CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 207997
Supplement #:	Not applicable (Original New Drug Application)
Drug Name:	Rydapt® (Midostaurin, PKC412) 25 mg capsules
Indication(s):	Advanced systemic mastocytosis
Applicant:	Novartis Pharmaceuticals Corporation
Date(s):	Submission date: August 29, 2016
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Review Priority:	Priority
Biometrics Division:	Division of Biometrics 5 (HFD-711)
Statistical Reviewer:	Chia-Wen Ko, Ph.D.
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Keywords: durable complete response, response criteria, single-arm trial design

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APPEARS THIS WAY ON ORIGINAL

1 EXECUTIVE SUMMARY

This is the statistical review for midostaurin original New Drug Application (NDA), seeking an indication for midostaurin as a single-agent therapy in patients with advanced systemic mastocytosis.

The proposed indication is mainly supported by the single-arm study D2201 conducted in 116 patients; 89 of those patients were considered evaluable for treatment response according to protocol-specified response criteria.

The primary efficacy endpoint of Study D2201 was overall response rate (ORR), defined as the proportion of patients with a best response of major response or partial response that initially occurred in the first 6 cycles of treatment with midostaurin as assessed by an external study steering committee using the modified Valent and Cheson criteria and that was confirmed at least 56 days later. The study continued to an expansion phase after rejecting a null hypothesis of ORR $\leq$ 30% based on a response rate of 60% from the first 40 evaluable patients. The overall ORR rate from the 89 evaluable patients was 59.6% (95% confidence interval [CI]: [48.6, 69.8]), including 40 patients who achieved a major response and 13 patients who achieved a partial response as the best response. The ORR was $\geq$ 50% across disease subtypes. The estimated median duration of response was 31.4 months in all responders, with the estimated median duration of response being not reached in patients who achieved a major response and being 7.4 months in patients who achieved a partial response.

Data on treatment response assessment according to the Internal Working Group (IWG) criteria were provided to the Agency during the review. The percentage of patients in Study D2201 who achieved either a complete or partial remission was 16.5% (95% CI: [10.3, 24.6]). The IWG criteria may not be directly comparable to the modified Valent and Cheson criteria, and therefore is not to be tested against the null ORR rate of 30% for interpretation of treatment efficacy.

Information on treatment response to midostaurin single-agent was also available from 26 patients with advanced systemic mastocytosis in a supportive single-arm study A2213. The overall response rate evaluated after 2 cycles of treatment by investigators was 73.1% (95% CI: [52.2, 88.4]).

There were no major statistical issues identified during the review.

Approval is recommended for midostaurin as a single-agent therapy in patients with advanced systemic mastocytosis.

2 INTRODUCTION

2.1 Overview

Product and Proposed Indication

RYDAPT® (midostaurin) is a protein kinase inhibitor, proposed for the following 2 indications:

1. Newly diagnosed acute myeloid leukemia (AML) that is FLT3 mutation-positive as detected by an FDA-approved test
2. Advanced systemic mastocytosis (Advanced SM)

There will be separate statistical reviews for the proposed indications. This review will focus on evaluations for proposed indication #2 in Advanced SM.

Disease Overview

Mastocytosis is a myeloproliferative neoplasm. According to the World Health Organization (WHO) classification system, 4 major variants of systemic mastocytosis are recognized: indolent systemic mastocytosis (ISM), SM with associated clonal hematologic non-mast cell lineage disease (SM-AHNMD), aggressive systemic mastocytosis (ASM), and mast cell leukemia (MCL). Advanced SM includes SM-AHNMD, ASM, and MCL.

Imatinib is the only drug currently approved for the treatment of adult patients with ASM lacking the D816V KIT mutation or with an unknown KIT mutation status. There is currently no approved therapy for SM with the D816V mutation or MCL.

Clinical Studies

Table 1 summarizes the clinical studies submitted to support the Advanced SM indication. The primary assessments for the treatment efficacy and safety of Midostaurin will be based on the pivotal study D2201. Findings from supportive study A2213 will be evaluated for consistency with the findings from the pivotal study. The supportive study will not be pooled with the pivotal study to support efficacy claim in the proposed indication, because overall response rate (ORR) in Study A2213 was assessed over the first 2 cycles of treatment based on investigator assessment, while ORR in Study D2201 was assessed over the first 6 cycles of treatment by the study steering committee using a standard response assessment criteria.

Table 1: Overview of Midostaurin Clinical Studies in Advanced Systemic Mastocytosis

Study	Population	Design	Midostaurin Dose	Primary Endpoint	Sample size
D2201 Pivotal study (phase II)	SM/MCL with or without AHNMD	Single-arm, monotherapy	100 mg bid	Overall response rate over 6 treatment cycles as assessed by SSC based on modified Valent/Cheson criteria	116
A2213 (phase II)	SM/MCL with or without AHNMD	Single-arm, monotherapy	100 mg bid	Overall response rate over 2 treatment cycles as assessed by investigators based on original Valent criteria	26

SM= systemic mastocytosis, MCL= mantel cell lymphoma, AHNMD= associated hematological clonal non-mast cell lineage disease, bid= twice daily, ORR= overall response rate, SSC= study steering committee

2.2 Data Sources

Materials reviewed for this application: protocols, statistical analysis plans, study reports, and submitted datasets for studies D2201 and A2213.

Reviewed data were provided electronically with legacy data formats. Datasets are located at: \\CDSESUB1\evsprod\NDA207997\0002\m5\datasets\pkc412d2201 (for Study D2201) and \\CDSESUB1\evsprod\NDA207997\0003\m5\datasets\pkc412a2213 (for Study A2213)

During the review cycle, the medical review team requested response data for studies D2201 and A2213 according to the most recent 2013 Internal Working Group response assessment criteria. Response to this request was provided on November 18 of 2016. Datasets containing the IWG best overall response are located at \\CDSESUB1\evspord\NDA207997\0040\m5\datasets.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Data from studies D2201 and A2213 were provided electronically with legacy (applicant company standard) formats. Data quality appeared to be acceptable in general.

3.2 Evaluation of Efficacy

The primary evaluation for treatment efficacy of midostaurin will be based on data from the pivotal study D2201. Efficacy findings from the supportive study A2213 will be presented for checking the consistency with findings from the pivotal study.

3.2.1 Study Design and Endpoints

The pivotal study D2201 was a multicenter, single-arm, multi-stage, open-label phase II study in 116 patients with advanced SM. Midostaurin was administrated orally at 100 mg twice daily until disease progression or intolerable toxicity. The primary endpoint was overall response rate (ORR), defined as the proportion of patients with a best response of major response or partial response that initially occurred in the first 6 cycles of treatment as assessed by an external study steering committee using the modified Valent and Cheson criteria and that was confirmed at least 56 days later. Secondary endpoints included duration of response and overall survival. In addition, patient-reported outcomes were assessed as exploratory endpoints using the Memorial Symptom Assessment Scale (MSAS) and the Short Form (SF-12) questionnaires. The study used a 2-stage+expansion design, with up to 2 stages of patient enrollment to test against the null hypothesis of an ORR $\leq$ 30%, followed by additional patient enrollment into expansion phase for better estimation of ORR.

The supportive study A2213 was a multicenter, single-arm, open-label phase II study of 26 patients with advanced SM. Midostaurin was administrated orally at 100 mg twice a day. Treatment was discontinued in patients who did not achieve a major or partial response by the

end of the second cycle of study treatment. The primary endpoint was ORR assessed by investigators after 2 cycles of treatment based on the original Valent criteria.

3.2.2 Statistical Methodologies

Protocol Defined Analyses

The protocol-defined primary analysis population for the pivotal study D2201 consisted of 89 patients who received study drug, met the diagnostic criteria for advanced SM, and had at least one measurable C-finding at study entry as confirmed by the study steering committee based on the modified Valent and Cheson criteria. ORR with the exact 2-sided 95% confidence interval was summarized for overall and by phase of the study. Time-to-event endpoints were estimated using Kaplan-Meier methodology. Patient-reported quality of life outcomes were summarized based on percentage of patients that had a meaningful improvement, defined as having ≥50% reduction from baseline in outcome score that was maintained for at least 168 days.

Study D2201 calculated a sample size of 40 response evaluable patients for Stage 1 and another 20 response evaluable patients for Stage 2 if study continued to Stage 2, in order to test the null hypothesis of ORR ≤ 30% versus alternative hypothesis of ORR ≥ 50% at an overall type I error of 0.05 with a power of approximately 85%. The null hypothesis would be rejected if more than 19 patients responded in Stage 1; otherwise, the study continued to Stage 2, and the null hypothesis would be rejected if more than 27 patients responded in Stage 1+ Stage 2. Once the null hypothesis was rejected, the study continued for expansion to reach a total of 80 evaluable patients for ORR estimation. There was no formal sample size calculation for the expansion phase.

For the supportive study A2213, response rates were summarized descriptively and there were no formal hypotheses for sample size determination.

Additional Analysis for This Review

Because the 2013 International Working Group (IWG) response assessment criteria was not developed yet at the time Study D2201 was being conducted, the responses in Study D2201 were not evaluated according to IWG criteria. The medical review team requested the applicant to provide response data according to the IWG criteria. The estimated ORR with exact confidence interval based on the provided IWG response dataset will be presented in the review.

Reviewer Comments:

- [redacted] (b) (4)
- *The historical benchmark of 30% for the null hypothesis in Study D2201 was determined by the applicant based on literature from studies using treatments other than midostaurin.*
- *In the original and modified Valent response criteria for advanced SM, the evaluation of clinical findings of organ damage (also known as C findings) was the foundation for distinguishing levels of response. Therefore, patients who did not have measurable C-*

findings were excluded from the protocol-specified primary analysis population in study D2201. In the IWG criteria, C-findings are no longer required for assessing responses.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

The pivotal study D2201 enrolled a total of 116 patients. At the time of data cut-off (01-Dec-2014), treatment was ongoing in 21 patients (18.1%). The most common reasons for treatment discontinuation were disease progression and adverse events. Patient disposition in the protocol-defined primary analysis population, which excluded 27 patients for not meeting the disease diagnosis per study steering committee, was similar to the population of all enrolled patients.

Table 2: Study D2201 Patient Disposition

	All enrolled N = 116 n (%)	**Primary analysis population N = 89 n (%)**
Patient Treated		
Treatment ongoing (data cut-off: 01-Dec-2014)	21 (18.1)	15 (16.9)
Treatment discontinued	95 (81.9)	74 (83.1)
Primary reason for treatment discontinuation		
Disease progression	44 (37.9)	35 (39.3)
Adverse Event(s)	28 (24.1)	22 (24.7)
Patient withdrew consent	10 (8.6)	8 (9.0)
Death	8 (6.9)	7 (7.9)
Other[1]	5 (4.3)	2 (2.2)

[1] Other reasons included: protocol deviation, lost to follow-up and administrative problems

Table 3 gives a summary on demographics and other baseline characteristics for patients in Study D2201. The median age was 63 years (range: 25 to 82 years). Approximately one-third of the patients were enrolled in the North America. The baseline characteristics of patients in the protocol-defined primary analysis population were similar to those of all enrolled patients.

Table 3: Study D2201 Demographics and Other Baseline Factors

Factor	**All enrolled N = 116**	**Primary analysis population N = 89**
Age (years)		
<65 / ≥65	65 / 51 (56 / 44 %)	46 / 43 (52 / 48 %)
mean (SD), median, min-max	62 (11.8), 63, 25-82	63 (11.6), 64, 25-82
Gender		
Female / Male	40 / 76 (34 / 66 %)	32 / 57 (36 / 64 %)
Race		
White / Other / Unknown	111 / 3 / 2 (96 / 3 / 1 %)	86 / 2 / 1 (97 / 2 / 1 %)
Region		
North America / Other	37 / 79 (32 / 68 %)	28 / 61 (31 / 69 %)
D816V KIT mutation		
Yes / No / Unknown	94 / 17 / 5 (81 / 15 / 4 %)	73 / 14 / 2 (82 / 16 / 2 %)
Prior anti-neoplastic medication for SM		

Factor	All enrolled N = 116	Primary analysis population N = 89
Yes / No	47 / 69 (41 / 59 %)	32 / 57 (36 / 64 %)
ECOG performance status		
0-1 / ≥2	77 / 39 (66 / 34 %)	57 / 32 (64 / 36 %)

SD: standard deviation, SM: systemic mastocytosis, ECOG: Eastern Cooperative Oncology Group.

3.2.4 Efficacy Results

3.2.4.1 Treatment Response

The pivotal study D2201 continued to expansion phase after rejecting the null ORR rate of 30% based on an ORR of 60% from the 40 patients enrolled in Stage I, including 20 patients with a major response (MR) and 4 patients with a partial response (PR) as adjudicated by the study steering committee using the modified Valent and Cheson criteria.

The primary analysis of ORR was conducted in the primary analysis population of 89 patients. Overall, 53 patients achieved a confirmed response (MR or PR) during the first 6 cycles of treatment for an ORR of 59.6% (95% CI: [48.6, 69.8]), including 40 patients achieved a MR and 13 patients achieved a PR as the best response. The ORR was ≥50% across disease subtypes.

Almost all the study patients were evaluable for response under the IWG criteria, which does not require at least one measurable C-fining. Based on the IWG criteria determined response data provided by the applicant during the review cycle, the percentage of patients who achieved either a complete or partial remission was 16.5% (95% CI: [10.3, 24.6]).

The distribution for duration of response (DOR) is plotted in Figure 1. The overall median DOR in the primary analysis population of 89 patients was 31.4 months. The median DOR was not reached in major responders, and was 7.4 months in partial responders. Distribution for DOR according to the IWG criteria is not plotted, because only one responder had disease progression.

Table 4: Study D2201 Treatment Response Result per Modified Valent/Cheson Criteria

	All N = 89	SM-AHNMD N = 57	ASM N = 16	MCL N = 16
Best response within 6 cycles of treatment				
Major response, n (%)	40 (44.9)	23 (40.4)	10 (62.5)	7 (43.8)
Partial response, n (%)	13 (14.6)	10 (17.5)	2 (12.5)	1 (6.3)

	All N = 89	SM-AHNMD N = 57	ASM N = 16	MCL N = 16
Best response within 6 cycles of treatment				
Stable disease, n (%)	11 (12.4)	7 (12.3)	1 (6.3)	3 (18.8)
Progressive disease, n (%)	10 (11.2)	6 (10.5)	1 (6.3)	3 (18.8)
Not evaluable, n (%)	15 (16.9)	11 (19.3)	2 (12.5)	2 (12.5)
ORR, n (%) [95% CI]	53 (59.6) [48.6, 69.8]	33 (57.9) [44.1, 70.9]	12 (75.0) [47.6, 92.7]	8 (50.0) [24.7, 75.4]
Duration of response[1], month				
Events[2] / Responders	22 / 53	18 / 33	2 / 12	2 / 8
Median (95% CI)	31.4 (10.8, NE)	12.7 (7.4, 31.4)	NR (24.2, NE)	NR (3.6, NE)
Range: min – max	1.9 – 66.9	1.9 – 52.1	2.3 – 66.9	3.6 – 65.8

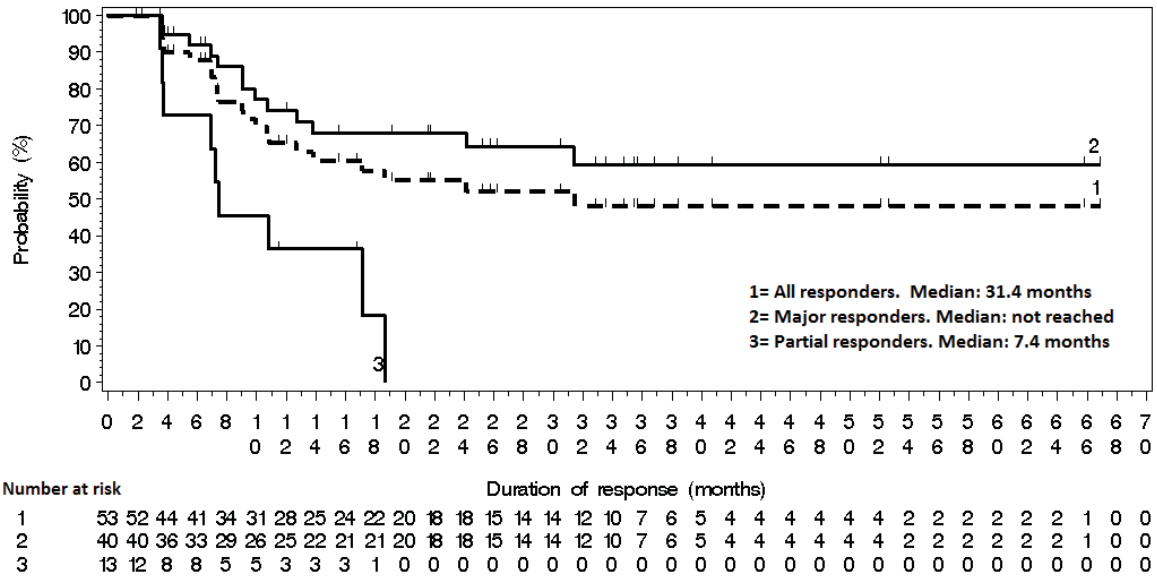
SM-AHNMD: systemic mastocytosis with associated non-mast cell lineage disorder; ASM: aggressive systemic mastocytosis; MCL: mast cell leukemia; ORR: overall response rate = proportion of patients achieved a major or partial response; CI: confidence interval; min: minimum; max: maximum; NR: not reached; NE: not estimable
[1] Defined only for responders; [2] An event was defined to be occurrence of disease progression or death

Table 5: Study D2201 Treatment Response Result per IWG Criteria

	All N = 115	SM-AHNMD N = 72	ASM N = 16	MCL N = 21
Best response within 6 cycles of treatment				
Complete remission, n (%)	2 (1.7)	0 (0.0)	1 (6.3)	1 (4.8)
Partial remission, n (%)	17 (14.8)	8 (11.1)	4 (25.0)	3 (14.3)
Clinical improvement, n (%)	20 (17.4)	13 (18.1)	3 (18.8)	3 (14.3)
Stable disease, n (%)	35 (30.4)	21 (29.2)	5 (31.3)	7 (33.3)
Progressive disease, n (%)	28 (24.4)	21 (29.2)	2 (12.5)	5 (23.8)
Not evaluable, n (%)	13 (11.3)	9 (12.5)	1 (6.3)	2 (9.5)
ORR, n (%) [95% CI]	19 (16.5) [10.3, 24.6]	8 (11.1) [4.9, 20.7]	5 (31.3) [11.0, 58.7]	4 (19.1) [5.5, 41.9]
Duration of response[1], month				
Events[2] / Responders	1 / 19	1 / 8	0 / 5	0 / 4
Median (95% CI)	NR (NE, NE)	NR (17.3, NE)	NR (NE, NE)	NR (NE, NE)
Range: min – max	6.8 – 60.5	6.8 – 51.8	10.2 – 36.4	8.6 – 55.9

SM-AHNMD: systemic mastocytosis with associated non-mast cell lineage disorder; ASM: aggressive systemic mastocytosis; MCL: mast cell leukemia; ORR: overall response rate = proportion of patients achieved a complete or partial remission; CI: confidence interval; min: minimum; max: maximum; IWG: Internal Working Group; NR: not reached; NE: not estimable
[1] Defined only for responders; [2] An event was defined to be occurrence of disease progression or death

Figure 1: Kaplan-Meier Plot of Duration of Response (Study D2201, Primary Analysis Population)



For the supportive study A2213, ORR evaluated by the original Valent criteria during the first 2 cycles of treatment was 73.1% (19 out of 26 patients, 95% CI: [52.2, 88.4]).

Reviewer Comments:

- *In Study D2201, the estimated ORR based on IWG criteria was lower than the one based on the protocol-specified response assessment criteria. However, the IWG criteria and the modified Valent and Cheson criteria may not be directly comparable. In addition, the ORR results based on IWG criteria should not be used to test the null ORR rate of 30%, as the historical benchmark was developed based on literature of studies where treatment responses were assessed using the original or modified version of Valent response criteria.*
- *The ORR result from Study A2213 should not be compared directly against the ORR result from Study D2201, because these 2 studies assessed treatment responses after different durations of treatment and based on different response criteria.*

3.2.4.2 Treatment Response by Baseline Characteristics

Table 6 displays the results on ORR by key baseline characteristics subgroups other than SM subtypes (ORR by SM subtypes already presented in Table 4 and Table 5). The ORR was consistent across the key subgroups, with lower rates only in relatively small subgroups.

Table 6 : Study D2201 Overall Response Rate by Baseline Factors

Factor	Subgroup	Response Criteria	
		Modified Valent/Cheson r / n, % [95% CI]	IWG r / n, % [95% CI]
Age	< 65 years	27 / 46 (58.7) [43.2, 73.0]	15 / 65 (23.1) [13.5, 35.2]
	≥ 65 years	26 / 43 (60.5) [44.4, 75.0]	4 / 51 (7.8) [2.2, 18.9]

Factor	Subgroup	Response Criteria	
		Modified Valent/Cheson r / n, % [95% CI]	**IWG r / n, % [95% CI]**
Gender	Female	22 / 32 (68.8) [50.0, 83.9]	6 / 40 (15.0) [5.7, 29.8]
	Male	31 / 57 (54.4) [40.7, 67.6]	13 / 76 (17.1) [9.4, 27.5]
Region	North America	16 / 28 (57.1) [37.2, 75.5]	4 / 37 (10.8) [3.0, 25.4]
	Other	37 / 61 (60.7) [47.3, 72.9]	15 / 79 (19.0) [11.0, 29.4]
D816V KIT mutation	Yes	46 / 73 (63.0) [50.9, 74.0]	16 / 94 (17.0) [10.1, 26.2]
	No or Unknown	7 / 16 (43.8) [19.8, 70.1]	3 / 22 (13.6) [2.9, 34.9]
Prior anti-neoplastic therapy for SM	Yes	21 / 32 (65.6) [46.8, 81.4]	8 / 47 (17.0) [7.7, 30.8]
	No	32 / 57 (56.1) [42.4, 69.3]	11 / 95 (11.6) [5.9, 19.8]
ECOG performance status	0-1	38 / 57 (66.7) [52.9, 78.6]	14 / 76 (18.4) [10.5, 29.0]
	>=2	15 / 31 (48.4) [30.2, 66.9]	5 / 39 (12.8) [4.3, 27.4]

r / n: number of responders / number of eligible patients according to the respective response criteria;

SM: systemic mastocytosis; CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; IWG: International Working Group

3.2.4.3 Overall Survival

Table 7 presents the overall survival result from patients in Study D2201 primary analysis population. At the time of data cut-off (01-Dec-2014), 54 patients (61%) had died. The median overall survival was 26.8 months (95% CI: 17.6, 34.7).

The median follow-up time for overall survival, calculated as the time from treatment initiation to end of survival follow-up (date of death or the last contact), was 20.7 months. The median survival in patients that had died was 14.9 months, and the median follow-up in surviving patients was 37.3 months.

Table 7: Study D2201 Patient Overall Survival

	Primary Analysis Population N =89
Overall Survival[1]	
Events / Censored	54 / 35
Median (95% CI)	26.8 months (17.6, 34.7)
Survival Rate, % (95% CI)	
6 months	89.6 % (81.0, 94.5)
12 months	70.2% (59.2, 78.8)
18 months	59.1% (47.8, 68.8)
24 months	50.5% (39.3, 60.7)
Follow-up[2] for Survival, median (range)	
In all patients	20.7 months (0.4 – 68.3)
In patients that had died	14.9 months (1.6 – 51.1)
In patients that were still alive	37.3 months (0.4 – 68.3)

CI = confidence interval

[1] Overall survival was measured form the start of treatment until death due to any cause or the date of last contact

[2] Follow-up time was calculated as the time from treatment initiation date to survival end date (date of death or last contact), regardless of survival status

Reviewer Comments:

- *Because Study D2201 is a single-arm trial, the overall survival (OS) result presented in this section is not interpretable on its own* (b) (4)
- *The overall survival result in all the 116 enrolled patients is similar to the result in the primary analysis population. The median is estimated at 28.7 months based on 67 events.*
- *The applicant provided overall survival data of 46 patients from a contemporary German registry to serve as historical data for comparison with OS result from Study D2201. Considering that the data provided are not useful to make a confirmatory comparison due to the small size and potential differences between studies, the OS result from the historical data is not presented in this review.*

3.2.4.4 Patient-Reported Outcomes

Study D2201 had assessed patients-reported quality of life outcomes as exploratory endpoints. The Memorial Symptom Assessment Scale (MSAS) total score is the average of all 32 symptom scores in the MSAS instrument. The Short Form (SF)-12 physical component and mental component scores are combination scores of 12 symptom scores from the SF-12 instrument, with more weights to the physical symptoms and mental symptoms, respectively.

Of the 89 patients in the primary analysis population, about 60% of them were considered evaluable for having assessments on the instruments for at least 168 days (i.e., 6 28-day cycles of treatment). Among the patients that were considered evaluable, 38% had ≥50% reduction in MSAS total symptom score, but less than 20% of them had ≥50% reduction in SF-12 scores.

Table 8 : Study D2201 Patients with Improvement in Patient-Reported Outcomes

	All patients in the primary analysis population	**Evaluable patients**
MSAS Total Score		
No. of patients	89	52
≥ 50% reduction from baseline[1], n (%)	20 (22.5%)	20 (38.5%)
SF-12 Physical Component Score		
No. of patients	89	53
≥ 50% reduction from baseline[1], n (%)	10 (11.2%)	10 (18.9%)
SF-12 Mental Component Score		
No. of patients	89	53
≥ 50% reduction from baseline[1], n (%)	3 (3.4%)	3 (5.7%)

MSAS: Memorial Symptom Assessment Scale; SF-12: Short Form 12 items

Evaluable patients: baseline score > 0, and evaluable for at least 168 days

[1] had a ≥ 50% decrease in score that was maintained for at least 168 days

Reviewer Comment:

(b) (4)

(1) the study did not have a control arm for comparison in order to interpret the patient-reported

outcomes; (2) missing data were substantial with only about 60% of patients in the primary analysis population were evaluable for the PRO outcomes; (3) there was no formal validation for the use of the instruments as quality of life assessment tools in this patient population; and (4) there was no formal justification to using 50% reduction as the threshold for meaningful improvement in quality of life. The PRO outcome results presented in this section are only to be considered as supportive evidence.

3.3 Evaluation of Safety

To support the proposed indication of midostaurin as a single-agent therapy for advanced SM, the evaluation of safety is mainly based on pooled safety database consists of 142 patients from studies D2201 and A2213 who were treated with single-agent midostaurin at a dose of 100 mg twice a day. There is no pre-specified hypothesis testing for safety.

Overall, the average treatment exposure was 19.3 months, with 69 (49%) of patients had at least 12 months of exposure. A total of 133 patients (94%) experienced at least one treatment-related adverse event and 59 patients (42%) experienced a Grade 3/4 treatment-related adverse event. The highest incidences of treatment-related adverse events were nausea (76%), vomiting (63%), and diarrhea (28%). A total of 16 patients (11%) had a treatment-related adverse event leading to treatment discontinuation. On-treatment deaths occurred in 26 patients (18%).

Please refer to the clinical review for detailed safety evaluation and clinical interpretation.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Please refer to Table 6 for the pivotal study D2201 best overall response rate results by gender, age, and geographic region. Subgroup analysis was not performed by race, because 96% of the study patients were white.

4.2 Other Special/Subgroup Populations

Please refer to Table 6 for pivotal study D2201 overall response rate results by other baseline factors, including: D816V KIT mutation status, prior anti-neoplastic medication, and ECOG performance status at baseline.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The proposed indication for single-agent midostaurin in advanced systemic mastocytosis is mainly supported by single-arm study D2201 conducted in 116 patients; 89 of those patients were evaluable for treatment response according to protocol-specified response criteria.

The primary treatment efficacy was evaluated in Study D2201 based on overall response rate (ORR), defined as the proportion of patients with a best response of major response or partial response that initially occurred in the first 6 cycles of treatment with midostaurin as assessed by an external study steering committee using the modified Valent and Cheson criteria and that was confirmed at least 56 days later. Based on a response rate of 60% from the first 40 evaluable patients, the study rejected a null hypothesis of ORR ≤ 30% and continued to expansion phase for final estimation of ORR. The overall ORR rate in the evaluable population was 59.6% (95% CI: [48.6, 69.8]), including 40 patients achieved a major response and 13 patients achieved a partial response as the best response. The ORR was ≥ 50% across disease subtypes. The estimated median duration of response was 31.4 months in all responders, with the estimated median duration of response being not reached in patients who achieved a major response and being 7.4 months in patients who achieved a partial response.

Patient survival and quality of life were assessed in Study D2201. However, because Study D2201 was a single-arm trial, the survival and quality of life outcomes were not interpretable (b) (4)

Data on treatment response assessment according to the IWG criteria were provided to the Agency during the review. The percentage of patients in Study D2201 who achieved either a complete or partial remission was 16.5% (95% CI: [10.3, 24.6]). The IWG criteria may not be directly comparable to the modified Valent and Cheson criteria, and therefore is not to be tested against the null ORR rate of 30% for interpretation of treatment efficacy.

For the supportive study A2213, the overall response rate in 26 patients was 73.1% (95% CI: [52.2, 88.4]). This ORR result supports treatment benefit of midostaurin. However, data from Study A2213 should not be pooled with data from Study D2201 for estimation of ORR, because these 2 studies assessed treatment responses after different durations of treatment and based on different response criteria.

There were no major statistical issues identified during the review.

5.2 Conclusions and Recommendations

Approval is recommended for midostaurin as a single-agent therapy in patients with advanced systemic mastocytosis.

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/s/

CHIA-WEN KO
02/01/2017

LEI NIE
02/01/2017

RAJESHWARI SRIDHARA
02/01/2017

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 207997
Supplement #:	Not applicable (Original New Drug Application)
Drug Name:	RYDAPT® (Midostaurin, PKC412) 25 mg capsules
Indication(s):	Newly diagnosed acute myeloid leukemia (AML) that is FLT3 mutation-positive as detected by an FDA-approved test
Applicant:	Novartis Pharmaceuticals Corporation
Date(s):	Submission date: August 29, 2016
	PDUFA date: April 28, 2017
	Review completion date: February 1, 2017
Review Priority:	Priority
Biometrics Division:	Division of Biometrics 5 (HFD-711)
Statistical Reviewer:	Chia-Wen Ko, Ph.D.
Concurring Reviewers:	Lei Nie, Ph.D., Team Leader
	Rajeshwari Sridhara, Ph.D., Division Director
Medical Division:	Division of Hematology Products
Clinical Team:	Ashly Ward, M.D., reviewer
	Donna Przepiorka, M.D., team leader
Project Manager:	Kimberly Scott

Keywords: overall survival, imprecise median estimation, transplantation, gender effect

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1 EXECUTIVE SUMMARY

This is the statistical review for RYDAPT® (midostaurin) initial New Drug Application (NDA) seeking the approval of midostaurin in combination with standard induction and consolidation chemotherapy [redacted](b)(4) for adult patients with newly diagnosed acute myeloid leukemia (AML) who are FLT3 mutation-positive, as detected by a FDA approved test.

The pivotal study A2301 supporting this application was a randomized, double-blind, placebo-controlled study in 717 patients 18-60 years of age with newly diagnosed FLT3-mutated AML to assess the efficacy and safety of midostaurin in combination with standard induction and consolidation chemotherapy [redacted](b)(4). The standard chemotherapy used in Study A2301 was the cytarabine and daunorubicin 7+3 induction therapy, followed by high-dose cytarabine consolidation therapy. Patients were randomized prior to induction at 1:1 ratio, with stratification on FLT3 mutation status, to receive midostaurin or placebo in addition to standard chemotherapy during induction and consolidation followed by monotherapy midostaurin or placebo during a continuation phase. Patients who entered the continuation phase received their initial treatment assignment, without being re-randomized.

Study A2301 primary efficacy endpoint was overall survival, defined as the time from randomization to death from any cause. Event-free survival was the only multiplicity adjusted key secondary endpoint. An EFS event was defined as a failure to obtain a complete remission within 60 days of initiation of protocol therapy, or relapse, or death from any cause. Other secondary endpoints included complete remission rate within 60 days of start of treatment, disease-free survival, and stem cell transplantation rate.

Study A2301 met its primary objective to demonstrate that midostaurin is superior to placebo in combination with standard chemotherapy regimen in prolongation of overall survival (hazard ratio [95% confidence interval]: 0.77 [0.63, 0.95], 2-sided p-value: 0.016). Treatment benefit is also supported by significant improvement in event-free survival. In addition, all other secondary endpoints are in favor of midostaurin over placebo and the incidences of treatment-emergent adverse events are similar between midostaurin and placebo arms. However, because survival curves plateaued before reaching the medians (see Figure 1); the estimated median survival times are not reliable. The table below summarizes the efficacy results.

Efficacy Endpoint	Midostaurin + SOC N=360	Placebo + SOC N=357	Hazard Ratio[1] [95% CI]	P-value[2] (2-sided)
Median overall survival	74.4 months	25.6 months	0.77 [0.63, 0.95]	0.016
Median event-free survival	8.2 months	3.6 months	0.78 [0.66, 0.93]	0.004
Median disease-free survival	26.7 months	15.5 months	0.71 [0.55, 0.92]	0.010
Complete remission by Day 60	58.9% (212/360)	53.5% (191/357)	-	0.146
Stem cell transplantation	59.4% (214/360)	55.2% (197/357)	-	0.250

[1] Hazard ratios for midostaurin over placebo in time-to-event endpoints, estimated based on Cox regression models stratified by FLT3 mutation status at randomization. [2] The p-values for time-to-event endpoints (including overall survival, event-free survival, and disease-free survival) are from log-rank tests stratified by FLT3 mutation status at randomization. The p-values for comparisons in complete remission and transplantation rates are from exact Cochran-Mantel-Haenszel tests adjusted for FLT3 mutation status at randomization.

This review has evaluated 4 issues with the efficacy results from Study A2301, including: (1) gender effect on overall survival; (2) substitute for estimated median survival times; (3) impact from high transplantation rate on overall survival result; and (4) use of midostaurin monotherapy for maintenance. Please refer to section 3.2.4.4 for detailed evaluations. The following summarizes major findings from the evaluations:

- Although benefit of midostaurin in survival was suggested for male patients but not for female patients, the overall efficacy results were in favor of midostaurin regardless gender to warrant a limitation of use in female patients.
- The difference in early overall survival percentiles and the difference in restricted mean survival times were investigated as alternatives to the difference in median survival times to describe benefit of midostaurin on a time scale. Both alternatives were in favor of midostaurin; however, just like the difference in median survival times, both alternatives produced results that were inconsistent with the overall treatment benefit as estimated by hazard ratio. (b)(4)
- The primary overall survival result appeared to be robust against the occurrence of stem cell transplantations.
- The design of Study A2301 was not appropriate to justify midostaurin monotherapy as a stand-alone maintenance therapy in patients with AML (in other words, a maintenance therapy that can be given to any patients regardless what induction and consolidation therapy they had received).

Based on the overall positive efficacy findings from the pivotal study, this reviewer recommends approving this application for the proposed indication. The median overall survival times; (b) (4) could not be reliably estimated from the pivotal study. (b) (4) The design of the pivotal study could not confirm the separate benefit of midostaurin for maintenance, and therefore midostaurin monotherapy should only be used for maintenance following midostaurin in combination with standard induction and consolidation chemotherapy.

2 INTRODUCTION

2.1 Overview

Product and Proposed Indication

RYDAPT® (midostaurin) is a protein kinase inhibitor, proposed for the following 2 indications:

1. Newly diagnosed acute myeloid leukemia (AML) that is FLT3 mutation-positive as detected by an FDA-approved test
2. Advanced systemic mastocytosis (Advanced SM)

There will be separate statistical reviews for the proposed indications. This review will focus on evaluations for proposed indication #1 in AML.

Disease Overview

AML is a type of blood cancer. The disease starts in the bone marrow when immature bone marrow cells (often called blast cells) keep building up. As an acute disease, AML can quickly be fatal if without treatment. Prognosis of the disease depends on age, history of blood disorders or cancers, and status of certain gene mutations such as FLT3 gene mutation. Initial therapy has been the '7+3' chemotherapy induction regimen with cytarabine and an anthracycline, followed by post-remission therapy with additional intensive chemotherapy such as high dose cytarabine.

Clinical Studies

Table 1 summarizes the clinical studies submitted to support the AML indication. The primary assessments for the treatment efficacy and safety of midostaurin will be based on the pivotal study A2301. The supportive studies will be pooled for the safety evaluation of midostaurin used as a monotherapy or used in combination with chemotherapy; however, they will not be evaluated to support efficacy claim in the proposed indication for AML because they are different from the pivotal study either in patient population or in dosing regimen.

Table 1: Overview of Midostaurin Clinical Studies in AML

Study	Population	Design	Midostaurin Dose	Primary Endpoint	Sample size
A2301 Pivotal study (phase III)	Newly diagnosed FLT3-mutated AML, age 18-60	Randomized, double-blind, midostaurin vs. placebo with standard induction and consolidation chemotherapy, followed by single-agent maintenance	50 mg bid	OS	717
A2106 (phase IB)	Newly diagnosed or refractory AML, age 18-60	Sequential or concomitant administration with standard induction chemotherapy	100 mg bid	Safety	69
A2104E1 (phase II)	Relapsed AML and high risk MDS, age >18	Randomized between 2 doses, monotherapy	50 mg bid 100 bid	Tumor response	95

Study	Population	Design	Midostaurin Dose	Primary Endpoint	Sample size
A2104 (phase II)	Relapsed FLT3-mutated AML, age >18	Single-arm, monotherapy	75 mg bid	Clinical response rate	20
A2104E2 (phase II)	Relapsed AML and high risk MDS, age >18	Monotherapy Intra-patient dose escalation vs combination with Itraconazole	Up to 300 mg bid	Safety	29

* AML= acute myeloid leukemia, FLT3= Fms-like tyrosine kinase-3, MDS= myelodysplastic syndrome, bid= twice daily, OS= overall survival, ORR= overall response rate

2.2 Data Sources

Materials reviewed for this application: protocols, statistical analysis plans, study reports, and submitted datasets for Study A2301 and integrated safety analysis (ISS).

Reviewed data were provided electronically with legacy data formats. Datasets are located at: \\CDSESUB1\evsprod\NDA207997\0002\m5\datasets\pkc412a2301 (for Study A2301) and \\CDSESUB1\evsprod\NDA207997\0003\m5\datasets\iss (for ISS)

There were issues with the datasets define files, including multiple files for the same study and incomplete or missing information on variable codes. The issues were conveyed to the applicant on 09/30/2016. Response from applicant received on 10/20/2016 had addressed the issues.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Data from Study A2301 were provided electronically with legacy (applicant company standard) formats. There were issues with the data define documentation, including incomplete or missing variable coding. The issues had been addressed by applicant during the review cycle. Data quality appeared to be acceptable in general with no errors identified for randomization and deviation of major study endpoints.

3.2 Evaluation of Efficacy

The evaluation for treatment efficacy of midostaurin will be based on data from the 717 patients randomized in the pivotal study A2301.

3.2.1 Study Design and Endpoints

Study A2301 was a randomized, double-blind, placebo-controlled study examining the efficacy and safety of midostaurin in combination with standard of care induction and consolidation

chemotherapy followed by midostaurin single-agent as maintenance therapy in patients <60 years of age with newly diagnosed FLT3-mutated AML. Patients were randomized prior to induction at 1:1 ratio, with stratification on FLT3 mutation status (i.e. FLT3-ITD allelic ratio <0.7, FLT3-ITD allelic ratio ≥0.7, or FLT3-TKD), to receive midostaurin or placebo in addition to standard of care chemotherapy during induction and consolidation followed by monotherapy midostaurin or placebo during a continuation phase. Patients who entered the continuation phase received their initial treatment assignment, without being re-randomized.

The study treatment was 200 mg/m^2/day cytarabine (Days 1-7) and 60 mg/m^2/day daunorubicin (Days 1-3) and 50 mg twice a day midostaurin/placebo (Days 8-21) during the induction phase. Patients who achieved a complete remission after up to 2 cycles of induction therapy received up to 4 cycles of consolidation therapy with high-dose cytarabine (3 g/m^2 i.v. every 12 hours on Days 1, 3 and 5 of each cycle) followed by midostaurin/placebo 50 mg twice a day on Days 8-21. Patients who continued to maintain a complete remission after consolidation therapy received continuation therapy with midostaurin 50 mg or placebo twice a day for a maximum of 12 cycles of 28 days each. In the event that a patient received non-protocol therapy directed against their leukemia (e.g. transplant), midostaurin/placebo therapy would be discontinued.

Study A2301 primary efficacy endpoint was overall survival (OS), defined as the time from randomization to death from any cause. Event-free survival (EFS) was the only multiplicity adjusted key secondary endpoint. An EFS event was defined as a failure to obtain a complete remission (CR) within 60 days of initiation of protocol therapy, or relapse, or death from any cause. Other secondary endpoints included CR rate within 60 days of start of treatment, disease-free survival (DFS), and stem cell transplantation (SCT) rate.

Quality of life assessments were not collected on Study A2301.

3.2.2 Statistical Methodologies

The primary analysis population supporting the proposed AML indication included all randomized patients in Study A2301. They were analyzed according to the treatment arm assigned at randomization.

The primary comparison between treatment arms in OS was based on log-rank test and Cox regression model stratified for FLT3 mutation status used in the randomization. OS was not censored at the time of SCT in the primary analysis. The primary analysis of EFS was conducted using the same methodology as the primary analysis of OS. For the control of Type I error, comparison in EFS was tested for statistical significance after comparison in OS was significant.

Study A2301 planned to enroll at least 714 patients, in order to have 509 OS events at the final analysis to demonstrate a hazard ratio of 0.78 for midostaurin versus placebo (or correspondingly a 4.6-month improvement in median OS from 16.3 months in placebo arm to 20.9 months in midostaurin arm) with approximately 85% power at an overall 2-sided alpha level of 0.05. The sample size calculation also accounted for one planned interim analysis of OS at 50% of events.

Due to slow occurrence of death events, Study A2301 protocol was amended to perform the final OS analysis with a data cut off of 01-April-2015. The critical 2-sided p-value to declare statistical significance was calculated to be 0.047 for the maintenance of overall 2-sided alpha at 0.05, based on total of 357 events occurred up to April 2015 and the alpha already spent (fixed at 2-sided 0.01) at the interim analysis.

Reviewer Comments:

- *The primary analysis of OS did not censor for stem cell transplantation. The applicant; however, did recognize that transplantations may impact a patient's overall survival, and therefore had proposed several sensitivity analyses including an analysis in which OS was censored at the time of transplantation. Those analyses will be presented and compared to the primary analysis later in this review.*
- *The planned interim analysis for OS was conducted with 255 death events. The result was not significant with a 2-sided p-value of 0.0252. The study continued, but the event occurrence became very slow. In March 2015, 350 events had been observed with only one death in the prior 6 months.*

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

The pivotal study A2301 enrolled a total of 717 patients: 360 patients randomized to the midostaurin arm, and 357 patients randomized to the placebo arm.

A total of 709 patients received at least one dose of study treatment in the induction phase: 355 in the midostaurin arm and 354 in the placebo arm. Treatment discontinuation rate was high but comparable between treatment arms (79.4% in the midostaurin arm, 84.6% in the placebo arm). The most common reasons for treatment discontinuation was the decision to obtain alternative therapy (including SCT) followed by disease progression.

Table 2: Study A2301 Patient Disposition

	Midostaurin N = 360 n (%)	**Placebo N = 357 n (%)**
Patient Treated	355 (98.6)	354 (99.2)
Received induction therapy	355 (98.6)	354 (99.2)
Received consolidation therapy	231 (64.2)	210 (58.8)
Received continuation therapy	120 (33.3)	85 (23.8)
Treatment completed	69 (19.2)	52 (14.6)
Treatment discontinued	286 (79.4)	302 (84.6)
Phase of treatment discontinuation		
Induction	122 (33.9)	144 (40.3)
Consolidation	113 (31.4)	124 (34.7)
Continuation	51 (14.2)	34 (9.5)
Primary reason for treatment discontinuation		
Alternative therapy	109 (30.3)	107 (30.0)
Disease progression	58 (16.1)	58 (16.2)
Patient withdrawal	22 (6.1)	40 (11.2)

	Midostaurin N = 360 n (%)	Placebo N = 357 n (%)
Adverse event/Complication	32 (8.9)	22 (6.2)
Death on study	18 (5.0)	18 (5.0)
Other	47 (13.1)	57 (16.0)

Table 3 gives a summary on demographics and other baseline characteristics for patients in Study A2301. The median age was 47 years (range: 18 to 60 years). Approximately one-third of the patients were enrolled in the North America. The two treatment arms were balanced for baseline characteristics, with the exception that the percentage of males was higher in the placebo arm.

Table 3: Study A2301 Demographics and Other Baseline Factors

Factor	Midostaurin N = 360	Placebo N = 357
Age (years)		
18-39 / 40-60	97 / 263 (27 / 73 %)	95 / 262 (27 / 73 %)
mean (SD), median, min-max	45 (10.4), 47, 19-59	46 (10.8), 48, 18-60
Gender		
Female / Male	186 / 174 (52 / 48 %)	212 / 145 (60 / 41 %)
Race		
White / Other / Unknown[1]	147 / 19 / 194 (41 / 5 / 54 %)	128 / 18 / 211 (36 / 5 / 57 %)
Region		
North America / Other	121 / 239 (34 / 66 %)	115 / 242 (32 / 68 %)
FLT3 mutation status		
TKD / ITD < 0.7 / ITD ≥ 0.7	83 / 164 / 112 (23 / 46 / 31 %)	80 / 165 / 109 (22 / 46 / 31 %)
MDS-related AML		
Yes / No	14 / 343 (4 / 96 %)	16 / 340 (4 / 96 %)
WBC count at baseline		
$<50x10^9$/L / $\geq 50x10^9$/L	217 / 134 (60 / 37 %)	207 / 143 (58 / 40 %)
ECOG performance status		
0-1 / ≥2	323 / 37 (90 / 10 %)	310 / 47 (87 / 13 %)

SD: standard deviation, FLT: Fms-like tyrosine kinase receptor, TKD: tyrosine kinase domain, ITD: internal tandem duplication, MDS: myelodysplastic syndrome, AML: acute myeloid leukemia, WBC: white blood count, ECOG = Eastern Cooperative Oncology Group. [1] Many countries did not collect data on race. Note: TKD, ITD < 0.7 and ITD >= 0.7 were the randomization strata

3.2.4 Efficacy Results

3.2.4.1 Study A2301 Efficacy Results – Primary Endpoint Overall Survival

The primary endpoint of the pivotal study A2301 was overall survival (OS), defined as the time from randomization to death due to any cause, without censoring for stem cell transplantations. The result was statistically significant with an estimated hazard ratio of 0.77 (95% CI: [0.63, 0.95]) and a 2-sided p-value of 0.016 (compared to 0.047 for statistical significance at the final analysis of OS).

The estimated 48.8 months of difference in median OS (74.4 months versus 25.6 months) is not consistent with the estimated treatment benefit in terms of hazard ratio. A hazard ratio of 0.77 with an estimated median OS of 25.6 months in the control arm and a proportional hazards assumption would correspond to a 7.6 months (7.6= (25.6/0.77 – 25.6)) difference in median OS. Based on the survival distributions as plotted in Figure 1 and the estimated survival rates as shown in Table 4, it appears the estimated large difference in median OS was due to the fact that the survival curves reached plateau at approximately 30 months with survival rate in the midostaurin arm was still above 50%, and therefore the median OS for the midostaurin arm could not be reliably estimated.

As of the data cut-off (01-April-2015), 357 patients in Study A2301 had died. The median follow-up time for overall survival was 26.1 months (range: 0.1 – 79.2). The median survival in patients that had died was 11.2 months (0.1 – 74.7), and the median follow-up in surviving patients was 56.8 months (0.1 – 79.2).

Table 4: Study A2301 Overall Survival Result

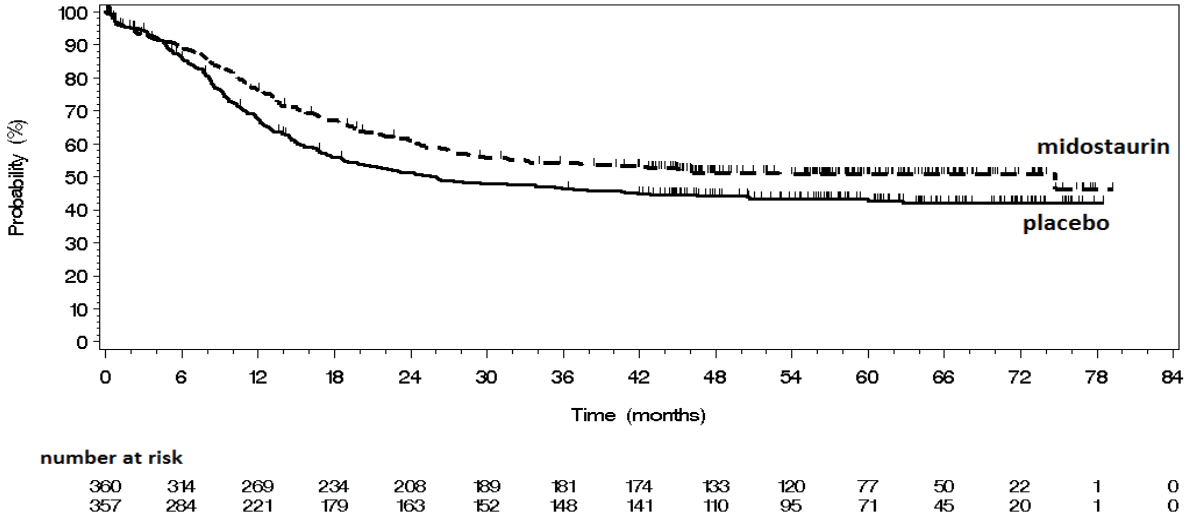
	All randomized patients	
	Midostaurin N = 360	Placebo N = 357
Number of events, n (%)	171 (47.5)	186 (52.1)
Number of censored, n (%)	189 (52.5)	171 (47.9)
Survival rate, % [95% CI]		
at 12 months	76.5 [71.7, 80.6]	67.7 [62.4, 72.5]
at 24 months	60.9 [55.6, 65.8]	51.2 [45.7, 56.5]
at 30 months	55.7 [50.3, 60.7]	47.8 [42.2, 53.1]
at 36 months	54.2 [NE, NE]	46.5 [41.0, 51.8]
at 48 months	51.3 [NE, NE]	44.2 [NE, NE]
at 60 months	50.9 [NE, NE]	43.3 [NE, NE]
Median survival, month [95% CI]	74.4 [31.5, NE]	25.6 [18.6, 42.9]
Hazard ratio, M/P [95% CI]	0.77 [0.63, 0.95]	
p-value	0.016	

CI= confidence interval; NE: not estimable

[1] Calculated using Cox regression model stratified by FLT3 mutation status at randomization

[2] 2-sided p-value for log-rank test stratified by FLT3 mutation status at randomization

Figure 1: Kaplan-Meier Plot of Survival Curves (Study A2301, All Randomized Patients)



Reviewer comment: *The median survival estimates were not reliable* (b) (4)

3.2.4.2 Study A2301 Efficacy Results – Secondary Endpoints

Table 5 summarizes Study 2301 results of secondary endpoints, including: event-free survival, disease-free survival, complete remission rate, and stem cell transplantation rate.

Event-free survival (EFS) was the only key secondary endpoint in Study A2301. Study A2301 defined an EFS event as a failure to obtain a complete remission (CR) within 60 days following initiation of protocol therapy, a relapse from CR, or death due to any cause. The estimated median EFS was 8.2 months for the midostaurin arm versus 3.6 months for the placebo arm. The estimated hazard ratio was statistically significant at 0.78 [0.66, 0.93] favoring midostaurin.

Disease-free survival (DFS) in Study A2301 was measured from the date of first CR to the date of relapse of death from any cause. The median DFS was 26.7 months in the midostaurin arm and 15.5 months in the placebo arm, and the estimated hazard ratio was 0.71 [0.55, 0.92].

A total of 403 patients (56.2%) achieved a CR by Day 60 of study treatment, and a total of 411 patients (57.3%) received stem cell transplantation. The complete remission and transplantation rates were comparable between the two treatment arms.

Because the primary endpoint OS was statistically significant, the statistically significant result of EFS can be used to support an efficacy claim in EFS. The other secondary endpoints; however, were not in pre-specified hierarchy of hypotheses testing (b) (4) .

Table 5: Study A2301 Results of the Secondary Efficacy Endpoints

Endpoint	Midostaurin (N = 360)	Placebo (N = 357)	Hazard ratio[1] [95% CI]	p-value[2]
Median EFS, month [95% CI]	8.2 [5.4, 10.7]	3.6 [0.03, 5.9]	0.78 [0.66, 0.93]	0.004
No CR by Day 60[3]	147 (40.8%)	166 (46.5%)		
Relapse	91 (25.3%)	90 (25.2%)		
Death	18 (5.0%)	24 (6.7%)		
Median DFS, month [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, n (% [95% CI])	212 (58.9 [53.6, 64.0])	191 (53.5 [48.2, 58.8])		0.146
SCT overall, n (% [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%)		

CI = confidence interval; EFS = event free survival; DFS = disease free survival; CR = complete remission; SCT = stem cell transplantation; CR1 = first complete remission; NE = not estimable

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

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

[3] For patients who did not achieve a CR by Day 60, Day 1 was assigned to be the event date

Reviewer Comments:

- *For patients who did not achieve a CR by Day 60, Study A2301 protocol defined the event date to be the date of last clinical assessment for the primary analysis of EFS. The review team defined Day 1 instead to be the event date in those patients, because those patients had not achieved a CR since Day 1 from a treatment perspective. The EFS result presented in Table 5 was based on the review team's definition. The result of EFS based on the protocol definition was similar (median: 8.2 months for the midostaurin arm versus 3.0 months for the placebo arm, hazard ratio: 0.78 [0.66, 0.93]).*
- *The transplantation rate was very high in Study A2301. The robustness of overall survival result against the occurrence of transplantation will be evaluated in section 3.2.4.4.*

3.2.4.3 Study A2301 Overall Survival Result by Subgroups

Study A2301 overall survival subgroup results did not show outliers with the overall population result, although differences were observed in some subgroups such as females (n=398, hazard ratio 1.01) versus males (n= 319, hazard ratio 0.53) and subgroups with small sizes.

Table 6 : Study A2301 Overall Survival Result by Subgroups

Factor	Subgroup	Midostaurin events n/N	Placebo events n/N	Hazard ratio[1] [95% CI]
Age	18-39 years	43/97	45/95	0.70 [0.46, 1.06]
	40-60 years	128/262	141/261	0.80 [0.63, 1.02]
Gender	Female	93/186	97/212	1.01 [0.76, 1.34]
	Male	78/174	89/145	0.53 [0.39, 0.72]
Race	White	82/147	74/128	0.87 [0.64, 1.20]
	Other	89/213	112/229	0.69 [0.53, 0.92]
Region	North America	65/121	68/115	0.75 [0.53, 1.05]
	Other	106/239	118/242	0.78 [0.60, 1.01]

Factor	Subgroup	Midostaurin events n/N	Placebo events n/N	Hazard ratio[1] [95% CI]
FLT mutation status	TKD	26/81	35/81	0.65 [0.39, 1.09]
	ITD<0.7	78/171	82/170	0.80 [0.59, 1.10]
	ITD>=0.7	67/108	68/106	0.80 [0.57, 1.12]
MDS-related AML	Yes	12/14	10/16	1.91 [0.78, 4.71]
	No	159/346	176/341	0.74 [0.60, 0.92]
WBC	<50x10^9/L	95/217	100/207	0.80 [0.60, 1.06]
	>=50x10^9/L	72/134	82/143	0.72 [0.53, 0.99]
ECOG performance status	0-1	148/323	159/310	0.74 [0.59, 0.93]
	>=2	23/37	27/47	1.04 [0.59, 1.85]

CI = confidence interval; MDS = myelodysplastic syndrome; AML = acute myeloid leukemia; WBC = white blood count at baseline; ECOG = Eastern Cooperative Oncology Group; TKD = tyrosine kinase domain; ITD = internal tandem duplication

[1] Hazard ratio estimated by Cox regression model, stratified by FLT mutation status

Note: overall survival not censored for stem cell transplantation

Reviewer Comment:

The overall survival subgroup analysis by gender suggested that the addition of midostaurin to standard chemotherapy may have a survival benefit in male patients but not in female patients. However, Study A2301 was not designed with a pre-specified hypothesis and sufficient power to test whether or not midostaurin had a gender effect on overall survival. Secondary endpoint results by gender will be presented in section 3.2.4.4, for overall consideration of midostaurin treatment benefit in female patients.

3.2.4.4 Evaluation of Issues with Efficacy Results

Four issues with efficacy results of pivotal study A2301 are discussed in this section, including: (1) gender effect on overall survival; (2) substitute for estimated median overall survival; (3) high transplantation rate; and (4) use of midostaurin monotherapy for maintenance.

3.2.4.4.1 Gender Effect on Overall Survival

As previously shown in Table 6, benefit of midostaurin in survival was suggested for males but not for females. Considering that the female patients accounted for 56% (398 out of 717) of the patients in the pivotal study, the gender difference in midostaurin effect on survival is an issue.

The reviewer evaluated this issue by several examinations, including: (1) examination of secondary endpoints results by gender, to see if there was overall evidence against the use of midostaurin in females; (2) examination of treatment by gender interaction on overall survival; and (3) examination of imbalance between the treatment arms in the status for Nucleophosmin (NPM1) mutation, which was indicated by the applicant as the most informative positive disease prognostic maker that co-occurs with FLT3 mutations.

Table 7 shows the results of Study A2301 secondary endpoints by gender. All the secondary endpoints were in favor of midostaurin regardless of gender.

The reviewer evaluated the treatment by gender interaction effect on overall survival using a Cox regression model including treatment, gender, and treatment by gender interaction terms. The

resulting 2-sided p-value for testing treatment by gender interaction on overall survival was 0.0113, suggesting that the impact on survival from midostaurin as an add-on therapy to standard chemotherapy may be different between males and females. Further examination of the survival curves in Figure 2 suggested that the treatment by gender interaction was because that male patients and female patients had different amounts of separation in overall survival between treatment arms, and that the survival prognosis in female patients was dramatically better than male patients.

In addition, gender difference on overall survival results were examined by NPM1 mutation status. The gender effect on overall survival could not be explained by NPM1 mutation, as the gender effect on survival remained after adjusting for the NPM1 mutation status and was observed within subgroups of patients defined by NPM1 mutation.

In summary, the overall efficacy results were in favor of midostaurin regardless gender. Although midostaurin might not provide additional benefit to standard chemotherapy in prolongation of long-term survival in female patients, it might be beneficial in short term endpoints for female patients.

Table 7: Study A2301 Efficacy Results by Gender

Endpoint	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]	
EFS				
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]	
SCT by Day 60				
SCT/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]	

OS = overall survival; EFS = event-free survival; DFS = disease-free survival; CR = complete remission; SCT = stem cell transplantation; CI = confidence interval; N = number of patients in the analysis
Note: For the EFS analysis, Day 1 was assigned to be the event date in patients who did not achieve a CR by Day 60

Figure 2: Study A2301 Gender-Specific Plots of Kaplan-Meier Survival Curves

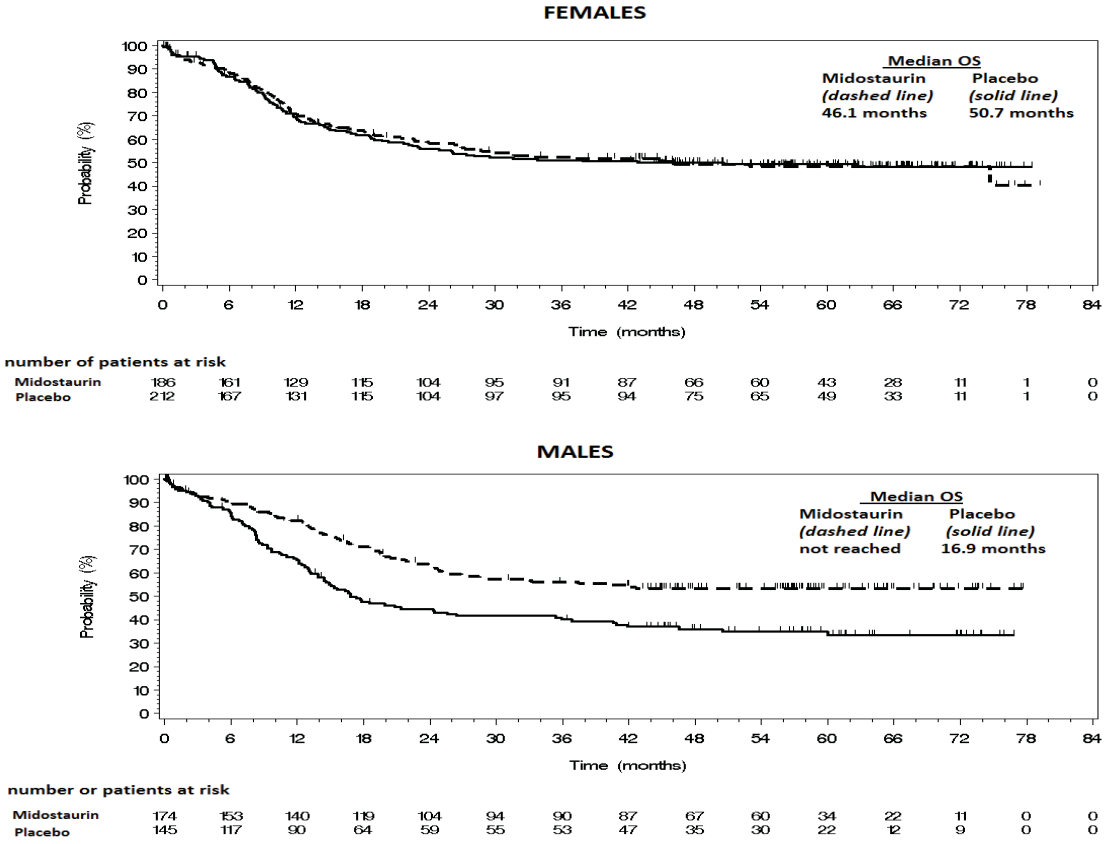


Table 8: Study A2301 Gender-specific Overall Survival Results by NPM1 Mutation Status

Overall Survival	Males		Females	
	Midostaurin	Placebo	Midostaurin	Placebo
NPM1 mutated patients				
Event/N (%)	24/71 (33.8)	28/52 (53.8)	39/91 (42.9)	47/110 (42.7)
Median	Not reached	26.4 months	Not reached	Not reached
HR[1] [95% CI]	0.51 [0.29, 0.88]		0.87 [0.57, 1.33]	
NPM1 wild type patients				
Event/N (%)	37/70 (52.9)	38/51 (74.5)	40/62 (64.5)	31/56 (55.4)
Median	40.1 months	12.0 months	18.3 months	23.2 months
HR[1] [95% CI]	0.47 [0.30, 0.75]		1.16 [0.72, 1.88]	
All randomized patients				
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
HR[1] [95% CI]	0.53 [0.39, 0.72]		1.01 [0.76, 1.34]	
NPM1-adjusted HR[2] [95% CI]	0.46 [0.33, 0.66]		0.98 [0.72, 1.35]	

CI = confidence interval; HR = hazard ratio; N = number of patients in analysis; NPM1 = Nucleophosmin

[1] Hazard ratio estimated from Cox regression model, stratified by FLT3 mutation status at randomization

[2] Hazard ratio estimated from Cox regression model, stratified by FLT3 mutation status at randomization, and adjusted for NPM1 mutation status as a covariate

Reviewer Comments:

- *Data collection on mutation profiling was performed according to a companion protocol to Study A2301. Data on NPM1 mutation status was provided by the applicant, as the most informative positive prognosis marker whose mutational profiling was consistently performed in the majority of study patients (563 or 79% of patients in Study A2310). However, since NPM1 mutation may co-occur with FLT3 mutation, results from FLT3 mutation stratified analyses with and without further adjusting for NPM1 mutation were similar.*
- *Because transplantation rate was similar between treatment arms in both male and female subgroups of patients in Study A2301, occurrence of transplantation was not evaluated as a factor that may explain the observed gender difference in midostaurin effect on survival.*

3.2.4.4.2 Substitute for Estimated Median Overall Survival

For a regulatory application based on a time to event endpoint such as overall survival, the difference in estimated median times between treatment arms is usually used to describe the size of treatment benefit, following the use of hazard ratio for making an inferential decision on overall treatment benefit. For this particular application; however, the difference in estimated median overall survival times between treatment arms in Study A2301 may not be reliable due to the fact that the survival curves reached a plateau prior to medians.

The reviewer evaluated 2 options as time-scaled alternatives to the difference in median times for description of treatment benefit. Option 1 is to use difference in earlier percentiles. Option 2 is to use difference in a mean-based measure such as the restricted mean survival time, which represents the average survival up to a specific time of follow-up.
Table 9 shows the difference between Study A2301 treatment arms in survival percentiles before the median (the 50th percentile). Except for the very early 25th and 30th percentiles, the large differences between treatment arms in other percentile times were not consistent with the overall treatment benefit as estimated by the hazard ratio of 0.77.

Table 10 shows the difference between Study A2301 treatment arms in restricted mean survival times for duration of survival follow-up ranging from the minimum follow-up of 3 years to the maximum follow-up of approximately 6 years at the data cut-off. With the ratio of restricted means between treatment arms to be about 0.90 regardless of duration of follow-up, a significant benefit of midostaurin was not supported by the results of restricted means.

In summary, both options may not be good alternatives for this particular application. Although both were in favor of midostaurin over placebo, the results were not consistent with estimated hazard ratio for the overall estimation of treatment survival benefit.

Besides the time-scaled alternatives, one option is to present observed survival rates such as the ones presented in Table 4 for description of survival distributions.

Table 9: Comparison in Survival Percentiles between Treatment Arms in Study A2301

Percent	Midostaurin (N = 360)		Placebo (N = 357)		Comparison in percentile times between treatment arms	
	Time* (months)	# Events	Time* (months)	# Events	Difference: M - P	Ratio: P / M
25	12.9	89	9.3	85	3.6 months	0.72
30	15.5	106	11.0	100	4.5 months	0.71
35	19.5	124	12.9	116	6.6 months	0.66
40	24.6	141	15.1	132	9.5 months	0.61
45	33.0	158	18.7	148	14.3 months	0.57
50 (median)	74.7	171	25.6	164	49.1 months	0.34

M = Midostaurin; P = Placebo

* Percentile survival times estimated based on Kaplan-Meier survival curves

Table 10: Comparison in Restricted Mean Survival Times between Treatment Arms in Study A2301

Follow-up (year)	Midostaurin (N = 360)		Placebo (N = 357)		Comparison in restricted means between treatment arms	
	Time (months)	[95% CI]	Time (months)	[95% CI]	Difference: M – P	Ratio: P / M
3.0	25.5	[9.2, 11.9]	22.9	[11.7, 14.6]	2.6	0.90
3.5	28.7	[11.7, 15.0]	25.6	[14.6, 18.1]	3.1	0.89
4.0	31.8	[14.3, 18.1]	28.3	[17.7, 21.8]	3.5	0.89
4.5	34.9	[16.9, 21.3]	30.9	[20.7, 25.4]	4.0	0.89
5.0	37.9	[19.6, 24.6]	33.5	[23.8, 29.1]	4.4	0.88
5.5	41.0	[22.2, 27.8]	36.1	[27.0, 32.9]	4.9	0.88
6.0	44.0	[24.9, 31.1]	38.6	[30.2, 36.7]	5.4	0.88

M = Midostaurin; P = Placebo; CI = confidence interval

* Restricted mean survival times estimated based on the area under Kaplan-Meier survival curves up to the specific follow-up

3.2.4.4.3 High Transplantation Rate

The stem cell transplantation rate was high for both treatment arms in Study A2301. The primary analysis of overall survival was not adjusted for the occurrence of transplantation.

The applicant did acknowledge the high transplantation rate, and performed several sensitivity analyses to evaluate the robustness of overall survival result against stem cell transplantations. The sensitivity analyses include an analysis having overall survival censored at the time of transplantation, an analysis considering the occurrence of transplantation as a time-dependent covariate, and another analysis only in the patients who had received transplantation in complete remission. The results from these analyses, as shown in Table 11, did not contradict to the result from the primary analysis.

Table 11: Study A2301 Overall Survival Analyses regarding Stem Cell Transplantation

Analysis	Midostaurin	Placebo
OS not censored for SCT (primary analysis)		
Number of events/N (%)	171/360 (47.5)	186/357 (52.1)
Hazard ratio, M/P [95% CI]	0.77 [0.63, 0.95]	
OS censored at time of SCT		
Number of events/N (%)	71/360 (19.7)	81/357 (22.7)
Hazard ratio, M/P [95% CI]	0.75 [0.54, 1.03]	
OS with SCT as a time-dependent covariate		
Number of events/N (%)	171/360 (47.5)	186/357 (52.1)
Hazard ratio, M/P [95% CI]	0.79 [0.61, 0.98]	
OS from start of SCT in first complete remission		
Number of events/N (%)	28/92 (30.4)	32/75 (42.7)
Hazard ratio, M/P [95% CI]	0.63 [0.38, 1.05]	

OS = overall survival; SCT = stem cell transplantation; M = Midostaurin; P = Placebo; CI = confidence interval

3.2.4.4.4 Use of Midostaurin Monotherapy for Maintenance

(b) (4)

(b) (4)

There were no data from a proper randomized maintenance study to assess the value of midostaurin monotherapy as maintenance in patients with FLT3-mutated AML in first remission. There were 205 patients received continuation therapy in Study A2301 (120 patients in the midostaurin arm and 85 patients in the placebo arm); however, they received continuation therapy with midostaurin or placebo according to their assignment without re-randomization. Although a comparison between treatment arms in overall survival after start of continuation therapy was in favor of midostaurin (hazard ratio [95% CI]: 0.80 [0.50, 1.28]), the comparison can only be viewed as exploratory.

3.3 Evaluation of Safety

There is no formal pre-specified hypothesis testing for safety. The evaluation of safety for midostaurin in combination with standard induction and consolidation chemotherapy for the treatment of newly diagnosed AML is mainly based on safety data from Study A2301.

There were a total of 680 patients received a least one dose of study drug in Study A2301; 345 patients in the midostaurin arm and 335 patients in the placebo arm. The percentage of patients who were exposed to study drug for at least 12 months was higher in the midostaurin arm at 21.2% compared to 15.2% in the placebo arm. The percentage of patients who experienced at least one grade 3/4 treatment-emergent adverse event was similar between study arms; 78.0% in the midostaurin arm and 75.2% in the placebo arm. Grade 3/4 events that occurred with at least 3% higher incidence in the midostaurin arm compared to the placebo arm included dermatitis exfoliative (7.2% versus 2.7%) and aspartate amino transferase increase (4.9% versus 1.8%).

The percentage of patients died during treatment was lower in the midostaurin arm than in the placebo arm: 15 patients (4.3%) versus 21 patients (6.3%), respectively.

Supportive study A2106 provided additional safety data for midostaurin in combination with chemotherapy in patients with previously untreated AML. Supportive studies A2104, A2104E1 and A2104E2 provided safety data for single-agent midostaurin in patients with relapsed or refractory AML. None of the supportive studies had reported an incidence of treatment-emergent adverse events to be higher than the one reported for Study A2301.

Please refer to the clinical review for detailed safety results and clinical interpretation.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Overall survival result from pivotal study A2301 by subgroups of patients defined by gender, race, age, and geographic region are displayed in Table 6. There were no outlier subgroups except that a difference was observed between male and female patients.

To further evaluate any potential differences between male and female patients in treatment benefit of midostaurin, subgroup analyses of secondary efficacy endpoints from Study A2301 are performed by gender. The results, as shown in Table 7, do not suggest a limitation of use should be considered for midostaurin in female patients.

4.2 Other Special/Subgroup Populations

Overall survival result from pivotal study A2301 by other subgroups of patients defined by FLT mutation status, myelodysplastic syndrome related disease status, white blood count, and medical performance status are displayed in Table 6. There were no outlier subgroups.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

In summary, the overall risk and benefit results from the pivotal study A2301 were supportive of approval for midostaurin in combination with standard chemotherapy as a treatment for patients with newly diagnosed FLT3-mutated AML. Study A2301 demonstrated a statistically significant result in its primary endpoint overall survival (OS), defined as the time from randomization to death due to any cause, without censoring for stem cell transplantations. The estimated hazard ratio for midostaurin arm over placebo arm in OS was 0.77 (95% CI: [0.63, 0.95], 2-sided log-rank test p-value: 0.016). All the secondary endpoints in Study A2301 were in favor of the addition of midostaurin, and the incidences of treatment-emergent adverse events were similar

between patients who received and patients who did not receive midostaurin in addition to the standard chemotherapy used in Study A2301.

Four issues with the efficacy results from Study A2301 were evaluated in this review:

1. Gender effect on overall survival: Benefit of midostaurin in survival was suggested for males but not for females. This issue was evaluated by examining the secondary endpoints results by gender, the treatment by gender interaction on overall survival, and the imbalance between treatment arms in an important disease prognosis marker NPM1 mutation status. The evaluations found that overall efficacy results were in favor of midostaurin regardless gender to warrant a limitation use in female patients.
2. Substitute for estimated median overall survival: The difference in estimated median overall survival times between treatment arms in Study A2301 was not reliable due to the fact that the survival curves plateaued before reaching medians. Two time-scaled alternatives were evaluated: difference in earlier percentiles, and difference in restricted mean survival times. The evaluations found that both may not be good alternatives for this particular application. Although both were in favor of midostaurin over placebo, the results were not consistent with estimated hazard ratio for the overall estimation of treatment survival benefit.
3. High transplantation rate: The stem cell transplantation rate was as high as 57% in Study A2301. The robustness of overall survival result against stem cell transplantations was evaluated through sensitivity analyses. Results from the sensitivity analyses did not contradict to the result from the primary analysis.
4. Use of midostaurin monotherapy for maintenance: (b) (4)

   Because patients in Study A2301 were given continuation therapy with midostaurin or placebo according to their assignment without re-randomization, Study A2301 was not appropriate (b) (4)

5.2 Conclusions and Recommendations

Based on the overall positive efficacy findings from the pivotal study, approval is recommended for the proposed indication of midostaurin in combination with standard induction and consolidation chemotherapy for adult patients with newly diagnosed AML who are FLT3 mutation positive.

The median overall survival times for midostaurin versus placebo in combination with standard chemotherapy (b) (4) could not be reliably estimated from the pivotal study. (b) (4) The design of the pivotal study could not confirm the separate benefit of midostaurin for maintenance, and therefore midostaurin monotherapy should only be used for maintenance following midostaurin in combination with standard induction and consolidation chemotherapy.

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