent with the primary and key secondary analyses. Transplantation rates were slightly higher on the midostaurin arm.

Table 11: Study A2301 – Results of Additional Efficacy Endpoints

	Midostaurin (n=360)	Placebo (n=357)	Hazard Ratio ¹ [95% CI]	p- value ²
Median DFS, m [95% CI]	26.7 [19.4, NE]	15.5 [11.3, 23.5]	0.71 [0.55, 0.92]	0.010
CR by Day 60 [95% CI]	212 (58.9%) [53.6, 64.0]	191 (53.5%) [48.2, 58.8]		0.146
HSCT overall [95% CI])	214 (59.4%) [54.2, 64.6]	197 (55.2%) [49.9, 60.4]		0.250
In patients without CR	86 (23.9%)	89 (24.9%)		
During CR1	80 (22.2%)	69 (19.3%)		
After relapse	48 (13.3%)	39 (10.9%)		

Source: FDA statistical reviewer

¹ Hazard ratio for midostaurin over placebo, estimated by Cox regression model stratified by FLT3 mutation status

² For DFS, 2-sided p-value was calculated by log-rank test stratified by FLT3 mutation status. For CR and HSCT rates, 2-sided p-value was calculated by Cochran-Mantel-Haenszel test stratified by FLT3 mutation status

Dose/Dose Response

With the exception of dose reductions for prolongation of QT interval, and dose reductions for neutropenia during the maintenance phase (both of which occurred infrequently), dose modifications were not allowed on Study A2301. All patients received 50 mg bid on scheduled days, except during treatment interruptions. See the clinical pharmacology review for an evaluation of exposure-response.

Additional Analyses Conducted on the Individual Trial

Figure 3 suggested that midostaurin improved survival in males but not in females. To further explore this observation, the FDA performed two additional analyses. The first was an analysis of secondary endpoints by gender, to determine whether Study A2301 provides consistent

Clinical Review

Ashley Ward, MD

NDA 207997

Rydapt® (midostaurin)

evidence against the use of midostaurin in females across endpoints. The second was an analysis of NPM1 mutations by gender and treatment arm, since NPM1 mutations are a positive prognostic indicator that frequently co-occurs with FLT3 mutations, are more common in women, and could, in theory, be a predictor of response to midostaurin since midostaurin is a multi-kinase inhibitor with broad in vitro effects.

A summary of efficacy results from Study A2301 by gender is provided in Table 12. Women treated on the midostaurin arm appeared to have prolonged EFS, prolonged DFS, increased CR rates, and increased likelihood of HSCT by day 60 compared with women on the placebo arm. These secondary endpoints all point to consistent clinical activity of midostaurin in women. The markedly superior survival of females compared to males on the placebo arm is surprising, and likely accounts for at least some of the discrepancy in overall survival benefit by gender.

Table 12: Study A2301 – Efficacy Results by Gender

	Males		Females	
	Midostaurin	Placebo	Midostaurin	Placebo
OS				
OS Event/N (%)	78/174 (44.8)	89/145 (61.4)	93/186 (50.0)	97/212 (45.8)
Median	Not reached	16.9 months	46.1 months	50.7 months
Hazard ratio [95% CI]	0.53 [0.39, 0.72]		1.01 [0.76, 1.34]	
EFS¹				
EFS Event/N (%)	118/174 (67.8)	110/145 (75.9)	138/186 (74.2)	170/212 (80.2)
Median	10.7 months	5.9 months	5.9 months	1.0 months
Hazard ratio [95% CI]	0.78 [0.60, 1.01]		0.81 [0.65, 1.02]	
DFS				
DFS Event/N (%)	49/104 (47.1)	50/85 (58.8)	60/108 (55.6)	64/106 (60.4)
Median	61.0 months	17.6 months	20.8 months	14.1 months
Hazard ratio [95% CI]	0.59 [0.40, 0.88]		0.86 [0.60, 1.22]	
CR by day 60				
CR/N (%)	104/174 (59.8)	85/145 (58.6)	108/186 (58.1)	106/212 (50.0)
Rate difference [95% CI]	1.2 [-9.7, 12.0]		8.1 [-1.7, 17.8]	
HSCT by day 60				
HSCT/N (%)	101/174 (58.1)	82/145 (56.6)	113/186 (60.7)	115/212 (54.2)
Rate difference [95% CI]	1.5 [-9.4, 12.4]		6.5 [-3.2, 16.2]	

Source: FDA Statistical Reviewer

¹ For EFS analysis, patients who did not achieve a CR by day 60 were assigned an event date of day +1

The FDA has concerns regarding whether the presence of a FLT3 mutation is the best predictor of clinical benefit from midostaurin, since midostaurin inhibits multiple kinases that have been implicated in AML pathogenesis, and the applicant has collected only minimal data in FLT3 wild type AML in support of their development in a diagnostically selected patient population.

In response (dated November 30, 2016, SDN 44) to an FDA information request, the applicant

Clinical Review

Ashley Ward, MD

NDA 207997

Rydapt® (midostaurin)

submitted results of their analysis of NPM1 mutations in patients on Study A2301. In this response, the applicant showed that NPM1 mutations were a positive predictor of overall survival (consistent with the literature), and that the treatment effect of midostaurin on OS was present in both NPM1 wild type (HR 0.74, $p=0.038$) and NPM1 mutated patients (HR 0.72, $p=0.029$). However, the treatment effect of midostaurin on EFS was only observed in patients with mutant NPM1 (HR 0.66, $p=0.001$), with little to no effect on EFS in patients with wild type NPM1 (HR 0.92, $p=0.282$). Furthermore, midostaurin improved CR rates in patients with mutant NPM1 (60% vs 40%, $p=0.010$), but not in patients with wild type NPM1 (46% vs 48%, $p=0.589$). This discrepancy between efficacy variables raised the concern that the overall survival benefit observed in patients with wild type NPM1 was due to factors other than the study treatment.

Additional information was requested from the applicant. In their response (dated January 25, 2016, SDN 70), additional sensitivity analyses performed by the applicant, which were confirmed by the FDA, showed that if the standard definition of CR is used (CR after 1 or 2 cycles of induction) rather than the protocol defined CR within 60 days, midostaurin improves CR rates in wild type NPM1 patients (57% vs 51%) and also improved EFS in wild type NPM1 patients (HR 0.72, 95% CI: 0.53, 0.96), with effect size now more similar to that in NPM1 mutant patients. Taken together, this data suggest that while NPM1 mutations are a positive prognostic indicator in AML, they do not appear to be a predictor of clinical benefit to midostaurin, and that midostaurin provides clinical benefit to AML patients with wild type and mutant NPM1.

The frequency of NPM1 mutations in women on Study A2301 was approximately 59% on the midostaurin arm and 66% on the placebo arm, while the frequency of NPM1 mutations in men was approximately 50% on both arms. This increased frequency of NPM1 mutations in women, and particularly in women on the placebo arm, combined with the disproportionate number of women randomized to the placebo arm, provides a plausible biologic explanation for the unexpectedly high survival of women on the placebo arm of the trial. These findings suggest that women are likely to benefit from the addition of midostaurin to standard chemotherapy in the treatment of their AML, although further studies to elucidate the magnitude of this benefit in patients with NPM1 mutations would be useful for defining the most appropriate patient population to receive midostaurin.

6.2. Study A2106

6.2.1. Study Design

Overview

Study A2106 was a phase I, open-label study to determine the safety, tolerability and pharmacokinetics of several different doses and schedules of midostaurin administered in combination with standard chemotherapy in patients with newly diagnosed AML. Evaluation of efficacy was a secondary objective. The study was conducted at a total of six sites in the United

Clinical Review

Ashley Ward, MD
NDA 207997
Rydapt® (midostaurin)

States and Germany between April 2003 and June 2011. The last treatment for the last patient was administered in September 2008.

Trial Design

Patients age ≥ 18 and ≤ 60 years with newly diagnosed AML (FLT3 mutation allowed but not required) were alternately assigned to one of two treatment arms. All patients received induction with daunorubicin 60 mg/m²/day IV over 30 minutes on each of days 1-3 and cytarabine 200 mg/m²/day over 24 hours for 7 days continuous infusion. If a second cycle of induction therapy was required due to inadequate response, daunorubicin and cytarabine were administered on days 1-2 and days 1-5, respectively. Patients who obtained a CR after 1 or 2 cycles of induction received up to 3 cycles of consolidation therapy with cytarabine 3 g/m² IV over 3 hours every 12 hours on days 1, 3 and 5 (total of 6 doses).

When the study started, midostaurin was administered during all cycles of induction and consolidation as follows:

- Arm 1: Sequential administration (midostaurin 100 mg bid days 8-28)
- Arm 2: Concomitant administration (midostaurin 100 mg bid days 1-28)

After patients completed consolidation, midostaurin was administered as single-agent maintenance therapy on the same schedule until relapse, unacceptable toxicity, or a maximum of 3 years. As the study progressed, the protocol was amended several times to adjust the treatment regimen, first to reduce the duration of midostaurin dosing (to days 8-21 on Arm 1 and to days 1-7 and 15-21 on Arm 2), then to reduce the midostaurin dose (from 100 mg bid to 50 mg bid on both arms).

Patients were continuously monitored for adverse events and had blood counts at least 3x weekly and serum chemistries at least weekly during induction and consolidation cycles. An echocardiogram was obtained at baseline and at the end of study. Response assessments were performed after every treatment cycle.

6.2.2. Study Results

Compliance with Good Clinical Practices

The applicant provided attestation that this study was conducted in accordance with U.S. regulations governing the protection of human subjects, institutional review boards, and the obligations of clinical investigators in accordance with good clinical practice (GCP).

Financial Disclosure

A summary of financial disclosures for Study A2106 is provided in the appendix (Section 13.2). The applicant was unable to obtain financial disclosure information from 7 of the 40

Clinical Review

Ashley Ward, MD

NDA 207997

Rydapt® (midostaurin)

investigators on Study A2106. All were sub-investigators at a single study site, which enrolled (b) (6) % of the subjects on the clinical trial. No financial interests or arrangements were reported in the other investigators.

Patient Disposition

The study screened 73 patients and enrolled 69 patients (34 in Arm 1 and 25 in Arm 2). The applicant's summary of patient disposition on Study A2016 is reproduced in Table 13. Study completion rate was highest (65%) in patients who received midostaurin 50 mg bid on days 8-21 of each cycle of therapy. Further detail about the reasons for treatment discontinuation was not provided in the applicant's submission, with the exception of adverse events that prompted treatment discontinuation, which are included in the discussion of safety below.

Table 13: Study A2106 – Disposition of Patients

	Midostaurin 100 mg bid initial schedule	Midostaurin 100 mg bid reduced frequency	Midostaurin 50 mg bid	Total
Arm 1 (sequential)	N=7	N=7	N=20	N=34
Completed study ¹	2 (29%)	2 (29%)	13 (65%)	17 (50%)
Discontinued study	5 (71%)	5 (71%)	7 (35%)	17 (50%)
Adverse event(s)	1 (14%)	1 (14%)	1 (5%)	3 (9%)
Unsatisfactory effect	3 (43%)	1 (14%)	4 (20%)	8 (24%)
No longer requires study drug	0	0	2 (10%)	2 (6%)
Protocol violation	0	0	0	0
Withdrew consent	1 (14%)	3 (43%)	0	4 (12%)
Arm 2 (concomitant)	N=7	N=8	N=20	N=35
Completed study ¹	1 (14%)	1 (13%)	9 (45%)	11 (31%)
Discontinued study	6 (86%)	7 (88%)	11 (55%)	24 (69%)
Adverse events	2 (29%)	1 (13%)	4 (20%)	3 (9%)
Unsatisfactory effect	2 (29%)	2 (25%)	4 (20%)	8 (23%)
No longer requires study drug	0	1 (13%)	2 (10%)	3 (9%)
Protocol violation	1 (14%)	0	1 (5%)	2 (6%)
Withdrew consent	1 (14%)	3 (38%)	2 (10%)	6 (17%)

Source: A2106 Clinical Study Report Table 10-1 dated 04-Dec-2014

¹ Per investigator. Two subjects did not receive all cycles of consolidation.

Demographic Characteristics

Study A106 enrolled equal numbers of men (n=35, 51%) and women (n=34, 49%). Most of the study subjects were white (n=58, 84%). The median age of study participants was 49 (range 20-65). One 65-year old subject was treated on the study which constituted a major protocol violation as the eligibility criteria required age ≤ 60.

Clinical Review

Ashley Ward, MD

NDA 207997

Rydapt® (midostaurin)

Other Baseline Characteristics

According to information recorded in the CRFs, 19 patients (28%) had FLT3 mutations at baseline. Of these, 13 had a FLT3-ITD and 6 had FLT3-TKD. The results for the central FLT3 mutation status assessment were consistent with that reported in the CRF for the majority of patients. A divergent baseline result was reported for 2 patients, both of whom had FLT3 mutations according to the investigator, but were FLT3 wild type according to the central laboratory. For an additional 2 patients assessed as FLT3 wild type by the investigator, FLT3 status could not be confirmed by central testing (central result: unknown).

Efficacy Results - Primary Endpoint

The primary efficacy variable in this study was CR, defined as an ANC $\geq 1500/\mu\text{L}$ (with no G-CSF for at least 5 days), platelet count $\geq 100 \times 10^9/\text{L}$, no leukemic blasts in the peripheral blood and transfusion independence, as well as a bone marrow with adequate (>20%) cellularity that showed < 5% blast cells and no extra-medullary leukemia. The applicant's analysis included all CRs that occurred within 42 days of treatment discontinuation, which included 5 subjects that obtained a CR during consolidation therapy. However, for consistency with the analysis of Study A2301, the FDA analyzed only those CRs that occurred after cycle 1 or 2. By this definition, a total of 34 patients (49%) achieved a CR. The CR rate was highest in patients who received midostaurin at 50 mg bid (Table 14).

Table 14: Study A2106 – Complete Responses

	Midostaurin 100 mg bid initial schedule	Midostaurin 100 mg bid reduced frequency	Midostaurin 50 mg bid	Total
Arm 1 (sequential)	N=7	N=7	N=20	N=34
CR ¹	3 (43%)	3 (43%)	11 (55%)	17 (50%)
Arm 2 (concomitant)	N=7	N=8	N=20	N=35
CR ¹	3 (43%)	2 (25%)	12 (60%)	17 (49%)

Source: FDA analysis

¹ Only CRs obtained after 1 or 2 cycles of induction were included

Historical rates of CR after standard induction chemotherapy (without midostaurin) in patients with unselected, previously untreated AML are 60-70% in patients age 40-60 and approximately 50% in patients older than 60 (Mayer et al, NEJM 1994). The lower CR rates observed on this study, which enrolled only patients younger than 60, may reflect small sample size and high study discontinuation rates, particularly in patients receiving 100 mg bid of midostaurin. Prior studies have generally found no difference in CR rates between wild-type and mutant FLT3 AML (Levis and Small, Leukemia 2003).

Clinical Review

Ashley Ward, MD
NDA 207997
Rydapt® (midostaurin)

Reviewer comment: The results of Study A2106 support the selection of the 50 mg bid dose of midostaurin, administered after chemotherapy (sequentially) in each cycle of standard induction with daunorubicin and cytarabine and consolidation with high dose cytarabine, for pivotal Study A2301.

By FDA analysis of the datasets provided by the applicant, CR rate was higher in patients with a baseline FLT3 mutation by central assessment (14 out of 19, 74%) than in those with wild type FLT3 (19 out of 50, 40%). The 2 patients assessed as FLT3 wild type by the investigator without central confirmation were included in the FLT3 wild type subset for the purposes of this analysis.

Reviewer comment: While the numbers are small and the analysis post-hoc, the observation that CR rates after 1 or 2 cycles of induction therapy were higher for patients with baseline FLT3 mutations compared to patients with wild type FLT3 makes the applicant's decision to study midostaurin further only in FLT3 mutated patients understandable. However, it is important to note that while CR rates after induction have been thought to predict long-term survival in AML, several recent studies of new drugs in AML have reported increased CR rates compared with controls but no corresponding increase in survival (Estey et al, Leukemia 2016), raising concerns about the utility of CR as a predictive biomarker.

6.3. Study ADE02T

6.3.1. Study Design

Overview

Study ADE02T was an investigator-sponsored, phase II, single-arm, open-label, multi-center study designed to evaluate the safety and efficacy of midostaurin administered in combination with standard chemotherapy in patients with newly diagnosed, FLT3-ITD, positive AML. The primary endpoint was EFS, with secondary efficacy endpoints including CR rate, relapse-free survival, and overall survival. Of note, the trial was not randomized and the intent was to compare the results observed on the study with historical controls. The interim clinical study report (CSR) states that the historical control population consisted of 588 intensively treated patients with FLT3-ITD and a concurrent NPM1 mutation, which had a 70% CR rate and 25% 2-year EFS, although a reference was not cited. Evaluation of efficacy included pre-defined (by protocol amendment) subgroup analyses in age groups 18-60 years and 61-70 years. The study was initiated in June 2012 and is ongoing at 49 sites in Germany and 5 sites in Austria. For the interim report provided in the submission, a summary of data received up to the data cut-off date of December 31, 2015 was reported.

Reviewer comment: Time-to-event variables cannot be evaluated on a single arm trial. Furthermore, it is not clear that the stated historical control population, which consisted of

Clinical Review

Ashley Ward, MD

NDA 207997

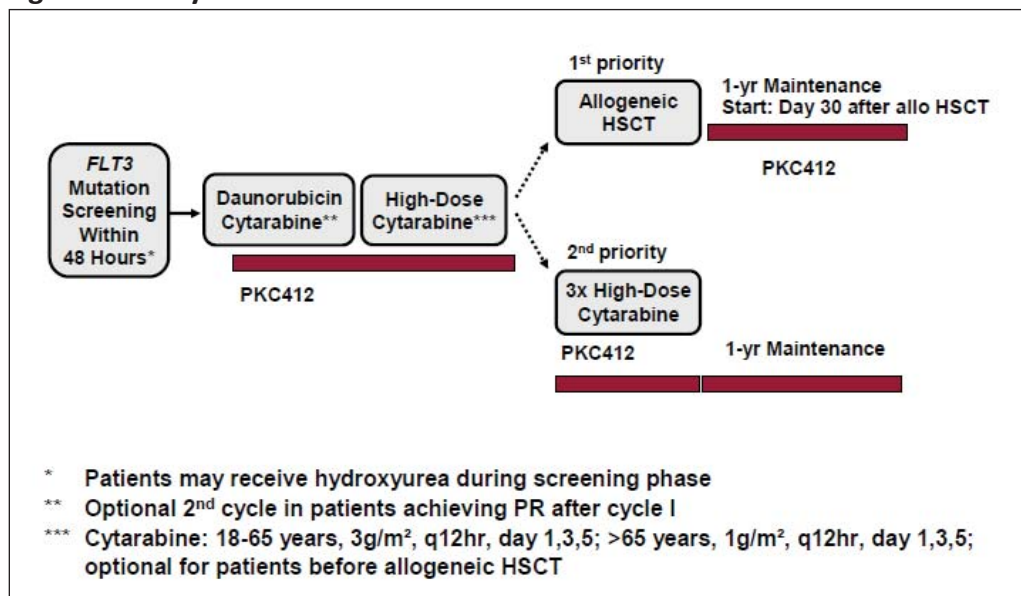
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patients with **NPM1 mutations (known positive prognostic indicator)**, is relevant for this study.

Trial Design

The trial schema for Study ADE02T is provided in Figure 6. Patients age 18 to 70 with newly diagnosed AML and FLT3-ITD as assessed by a central laboratory were eligible for the study, except for patients with t(8;21)(q22;q22), inv(16)(p13.1q22), t(16;16)(p13.1;q22), *PML-RARA* or any other variant translocations with other *RARA* gene fusions. Patients were required to have a WHO performance status of ≤ 2 .

Figure 6: Study ADE02T – Trial Schema



Source: ADE02T Interim Clinical Study Report Table 10-1 dated April 30, 2016

All patients received at least one dose of induction with daunorubicin 60 mg/m²/day IV over 30 minutes on each of days 1-3 and cytarabine 200 mg/m²/day over 24 hours for 7 days continuous infusion. Patients in a CR after 1 or 2 cycles of induction went on to consolidation therapy. Where possible, patients underwent allogeneic HSCT, ideally after one cycle of high-dose cytarabine. Patients without a donor or who were otherwise ineligible for transplantation were intended to receive four cycles of high-dose cytarabine. Cytarabine dose in consolidation was age-adjusted as described in Figure 6.

Midostaurin was administered at 50 mg bid starting on day 8 (for induction cycles) or day 6 (for consolidation cycles) through 48h prior to the start of the next chemotherapy cycle.

Maintenance therapy (50 mg bid continuously for one year) was intended for all patients, to

Clinical Review

Ashley Ward, MD
NDA 207997
Rydapt® (midostaurin)

begin immediately after the last consolidation cycle or, at earliest, 30 days after allogeneic HSCT.

Patients were continuously monitored for adverse events and had blood counts at least 3x weekly and serum chemistries at least weekly during induction and consolidation cycles. An echocardiogram was obtained at baseline and at the end of study. Response assessments were performed after every treatment cycle of induction and consolidation, and every 3 months during maintenance therapy. Response was evaluated using standard International Working Group (IWG) criteria (Cheson et al, JCO 2003).

6.3.2. Study Results

Compliance with Good Clinical Practices

The study sponsor provided attestation that this study was conducted in accordance with U.S. regulations governing the protection of human subjects, institutional review boards, and the obligations of clinical investigators in accordance with good clinical practice (GCP).

Financial Disclosure

Study ADE02T was an investigator-sponsored trial. Financial disclosure information for this trial was not provided by the applicant.

Patient Disposition

A total of 153 subjects enrolled on Study AADE01T. A summary of patient disposition was provided by the applicant and is adapted in Table 15.

Table 15: Study ADE01T – Disposition of Patients

Disposition	Age ≤ 60 years (n=105)	Age > 60 years (n=48)	All patients (n=153)
Excluded from interim analysis	6 (6%)	2 (4%)	8 (5%)
Completed study	10 (10%)	7 (15%)	17 (11%)
Discontinued study	89 (85%)	39 (81%)	128 (84%)
Adverse event	35 (33%)	15 (31%)	50 (33%)
Refractory disease	16 (15%)	6 (13%)	22 (14%)
Patient decision	13 (12%)	4 (8%)	17 (11%)
Death	8 (8%)	8 (17%)	16 (10%)
Relapse	8 (8%)	2 (4%)	10 (7%)
Other reason	7 (7%)	4 (8%)	11 (7%)
Withdrew consent	2 (2%)	0	2 (1%)

Source: Adapted from ADE02T Interim Clinical Study Report Section 8.1.1 dated April 30, 2016

Clinical Review

Ashley Ward, MD

NDA 207997

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Eight patients (5%) were excluded from all other analyses by the study sponsor, leaving 145 patients evaluated for safety and efficacy. Five patients were excluded for not meeting inclusion criteria; of these, 2 received no study therapy and the other 3 received study therapy but no midostaurin. One patient was excluded after withdrawing informed consent on day 4 of induction therapy, and 2 patients were excluded because no CRF data were available. The sponsor provided no additional data to the FDA regarding these 8 patients.

Demographic Characteristics

According to an analysis performed by the study sponsor, Study ADE02T enrolled more women (84, 58%) than men (61, 42%). Race and ethnicity data were not collected. The median age of study participants was 54 (range 20-69). More subjects were ≤ 60 years (99, 68%) than > 60 years (46, 32%).

Other Baseline Characteristics

According to an analysis performed by the study sponsor, most patients (125, 87%) had de novo AML. AML after MDS and AML after chemo and/or radiation therapy were less frequent (7% and 6%, respectively). Secondary AML was more common in patients age > 60 years (9, 20%) than in patients age ≤ 60 years (9, 9%). NPM1 mutations were present in 89 patients (61%), with a higher incidence in younger patients (65% vs 54%). The proportion of patients with FLT3 ITD allelic ratio ≥ 0.51 was approximately 52% in both age groups.

Efficacy Results - Primary Endpoint

At the time of the data cutoff, with a median follow-up time of 25.2 months, a total of 95 EFS were observed in the 145 patients. The study sponsor stated that the 2-year EFS was 34.6% for the entire study population (median EFS 10.7 months). The 2-year EFS was 38.2% in patients age ≤ 60 years (median EFS 13.8 months), and 27.1% in patients age > 60 years (median EFS 9.3 months). A breakdown of observed EFS events provided by the study sponsor is reproduced in Table 16. Older patients were more likely to die during induction therapy (17% vs 3%) and more likely to relapse (28% vs 18%) than younger patients. There was no difference in EFS between patients with high and low FLT3-ITD allelic ratio, regardless of whether the cutoff used was 0.7 or 0.51.

Clinical Review

Ashley Ward, MD

NDA 207997

Rydapt® (midostaurin)

Table 16: Study ADE02T – EFS Events

	Age ≤ 60 (n=99)	Age > 60 (n=46)	All patients (n=145)
Number of patients with at least one EFS event	60 (61%)	35 (76%)	95 (66%)
Death during induction therapy	3 (3%)	8 (17%)	11 (7%)
Refractory disease after first induction	16 (16%)	6 (13%)	22 (15%)
Refractory disease after second induction	4 (4%)	1 (2%)	5 (3%)
Relapse	18 (18%)	13 (28%)	31 (21%)
Death in CR	19 (19%)	7 (15%)	26 (18%)

Source: ADE02T Interim Clinical Study Report Section 9.3.2.1.1 dated April 30, 2016

Data Quality and Integrity - Reviewers' Assessment

Data sets for Study ADE02T were not provided by the applicant, so an assessment of data integrity cannot be made. Lack of detail in some of the analyses made interpretation of the efficacy data difficult.

Efficacy Results - Secondary and other relevant endpoints

The results of selected other secondary endpoints, as assessed by the study sponsor, are summarized in Table 17.

Table 17: Study ADE02T – Other Endpoints

Endpoint	Age ≤ 60 years (n=99)	Age > 60 years (n=46)	All patients (n=145)
CR/CRi after induction therapy ¹	76 (77%)	31 (67%)	31 (67%)
Median OS ²	28.5 months	15.5 months	24.7 months
2-year OS	53.7%	45.2%	51.0%
% of patients proceeding to HSCT in first CR	45%	23%	50%

Source: ADE02T Interim Clinical Study Report Section 9.3.2.2.1 dated April 30, 2016

¹ The applicant did not provide the breakdown by CR and CRi, nor did they specify whether the indicated number included patients who required a second induction therapy.

² A total of 74 OS events were observed, 46 in patients age ≤ 60 and 28 in patients age > 60.

Reviewer comment: Study A2301 excluded patients age > 60 due to the presumption that older patients with AML should not receive intensive chemotherapy. However, intensive chemotherapy is increasingly being used successfully in fit older patients with AML, and age by itself is no longer considered an acceptable reason to disqualify a patient from receiving it (Ferrara et al, Leukemia 2013). The FDA analyzed data summarized in the CSR from Study ADE02T to determine whether it would help support an indication for midostaurin in untreated AML without age restriction, even though the pivotal study was conducted in patients age < 60 years.

Clinical Review

Ashley Ward, MD

NDA 207997

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Time-to-event endpoints cannot be interpreted on single arm trials, and since CR rate was lumped together with CRi rate, the data as presented in the ADE02T CSR are challenging to compare with historical controls. However, the difference in 2-year OS between patients who were ≤ 60 years and those who were > 60 years was just 8.5%, which compares favorably to the approximately 20% difference in 2-year OS between patients age ≤ 60 and > 60 who were treated with intensive chemotherapy in a large retrospective review of patients in France treated between January 1, 2000 and December 31, 2009 (Bertolli et al, Blood 2013). It also compares favorably to the estimated 30% difference in 2-year OS between the patients age ≤ 60 and > 60 that has been estimated from literature reviews (Fernandez et al, NEJM 2009 and Estey, JCO 2006). As there does not appear to be a decrease in expected 2-year survival in younger patients compared to historical controls (with the caveat regarding interpretation of time-to-event endpoints noted earlier), it is unlikely that this narrowing of expected OS between the two age groups is due to underperformance of the treatment regimen in the younger patients on Study ADE02T.

This study thus provides limited evidence that the addition of midostaurin to intensive chemotherapy does not appear to adversely impact efficacy in patients age > 60 years, and in fact may improve it, and that it may therefore be reasonable to extrapolate survival data from Study A2301 to a broader patient population.

6.4. Studies A2104, A2104E1, and A2014E2

6.4.1. Study Design

Study A2104

Study A2014 was a phase II, open-label proof-of-concept trial of midostaurin monotherapy in patients with FLT3-mutated AML or MDS. The study population included patients age ≥ 18 years with untreated AML who were not candidates for myelosuppressive chemotherapy, patients with relapsed or refractory AML, and patients with high risk MDS. Patients who had undergone HSCT within the last 2 months or had had more than 2 prior regimens were ineligible.

A total of 20 patients (18 with AML and 2 with MDS) were treated on this study between January 2002 and September 2003 at 3 study sites in the United States. Of these, 7 (35%) had untreated disease. All received midostaurin monotherapy at a dose of 75 mg TID until disease progression or unacceptable toxicity. Safety evaluations were conducted at least weekly, and marrow evaluations were performed at the beginning of every 28-day treatment cycle and at the time of treatment discontinuation. The primary efficacy endpoint was investigator-determined best clinical response, according to National Cancer Institute definitions for AML (Cheson 1990) and WHO-IWG for MDS (Cheson, 2000). The study is complete.

Clinical Review

Ashley Ward, MD

NDA 207997

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Study A2104E1

Study A2014E1 was conducted as an extension of study A2014 (via protocol amendment #3). It was a phase II, open-label, randomized trial of midostaurin monotherapy in patients with AML or MDS. The study population was virtually identical to that enrolled on Study A2014, except that patients with either wild type or mutant FLT3 were eligible and patients were not allowed to have received a prior FLT3 inhibitor.

A total of 95 patients (85 with AML and 10 with MDS) were treated on this study between March 2003 and September 2004 at 4 study sites in the United States and 2 in Germany. Of these, 52 patients (55%) had previously untreated disease (12 with FLT3 mutations and 40 with wild type FLT3). Patients were randomized 1:1 to receive either 50 mg or 100 mg of midostaurin bid in continuous, 28-day cycles. Safety evaluations were conducted at least weekly, and marrow evaluations were performed at the beginning of every 28-day treatment cycle and at the time of treatment discontinuation. The primary efficacy endpoint was investigator-determined best clinical response measured on or after cycle 1, day 8, according to NCI definitions for AML (Cheson 1990) and WHO-IWG for MDS (Cheson, 2000). The study is complete.

Study A2104E2

Study A2014E2 was conducted as a second extension of study A2014 (via protocol amendment #4). It was a phase I/II, open-label, proof-of-concept trial of midostaurin monotherapy administered via intra-patient dose escalation or in combination with itraconazole in patients with AML or MDS. The study population was virtually identical to that enrolled on Study A2014, except that patients with either wild type or mutant FLT3 were eligible and patients were not allowed to have received a prior FLT3 inhibitor.

A total of 29 patients (all with AML) were treated on this study between August 2003 and March 2008 at 3 study sites in the United States and 2 in Germany. Of these, 16 patients (55%) had previously untreated disease (5 with FLT3 mutations and 11 with wild type FLT3). Sixteen of the patients (including 2 who had been receiving therapy on Study A2104E1 at the time of the amendment) were enrolled on the midostaurin dose escalation arm, in which patients started midostaurin at 100 mg bid for two weeks, then, in the absence of Grade 3 or 4 adverse events, increased their dose by 50mg bid every two weeks to a maximum dose of 300 mg bid. Midostaurin monotherapy was continued until disease progression or unacceptable toxicity. The other 13 patients were enrolled to evaluate the effects of combining midostaurin with itraconazole. These patients received midostaurin at 100 mg bid for the first two days, followed by 50 mg bid. On cycle 1, day 22, itraconazole was started at a dose of 100 mg bid. Both study medications were continued until disease progression or unacceptable toxicity. Safety evaluations were conducted at least weekly, and marrow evaluations were performed at the beginning of every 28-day treatment cycle and at the time of treatment discontinuation. The

Clinical Review

Ashley Ward, MD
NDA 207997
Rydapt® (midostaurin)

primary efficacy endpoint was investigator-determined best clinical response measured on or after cycle 1, day 8, according to NCI definitions for AML (Cheson 1990) and WHO-IWG for MDS (Cheson, 2000). The study is complete.

6.4.2. Study Results

Compliance with Good Clinical Practices

The applicant provided attestation that these studies were conducted in accordance with U.S. regulations governing the protection of human subjects, institutional review boards, and the obligations of clinical investigators in accordance with good clinical practice (GCP).

Financial Disclosure

A summary of financial disclosures for Studies A2104, A2104E1 and A2014E2 are provided in the appendix (Section 13.2). The applicant was unable to obtain financial disclosure information from 1 U.S. sub-investigator. The principal investigator at one study site (b) (6) on Study A2104E1 reported a grant in excess of \$25,000 from the study sponsor to the investigator to fund ongoing research. His study site enrolled (b) (6) of the 95 subjects (b) (6) % on Study A2014E1. No financial interests or arrangements were reported in the other investigators.

Patient Disposition

On Study A2104, the median duration of treatment was 35.5 days. Nine patients (45%) received a maximum of one cycle of midostaurin. Only one patient received ≥ 6 cycles of midostaurin. All patients discontinued the study, the majority due to lack of efficacy (n=13, 65%).

On Study A2104E1, the median duration of treatment was 46 days in FLT3 mutated patients and 53 days in FLT3 wild type patients. Most patients (n=55, 58%) received 1-2 cycles of midostaurin. Twelve patients received ≥ 6 cycles of midostaurin. All patients discontinued the study except for the two patients that were rolled over onto Study A2104E2. The most frequent reason for discontinuation was lack of efficacy (n=62, 65%).

On Study A2104E2, the median duration of treatment was 29 days in the inpatient dose escalation arm and 24 days in the midostaurin + itraconazole arm. Most patients (n=16, 55%) received 1-2 cycles of midostaurin. Six patients received ≥ 6 cycles of midostaurin. All patients discontinued the study, primarily due to lack of efficacy (13, 45%) or adverse events (8, 28%).

Efficacy Results

Key response data from Studies A2014, A2014E1 and A2104E2 as reported by the applicant are summarized shown in Table 18.

Clinical Review

Ashley Ward, MD

NDA 207997

Rydapt® (midostaurin)

Table 18: Studies A2104, A2104E1 and A2104E2 – Complete and Partial Responses

Study	Baseline FLT3 Status	N	Complete Response	Partial Response
A2104	Mutated	20	0	0
A2014E1	Mutated	35	0	1 (3%)
	Wild Type	57	0	0
A2014E2	Mutated	16	0	0
	Wild Type	13	1 (8%)	0

Source: Slides provided by the applicant for the application orientation meeting in September 2016.

Reviewer comment: Studies A2104, A2104E1 and A2104E2 provide substantial evidence of lack of efficacy of midostaurin monotherapy in patients with de novo and relapsed/refractory AML.

7 Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

7.1.1. Primary Endpoints

Midostaurin, administered at 50 mg by mouth twice daily on days 8-21 of each cycle of induction (daunorubicin and cytarabine) and consolidation (high-dose cytarabine) chemotherapy to patients with previously untreated FLT3+ AML confers a survival advantage when compared to placebo (HR 0.77, p=0.016). Due to plateauing of the OS curves, estimates of median OS are not reliable, but the restricted mean survival advantage ranges from 2.6 - 5.4 months depending on time of follow-up. Although the pivotal study was conducted in patients age < 60, data from an investigator-sponsored trial of midostaurin in combination with intensive chemotherapy in older adults with AML lend support for a broad indication without age restriction.

Data from several studies consistently showed that midostaurin does not produce any complete responses when administered as monotherapy across a wide range of doses in patients with previously untreated or relapsed/refractory AML.

7.1.2. Secondary and Other Endpoints

In the pivotal study, event-free survival (8.2 months vs 3.6 months) and rates of complete response by day 60 (59% vs 54%) were both also higher on the midostaurin arm, revealing consistent benefit of midostaurin in combination with chemotherapy in untreated AML.

Clinical Review

Ashley Ward, MD

NDA 207997

Rydapt® (midostaurin)

7.1.3. Dose and Dose-Response

Study A2106 was the only dose-ranging study in patients with previously untreated AML. As summarized in Section 6.2.2, administration of midostaurin at 50 mg bid on days 8-21 of each cycle of induction and consolidation chemotherapy was better tolerated and more effective than higher doses or when administered concomitantly (during week 1) with chemotherapy. Literature search reveals biologic support for these observations, independent of toxicity: experiments with FLT3 mutated cell lines treated with lestaurtinib (a multikinase inhibitor somewhat related to midostaurin), showed synergy when lestaurtinib was given in combination with or after chemotherapy agents, but antagonism when administered before chemotherapy agents (Levis et al Blood 2003). Dose modifications for toxicity or lack of efficacy were not studied in patients with previously untreated AML eligible for standard intensive chemotherapy.

7.1.4. Onset, Duration, and Durability of Efficacy Effects

Most of the CRs that were observed on Study A2301 occurred after 1 or 2 cycles of induction, which is typical for intensive chemotherapy regimens. Duration of response is relatively uninformative since this trial had a high rate of patients who went on to HSCT, but the study demonstrated a statistically significant overall survival advantage of 2.6 to 5.4 months (depending on follow-up time) with the addition of midostaurin to a standard chemotherapy regimen in previously untreated AML. See Section 6.2.2 for a discussion of the lack of evidence for continuing midostaurin beyond induction and consolidation therapy in this indication.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

While patients who enroll on clinical trials tend to differ in various ways from the broader population of patients with cancer, there is no indication that efficacy would be lower in patient populations underrepresented on Study A2301. As patients receiving intensive induction and consolidation therapy for AML are typically treated as inpatients, compliance in the post-market setting is expected to be high.

7.3. Integrated Assessment of Effectiveness

The efficacy of midostaurin in AML has been established, based primarily on the results of a single randomized, phase III study in patients age 18-60 with previously untreated FLT3+ AML, in which patients who received 50 mg bid of midostaurin sequentially in combination with intensive chemotherapy had longer overall survival than patients who received placebo (HR 0.77, p=0.019). The median OS estimates are uninformative due to plateau of the survival curves, but the RMST analysis demonstrates that midostaurin confers a survival advantage of approximately 2.6 to 5.4 months. As the study did not re-randomize patients at the start of

Clinical Review

Ashley Ward, MD

NDA 207997

Rydapt® (midostaurin)

maintenance therapy, and the OS benefit appears to be explained primarily by treatment effects observed during the period of intensive chemotherapy, Study A2301 does not support maintenance dosing of midostaurin.

The dose and regimen used in the pivotal study are supported by the data from Study A2106, in which patients who received higher doses of midostaurin (100 mg bid) in combination with chemotherapy experienced worse outcomes. Although Study A2301 was restricted to patients age ≤ 60 years, the expansion of the indication to include adult patients who are candidates for intensive chemotherapy regardless of age is supported by the data from Study ADE02T, in which patients age > 60 appeared to have improved survival with the proposed regimen relative to patients age ≤ 60 , compared to historical data. Data from Studies A2014, A2014E1 and A2104E2 demonstrate lack of efficacy of midostaurin as monotherapy in patients with de novo and relapsed/refractory AML, and support a limitation of use statement in the product label.

8 Review of Safety

8.1. Safety Review Approach

Although review emphasis was placed on safety data from Study A2301, results from all 24 trials listed in Table 2 were used to support the analysis of safety. Pooled safety data from all trials of midostaurin monotherapy and the two trials of midostaurin in combination with intensive chemotherapy for AML are summarized where relevant in Section 8.4.

Several studies for which databases were not available were also considered relevant for the proposed indication. Patients with previously untreated AML on Study ADE02T (n=143) as well as 22 healthy volunteers on Study 001 and 1 healthy volunteer on study A2120 were exposed to midostaurin on these studies. While they are not included in the pooled analysis, portions of the clinical study reports from these studies are also summarized where relevant in Section 8.4.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

A total of 1,298 patients were exposed to midostaurin across the midostaurin clinical development program and included in the pooled safety analysis (Table 19).

Clinical Review

Ashley Ward, MD

NDA 207997

Rydapt® (midostaurin)

Table 19: Pooled Safety Database – Safety Population, Size and Denominators

Clinical Trial Groups	Midostaurin (N=1,298)	Active Control (N=379)	Placebo (N=131)
Controlled trials conducted for this indication ¹	345	335	0
Uncontrolled trials conducted for this indication ²	68	0	0
Uncontrolled trials conducted for other malignant indications ³	359	0	0
Healthy volunteers and patients without cancer ⁴	526	44	131

Source: FDA analysis

¹ Study A2301

² Study A2106

³ Studies A2104, A2104E1, A2104E2, D2201, A2213, A0002, A0006, and A2114

⁴ Studies A1101, A2107, A2108, A2109, A2110, A2111, A2112, A2113, A2116, C99-001, and A0003

A summary of exposure to midostaurin in Study A2301 and in the pooled safety database is provided in Table 20. In Study A2301, the median duration of exposure to midostaurin was 1.4 months (mean 4.5 months), with a maximum exposure time of 18.9 months. In the pooled safety database, the median duration of exposure was 0.9 months (mean 4.4 months), with a maximum duration of exposure of 87.3 months. Fifty-two patients were exposed to midostaurin for greater than 2 years. Most of these patients (48, 92%) had aggressive systemic mastocytosis or mast cell leukemia, the other 4 had relapsed or refractory AML/MDS.

Table 20: Duration of Exposure¹ to Midostaurin in the Safety Population

	0-3 months	>3 to 6 months	>6 to 12 months	> 12 months
Study A2301 (n=345)	227	23	22	73
Pooled safety database (n=1,298)	982	111	56	149

Source: FDA analysis

¹ Irrespective of dose or regimen

Forty-three percent (n=554) of the patients in the pooled safety database received a total of 100 mg of midostaurin daily, the same dose administered on Study A2301 (Table 21). Another 459 (35%) received >100 mg daily and 285 (22%) received <100 mg daily.

Clinical Review

Ashley Ward, MD

NDA 207997

Rydapt® (midostaurin)

Table 21: Planned Total Daily Dose of Midostaurin in the Safety Population

Planned total daily dose	Study A2301 (n=345)	Pooled safety database (n=1,298)
12.5 mg	0	3
25 mg	0	18
50 mg	0	256
75 mg	0	8
100 mg	345	554
150 mg	0	135
200 mg	0	241
225 mg	0	51
300 mg	0	16
Inpatient dose escalation	0	16

Source: FDA analysis

8.2.2. Relevant characteristics of the safety population:

Demographic information for patients enrolled on Study A2301 as well as those that compose the entire pooled safety database is summarized in Table 22. For Study A2301, the demographics of the safety population on the midostaurin and control arms are virtually identical to those of the efficacy population. The two arms of the study are well-balanced, except that the placebo arm has more females than the midostaurin arm (59% vs 51%), and the Eastern Cooperative Oncology Group (ECOG) performance status is slightly worse, on average, on the placebo arm than in the midostaurin arm. The demographics of the pooled safety database are very similar to that of Study A2301, except that males are comparatively over-represented, and the pooled safety database comprises patients with a wider age range.

Table 22: Demographics of the Safety Population

	Study A2301 Midostaurin (n=345)	Study A2301 Placebo (n=335)	Pooled Safety Database ¹ (n=1,298)
Sex			
Female	176 (51%)	196 (59%)	532 (41%)
Male	169 (49%)	139 (41%)	766 (59%)
Age (years)			
Mean	45	46	49
Median	46	49	49
Min, Max	19, 59	18, 60	0.5, 94
ECOG Performance Status²			
0	162 (47%)	133 (40%)	
1	150 (43%)	160 (48%)	
2	27 (8%)	32 (10%)	
3	5 (1%)	8 (2%)	
4	1 (<1%)	2 (<1%)	

Clinical Review

Ashley Ward, MD

NDA 207997

Rydapt® (midostaurin)

	Study A2301 Midostaurin (n=345)	Study A2301 Placebo (n=335)	Pooled Safety Database ¹ (n=1,298)
Race			
White	140 (41%)	121 (36%)	890 (69%)
Unknown or not reported ¹	189 (55%)	199 (59%)	193 (15%)
Black or African-American	7 (2%)	9 (3%)	124 (10%)
Asian	7 (2%)	5 (1%)	48 (4%)
Other or more than one race	2 (<1%)	1 (<1%)	43 (3%)
Ethnicity			
Unknown, other, or not reported ¹	237 (69%)	227 (68%)	1183 (91%)
Hispanic or Latino	9 (3%)	6 (2%)	16 (1%)
Not Hispanic or Latino	99 (29%)	102 (30%)	99 (8%)
Region			
North America			
United States	112 (32%)	101 (30%)	518 (40%)
Canada	4 (1%)	8 (2%)	9 (<1%)
Non-North America	229 (66%)	226 (67%)	771 (59%)
Weight Group			
< 55 kg	20 (6%)	19 (6%)	83 (6%)
55-100 kg	277 (80%)	269 (80%)	1073 (83%)
> 100 kg	48 (14%)	47 (14%)	116 (9%)
Missing	0	0	26 (2%)

Source: FDA analysis

¹ Includes patients treated with midostaurin only

² Data not relevant or collected for non-oncology studies

Due to the substantial amount of missing baseline laboratory data, missing normal lab ranges, and implausible lab values noted in the laboratory datasets provided by the applicant, it was not possible to determine the number of patients on Study A2301 and in the pooled safety database that had baseline hepatic or renal dysfunction.

8.2.3. Adequacy of the safety database:

The size of the safety database is adequate to provide a reasonable estimate of adverse reactions that may be observed with midostaurin, and the duration of treatment is adequate to allow assessment of adverse reactions over time. Study A2301 randomizes midostaurin against placebo, which is very helpful in understanding the contribution of the underlying disease to adverse reactions. Study A2301 and the safety pool are representative of typical patients with AML that participate on clinical trials. However, non-white patients are under-represented compared to the overall AML population in the United States. Please see section 8.3.1 for a discussion of the quality of the safety database.

Clinical Review

Ashley Ward, MD

NDA 207997

Rydapt® (midostaurin)

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

On the pivotal study A2301, the collection of adverse events and severe adverse events differed between clinical trial sites in North America and those in other regions due to differences in sponsorship. This discrepancy in adverse event collection was not pre-specified by the protocol. Clinical trial sites in North America collected all grade ≥ 3 adverse events, but only collected grade 1 and 2 adverse events for 13 pre-specified adverse events (neutrophils/granulocytes, platelets, hemoglobin, febrile neutropenia, ataxia, rash/desquamation, diarrhea, nausea, vomiting, keratitis, fatigue, left ventricular systolic dysfunction and mucositis/stomatitis). Clinical trial sites outside of North America collected all adverse events regardless of grade. Adverse events, regardless of clinical trial site, were recorded by reporting period (cycle) but start and stop dates were not collected. If an event happened intermittently or repeatedly within one reporting period, the site was only required to report the worse National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) grade observed for that event during the reporting period. Seriousness of the adverse events was not captured by the investigator on the CRF, although serious adverse events (with the exception of myelosuppression, febrile neutropenia, nausea, vomiting and hospitalization resulting from these) were required to be reported to the study sponsor and were collected in the Novartis safety database.

The collection of post-baseline laboratory values was initiated after the start of the study, and the data were collected retrospectively for only those sites outside of North America. The database of laboratory values provided by the sponsor is of poor quality, with many missing baseline values, missing normal lab ranges, and implausible lab values recorded.

8.3.2. Categorization of Adverse Events

Adverse events (AE) were coded by the Investigators in the CRF using the Medical Dictionary for Regulatory Activities (MedDRA) version 6.0, and re-coded by Novartis using the latest MedDRA version 18.1. Adverse events were graded by the investigators in the CRF using the NCI-CTCAE for AEs version 3.0 until Oct-2011, and thereafter using version 4.0. The seriousness for each AE was not recorded in the CRF.

The FDA compared the verbatim adverse event term with the MedDRA preferred term for all adverse events reported on Study A2301 and did not identify any irregularities. The applicant did not group preferred terms in their analysis. The FDA grouped related preferred terms for all analyses; a listing of these grouped terms can be found in Appendix 13.3. Standard MedDra Query (SMQ) analysis was performed using MAED, and no additional safety signals were identified beyond those discussed below.

Clinical Review

Ashley Ward, MD

NDA 207997

Rydapt® (midostaurin)

8.3.3. Routine Clinical Tests

See Section 6 for a description of the frequency of clinical assessments for the studies conducted in patients with AML. The frequency of clinical assessments in the other studies included in the safety pool varied, but is adequate to assess the risks of serious safety events.

8.4. Safety Results

8.4.1. Deaths

The FDA identified 398 deaths among the 1,298 subjects exposed to midostaurin (Table 23). Most deaths occurred more than 28-30 days after the last dose of midostaurin (304 subjects, 23%), leaving 94 on-treatment deaths.

Table 23: Deaths in the Safety Pool

Population / Treatment	On or within 30 days of last dose of midostaurin	More than 28 days after last dose of midostaurin ¹
AML / Combination (N=143)	16 (4%)	185 (49%)
AML/MDS/ALL / Monotherapy (N=164)	52 (32%)	66 (40%)
ASM/MCL / Monotherapy (N=142)	26 (18%)	52 (37%)
Other indications / Mixed (N=53)	0	1 (2%)
Healthy Volunteers / Mixed (N=171)	0	0
Total (N=1,298)	94 (7%)	304 (23%)

Source: FDA analysis

¹ More than 30 days after the last dose of midostaurin for subjects on Study A2301

The applicant identified the underlying malignancy as the cause of death in 46 of the 94 on-treatment deaths (49%) in subjects exposed to midostaurin. The other frequently reported causes of on-treatment death were sepsis (13 subjects), cardiac and/or respiratory failure (7 subjects), multiorgan failure (6 subjects), cardiac arrest (4 subjects) and pneumonia (3 subjects).

The FDA identified 347 deaths among the 680 subjects on Study A2301 who received at least one dose of midostaurin or placebo. Most deaths occurred more than 30 days after the last dose of midostaurin (147 subjects, 43%) or placebo (164 subjects, 49%) (Table 24).

Table 24: Study A2301 – Deaths by Treatment Phase

Study Phase	Midostaurin (N=345)	Placebo (N=335)
Induction	14 (4%)	11 (3%)
Consolidation	1 (<1%)	9 (3%)
Maintenance	0	1 (<1%)
> 30 days after last dose of midostaurin/placebo	147 (43%)	164 (49%)

Source: FDA analysis

Clinical Review

Ashley Ward, MD

NDA 207997

Rydapt® (midostaurin)

The FDA reviewed individual patient narratives from the remaining 36 subjects to confirm the cause of on-treatment deaths. Narratives were not available for deaths that occurred more than 30 days after the last dose of midostaurin. In general, the narratives were poorly written, consisting of a reiteration in paragraph form of labs, adverse events and concomitant medications already provided in data sets. In patients with AML, particularly those treated with intensive chemotherapy, root cause of death early in the course of treatment was generally difficult to determine due to the high incidence of baseline comorbid conditions, many caused by the underlying disease. With those caveats, the FDA concluded that 12 of the 15 deaths (80%) on the midostaurin arm and 14 of the 21 of the deaths (67%) on the placebo arm were likely attributable to complications of infection (Table 25). The other three patients on the midostaurin arm died from pulmonary hemorrhage, progressive disease and hemorrhagic colitis, none of which are unusual causes of death in patients with AML receiving intensive chemotherapy.

Table 25: Study A2301 – Causes of Deaths Occurring Within 30 Days of Treatment

Arm	Subject	Day of Death	FDA Root COD	Investigator COD
Midostaurin	5017-119613	12	Infection	Pneumonitis, Acute respiratory failure, Septic shock
Midostaurin	2918-117246	14	Infection	Sepsis
Midostaurin	5036-115463	16	Infection	Sepsis, Vomiting
Midostaurin	5017-119017	22	Infection	Myocardial infarction
Midostaurin	0535-113109	23	Infection	Colitis
Midostaurin	2920-113671	25	Infection	Sepsis
Midostaurin	5239-123150	25	Infection	Pulmonary hemorrhage
Midostaurin	5022-125363	25	Infection	Infectious colitis
Midostaurin	2902-117170	42	Infection	ARDS
Midostaurin	5453-123147	43	Infection	Cardiac arrest
Midostaurin	0176-126204	45	Pulmonary hemorrhage	Multi-organ failure
Midostaurin	5487-120166	48	AML	AML
Midostaurin	0342-114365	49	Infection	Sepsis
Midostaurin	2953-113990	56	Hemorrhagic colitis	Multi-organ failure
Midostaurin	5071-127110	96	Infection	Neutropenic sepsis
Placebo	5982-126679	13	Unknown	Sudden death
Placebo	2961-125715	15	Infection	Sepsis, Hypokalemia
Placebo	2942-114452	20	Infection	Sepsis
Placebo	0176-124273	20	Infection	Sepsis
Placebo	5021-127326	21	Infection	Sepsis
Placebo	5028-122540	22	Infection	Opportunistic infection
Placebo	5034-119534	24	Infection	Septic shock
Placebo	5029-116863	30	Infection	Sepsis
Placebo	2923-118050	38	Infection	Pulmonary hemorrhage
Placebo	5210-127203	47	PRES	Cerebral hemorrhage
Placebo	2938-115109	58	Infection	Infectious colitis

Clinical Review

Ashley Ward, MD

NDA 207997

Rydapt® (midostaurin)

Arm	Subject	Day of Death	FDA Root COD	Investigator COD
Placebo	0006-114316	81	Infection	Multi-organ failure
Placebo	2937-126394	93	AML	Hemorrhagic stroke
Placebo	0525-126654	124	Infection	Large intestine perforation
Placebo	2913-113776	143	Infection	Multi-organ failure
Placebo	5982-124330	144	Cardiac arrest	Myocardial ischemia
Placebo	0372-115835	147	Hemorrhagic stroke	Hemorrhagic stroke
Placebo	0372-116234	160	Infection	Sepsis
Placebo	2902-119309	179	AML	AML
Placebo	2911-116162	188	Infection	Multi-organ failure
Placebo	5048-122525	233	AML	AML

Source: FDA analysis

Abbreviations: COD, cause of death; ARDS, acute respiratory distress syndrome; PRES, posterior reversible encephalopathy syndrome

On study ADE02T, 16 patients died during treatment with midostaurin or in the 30-day follow-up period (2 of these deaths occurred prior to initiation of midostaurin). Two patients died in maintenance, one of a hemorrhagic stroke and the other of relapsed disease. The other 14 patients died during induction (n=12) or consolidation (n=2). Cause of death in these patients was infection (n=9), hemorrhagic stroke (n=2), pulmonary hemorrhage (n=1), myocardial ischemia (n=1), or sudden cardiac death (n=1). While more patients age > 60 years died during study treatment (n=10, 22%) than patients age ≤ 60 (n=6, 6%), the addition of midostaurin to intensive chemotherapy did not appear to increase the early death rate in older patients compared to the 11-22% observed on other studies (Brandwein et al, Am J Blood Res 2013).

8.4.2. Serious Adverse Events

The seriousness of adverse events was not captured on CRFs by the investigators on Study A2301. Instead, serious adverse events (SAE) were reported individually to the study sponsor who captured them in a separate safety database. For this submission, the applicant manually reconciled adverse events in the clinical trial database with those reported in the company's safety database to flag events in the clinical trial database that were reported as serious. Myelosuppression, febrile neutropenia, nausea, vomiting and hospitalization from these were exempt from reporting, and thus are not included in the applicant's analysis of SAE. The applicant performed several sensitivity analyses in an effort to mitigate the inherent risk of under-reporting of SAE, including all non-reconciled grade 3-4 adverse events in the clinical data base without a match in the safety database (excluding those exempt from reporting as described above) and all of the non-reconciled adverse events in the safety database. The applicant stated that results of these sensitivity analyses did not change their conclusion that the overall incidence of serious adverse events, the incidence of serious infections, and the incidence of serious episodes of pneumonia and pneumonitis were similar between the two treatment groups (Study A2301 Clinical Study Report Section 12.3.6 dated July 5, 2016).

Clinical Review

Ashley Ward, MD

NDA 207997

Rydapt® (midostaurin)

The applicant identified 34 fatal adverse events in 30 subjects that occurred on study therapy or within 30 days after the last dose of midostaurin/placebo on Study A2301. Fourteen subjects (4%) on the midostaurin arm and 16 subjects (5%) on the placebo arm experienced at least one fatal adverse event. The most commonly reported fatal adverse events on the midostaurin arm were sepsis (4 subjects), colitis (3 subjects) and multiorgan failure (2 subjects). The most commonly reported fatal adverse events on the placebo arm were sepsis (6 subjects) and multiorgan failure (3 subjects).

FDA performed an analysis of serious adverse events reported in the clinical trial database (which is subject to the limitations described above) using grouped preferred terms (see Appendix Section 13.3). The most frequently occurring ($\geq 5\%$) serious adverse events were febrile neutropenia (107, 16%), sepsis (67 (10%), neutrophil count decreased (62, 9%), pneumonia (60, 9%), platelet count decreased (54, 8%), diarrhea (40, 6%), and device-related infection (40, 6%). The only serious adverse events occurring $\geq 2\%$ more frequently on the midostaurin arm than the placebo arm were device-related infection (7% vs 4%), hypotension (4% vs 1%), hypertransaminasemia (3% vs 1%), rash (3% vs 1%) and pneumonitis (6% vs 4%).

The FDA did not analyze serious adverse events in the pooled safety database, as the seriousness of events was not collected consistently across studies.

On study ADE02T, 94 patients (65%) experienced a serious adverse event. Serious adverse events were modestly more frequent in patients age > 60 years ($n=33$, 72%) than in those ≤ 60 years of age ($n=61$, 62%). SAEs occurring in $\geq 5\%$ of patients were sepsis ($n=11$), renal failure ($n=10$), pyrexia ($n=9$), diarrhea ($n=8$), prolonged QT interval ($n=7$), ALT elevation ($n=7$) and platelet count decreased ($n=7$).

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

On Study A2301, 57 patients (8%) discontinued the study due to an adverse event. Adverse events leading to discontinuation in more than one patient on the midostaurin arm are listed in Table 26, in order of frequency on the midostaurin arm. The most frequent reasons patients discontinued study treatment on the midostaurin arm were elevated transaminases ($n=4$), rash ($n=4$) and vomiting ($n=3$).

Clinical Review

Ashley Ward, MD

NDA 207997

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Table 26: Study A2301 – Adverse Events Leading to Discontinuation in ≥ 2 Patients

Preferred Term ¹	Midostaurin (N=345)	Placebo (N=335)
Hypertransaminasemia	4 (1%)	2 (<1%)
Rash	4 (1%)	0
Vomiting	3 (1%)	1 (<1%)
Arrhythmia	2 (<1%)	1 (<1%)
Myocardial ischemia	2 (<1%)	1 (<1%)
Nausea	2 (<1%)	1 (<1%)
Renal insufficiency	2 (<1%)	0

Source: FDA analysis

¹ Includes grouped terms (see Appendix 13.3)

On study ADE02T, 41 patients (28%) discontinued the study due to an adverse event. Discontinuations for AEs were modestly more frequent in patients age > 60 years (n=15, 33%) than in those ≤ 60 years of age (n=26, 27%). AEs leading to treatment discontinuation in > 2 patients were graft-versus-host disease (n=5), nausea (n=3) and platelet count decreased (n=3).

8.4.4. Treatment Emergent Adverse Events and Adverse Reactions

Treatment-emergent adverse events (TEAE) occurring either on study treatment or within 30 days after discontinuation of study treatment on Study A2301 are summarized by system organ class (SOC) in Table 27. All but one patient on the study experienced an adverse event, which is expected for patients with AML who are treated with intensive chemotherapy. SOCs in which the frequency of AEs of any grade was ≥ 2% higher in the midostaurin arm included the gastrointestinal system disorders (Δ3%), infections and infestations (Δ2%), injuries, poisonings and procedural complications (Δ3%), musculoskeletal and connective tissue disorders (Δ3%), and psychiatric disorders (Δ2%).

Table 27: Study A2301 – TEAE Occurring in ≥ 10% of Patients by System Organ Class¹

System Organ Class ¹	Midostaurin (n=345)		Placebo (n=335)	
	All grades	Grade 3+	All grades	Grade 3+
Investigations	343 (99%)	343 (99%)	334 (100%)	334 (100%)
Blood and lymphatic system	342 (99%)	341 (99%)	334 (100%)	331 (99%)
Gastrointestinal	332 (96%)	98 (28%)	313 (93%)	102 (30%)
General & administrative site conditions	287 (83%)	47 (14%)	283 (84%)	58 (17%)
Skin and subcutaneous tissue	275 (80%)	57 (17%)	267 (80%)	35 (10%)
Infections and infestations	242 (70%)	188 (54%)	228 (68%)	181 (54%)
Injury, poisoning and proc. complications	215 (62%)	43 (12%)	198 (59%)	51 (15%)
Metabolism and nutrition	192 (56%)	110 (32%)	198 (59%)	124 (37%)
Respiratory, thoracic and mediastinal	167 (48%)	55 (16%)	164 (49%)	50 (15%)
Nervous system	156 (45%)	34 (10%)	157 (47%)	32 (10%)

Clinical Review

Ashley Ward, MD

NDA 207997

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System Organ Class ¹	Midostaurin (n=345)		Placebo (n=335)	
	All grades	Grade 3+	All grades	Grade 3+
Vascular	124 (36%)	40 (12%)	122 (36%)	30 (9%)
Musculoskeletal and connective tissue	121 (35%)	25 (7%)	108 (32%)	11 (3%)
Hepatobiliary	76 (22%)	27 (8%)	89 (27%)	29 (9%)
Cardiac	82 (24%)	28 (8%)	77 (23%)	19 (6%)
Psychiatric	78 (23%)	3 (1%)	69 (21%)	4 (1%)
Eye	71 (21%)	5 (1%)	68 (20%)	4 (1%)
Renal and urinary	63 (18%)	19 (6%)	56 (17%)	13 (4%)
Immune system	51 (15%)	6 (2%)	47 (14%)	6 (2%)
Reproductive system and breast	39 (11%)	11 (3%)	43 (13%)	8 (2%)

Source: FDA analysis

¹ Includes only SOCs for which > 10% of patients experienced an adverse event

² Includes grouped terms (see Appendix 13.3)

Treatment-emergent adverse events occurring either on study treatment or within 30 days after discontinuation of study treatment on Study A2301 are summarized by preferred term in Table 28. AEs, regardless of grade, occurring in at least 10% of patients and at least 2% more frequently on the midostaurin arm are included in the table. Nausea (Δ 9%), device-related infection (Δ 6%), vomiting (Δ 5%) and petechiae (Δ 5%) were the only adverse events that occurred at least 5% more frequently in the midostaurin arm than in the placebo arm. The severity of rash, device-related infection and musculoskeletal pain appeared to be higher on the midostaurin arm, with $\geq$ 5% more grade $\geq$ 3 events reported than on the placebo arm. The spectrum, frequency and severity of TEAE observed on Study A2301 are consistent with those expected in the general AML population receiving intensive chemotherapy.

Table 28: Study A2301 – TEAE in $\geq$ 10% of Patients and $\geq$ 2% More Frequently on the Midostaurin Arm by Preferred Term

Preferred Term ¹	Midostaurin (n=345)		Placebo (n=335)	
	All grades	Grade 3+	All grades	Grade 3+
Anemia	336 (97%)	321 (93%)	327 (98%)	297 (89%)
Nausea	285 (83%)	20 (6%)	248 (74%)	34 (10%)
Rash	238 (69%)	50 (14%)	239 (71%)	28 (8%)
Vomiting	213 (62%)	11 (3%)	191 (57%)	15 (4%)
Mucositis	208 (60%)	40 (12%)	193 (58%)	46 (14%)
Headache	124 (36%)	9 (3%)	109 (33%)	10 (3%)
Hypertransaminasemia	117 (34%)	51 (15%)	106 (32%)	36 (11%)
Musculoskeletal pain	98 (28%)	19 (6%)	87 (26%)	5 (1%)
Petechiae	89 (26%)	4 (1%)	69 (21%)	2 (1%)
Hyperglycemia	79 (23%)	24 (7%)	68 (20%)	20 (6%)
Device-related infection	74 (21%)	56 (16%)	51 (15%)	35 (10%)

Clinical Review

Ashley Ward, MD

NDA 207997

Rydapt® (midostaurin)

Preferred Term ¹	Midostaurin (n=345)		Placebo (n=335)	
	All grades	Grade 3+	All grades	Grade 3+
Epistaxis	73 (21%)	9 (3%)	60 (18%)	2 (1%)
Upper respiratory tract infection	58 (17%)	14 (4%)	45 (13%)	14 (4%)
Hypotension	54 (16%)	19 (6%)	46 (14%)	11 (3%)
Arthralgia	39 (11%)	1 (<1%)	20 (6%)	1 (<1%)
Hemorrhoids	36 (10%)	5 (1%)	27 (8%)	0
Insomnia	36 (10%)	0	24 (7%)	0
Hyperhidrosis	36 (10%)	0	22 (7%)	0
Cellulitis	32 (9%)	16 (5%)	23 (7%)	14 (4%)
Thrombosis	19 (6%)	12 (3%)	10 (3%)	8 (2%)
Weight increased	19 (6%)	3 (1%)	8 (2%)	1 (0%)

Source: FDA analysis

¹ Includes grouped terms (see Appendix 13.3)

Study A2301 included a maintenance phase in which patients still in remission received either midostaurin or placebo monotherapy. The most commonly occurring TEAEs on the maintenance phase of the study are summarized in Table 29 as a percentage of patients who entered maintenance therapy. Nausea occurred more frequently on the midostaurin arm than on the placebo arm (53% vs 22%), as did vomiting (24% vs 11%), but only one patient on each arm discontinued study therapy due to nausea/vomiting. With the exception of grade ≥ 3 elevated transaminases, which occurred in 5% of patients on both treatment arms, and grade ≥ 3 lymphopenia, which occurred in 7% of the patients on the midostaurin arm (vs 2% on the placebo arm), most adverse events during maintenance were mild to moderate in intensity.

Table 29: Study A2301 – TEAE in $\geq 10\%$ of Patients and $\geq 2\%$ More Frequently on the Midostaurin Arm During Maintenance Therapy

Preferred Term ¹	Midostaurin (n=120)		Placebo (n=85)	
	All grades	Grade 3+	All grades	Grade 3+
Nausea	64 (53%)	0	19 (22%)	0
Diarrhea	36 (30%)	1 (1%)	19 (22%)	2 (2%)
Fatigue	36 (30%)	1 (1%)	24 (28%)	1 (1%)
Hypertransaminasemia	33 (28%)	6 (5%)	16 (19%)	4 (5%)
Vomiting	29 (24%)	0	9 (11%)	0
Musculoskeletal pain	23 (19%)	2 (2%)	14 (16%)	0
Hyperglycemia	22 (18%)	3 (3%)	11 (13%)	5 (6%)
Lymphopenia	17 (14%)	8 (7%)	6 (7%)	2 (2%)
Leukopenia	17 (14%)	3 (3%)	8 (9%)	0
Headache	16 (13%)	0	9 (11%)	0
Abdominal pain	13 (11%)	1 (1%)	7 (8%)	0

Source: FDA analysis

¹ Includes grouped terms (see Appendix 13.3)

Clinical Review

Ashley Ward, MD

NDA 207997

Rydapt® (midostaurin)

As a sensitivity analysis, the FDA analyzed AEs in the pooled safety database, excluding patients enrolled on Study A2301 (which otherwise dominated the results due to the high frequency of toxicities associated with intensive chemotherapy). This analysis was not performed using grouped preferred terms. Table 30 lists AEs occurring in $\geq 10\%$ of the patients in the safety pool.

Table 30: Safety Pool – Adverse Events Occurring in $\geq 10\%$ of Patients

Preferred Term	Any Grade (n=918)	Grade 3-4 (n=918)
Nausea	488 (53%)	26 (3%)
Diarrhea	353 (38%)	26 (3%)
Vomiting	321 (35%)	22 (2%)
Headache	197 (21%)	11 (1%)
Fatigue	158 (17%)	28 (3%)
Pyrexia	149 (16%)	24 (3%)
Anemia	137 (15%)	91 (10%)
Thrombocytopenia	125 (14%)	104 (11%)
Constipation	123 (13%)	3 (<1%)
Abdominal pain	112 (12%)	13 (1%)
Peripheral edema	111 (12%)	7 (1%)
Hypokalemia	104 (11%)	35 (4%)
Cough	102 (11%)	6 (1%)
Dyspnea	96 (10%)	25 (3%)
Febrile neutropenia	92 (10%)	81 (9%)
Dizziness	90 (10%)	3 (<1%)

Source: FDA analysis

Note: Analysis excludes patients on Study A2301

The results of this analysis demonstrate a safety profile generally consistent with that observed on Study A2301, with the exception of cough and dyspnea, which were not prominent toxicities on the midostaurin arm compared to the placebo arm on Study A2301. The applicant proposed a Warning and Precaution of pulmonary toxicity / interstitial lung disease. In a response (dated December 29, 2016, SDN 61) to an FDA information request, the applicant reported 57 cases of possible interstitial lung disease from patients in the safety pool based on an Interstitial Lung Disease MedDRA standardized query. The majority of these cases (37, 65%), and all but one of the grade ≥ 3 events, occurred on Study A2301. FDA analysis of the safety data from Study A2301 using grouped terms did not reveal an imbalance between treatment arms with respect to pneumonitis (12% in both arms) or pneumonia (17% on the midostaurin arm and 18% on the placebo arm). All other cases occurred on other studies of midostaurin in patients with AML, advanced systemic mastocytosis, or mast cell leukemia.

Reviewer comment: Although lung toxicity does not appear to be a prominent toxicity of midostaurin in patients with untreated AML based on findings from Study A2301, given the

Clinical Review

Ashley Ward, MD

NDA 207997

Rydapt® (midostaurin)

lung findings observed in the nonclinical toxicology findings, and the observation of respiratory symptoms (cough, dyspnea) in the pooled safety analysis, this reviewer is not opposed to the sponsor's proposal of a Warning and Precaution for possible pulmonary toxicity in the product label.

8.4.5. Laboratory Findings

As the laboratory datasets submitted by the applicant were poorly defined, and missing many test results, normal ranges and test grades, and there appeared to be inconsistent application of the implausible result flag, the FDA was unable to independently analyze all laboratory findings on Study A2301 and in the safety pool. However, the FDA reproduced the analysis for selected lab abnormalities and results were generally consistent with those of the applicant.

On Study A2301, the applicant found that the only chemistry abnormality that was new or worsening in at least 10% of patients and at least 2% more frequently on the midostaurin arm was hypernatremia (21% vs 16%). Although the frequency of all grade ALT elevation was virtually identical on the midostaurin and placebo arms (69% vs 68%, respectively), the frequency of grade ≥ 3 ALT elevation was higher on the midostaurin arm (20% vs 16%). During induction and consolidation, most patients on both arms experienced profound pancytopenia, as would be expected, and there were no differences between the treatment arms.

The applicant did a more in-depth analysis of newly occurring liver function abnormalities on Study A2301, reproduced in Table 31. While there appears to be a slight increase in frequency of ALT or AST elevations $\leq 8x$ ULN on the midostaurin arm compared to the placebo arm, ALT or AST elevations $> 8x$ ULN and cases of Hy's law appear slightly higher on the placebo arm. According to the sponsor's analysis, only two patients (one on each arm) experienced ALT or AST elevations $> 8x$ ULN during maintenance, and none experienced elevations $> 10x$ ULN.

Table 31: Study A2301 – Newly Occurring Liver Function Abnormalities

	Midostaurin (n=345) ¹	Placebo (n=335) ¹
ALT or AST $> 3x$ ULN	132/304 (43%)	111/306 (36%)
ALT or AST $> 5x$ ULN	67/318 (21%)	53/318 (17%)
ALT or AST $> 8x$ ULN	24/325 (7%)	19/322 (6%)
ALT or AST $> 10x$ ULN	10/326 (3%)	12/323 (4%)
ALT or AST $> 20x$ ULN	3/327 (1%)	5/324 (2%)
ALT or AST $> 3x$ ULN and TBili $> 2x$ ULN and Alk Phos $\leq 2x$ ULN	9/315 (3%)	15/314 (5%)

Source: From A2301 Clinical Study Report Table 12-20 dated 05-Jul-2016

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase, ULN, upper limit of normal; Tbili, total bilirubin; Alk Phos, alkaline phosphatase

¹ Percentages calculated using a denominator consisting of patients having a baseline measurement not meeting the criterion or missing, but at least 1 post-baseline measurement

Clinical Review

Ashley Ward, MD

NDA 207997

Rydapt® (midostaurin)

8.4.6. Vital Signs

The Applicant did not collect vital signs, other than weight, on Study A2301.

In their integrated analysis of safety, the applicant described vital sign changes in patients with aggressive systemic mastocytosis or mast cell leukemia on studies D2201 and A2213. According to the applicant, the only notable finding was a transient decrease in diastolic blood pressure in the first 3 months of treatment, which appeared to correlate with an increased incidence of hypotension and dizziness reported in the first 6 months of treatment.

The FDA used the pooled safety database to evaluate vital signs in patients exposed to midostaurin on studies other than A2301. Although the safety pool is somewhat skewed given the inclusion of healthy volunteers, and the analysis is limited to due lack of randomized comparison with placebo, there do not appear to be any vital sign abnormalities in patients treated with midostaurin beyond what would be expected in the general population (Table 32). With the exception of lower heart rate in younger patients and in men, and higher blood pressure in older patients, which are all consistent with the general population, there does not appear to be an age- or gender-specific impact of midostaurin on vital signs.

Table 32: Pooled Safety Database – Vital Signs

	Pooled safety database (n=1,298)				
	Total ¹ (n=952)	Age < 60 (n=618)	Age ≥ 60 (n=334)	Male (n=597)	Female (n=355)
SBP ≥ 160 mm Hg	119 (13%)	31 (5%)	88 (26%)	67 (11%)	52 (15%)
SBP < 90 mm Hg	36 (4%)	24 (4%)	12 (4%)	17 (3%)	19 (5%)
DBP ≥ 100 mm Hg	42 (4%)	18 (3%)	24 (7%)	24 (4%)	18 (5%)
Heart rate < 50 bpm	49 (5%)	41 (7%)	8 (2%)	42 (7%)	7 (2%)
Heart rate > 120 bpm	35 (4%)	28 (5%)	7 (2%)	14 (2%)	21 (6%)

Source: FDA analysis

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; bpm, beats per minute

¹ Includes only those patients for whom vital sign data was collected

8.4.7. Electrocardiograms (ECGs)

ECGs were obtained at baseline, several times per cycle during induction and consolidation, and at the beginning of each cycle of maintenance therapy on Study A2301. Arrhythmias (most frequently sinus tachycardia (n=60, 9%) were noted in 43 patients (12%) on the midostaurin arm and 54 patients (16%) on the placebo arm. Myocardial ischemia was reported in 8 patients (2%) on the midostaurin arm and 6 patients (2%) on the placebo arm. All other ECG-related adverse events reported were rare (occurring in ≤ 4 patients), and were evenly distributed on both study arms.

Clinical Review

Ashley Ward, MD

NDA 207997

Rydapt® (midostaurin)

8.4.8. QT

According to the applicant, midostaurin and its active metabolites (CGP62221 and CGP52421) were evaluated in vitro in the human ether-a-go-go (hERG) assay for the potential to cause QTc prolongation. The hERG IC50 for midostaurin and its metabolites could not be determined at the limit of solubility. As the concentrations tested in vitro exceed the levels that patients would be exposed to, the applicant concluded that the risk of QTc interval prolongation at therapeutic exposures is considered low. Long-term toxicology studies in dogs revealed some cardiotoxicity (decreased heart rate, myocardial degeneration, myocarditis and P-Q prolongation) but no effects of midostaurin on the QT interval.

The FDA Interdisciplinary Review Team (IRT) for QT Studies reviewed the thorough QT study. The effect of midostaurin (75 mg BID for 3 days) on the QTc interval was evaluated in a randomized, placebo and moxifloxacin controlled, multiple-dose, blinded, parallel study. There was no clinically significant prolongation of QTc interval or relationship between changes in QTc and concentrations for midostaurin and its active metabolites (CGP62221 and CGP52421). The study duration was not long enough to estimate the effects of the metabolite CGP52421 on the QT/QTc interval. The IRT concluded that there is no evidence that midostaurin affects the QTc interval.

In a randomized placebo-controlled study in patients with AML (Study A2301), the proportion of patients with QTc prolongation was higher in patients randomized to midostaurin as compared to placebo (QTcF > 480 ms: 10.1% vs 5.7%; QTcF > 500 ms: 6.2% vs 2.6%; Δ QTcF > 60 ms: 18.4% vs 10.7%). However, as information collected about concomitant medications did not include reliable start and stop dates, it is difficult to assess the impact of concomitant medication use on these findings.

Reviewer comment: Given that the thorough QT study had a minor limitation in that it was not long enough to estimate the effects of the metabolite CGP52421 on the QT interval, and that many patients with AML receive concomitant therapies that may prolong the QT interval, it would be reasonable to recommend QT monitoring as part of the intensive inpatient monitoring that AML patients receive while undergoing therapy.

8.5. Analysis of Submission-Specific Safety Issues

8.5.1. Embryo-fetal toxicity

Animal reproductive studies of midostaurin demonstrated that midostaurin caused embryo-fetal toxicities, including late embryo-fetal death and reduced fetal birth weight, with delays in fetal growth at doses lower than the recommended human dose. As the chemotherapy regimen used with midostaurin in Study A2301 is used in pregnant women during their second and third trimesters, it will be important to remind prescribers that midostaurin should not be

Clinical Review

Ashley Ward, MD

NDA 207997

Rydapt® (midostaurin)

administered to pregnant women. After consultation with the Division of Maternal and Pediatric Health (DMPH), we recommend a boxed warning. See Section 8.8.2 for further details.

8.5.2. Nausea and vomiting

Nausea and vomiting are frequent adverse events associated with intensive chemotherapy for AML, but the addition of midostaurin appears to increase their frequency. On Study A2301, 83% of the patients on the midostaurin arm reported nausea (6% grade ≥ 3) compared to 74% of the patients on the placebo arm (10% grade ≥ 3). Similarly, 62% of the patients on the midostaurin arm reported vomiting (3% grade ≥ 3) compared to 57% of the patients on the placebo arm (4% $\geq$ grade 4). This effect of midostaurin was more noticeable in the maintenance phase of the clinical trial, after completion of intensive chemotherapy, where the rate of nausea was 53% (22% on the placebo arm) and the rate of vomiting was 24% (compared to 11% on the placebo arm). While these events were generally low-grade and did not prompt frequent study treatment discontinuations, prescribers should be encourage to use anti-emetic therapy in patients taking midostaurin.

8.6. Safety Analyses by Demographic Subgroups

As reporting of race and ethnicity were sparse across all trials, safety was not analyzed by these variables. An analysis of TEAEs by gender on Study A2301 is summarized in Table 33, in order of the magnitude in difference in rate of the TEAE between the two genders. Vomiting, diarrhea, nausea, abdominal pain and rash were more common in females than males on both treatment arms, as were events physiologically associated with female gender (vaginal hemorrhage, urinary tract infection, and menorrhagia). The delta between rates for men or women was similar on both treatment arms, suggesting that there are no toxicities from midostaurin that are highly specific to women.

Of the adverse events observed more commonly in males on the midostaurin arm, several were observed less commonly in males on the placebo arm, raising the possibility of toxicities from midostaurin that are more specific to men. PTT prolongation, decreased appetite and arrhythmias were particularly pronounced in this respect. However, as overall survival benefit in men who received midostaurin was, if anything, better than that of women on Study A2301, the clinical significance of this post-hoc subgroup analysis is dubious.

Table 33: Study A2301 – TEAEs Occurring ≥ 5% More Frequently in One Gender on the Midostaurin Arm

Preferred Term	Midostaurin		Placebo	
	Male (n=169)	Female (n=176)	Male (n=139)	Female (n=196)
Events more common in males				
PTT prolongation	26 (15%)	8 (5%)	9 (6%)	19 (10%)
Hyperbilirubinemia	43 (25%)	26 (15%)	38 (27%)	47 (24%)
Decreased appetite	31 (18%)	15 (9%)	21 (15%)	41 (21%)
Leukopenia	53 (31%)	42 (24%)	48 (35%)	55 (28%)
Fatigue	127 (75%)	120 (68%)	98 (71%)	147 (75%)
Arthralgia	25 (15%)	14 (8%)	10 (7%)	10 (5%)
Hyperuricemia	17 (10%)	6 (3%)	7 (5%)	9 (5%)
Pyrexia	51 (30%)	42 (24%)	39 (28%)	52 (27%)
Hyperglycemia	44 (26%)	35 (20%)	30 (22%)	38 (19%)
Hyponatremia	36 (21%)	27 (15%)	31 (22%)	31 (16%)
Arrhythmia	31 (18%)	22 (13%)	14 (10%)	40 (20%)
Fungal infection	18 (11%)	9 (5%)	12 (9%)	12 (6%)
Dyspnea	27 (16%)	20 (11%)	15 (11%)	31 (16%)
Events more common in females				
Vomiting	92 (54%)	121 (69%)	63 (45%)	128 (65%)
Diarrhea	119 (70%)	144 (82%)	98 (71%)	161 (82%)
Vaginal hemorrhage	0	18 (10%)	0	22 (11%)
Urinary tract infection	7 (4%)	25 (14%)	6 (4%)	41 (21%)
Nausea	131 (78%)	154 (88%)	98 (71%)	150 (77%)
Abdominal pain	43 (25%)	61 (35%)	35 (25%)	74 (38%)
Rash	109 (64%)	129 (73%)	94 (68%)	145 (74%)
Petechiae	39 (23%)	50 (28%)	23 (17%)	46 (23%)
Menorrhagia	0	8 (5%)	0	4 (2%)

Source: FDA analysis

8.7. Specific Safety Studies/Clinical Trials

No studies or trials were conducted to evaluate a specific safety concern.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

A formal human carcinogenicity study was not conducted for midostaurin. Neoplasms (identified using the Neoplasms, Benign, Malignant and Unspecified SOC) were rare on Study A2301. 6 patients (2%) on the midostaurin arm and 6 (2%) on the placebo arm developed a neoplasm. Most were benign. Second primary malignancies (colon cancer, myelodysplastic syndrome, and a testicular neoplasm) developed in 3 patients on the placebo arm. A second

Clinical Review

Ashley Ward, MD

NDA 207997

Rydapt® (midostaurin)

primary malignancy (pineal neoplasm) was reported in only one patient on midostaurin. Based on these data, no secondary cancer safety signal was identified.

8.8.2. Human Reproduction and Pregnancy

In animal reproduction studies, oral administration of midostaurin to pregnant rats and rabbits during organogenesis caused embryo-fetal toxicities, including late embryo-fetal death and reduced fetal birth weight, with delays in fetal growth at doses lower than the recommended human dose. The DMPH reviewer identified 8 pregnancies on subjects in clinical trials of midostaurin. Three of these patients reported definite or possible fetal exposure to midostaurin and underwent elective abortions at ≤ 12 weeks gestational age. Fetal outcomes were not reported. One patient delivered a healthy term baby 2 years after the last intake of midostaurin. The remaining 4 patients did not have fetal exposure to midostaurin (3 received placebo, 1 was pregnant at diagnosis and began treatment after delivery).

DMPH recommends that a boxed warning for embryo-fetal toxicity be added to labeling for midostaurin and recommends verification of pregnancy status prior to treatment in females of reproductive potential. Since the “7+3” regimen is the most common regimen used in pregnant women in their 2nd and 3rd trimesters, this reviewer agrees with their recommendation. DPMH also recommends effective contraception during treatment and for 4 months following the last dose of midostaurin.

Midostaurin may also adversely impact male fertility based on nonclinical findings as reviewed in Section 4.3.

8.8.3. Pediatrics and Assessment of Effects on Growth

The applicant was granted Orphan Designation for midostaurin for the treatment of patients with AML and is therefore exempt from pediatric studies under the Pediatric Research Equity Act (PREA). (b) (4)

[REDACTED]

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The applicant did not provide any reported cases of overdose of midostaurin in the AML population. Midostaurin does not have abuse potential.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

Clinical Review

Ashley Ward, MD

NDA 207997

Rydapt® (midostaurin)

Midostaurin is not marketed in any country, and there is no postmarket experience.

8.9.2. Expectations on Safety in the Postmarket Setting

Safety in the postmarket setting is expected to be similar to that observed on the clinical trials reviewed in this Application.

8.10. Additional Safety Issues From Other Disciplines

No additional safety issues were identified by other disciplines.

8.11. Integrated Assessment of Safety

The primary data in support of safety for the proposed indication came from Study A2301, in which 345 patients with previously untreated AML were exposed to midostaurin + chemotherapy, and 335 were exposed to placebo + chemotherapy. The median duration of exposure to midostaurin on this study was 1.4 months (mean 4.5 months), with a maximum exposure time of 18.9 months. Data from an additional 953 patients who were exposed to midostaurin across the development program was included in the integrated safety database.

The study population was monitored for deaths, serious adverse events, common adverse events, and common laboratory tests. A thorough QT study was conducted. Fourteen patients on the midostaurin arm died during or within 30 days after study treatment (compared to 21 on the placebo arm). The most frequent cause of death on both arms was infection, which is typical in this patient population and is considered related to the underlying disease.

Midostaurin was generally well-tolerated. The most common non-laboratory TEAEs (incidence $\geq 20\%$ and $\geq 2\%$ more frequent on the midostaurin arm) were rash, vomiting, mucositis, headache, musculoskeletal pain, petechiae, device-related infection and epistaxis. The most frequent Grade 3/4 adverse reactions (incidence $\geq 10\%$ and $\geq 2\%$ more frequent on the midostaurin arm) were febrile neutropenia, diarrhea, device-related infection, sepsis, rash, pneumonia and mucositis. The most frequent serious adverse reaction was febrile neutropenia, which occurred at similar rates in the midostaurin (16%) and placebo arms (16%).

Gastrointestinal toxicities were more noticeable on the maintenance phase of the study, in which midostaurin/placebo was administered as a monotherapy. In maintenance 53% of patients on the midostaurin arm reported nausea (vs 22% on the placebo arm). Other adverse events occurring in $\geq 20\%$ of the patients in the midostaurin arm and $\geq 2\%$ more frequently than in patients on the placebo arm were diarrhea (30% vs 22%), fatigue (30% vs 28%), elevated transaminases (28% vs 19%) and vomiting (24% vs 11%). Almost all of these events were mild-moderate in severity.

Clinical Review

Ashley Ward, MD

NDA 207997

Rydapt® (midostaurin)

Discontinuation due to adverse reaction occurred in 8% of patients on the midostaurin arm versus 5% on the placebo arm. The most frequent Grade 3/4 adverse reactions leading to discontinuation of midostaurin were elevated transaminases (1.4%) and exfoliative dermatitis (1.2%).

Study ADE02T provided data supporting the use of midostaurin in combination with intensive chemotherapy in older patients with untreated AML. On this study, serious adverse events were modestly more frequent in patients age > 60 years (33, 72%) than in those ≤ 60 years of age (61, 62%). Discontinuations for adverse events were also modestly more frequent in patients age > 60 years (15, 33%) than in those ≤ 60 years of age (26, 27%). Given the historically poor overall survival in older patients with AML, this level of toxicity is acceptable for the clinical benefit observed.

9 Advisory Committee Meeting and Other External Consultations

This Application was not presented to the Oncologic Drug Advisory Committee or any other external consultants.

10 Labeling Recommendations

10.1. Prescribing Information

The following are recommended major changes to the midostaurin prescribing information proposed by the applicant based on this review:

- **HIGHLIGHTS:** Add a boxed warning describing embryo-fetal toxicity.
- **1 INDICATIONS AND USAGE:** (b) (4) Add a limitation of use: midostaurin should not be used as monotherapy in patients with AML.
- **2 DOSAGE AND ADMINISTRATION:** (b) (4) . Add a recommendation to administer prophylactic anti-emetics.
- **5 WARNINGS AND PRECAUTIONS:** Remove (b) (4)
- **6 ADVERSE REACTIONS:** Modify the tables of adverse reactions and laboratory

Clinical Review

Ashley Ward, MD

NDA 207997

Rydapt® (midostaurin)

abnormalities to include (b) (4) those occurring in $\geq 10\%$ of patients and at a rate $\geq 2\%$ higher than the placebo arm. Preferred terms should be grouped.

- **14 CLINICAL STUDIES:** (b) (4) Revise EFS such that patients who did not have a CR documented by day 60 are assigned a date of treatment failure as day 1. (b) (4)

10.2. Patient Labeling

Review of the patient labeling by the Division of Medical Policy Programs in the Office of Medical Policy is ongoing. The risks of the product do not warrant a Patient Medication Guide.

11 Risk Evaluation and Mitigation Strategies (REMS)

Given the favorable safety profile of midostaurin, there are no additional risk management strategies beyond recommended labeling. The Division of Risk Management in the Office of Surveillance and Epidemiology concurs with this assessment.

12 Postmarketing Requirements and Commitments

No post-marketing requirements or commitments are recommended for this application.

13 Appendices

13.1. References

Bacher U, Haferlach C et al. 2008. Prognostic relevance of FLT3-TKD mutations in AML: the combination matters – an analysis of 3082 patients. *Blood* 111:2527-2537.

Bertoli S, Berard E et al. 2013. Time from diagnosis to intensive chemotherapy initiation does not adversely impact the outcome of patients with acute myeloid leukemia. *Blood* 121:2618-2626.

Brandwein JM, Geddes M et al. 2013. Treatment of older patients with acute myeloid leukemia (AML): A Canadian consensus. *Am J Blood Res* 3:141-164.

Clinical Review

Ashley Ward, MD
NDA 207997
Rydapt® (midostaurin)

Cheson BD, Bennett JM et al. 2003. Revised recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. *JCO* 21:4642-9.

Cheson, BD, Bennett BD et al. 2000. Report of an international working group to standardize response criteria for myelodysplastic syndromes. *Blood* 96:2671-3674.

Cheson BD, Cassileth PA et al. 1990. Report of the National Cancer Institute-sponsored workshop on definitions of diagnosis and response in acute myeloid leukemia. *JCO* 8:813-819.

Estey E, Othus M et al. 2016. New drug approvals in acute myeloid leukemia: what's the best end point? *Leukemia* 30:521-525.

Estey E. 2006. Acute myeloid leukemia and myelodysplastic syndromes in older patients. *JCO* 25:1908-1915.

Fernandez HF, Sun Z et al. 2009. Anthracycline dose intensification in acute myeloid leukemia. *NEJM* 361:1249-1259.

Ferrara F, Barosi G et al. 2013. Editorial: Consensus-based definition of unfit to intensive and non-intensive chemotherapy in acute myeloid leukemia: a project of SIE, SIES and GITMO group on a new tool for therapy decision making. *Leukemia* 27:997-999.

Levis M, Pham R et al. 2003. CEP-701, a selective FLT3 tyrosine kinase inhibitor that is cytotoxic to FLT3/ITD-expressing leukemia cells, is synergistic with chemotherapeutic agents in vitro when used in time-sequential fashion. *Blood* 102:66a (abstract 220).

Levis M and Small D. 2003. FLT3: ITD Does matter in leukemia. *Leukemia* 17:1738-1752.

Levis M. 2013. FLT3 mutations in acute myeloid leukemia: what is the best approach in 2013? *Hematol Am Soc Hematol Educ Program* 2013:220-226.

Oran B and Weisdorf D. 2012. Survival for older patients with acute myeloid leukemia: a population-based study. *Haematologica* 97:1916-24.

Ravandi F. 2011. Primary refractory acute myeloid leukemia – in search of better definitions and therapies. *Br J Haematol* 155:413-419.

Schnittger S, Schoch C et al. 2002. Analysis of FLT3 length mutations in 1003 patients with acute myeloid leukemia: correlation to cytogenetics, FAB subtype, and prognosis in the AMLCG study

Clinical Review

Ashley Ward, MD

NDA 207997

Rydapt® (midostaurin)

and usefulness as a marker for the detection of minimal residual disease. *Blood* 100:59-66.

Thiede C, Steudel C et al. 2002. Analysis of FLT3-activating mutations in 979 patients with acute myelogenous leukemia: association with FAB subtypes and identification of subgroups with poor prognosis. *Blood* 99:4326-4335.

Yates J, Wallace H et al. 1973. Cytosine arabinoside (NSC-63878) and daunorubicin (NSC-83142) therapy in acute nonlymphocytic leukemia. *Cancer Chemother Rep Part 1* 57:485-488.

Clinical Review

Ashley Ward, MD

NDA 207997

Rydapt® (midostaurin)

13.2. Financial Disclosure**Covered Clinical Study (Name and/or Number): Study A2301**

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>1488</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>5</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u> Significant payments of other sorts: <u>4</u> Proprietary interest in the product tested held by investigator: <u>1</u> Significant equity interest held by investigator in Sponsor of covered study: <u>0</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>31</u>		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Clinical Review

Ashley Ward, MD

NDA 207997

Rydapt® (midostaurin)

Covered Clinical Study (Name and/or Number): Study A2601

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>40</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u> Significant payments of other sorts: <u>0</u> Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator in Sponsor of covered study: <u>0</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>7</u>		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Clinical Review

Ashley Ward, MD

NDA 207997

Rydapt® (midostaurin)

Covered Clinical Study (Name and/or Number): A2104/A2014E1/A2104E2

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>102</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>1</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u> Significant payments of other sorts: <u>1</u> Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator in Sponsor of covered study: <u>0</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>2</u>		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

13.3. Grouped Preferred Terms

Grouped Term	Preferred Terms
Abdominal pain	Abdominal pain, Abdominal pain lower, Abdominal pain upper, Abdominal tenderness, Gastrointestinal pain
Anemia	Anemia, Erythropenia, Hematocrit decreased, Hemoglobin decreased, Red blood cell count decreased
Arrhythmia	Arrhythmia, Atrial fibrillation, Atrial flutter, Atrial tachycardia, Bradycardia, Sinus bradycardia, Sinus tachycardia, Supraventricular extrasystoles, Supraventricular tachycardia, Tachycardia, Ventricular arrhythmia, Ventricular extrasystoles, Ventricular fibrillation, Ventricular tachycardia
Cardiac failure	Left ventricular dysfunction, Left ventricular failure, Diastolic dysfunction, Cor pulmonale, Cardiac failure congestive, Cardiac failure
Cellulitis	Anorectal cellulitis, Catheter site cellulitis, Cellulitis, Cellulitis orbital, Erysipelas, Injection site cellulitis, Periorbital cellulitis, Vaginal cellulitis
Chest pain	Angina pectoris, Chest discomfort, Chest pain
Clostridial infection	Clostridial infection, Clostridium colitis, Clostridium difficile colitis, Clostridium difficile infection
Conduction disorder	Atrioventricular block, Atrioventricular block first degree, Bundle branch block right
Cough	Cough, Productive cough
Diarrhea	Colitis, Diarrhea, Enteritis, Enterocolitis, Gastroenteritis, Neutropenic colitis
Dyspnea	Acute respiratory failure, Bronchospasm, Dyspnea, Dyspnea exertional, Respiratory failure, Respiratory rate increased
Edema	Face edema, Generalized edema, Edema, Edema peripheral, Peripheral swelling, Swelling face
Eye irritation	Dry eye, Eye irritation, Eye pain, Eye pruritus, Keratitis
Fatigue	Asthenia, Fatigue
Fungal infection	Aspergillus infection, Bronchopulmonary aspergillosis, Candida infection, Candida sepsis, Fungal infection, Fungal skin infection, Gastrointestinal candidiasis, Hepatic candidiasis, Hepatic infection fungal, Oral candidiasis, Oral fungal infection, Pneumonia fungal, Respiratory moniliasis, Splenic infection fungal, Systemic candida
Gastrointestinal hemorrhage	Anal hemorrhage, Esophageal hemorrhage, Gastric hemorrhage, Hematemesis, Hematochezia, Hemorrhoidal hemorrhage, Large intestinal hemorrhage, Lower gastrointestinal hemorrhage, Mouth hemorrhage, Rectal hemorrhage, Small intestinal hemorrhage, Upper gastrointestinal hemorrhage
Hemorrhage intracranial	Cerebral hemorrhage, Hemorrhagic stroke, Subarachnoid hemorrhage
Herpesvirus infection	Genital herpes, Herpes simplex, Herpes simplex pneumonia, Herpes virus infection, Herpes zoster, Oral herpes, Varicella zoster virus infection
Hyperbilirubinemia	Blood bilirubin increased, Hyperbilirubinaemia, Jaundice

Clinical Review

Ashley Ward, MD

NDA 207997

Rydapt® (midostaurin)

Grouped Term	Preferred Terms
Hyperglycaemia	Diabetes mellitus, Hyperglycaemia
Hypersensitivity	Anaphylactic reaction, Drug eruption, Drug hypersensitivity, Erythema multiforme, Hypersensitivity, Urticaria
Hypertransaminasemia	Alanine aminotransferase increased, Aspartate aminotransferase decreased, Hepatic enzyme abnormal, Transaminases increased
Hypoalbuminemia	Blood albumin decreased, Hypoalbuminaemia
Injection site reaction	Injection site erythema, Injection site extravasation, Injection site hematoma, Injection site pain, Injection site reaction
Mucositis	Anal inflammation, Anal ulcer, Anorectal discomfort, Aphthous ulcer, Esophageal ulcer, Esophagitis, Esophageal pain, Gingival pain, Laryngeal discomfort, Laryngeal inflammation, Laryngeal pain, Mouth ulceration, Mucosal inflammation, Mucosal pain, Oral mucosal blistering, Oral pain, Oropharyngeal pain, Pharyngeal inflammation, Proctalgia, Proctitis, Radiation mucositis, Stomatitis, Vaginal inflammation
Musculoskeletal pain	Back pain, Bone pain, Musculoskeletal chest pain, Musculoskeletal pain, Neck pain, Pain, Pain in extremity
Myocardial ischemia	Acute myocardial infarction, Myocardial infarction, Myocardial ischaemia, Troponin I increased, Troponin T increased
Phlebitis	Injection site phlebitis, Phlebitis, Phlebitis infective, Phlebitis superficial
Pneumonia	Atypical pneumonia, Lung infection, Pneumonia, Pneumonia aspiration, Pneumonia bacterial, Pneumonia klebsiella
Pneumonitis	Pneumonitis, Acute respiratory distress syndrome, Pulmonary toxicity, Pneumonitis chemical
Rash	Dermatitis, Dermatitis acneiform, Dermatitis allergic, Dermatitis contact, Dermatitis exfoliative, Exfoliative rash, Rash, Rash Erythematous, Rash Macular, Rash maculo-papular, Rash papular, Rash pruritic, Rash pustular, Rash vesicular, Skin exfoliation, Skin reaction, Toxic skin eruption
Renal insufficiency	Acute kidney injury, Blood creatinine increase, Glomerular filtration rate decreased, Renal disorder, Renal failure
Sepsis	Bacteremia, Device related sepsis, Enterobacter sepsis, Enterococcal infection, Escherichia bacteremia, Escherichia infection, Escherichia sepsis, Neutropenic infection, Neutropenic sepsis, Pulmonary sepsis, Sepsis, Septic shock, Staphylococcal infection, Stenotrophomonas infection (for all PTs with "infection", events only included if verbatim term specified blood infection)
Thrombosis	Deep vein thrombosis, Thrombosis, Thrombosis in device
Transfusion reaction	Allergic transfusion reaction, Febrile nonhaemolytic transfusion reaction, Transfusion reaction
Upper respiratory tract infection	Acute sinusitis, Chronic sinusitis, Laryngitis, Nasopharyngitis, Pharyngitis, Pharyngitis streptococcal, Rhinitis, Sinusitis, Tonsillitis, Upper respiratory tract infection, Upper respiratory tract infection bacterial
Urinary tract infection	Cystitis, Escherichia urinary tract infection, Kidney infection, Pyelonephritis, Renal abscess, Urinary tract infection, Urinary tract infection bacterial, Urinary tract infection enterococcal

Clinical Review

Ashley Ward, MD

NDA 207997

Rydapt® (midostaurin)

Grouped Term	Preferred Terms
Visual impairment	Diplopia, Hypermetropia, Vision blurred, Visual acuity reduced, Visual impairment

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/s/

ASHLEY F WARD
02/03/2017

DONNA PRZEPIORKA
02/03/2017

I concur with the primary reviewer's recommendation for regular approval of midostaurin, in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation chemotherapy for the treatment of adult patients with newly-diagnosed AML who are FLT3 mutation-positive.