CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Midostaurin (Rydapt) for Systemic Mastocytosis

April 2, 2020

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ABBREVIATIONS

advSM	Advanced systemic mastocytosis
AE	Adverse event
AESI	Adverse event of special interest
AHNMD	Associated hematological clonal non-mast cell lineage disease
AHN	Associated hematological neoplasm
ALT	Alanine transaminase
ASCO	American Society of Clinical Oncology
ASH	American Society of Hematology
ASM	Aggressive systemic mastocytosis
AST	Aspartate transaminase
BM	Bone marrow
CI	Confidence interval
CVD	Cardiovascular disease
DCR	Disease control rate
DOR	Duration of response
ECOG	European Cooperative Oncology Group
EHA	European Hematology Association
EPAR	European Public Assessment Report
FAS	Full analysis set
FDA	Food and Drug Administration
GI	Gastrointestinal
HCT	Hematopoietic cell transplant
HGF	Hematopoietic growth factor
HRQoL	Health-related quality of life
INV	Investigator
ITT	Intention-to-treat
IWG-MRT-ECNM	International Working Group-Myeloproliferative Neoplasms Research and Treatment-European Competence Network on Mastocytosis
KIT	Tyrosine kinase encoded by the KIT proto-oncogene
LVEF	Left ventricular ejection fraction
MCL	Mast cell leukemia
MCS	Mental component summary score of the SF-12
MDS	Myelodysplastic syndrome

MR	Major response
MSAS	Memorial Symptom Assessment Scale
NA	Not applicable
NE	Not estimable
NR	Not reported
ORR	Overall response rate
OS	Overall survival
PCS	Physical component summary score of the SF-12
PD	Progressive disease
PEP	Primary efficacy population
PFS	Progression-free survival
PR	Partial response
PRO	Patient-reported outcome
PS	Performance status
RBC	Red blood cell
RCT	Randomized controlled trial
SD	Stable disease
SF-12	Short form health survey-12
SM	Systemic mastocytosis
SM-AHN	Systemic mastocytosis associated with hematologic neoplasm
SSC	Study steering committee
TMAS	Total Memorial Symptom Assessment Score
TTR	Time to response
ULN	Upper limit of normal
WDAE	Withdrawal due to adverse event
WHO	World Health Organization

1 GUIDANCE IN BRIEF

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding midostaurin for advanced systemic mastocytosis. The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the CADTH website (www.cadth.ca/pcodr).

This Clinical Guidance is based on: a systematic review of the literature midostaurin for advanced systemic mastocytosis conducted by the Systemic Mastocytosis Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; input from Registered Clinicians; and supplemental issues relevant to the implementation of a funding decision.

The systematic review and supplemental issues are fully reported in Sections 6 and 7. A background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on midostaurin for advanced systemic mastocytosis, a summary of submitted Provincial Advisory Group Input on midostaurin for advanced systemic mastocytosis, and a summary of submitted Registered Clinician Input on midostaurin for advanced systemic mastocytosis, and are provided in Sections 2, 3, 4, and 5 respectively.

1.1 Introduction

The purpose of this review is to evaluate the efficacy and safety of midostaurin for the treatment of adult patients with aggressive systemic mastocytosis (ASM), aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated hematologic neoplasm (SM-AHN), or mast cell leukemia (MCL).

Midostaurin is an orally bioavailable, small-molecule multi-targeted protein kinase inhibitor, including c-KIT.[1]

Midostaurin has been issued a Health Canada marketing authorization without conditions that reflects the requested patient population for reimbursement; midostaurin is indicated for the treatment of adult patients with ASM, SM-AHN, or MCL.

The recommended dose of midostaurin is 100mg twice daily. Treatment should be continued as long as clinical benefit is observed or until unacceptable toxicity occurs.

Midostaurin should be taken orally, twice daily at approximately 12-hour intervals with food to help prevent nausea. Prophylactic anti-emetics should be administered in accordance with local medical practice as per patient tolerance.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

Two completed non-randomized phase II trials were identified that met the eligibility criteria for the systematic review. Study 2201 was a manufacturer-sponsored, single-arm, open-label, international, multicentre trial that included adult patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated hematologic neoplasm (SM-AHN), or mast cell leukemia (MCL); collectively referred to as advanced systemic mastocytosis (advSM). Study 2213 was an investigator-initiated and manufacturer-sponsored, single-arm, open-label, multicentre trial that also included adult patients with

ASM, SM-AHN, or MCL. In Study 2201 there were 116 patients included in the full analysis set [FAS[a]] and 89 patients included in the primary efficacy population [PEP]) whereas in Study 2213 there were 26 patients included in both the PEP and FAS.[2-4] Both trials enrolled patients irrespective of *KIT* D816V mutation status and required that patients have ≥ 1 C-findings, European Cooperative Oncology Group (ECOG) performance status between 0 to 3, and adequate renal and hepatic function.

Key exclusion criteria in both trials were serious cardiovascular disease (CVD) such as congestive heart failure and use of hematopoietic growth factor (HGF) support within two weeks of study entry. Study 2201 also excluded patients that had relapsed after ≥3 systemic mastocytosis (SM) treatments or had eosinophilia and known positivity for FIP1L1-PDGFRα fusion, unless the patient had relapsed or had disease progression on imatinib.

The intervention in both trials was oral midostaurin 100 mg twice daily administered over continuous 4-week cycles. In Study 2201, patients received up to six cycles of midostaurin after which they entered an extension phase. In Study 2213, patients received up to 12 cycles of midostaurin after which they also entered an extension phase, although if patients did not achieve a major response (MR) or partial response (PR) in the first two months, then treatment was discontinued. Otherwise in both trials, midostaurin treatment continued during the extension phases until disease progression or unacceptable therapeutic effect, unacceptable toxicity, or patient withdrawal. Assessment of efficacy and harms included patients enrolled in the initial stages of the trials and the extension phases.

Efficacy

The primary efficacy outcome in Study 2201 was the overall response rate (ORR) defined as the proportion of patients classified as confirmed responders (i.e., having a MR or PR during the first six cycles of midostaurin treatment as adjudicated by the SSC according to modified Valent[5] and Cheson[6,7] criteria and confirmed for ≥ 8 weeks in the PEP). Secondary outcomes included duration of response (DOR), time to response (TTR), progression-free survival (PFS), overall survival (OS), safety and tolerability, and histopathologic response based on bone marrow mast cell infiltration and serum tryptase levels. Exploratory outcomes included the assessment of patient-reported outcomes (PROs) using the Memorial Symptom Assessment Scale (MSAS)[8] and the Medical Outcomes Study 12-Item Short-Form Health Survey (SF-12).[9,10]

The primary outcome in Study 2213 was ORR defined as the proportion of patients with a best overall response of MR or PR by investigator assessment (INV) over the first two cycles of midostaurin treatment according to Valent criteria[11] and confirmed for ≥ 8 weeks. Secondary outcomes included safety and tolerability, pharmacokinetic parameters, *KIT* mutation status, OS, and PFS. [redacted]. (*Non-Disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the manufacturer that it can be publicly disclosed).*

[a] The FAS was defined as all patients to whom study drug was assigned in both Study 2201 and Study 2213; however, in Study 2201, the PEP comprised all patients in the FAS who met diagnostic criteria for ASM or MCL and presented with at least one measurable C-finding at study entry and/or patients with transfusion-dependent anemia due to their underlying disease as confirmed by the study steering committee (SSC). In Study 2213, the PEP was defined as all patients in the FAS who received at least 14 days of midostaurin treatment and who did not have any major protocol deviations. In Study 2213 the PEP and FAS were identical.

Baseline characteristics

In Study 2201 (PEP) (N=89), the median age was 64 years (range: 25 to 82), 64% of patients were male, and 36% of patients had an ECOG performance score of 2 or 3.[3] More than 50% of patients had not received any prior treatment for SM and most (87% in the PEP) were positive for a *KIT* D816 mutation. The PEP included 16 (18%) patients with ASM, 57 (64%) patients with SM-AHN, and 16 (18%) patients with MCL (of which six [7%] had MCL associated with AHN). All patients had at least one sign of organ damage and most (43% in the PEP) had three or more C-findings. Baseline median tryptase levels were 236 µg/mL (range: 27 to 12,069) and median bone marrow mast cell burden was 50% (range: 8 to 98) in the PEP.

In Study 2213, median age was 64.5 years (range: 24 to 79), 58% of patients were male, and 54% of patients had an ECOG performance score of 2 or 3.[4] Most patients (>80%) had received prior treatment and were positive (77%) for a *KIT* D816 mutation. Of the 26 patients in the FAS, 3 (12%) were diagnosed with ASM, 17 (65%) with SM-AHN, and 6 (23%) with MCL. All patients had at least one sign of organ damage with the largest category of patients (39%) having at least two C-findings.[4] Baseline median tryptase levels were 323 ng/mL (range: 22 to 1255) and median bone marrow mast cell burden was 50% (range: 5 to 95).[4]

Highlights of the key outcomes of Study 2201 and Study 2213 are provided in Table 1.1.

Table 1.1: Highlights of Key Outcomes of Study 2201 and Study 2213

	Study 2201		Study 2213	
Data cut-off	Dec 1, 2014		Dec 3, 2012	Mar 1, 2017
Median follow-up (range)	43 months (29 to 70)		73 months (31 to 89)	124 months (82 to 140)
Analysis population	PEP (N=89)	FAS (N=116)	FAS (N=26)	FAS (N=26)
Overall survival				
No. deaths, n (%)	54 (60.7)	67 (57.4)	[redacted]	22 (84.6)
Median OS, months (95% CI)	26.8 (17.6; 34.7)	28.7 (20.3; 38.0)	[redacted]	40.0 (27.3; 52.7)
Progression-free survival				
No. PFS events, n (%)	45 (50.6)	45 (38.8)	8 (30.8)	10 (38.5)
Median PFS, months (95% CI)	17.0 (10.2; 24.8)	17.0 (10.2; 24.8)	38.6 (11.3; NE)	41.0 (4.4; 77.6)
Overall response rate [a]				
ORR, n (%) (95% CI)	53 (59.6) (48.6; 69.8)	53 (45.7) (36.4; 55.2)	19 (73.1) (52.2; 88.4)	18 (69) (50; 88)
Major response, n (%)	40 (44.9)	40 (34.5)	13 (50.0)	13 (50)
Partial response, n (%)	13 (14.6)	13 (11.2)	6 (23.1)	5 (19)
Stable disease, n (%)	11 (12.4)	11 (9.5)	6 (23.1)	5 (19)
Progressive disease, n (%)	10 (11.2)	10 (8.6)	1 (3.8)	3 (12)
Not evaluable, n (%)	15 (16.9)	42 (36.2)	0 (0)	0 (0)
Patient-reported outcomes				
TMSAS scores				
≥50% decrease from BL, n (%)	20 (22.5)	NR	NA	NA
SF-12 scores				
≥50% increase from BL in PCS, n (%)	10 (11.2)	NR	NA	NA
≥50% increase from BL in MCS, n (%)	3 (3.4)	NR	NA	NA
Harms Outcome, n (%)	**SAS (N=116)[b]**		**SAS (N=26)[b]**	
Grade ≥3	103 (88.8)		16 (61.5)	
SAE	85 (73.3)		12 (46.2)	

	Study 2201	Study 2213
AE (any grade)	116 (100)	26 (100)
TRAE	108 (93.1)	25 (96.2)
WDAE	30 (25.9)	4 (15.4)

Abbreviations: AE = adverse event; BL = baseline; BM = bone marrow; CI = confidence interval; DOR = duration of response; FAS = full analysis set; HRQoL = health-related quality of life; MCS = mental component score of the SF-12; NA = not applicable; NE = not estimable; NR = not reported; ORR = overall response rate; OS = overall survival; PCS = physical component score of the SF-12; PFS = progression-free survival; PEP = primary efficacy population; SAE = serious adverse event; SAS = safety analysis set; SF-12 = Short form health survey-12; TMSAS = Total Memorial Symptom Assessment Score; TRAE = treatment-related AE; WDAE = withdrawal due to AE

Notes:

[a] The primary efficacy outcome in Study 2201 was ORR (MR + PR) by SSC adjudication and in Study 2213 was ORR (MR + PR) by investigator assessment

[b] Primary data cut-off date for SAS in Study 2201 is December 1, 2014 and in Study 2213 is December 3, 2012

(Non-Disclosable information was used in this pCODR Guidance Report and the manufacturer requested this efficacy information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the manufacturer that it can be publicly disclosed).

The results of Study 2201 have been analyzed, presented or published using data from five different data extraction dates: March 15, 2012,[13] December 1, 2012,[14] July 9, 2013,[3,15] December 1, 2014 (primary analysis),[2] and August 24, 2017 (final OS analysis only).[16] The sponsor confirmed that the only planned interim analysis was the analysis with data cut-off of March 15, 2012[13] which reported the results of n=62 patients enrolled in Stage 1.[17] The clinical data for Study 2201 presented in this report corresponds to the data cut-off date of December 1, 2014 (unless otherwise specified) as per the submitted Clinical Study Report (CSR) for Study 2201 and is in alignment with the data cut-off date for Study 2201 in the economic evaluation submitted by the sponsor.[2] Of note, data from the final OS analysis for Study 2201 (data cut-off date of August 24, 2017) are also reported. The median duration of follow-up as of December 1, 2014 was 43 months (range: 29 to 70) and 21 (18.1%) patients in the FAS and 15 (16.9%) patients in the PEP remained on treatment.[18] The median duration of follow-up as of August 24, 2017 (final OS analysis) was 76 months ([redacted]).[19] *(Non-Disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the manufacturer that it can be publicly disclosed).*

The results of Study 2213 have been analyzed, presented or published also using data from five different data extraction dates: June 1, 2006,[20] June 1, 2007,[21] and June 1, 2010[22] (all three data cuts mentioned are estimated by the sponsor) as well as December 3, 2012[2] and March 1, 2017.[4] As Study 2213 was an investigator-sponsored trial (whereby all abstracts and study publications were controlled strictly by the study investigators)[23], the sponsor was unable to confirm which of the data cut-offs were pre-specified.[17] The clinical data presented in this report for Study 2213 corresponds with a data cut-off of December 3, 2012 as reported in the CSR[2] and March 1, 2017,[4] the data cut-off for the main publication for Study 2213. The data cut-off date of March 1, 2017 is in alignment with the data cut-off date in the sponsor's economic evaluation.[2] The median duration of follow-up as of March 1, 2017 was 124 months (range: 82 to 140) and two (7.7%) of patients remained on treatment.

In Study 2201, based on the December 1, 2014 data cut-off, 54 patients (60.7%) in the PEP had died corresponding with a median OS of 26.8 months (95% CI: 17.6; 34.7).[18] In the final OS analysis (data cut-off August 24, 2017), median OS was similar: 26.8 months (95% CI: 17.6; 34.4) in the PEP.[24] Based on the December 1, 2014 data cut-off date, median PFS was 17.0 months (95% CI: 10.2; 24.8). For the primary efficacy outcome of ORR by SSC adjudication in the PEP, at the same data cut-off, 53 patients had a confirmed best response of MR (n=40) or PR (n=13) corresponding with an ORR of 59.6% (95% CI: 48.6; 69.8).

In Study 2213, [redacted] ([redacted])[12] whereas at the data cut-off of March 1, 2017, 22 patients (84.6%) had died and median OS was 40.0 (95% CI: 27.3; 52.7).[4] (*Non-Disclosable information was used in this pCODR Guidance Report and the manufacturer requested this efficacy information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the manufacturer that it can be publicly disclosed).* Median PFS was 38.6 months (95% CI: 11.3; NE) and 41.0 months (95% CI: 4.4; 77.6),[4] for the two data cut-offs, respectively. For the December 3, 2012 data cut-off, 13 patients (50.0%) had a MR and six patients (23.1%) had a PR corresponding with an ORR by INV (primary efficacy outcome) of 73.1% (95% CI: 52.2; 88.4). For the March 1, 2017 data cut-off, ORR was 69% (95% CI: 50; 88).[4]

For both, Study 2201 and Study 2213, pre-specified subgroup analyses of OS and ORR are of interest to this review (e.g., by SM sub-type, prior therapies, *KIT* mutation status) are reported in section 6.3.2.2; however, due to small sample sizes and lack of interaction testing, the results are associated with uncertainty and are considered to be exploratory.

Patient-reported outcomes

PROs measured by the MSAS and SF-12 were included in Study 2201 as exploratory outcomes. According to the statistical analysis plan, results were to be summarized using descriptive statistics only. The sponsor reported that 20 (38.5%) of 52 evaluable patients in the PEP had ≥ 50% decrease (improvement) from baseline in the total MSAS score and 10 (18.9%) of 53 evaluable patients and 3 (5.7%) of 53 evaluable patients had ≥ 50% increase (improvement) from baseline in the physical component score (PCS) and the mental component score (MCS) of the SF-12, respectively.

Data were available for approximately 60% of the patients in the PEP who were considered evaluable (i.e., had baseline scores > 0 and were evaluable for ≥ 168 days [six cycles]). There were increasingly fewer eligible patients with less than 50% of the patients providing PRO scores after cycle 12 and beyond.[25] Overall, the CADTH Methods Team concluded that no firm conclusions can be drawn based on the PRO results due to several limitations (see section 6 for more details).

Harms

Based on a pooled safety analysis of harms outcomes from Study 2201 and Study 2213, all (100%) patients in both studies experienced an adverse event (AE) and of these, 93.1% and 96.2%, respectively, were suspected to be treatment-related. The most frequent AEs suspected to be treatment-related were gastrointestinal (GI)-related (e.g., nausea, vomiting, diarrhea), the majority of which were of grade 1 or 2 severity. Furthermore, 88.8% (Study 2201) and 61.5% (Study 2213) of patients experienced AEs of grade 3-4

severity. The most frequent grade 3-4 AEs were due to myelosuppression (e.g., anemia, thrombocytopenia, and neutropenia).

Limitations

- Both Study 2201 and Study 2213 were non-randomized, single-arm, open-label trials. The non-randomized design complicates the interpretation of the efficacy and safety data for midostaurin because all patients received the same treatment which precludes the ability to assess relative benefit or harm in terms of clinical or statistical significance against a relevant comparator.

- The open-label design of the trials potentially increases the risk of performance and detection bias because both study personnel and patients were aware of the treatment allocation. The lack of blinding is expected to have the largest impact on subjective outcomes such as PROs and AEs.

- The patient populations in both Study 2201 (N=116 FAS) and Study 2213 (N=26 FAS) are small which is not unexpected given the rarity of advSM. Although many subgroup and sensitivity analyses were pre-specified in both trials, the results of these analyses are associated with substantial uncertainty as the resultant sample sizes in these analyses are even smaller and associated with wide confidence intervals (CIs). Further, the lack of statistical interaction testing and adjustments for multiple comparisons adds to the uncertainty associated with the results, which are considered to be exploratory.

- The primary and secondary efficacy and safety analyses in both Study 2201 and Study 2213 were assessed in all patients, regardless of SM sub-type. Combining all patients into one group, regardless of the SM sub-type, discounts the potential for clinical heterogeneity in disease processes or differences in prognostic heterogeneity based on the specific SM sub-type.[26] In addition, for the SM-AHN sub-type, the type of hematologic neoplasm can also have a large impact on clinical outcomes or prognosis.[26]

- Although OS and PFS were secondary outcomes in both included trials, it is challenging to interpret the OS and PFS results in a single-arm trial because it is unclear to what extent the outcomes can be attributed to the treatment effect of the drug.[27] In Study 2213, patients were followed up for survival for only one year, therefore, long-term survival beyond one year cannot reliably be determined from this trial. In Study 2201, there was a large proportion of patients (approximately 49% and 39%) censored from the PFS and OS analyses, respectively. Furthermore, in Study 2201 patients who discontinued midostaurin were able to receive subsequent antineoplastic therapy (i.e., 35 [39.3%] patients in the PEP received such therapies) which may have confounded the OS analysis.

- PROs (i.e., MSAS, SF-12) were only included in Study 2201 as exploratory outcomes and the results are limited by missing data and a lack of validation of the instruments and determination of the minimal clinically important differences in patients with advSM. As a result, no firm conclusions regarding the clinical significance of the PRO outcomes could be drawn.

1.2.2 Additional Evidence

See Section 3, Section 4, and Section 5 for a complete summary of patient advocacy group input, Provincial Advisory Group (PAG) Input, and Registered Clinician Input, respectively.

Patient Advocacy Group Input

One patient group, Mastocytosis Society Canada (MSC), with support of the Canadian Organization for Rare Disorders (CORD) provided input on midostaurin (Rydapt) for systemic mastocytosis (SM).

MSC and CORD noted that, from a patient's perspective, SM is a very aggressive and debilitating condition with limited treatment options for patients. Patients considered symptom control to be their biggest concern, as the disease has significantly impacted their ability to carry on their daily activities. Some of the most debilitating symptoms reported by patients include fatigue, headaches, lightheadedness, gastro-intestinal problems and skin-related issues such as lesions, hives, rashes and itching and allergic reactions. Patients reported that these symptoms have caused a significant amount of physical and psychological distress to not only themselves but also their caregivers and loved ones.

MSC and CORD commented that overall, current therapies do not appear to halt the progression of disease or control bouts of symptoms. Some of the most common therapies that have been used by patients to control symptoms included antihistamines (for skin and abdominal reactions), allergen immunotherapy or epinephrine for allergic reactions, steroids and chemotherapy. The survey results revealed very little patient awareness of midostaurin, as almost three-fourths (73%) of survey respondents reported that they had never heard of midostaurin and only 10% knew about the drug and how it was used. Overall, approximately five patients had indicated that they had experience with midostaurin. While some patients spoke highly favourable of midostaurin as it was reported to result in a significant improvement in their quality of life (i.e., helps with symptom control and gradual return to activities) others spoke of its benefits but were also challenged by the drug regimen and its side effects. Two patients reported that they had to discontinue the therapy with midostaurin due to side effects. MSC and CORD however cautioned against the generalizability of these reactions to the larger population due to the very small number of patients who have experience with midostaurin. When presented with the drug profile of midostaurin, the majority of patients (93%) responded favourably and said that it should be made available through drug plans. An overarching theme in patient responses was the ability to maintain a level of independence to be able to carry on their daily tasks. Patients value new therapies that would provide better symptom management, improve quality of life and survival, and would have minimal or manageable side effects.

Provincial Advisory Group (PAG) Input

Input was obtained from **all nine** provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation:

Clinical factors:

- No standard of care in this setting

Economic factors:

- High cost of midostaurin
- Additional pharmacy resources and clinic visits may be required

Registered Clinician Input

One individual clinician input was provided by a hematologist/oncologist from Cancer Care Ontario Hematology DAC for the review of midostaurin (Rydapt) 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 clinician asserted an unmet medical need considering that systemic mastocytosis is a very symptomatic disease with poor outcomes. Midostaurin was recommended as a first-line treatment as it appears to have better responses than other treatments and seems to be tolerable.

Summary of Supplemental Questions

- Critical appraisal of the sponsor's submitted naïve treatment comparison of midostaurin and standard of care (SOC) for the treatment of advanced systemic mastocytosis

In the submitted economic evaluation, the sponsor identified the comparator for midostaurin to be SOC which was defined as a combination of available therapies (i.e., interferon, hydroxyurea, cladribine, and cytarabine) that are used off-label in Canada for the treatment of adult patients with advSM.[2] The sponsor obtained estimates for the clinical inputs of OS and ORR for SOC in the submitted economic model from the published literature. The OS estimate for SOC was derived through hazard mapping using a published hazard ratio (HR) of 2.2 (95% CI: 1.08; 4.47) for OS in favour of midostaurin over control.[28] The HR for OS was based on a naïve comparison of survival data from 28 patients who received midostaurin through a compassionate-use program with that of 44 historical controls who did not receive midostaurin, all of whom were registered in the French Centre de Réfèrence National des Mastocytoses (CEREMAST) database.[28,29] For the comparison, patients were matched only on age at diagnosis and SM sub-type.[28,29] The sponsor was unable to confirm if propensity scoring was used to match patients in the analysis.[30] The CADTH Methods team identified differences among various baseline characteristics of the patients in the two groups, most notably that they were not matched on prior therapies. The historical controls were more heavily pre-treated than the midostaurin-treated patients which suggests that they may have been more refractory to treatment and thus predisposed to worse survival outcomes. For the ORR estimate for SOC (52.2%), a weighted average (by sample size) was calculated from the ORR of 50% (n=32) for cladribine reported in a retrospective cohort analysis by Barete et al., 2015[31] and the ORR of 57.1% (n=14) for interferon from a review paper by Valent et al., 2003 in which the authors calculated the average ORR of 14 patients derived from seven separate case reports.[5] Other limitations included methodological limitations of the studies from which data for the SOC were obtained (e.g., small sample sizes, limited data reporting, retrospective analyses, missing data elements).

The use of naïve treatment comparisons to compare drug therapies is associated with many limitations.[32] A major limitation of a naïve treatment comparison is that it is not possible to determine if any observed differences in efficacy or safety between therapies is solely due to the treatment or rather due to bias or confounding factors such as differences in study populations, definitions of outcomes, or study designs.[32] It would have been preferable for the sponsor to have conducted a matching-adjusted indirect comparison (MAIC) which uses individual patient level data to match baseline summary statistics of patients which is then used to compare treatment outcomes across balanced trial populations.[33] Due to the above limitations, the comparative efficacy estimates obtained for OS and ORR should be interpreted with caution and are likely biased. It is

difficult to quantify or identify the direction of the bias. As a result, the estimates may over- or underestimate the true treatment effect associated with midostaurin.

Refer to section 7.1 for the complete critical appraisal of the naïve treatment comparison.

- Critical appraisal of the sponsor's submitted pooled survival analysis of midostaurin clinical study data from Study 2201 and Study 2213 in patients with advSM compared with historical controls

An alternate source for the HR for OS which was derived from an unpublished pooled survival analysis by Reiter et al., 2017 was provided in the economic evaluation.[34] Information on the Reiter analysis was only available from the slides of an oral presentation submitted by the sponsor, therefore, methodological details are limited. In their analysis, the authors pooled OS data for midostaurin-treated patients with a known date of diagnosis from Study 2201 (n=63) and Study 2213 (n=26) and compared OS data for the pooled dataset (n=89) with that of historical controls (n=42) who did not receive midostaurin from a German registry. As a supportive analysis, propensity scoring was used to match midostaurin-treated patients (n=42) from the pooled dataset with historical controls (n=42) using age at diagnosis, WHO-defined SM sub-type (i.e., ASM, SM-AHN, and MCL), prior lines of treatment, and sex as factors. Midostaurin-treated patients and historical controls were matched 1:1 based on their assigned propensity score and a stratified Cox regression model using the matched pairs as strata was used to analyze the matched dataset. Median OS was 27.8 months (95% CI; 19.3; 44.6) in the pooled midostaurin-treated patients and 19.5 months (95% CI: 13.0; 35.3) in the historical controls, corresponding with a 36% lower risk of death in midostaurin-treated patients or a HR of 0.636 (95% CI: 0.326; 1.244). The inverse HR for OS, as provided in the economic evaluation, was 1.57 (95% CI, 0.80-3.07).

The Reiter analysis[34] may be a better source for the HR estimate for OS compared to the Chandesris study,[28] which was used in the sponsor's submitted economic evaluation. The Reiter analysis matched patients on more factors (i.e., age at diagnosis, WHO-defined SM sub-type, prior treatments, and sex), matched to a more contemporary group of patients (~95% of patients were diagnosed after 2005), had longer median follow-up for both the pooled midostaurin-treated patients and historical controls, and provided a more conservative HR estimate for OS than the Chandesris study. Key limitations identified with the Reiter analysis were lack of information on SOC or the specific treatments received by the historical controls and the pooling of data from Study 2201 and Study 2213 despite differences in study design such as the different length of follow-up for survival data. As with the Chandesris study, Reiter et al., did not conduct a systematic literature review to identify all potential studies, conduct a risk of bias assessment, or consider patient-reported outcomes or safety outcomes in their analysis. Due to the above limitations, the comparative efficacy estimates obtained for OS should be interpreted with caution and are likely biased.

Refer to section 7.2 for the complete critical appraisal of the pooled survival analysis

Comparison with Other Literature

The pCODR Clinical Guidance Panel and the pCODR Methods Team did not identify other relevant literature providing supporting information for this review.

1.2.3 Factors Related to Generalizability of the Evidence

Table 1.2 addresses the generalizability of the evidence and an assessment of the limitations and sources of bias can be found in Sections 6.3.2.1a and 6.3.2.1b (regarding internal validity).

Table 1.2: Assessment of generalisability of evidence of midostaurin for advanced SM.

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence from Study 2201[2,3a] and Study 2213[2,4b]</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td rowspan="4">Population</td><td>SM sub-type</td><td>Patients with ASM, SM-AHN, and MCL were combined in the primary and secondary efficacy analyses* in both trials.
SM sub-type, n (%)
<table>
<tr><th>Sub-type</th><th>2201 (N=89)</th><th>2213 (N=26)</th></tr>
<tr><td>ASM</td><td>16 (18)</td><td>3 (12)</td></tr>
<tr><td>SM-ANH:
CMML

MDS/MPN-U
MDS
CEL
Other</td><td>63 (71)
25 (28)
22 (25)
7 (8)
4 (4)
5 (6)</td><td>17 (65)
12 (46)
3 (12)
2 (8)
0 (0)
0 (0)</td></tr>
<tr><td>MCL</td><td>16 (18)</td><td>6 (23)</td></tr>
</table>
*Pre-specified subgroup analyses were also conducted by SM sub-type, but sample sizes are small and are considered to be exploratory.</td><td>Are the overall trial results generalizable to patients across all SM sub-types? Are there differences in clinical and prognostic factors with specific SM sub-types (e.g., the specific hematologic neoplasm associated with SM) that could affect the interpretation of the trial results? If so, what factors are these?</td><td>The CGP supports generalizing the study results to the three subgroups (i.e., ASM, SM-AHN, and MCL). Classification of SM has been shown to be useful in establishing prognosis. Survival is usually best in patients with ASM and worst in those with MCL. Major responses were achieved by patients on midostaurin across all SM sub-types (e.g., study 2201: ASM: 62.5%; SM-AHN: 40.4%; MCL: 43.8%) and there is no biological rationale to assume that outcomes on midostaurin would be markedly different between SM sub-types. However, the subgroup analyses by SM- subtype in studies 2201 and 2213 were inconclusive due to several limitations (e.g., small sample sizes, lack of adjustment for multiplicity, and lack of statistical interaction testing).</td></tr>
<tr><td>Organ dysfunction</td><td>Patients were required to have adequate hepatic and renal function in both trials. Approximately 70% of patients in both trials had hepatomegaly; 92% of patients in 2201 and 77% of patients in 2213 had splenomegaly.</td><td>Does the exclusion of patients with hepatic or renal dysfunction limit the interpretation of the trial results with respect to the target population (e.g., Canadian clinical practice, patients without the dysfunction, etc.)?</td><td>Given the generally well tolerated safety profile of midostaurin, the CGP suggests it is up to the discretion of the treating physician to apply some flexibility in terms of using midostaurin in patients with slightly lower lab parameters than those outlined in the trial.</td></tr>
<tr><td>Cardiovascular disease</td><td>Patients with CVD including CHF NYHA Class III or IV, LVEF < 50%, recent MI, poorly controlled hypertension, or heart block (Canada only) were excluded from the trials.</td><td>Does the exclusion of patients with CVD limit the interpretation of the trial results with respect to the target population (e.g., Canadian clinical practice, patients without CVD, etc.)?</td><td>Efficacy or safety of midostaurin was not studied in patients excluded from trial participation due to CVD. Therefore, the CGP cannot generalize treatment benefits to this patient population.</td></tr>
<tr><td>Biomarkers</td><td>Patients were included in both trials regardless of KIT D816V mutation status.</td><td>Is KIT D816V mutation status an effect modifier (i.e.,</td><td>The CGP supports generalizing the study results to patients regardless of their KIT</td></tr>
</table>

Table 1.2: Assessment of generalisability of evidence of midostaurin for advanced SM.

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence from Study 2201[2,3a] and Study 2213[2,4b]</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td></td><td>KIT D816V mutation status</td><td>KIT D816V mutation status, * n (%)
<table>
<tr><th>Study</th><th>Positive</th><th>Negative/ Unknown</th></tr>
<tr><td>2201 (N=89)</td><td>73 (82)</td><td>16 (18)</td></tr>
<tr><td>2213 (N=26)</td><td>20 (77)</td><td>5 (19) (n=1 patient with other KIT mutation)</td></tr>
</table>
*Pre-specified subgroup analyses were also conducted by KIT D816V mutation status but sample sizes are small and are considered to be exploratory.</td><td>differences in effect are expected due to biomarker status)? Are the results of the trial applicable to patients without a KIT D816V mutation or with a different KIT mutation equally?</td><td>D816 mutation status. While activating KIT mutations are frequently associated with mastocytosis, it remains unclear if such mutations alone are of prognostic relevance and explain the diverse clinical presentation of mastocytosis. ORR was achieved by patients who are KIT D816V mutation positive and negative (e.g., study 2201: KIT positive: ORR of 63.0%; KIT negative: ORR of 43.8%). However, pre-specified subgroup analyses by KIT D816V mutation in studies 2201 and 2213 were inconclusive due to several limitations (e.g., small sample sizes, lack of adjustment for multiplicity, and lack of statistical interaction testing).</td></tr>
<tr><td></td><td>Prior therapies</td><td>Patients who received investigational, targeted therapies, chemotherapy, interferon-α, or cladribine within 30 days prior to study start were excluded.</td><td>Are the trial results generalizable to patients who may be on the excluded therapies and who are transitioned to midostaurin within < 30 days?</td><td>Efficacy or safety of midostaurin was not studied in patients who received investigational, targeted therapies, chemotherapy, interferon-α, or cladribine within 30 days prior to study start. Therefore, the CGP cannot generalize treatment benefits to this patient population.</td></tr>
<tr><td></td><td></td><td>Patients who relapsed after ≥ 3 prior SM therapies were excluded from Study 2201.
Number of prior therapies, n (%)
<table>
<tr><th>Number</th><th>2201</th><th>2213</th></tr>
<tr><td>None</td><td>52 (58)</td><td>5 (19)</td></tr>
<tr><td>1</td><td>21 (24)</td><td>8 (31)</td></tr>
<tr><td>2</td><td>12 (13)</td><td>6 (23)</td></tr>
<tr><td>≥ 3</td><td>4 (4)</td><td>7 (27)</td></tr>
</table></td><td>Are the trial results generalizable to patients who have relapsed after ≥ 1 prior lines of therapy?</td><td>There are insufficient data specifically addressing the addition of midostaurin to patients who relapsed after ≥ 3 prior SM therapies and who have not previously received midostaurin. Therefore, the CGP cannot generalize treatment benefits to this patient population.
However, CGP considers that it would be reasonable to add midostaurin at the discretion of the treating physician to patients who have relapsed after 1 or 2 prior lines of therapy as per trial criteria. CGP would suggest using midostaurin as a salvage option for patients who are not responding to either interferon, cladribine or imatinib (KIT negative patients). Therefore, the CGP supports generalizing</td></tr>
</table>

Table 1.2: Assessment of generalisability of evidence of midostaurin for advanced SM.				
Domain	**Factor**	**Evidence from Study 2201[2,3a] and Study 2213[2,4b]**	**Generalizability Question**	**CGP Assessment of Generalizability**
				the study results to patients who relapsed after 1 or 2 prior SM therapies.
	Eosinophilia	Patients with ASM with eosinophilia and known positivity for FIP1L1-PDGFRα fusion unless relapse or disease progression on imatinib were excluded from Study 2201.	Are the trial results generalizable to patients with eosinophilia?	There are no data specifically addressing the addition of midostaurin to patients with ASM with eosinophilia and known positivity for FIP1L1-PDGFRα fusion. This is a very rare condition, and the vast majority of these patients respond well to imatinib.[35] However, in rare variants with imatinib resistance,[36] CGP considers that it would be reasonable to add midostaurin at the discretion of the treating physician.
Intervention	Midostaurin 100 mg twice daily in continuous 4-week cycles	Patients received oral midostaurin 100 mg (4 x 25 mg capsules) twice daily (i.e., 8 capsules total daily) with meals in both Study 2201 and Study 2213.	Is the trial dosage generalizable to patients across Canada? Are dosage modifications expected and is the pill burden anticipated to be problematic?	Results are relevant to Canada; the dosing in the trials would be acceptable to patients and physicians.

Table 1.2: Assessment of generalisability of evidence of midostaurin for advanced SM.				
Domain	**Factor**	**Evidence from Study 2201[2,3a] and Study 2213[2,4b]**	**Generalizability Question**	**CGP Assessment of Generalizability**
Comparator	No comparator	Both Study 2201 and Study 2213 were single-arm, non-comparative trials. There does not appear to be an identified standard of care for advanced SM in Canada. In the sponsor's submitted pharmacoeconomic evaluation, the standard of care was identified as a combination of available therapies including interferon, hydroxyurea, cladribine, and cytarabine. In order to assess the comparative efficacy of midostaurin compared with currently used therapies, the pCODR Methods Team reviewed a naive indirect treatment comparison. Refer to section 7 for more details.	Are there a relevant current standard of care option(s) in Canada that could have been used as an active comparator in the included trials?	Due to the lack of randomized comparative data, there is no reliable estimate of the comparative efficacy of midostaurin to current treatment options (including mostly interferon or cladribine, imatinib for KIT negative patients, and rarely hydroxyurea, cytarabine or fludarabine). The CGP noted that based on the published data, and on poor results with existing treatment options, it is likely that results with midostaurin will be equal to or better than current treatment options, with improved tolerability compared to options such as chemotherapy or allogeneic stem cell transplant. The CGP suggest that treatment toxicity profiles, patient values and preferences, co-morbidities, and treatment availability (provincial reimbursement) should guide treatment selection in clinical practice. Refer to section 1.2.4 for the CGP's interpretation of two studies (Chandesris et al., 2016[28] and Reiter at al., 2017[34]) that have attempted to compare the results achieved with midostaurin to matched historical cohorts. Refer to section 7 for the complete summary and critical appraisals of the Chandesris et al and Reiter et al studies. Data from these studies were used to elicit comparative efficacy estimates in the economic model.
Outcomes	Appropriateness of primary and Secondary Outcomes	<u>The primary efficacy outcome:</u> Studies 2201 & 2213: ORR.[c] <u>Secondary efficacy outcomes:</u> Study 2201:	Were the primary and secondary outcomes appropriate for the trial design?	Given that RCTs are likely not conducted in this rare disease, the CGP is of the opinion that an ORR of 59.6% with median duration of response of 31.4 months would likely translate into survival benefit given the currently high mortality of these patients.

Table 1.2: Assessment of generalisability of evidence of midostaurin for advanced SM.				
Domain	**Factor**	**Evidence from Study 2201[2,3a] and Study 2213[2,4b]**	**Generalizability Question**	**CGP Assessment of Generalizability**
		OS, PFS, DOR, time to response (TTR), safety and tolerability, and histopathologic response Study 2213: OS, PFS, safety and tolerability, pharmacokinetic parameters, *KIT* mutation status.		The CGP agrees that an ORR of nearly 60% would improve patient symptoms such as bone disease, ascites and liver dysfunction, skin disease, etc. The CGP is not concerned about the lack of complete remissions, which is very hard to obtain in these patients.
	Criteria used to define response	The primary efficacy outcome in both Study 2201 and Study 2213 was ORR.[c] In Study 2201, ORR was based on modified Valent response criteria[5] and Cheson criteria[6,7] and a confirmed response maintained for ≥ 8 weeks during the first six treatment cycles. In Study 2213, response was based on Valent response criteria confirmed for ≥ 8 weeks during the first two treatment cycles.[11] The US FDA required a re-analysis of Study 2201 using more stringent criteria for response based on IWG-MRT-ECNM criteria.[37]	Does the use of different criteria for definition of ORR limit the interpretation of the trial results with respect to the target population? Would these criteria be used in clinical practice in Canada to assess patients and determine response to treatment? If so, which would be the preferred criteria for definition of a treatment response in the Canadian setting?	CGP agrees that responses based on criteria such as modified Valent and Cheson, Valent, or IMG-MRT-ECNM are clinically meaningful and felt that any differences between these criteria are minimal.
Setting	Trial sites	Study 2201 was conducted at 29 sites in 12 countries including Canada (2 sites), Australia (2 sites), Austria (1 site), Belgium (1 site), France (2 sites), Germany (5 sites), Netherlands (1 site), Norway (1 site), Poland (1 site), Turkey (1 site), UK (3 sites), and USA (9 sites) Study 2213 was conducted at 3 sites in the USA.	Do the trial results apply to patients across Canada? Is there a known difference in effect based on ethnicity or demographics that might yield a different result in a Canadian setting? Are there any differences in practice patterns between the countries listed and Canada?	Overall, most patients were from the US and Western Europe, where practice patterns are similar to Canada. Even though the clinical trials were started several years ago (study 2201 first patient enrolment 2009; study 2213 first patient enrolment 2005) clinical practice patterns in this setting have stayed the same.
	Supportive medications	Patients were permitted to take prophylactic anti-emetic therapies concomitantly with midostaurin.	Are the results of the trial generalizable to a setting where different supportive medications, procedures, or care are used?	Administration of prophylactic anti-emetic therapies is considered standard of care in Canadian practice. Therefore, trial results are generalizable to the Canadian patient population.
		Patients who received HGF support within 14 days of study start were excluded from Study 2201 and Study 2213.	Are the results of the trials generalizable to patients who receive HGF support within < 14 days of start of treatment or	The CGP agrees that the trial results can be generalized to patients who received HGF support. Although G-CSF and other granulocyte stimulating agents could in

Table 1.2: Assessment of generalisability of evidence of midostaurin for advanced SM.

Domain	Factor	Evidence from Study 2201[2,3a] and Study 2213[2,4b]	Generalizability Question	CGP Assessment of Generalizability
			who may have concomitant HGF support with midostaurin treatment?	theory increase mast cell activity, CGP believes that midostaurin would likely still have biological activity and clinical efficacy in patients who have received HGF to recover from severe neutropenia.

Abbreviations: ASM = aggressive systemic mastocytosis; CEL = chronic eosinophilic leukemia; CHF = congestive heart failure; CMML = chronic myelomonocytic leukemia; CVD = cardiovascular disease; Duration of Response = DOR; ECOG PS = European Cooperative Oncology Group Performance Status; Hg = hemoglobin; HGF = hematopoietic growth factor; IWG-MRT-ECNM = International Working Group-Myeloproliferative Neoplasms Research and Treatment- European Competence Network on Mastocytosis; LVEF = left ventricular ejection fraction; MCL = mast cell leukemia; MDS = myelodyslastic syndrome; MPN-U = myeloproliferative neoplasm – unclassifiable; MI = myocardial infarction; NYHA = New York Heart Association; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; RBC = red blood cell; SM = systemic mastocytosis; SM-AHN = systemic mastocytosis with associated hematologic neoplasm; US FDA = United States Food and Drug Administration

Notes:
[a] For Study 2201 all baseline data reported is from the primary efficacy population (PEP)
[b] For Study 2213, all baseline data reported is from the full analysis set (FAS) equivalent to the intention-to-treat (ITT) population
[c] In Study 2201, the primary efficacy outcome was ORR by Study Steering Committee (SSC) adjudication in the PEP and in Study 2213 the primary efficacy outcome was ORR by Investigator Assessment (INV) in the FAS

1.2.4 Interpretation

Burden of Illness and Need

Advanced systemic mastocytosis (SM) comprises three related, rare mast cell neoplasms: aggressive systemic mastocytosis (ASM), SM with associated hematologic neoplasm (SM-AHM), and mast cell leukemia (MCL). The only Danish population-based study[38] to date estimates a combined incidence of 0.06 per 100,000 for advanced SM (0.01 for aggressive SM, 0.04 for SM-AHN and 0.01 for MCL). The estimated prevalence of advanced SM in this study was 0.4 per 100,000. Extrapolating the Danish population results[38] to Canada's population of 37 million, the CGP estimates that there would be 20 new cases per year (incidence 0.06 per 100,000) of patients with advanced SM for whom midostaurin might be considered. One caveat is that mastocytosis is likely under-recognized presently and this figure may underestimate the eligible patient population for midostaurin.

Advanced SM is associated with a poor prognosis and lacks effective treatment options. The multi-kinase inhibitor midostaurin inhibits KIT D816V, a primary driver of disease pathogenesis.

Advanced SM is an aggressive disease with high morbidity and mortality. The median overall survival is three-and-a-half years in patients with aggressive SM, two years in those with SM-AHN, and less than six months in those with MCL.[38-40] Cladribine and interferon alfa[41] have been associated with limited response rates and duration of response in mostly small, retrospective studies.[42-47] Although imatinib is approved by Health Canada for the treatment of aggressive subtypes of SM (ASM and SM-AHN) in patients without the *KIT* D816V mutation or with unknown *KIT* mutation status,[48] this indication is applicable to only about 10% of patients.[49,50] The orally active small-molecule agent midostaurin inhibits multiple kinases, including nonmutant and mutant KIT D816V and has shown promising activity in a phase II trial involving patients with advanced SM.

For currently available treatments, the respective overall response rates in indolent SM, aggressive SM, and SM-AHM were 60%, 60%, and 45% for interferon alfa (IFN-α), 0%, 0%, and 21% for hydroxyurea (HU), 14%, 50%, and 9% for imatinib (IM) and 56%, 50%, and 55% for cladribine (2-CdA).[47]

Further the Clinical Guidance Panel (CGP) agreed with PAG and the registered clinicians providing input for this submission that midostaurin would address an unmet need in these patients given the rarity of the disease and lack of better treatment options. According to the CGP's expert opinion midostaurin has been used by clinicians in Canada on a compassionate basis with some promising results. In addition, based on CGP's opinion, midostaurin may fulfill an unmet need by either preventing a need for allogeneic stem cell transplant or facilitating a bridge to allogeneic stem cell transplant in patients who are eligible for transplant.

Effectiveness

The efficacy of midostaurin in the treatment of adults with advanced SM was demonstrated in a single-arm, open-label, multinational, phase 2 trial study 2201.[3] At a median duration of follow-up of 43 months (range 29–70 months) at the clinical data cut-off date of Dec 1, 2014, the ORR in patients with mastocytosis-related organ damage (i.e. clinical findings associated with organ damage from infiltrating mast cells, referred to as C-findings) [n = 89; primary efficacy population (PEP)] was 60% (95% CI 49–70; p=0.001).[18] The ORR consisted of patients whose best overall response (according to modified Valent and Cheson criteria) was a major response (45% of patients; complete resolution of at least one C-finding) or a partial response (15% of patients; improvement of at least one C-finding) starting in the first six 4-week treatment cycles and lasting for ≥ 8 weeks.[18] Among patients with a major response, although no patients achieved a CR, 38% of patients with ASM, 16% of patients with SM-AHN, and 25% of patients with MCL achieved an incomplete remission. The ORR was similar irrespective of advanced SM subtype, KIT

D816V mutation status or history of prior therapy.[18] Among patients who had a response (major or partial response), the median duration of response (DOR) was 31.4 months (95% CI: 10.8; NE).[1] [redacted].[51] *(Non-Disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the manufacturer that it can be publicly disclosed).* Patients in the primary efficacy population (PEP) had a median OS of 26.8 months (95% CI: 17.6; 34.7) and a median PFS of 17.0 months (95% CI: 10.2; 24.8).[18] Patients with MCL, the most fatal variant of advanced SM, had a median OS of 9.4 months.[52] There were 34 patients (38.2%) in the PEP that experienced a ≥ 50% reduction in serum tryptase levels relative to baseline that were sustained for ≥ 56 days. There were 41 patients (46.1%) who experienced > 50% reduction in bone marrow mast cell infiltration relative to baseline.[52] In addition, midostaurin treatment was associated with reduced splenomegaly (among 39 patients who had splenomegaly at baseline and who had at least one postbaseline assessment), 77% of patients had a reduction in spleen volume, with 26% of patients having a reduction in spleen volume of at least 35%.[3]

While patient-reported outcomes (PRO) data was collected in Study 2201, the CGP agreed with the CADTH Methods Team that no firm conclusions can be drawn from these exploratory and descriptive analyses due to several limitations including the declining number of patients providing PRO data over the course of the first year, the open-label design of the trial, and the lack of a comparator group (see section 6 for more details). Interpreting the PRO data in the context of these limitations, the CGP agreed that midostaurin is unlikely to negatively affect quality of life.

The efficacy of midostaurin in the treatment of patients with advanced SM was also demonstrated in a smaller (n = 26), open-label, multicentre, phase 2 trial, Study 2213.[4] A confirmed ORR (according to Valent criteria) starting by two cycles and confirmed for at least 8 weeks was achieved by 69% of patients (18 out of 26). Of the 18 patients with either a MR or PR (as per the ORR definition), one patient was categorized as having ASM, 13 patients as SM-AHN, and four patients as MCL. Based on a data cut-off date of March 1, 2017, median DOR was formally reached at 132 months when a patient with SM- chronic myelomonocytic leukemia (CMML) who had been on midostaurin therapy for 11 years progressed to acute myeloid leukemia.[4]

Comparative Therapies considered

Direct randomized comparisons between midostaurin and currently used therapies are unlikely to take place in the setting of advanced SM. Consequently, attempts have been made to compare the results achieved with midostaurin to matched historical cohorts. Please see section 7 of the CGR for a detailed summary and critical appraisal of the Chandesris et al., 2016[28] and Reiter at al., 2017[34] studies, that have attempted to derive estimates of relative efficacy, i.e., overall survival hazard ratios, between midostaurin and currently used therapies. The CGP agreed with the CADTH Methods Team, that due to several limitations identified in the analyses by Chandesris et al., and Reiter et al, caution must be used in interpreting the comparative efficacy estimates. Given the absence of direct comparison, there is no robust evidence to ascertain which of the agents (i.e., midostaurin or currently available therapies) have superior efficacy.

The CGP noted that based on the published data, and on poor results with existing treatment options, it is likely that results with midostaurin will be equal to or better than current treatment options, with improved tolerability compared to options such as chemotherapy or allogeneic stem cell transplant. The CGP also acknowledged a trend for improved OS that was particularly striking

among patients with MCL. Although historical comparisons regarding the survival of patients with MCL are challenging because of its biologic and clinical heterogeneity.

Overall, the CGP concluded that there is insufficient evidence to determine the comparative effectiveness of midostaurin compared with currently used therapies and therefore patient values and preferences, co-morbidities, individual toxicity profiles, and treatment availability (provincial reimbursement) should guide treatment selection.

Safety

In a pooled analysis (n = 142) of patients with ASM, SM-AHN or MCL who received midostaurin as a single agent in study 2201 and 2213, the most common adverse events (AEs) (incidence 10% of patients) were GI-related toxicity (e.g., nausea, vomiting, diarrhea), infections, and myelosuppression.[18] The most frequent grade 3-4 AEs (e.g., anemia, thrombocytopenia, and neutropenia) were due to myelosuppression.[18] Serious AEs occurred in 68.3% of patients in the pooled dataset and common reasons included [redacted] ([redacted])[53], primarily pneumonia (7.0%), sepsis, (7.0%), and urinary tract infection (4.2%). *(Non-Disclosable information was used in this pCODR Guidance Report and the manufacturer requested this safety information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the manufacturer that it can be publicly disclosed).* Hematologic AEs were frequent in both Study 2201 and Study 2213. AEs leading to discontinuation were reported by 34 (23.9%) patients in the pooled dataset.[18] There was a total of 26 (18.3%) on-treatment deaths (i.e., deaths occurring on treatment and up to 28 days after the last dose of study drug) across both trials. Ten deaths were directly attributed to disease progression whereas other frequent primary causes were sepsis (n=5), cardiac disorders (n=5), and multi-organ failure (n=3).[18] Despite the clear limitations of comparisons between non-randomized studies, the CGP agreed that midostaurin is likely to have a favourable toxicity profile compared to chemotherapy. Chemotherapy in this advanced disease setting is associated with significant myelosuppression, with grade 3/4 neutropenia often occurring in over 50% of patients, occasionally resulting in infectious complications requiring inpatient and outpatient supportive care, which is largely avoided when midostaurin is used.

1.2.5 Conclusions

The CGP concluded that there may be a net clinical benefit with midostaurin, compared with currently available chemotherapy/ cytoreductive options, in the treatment of adult patients with ASM, SM-AHN, or MCL as a first line option. This conclusion is based on the non-comparative studies 2201 and 2213, which showed clinically meaningful overall response rates (approximately 60%), prolonged durability of responses, and encouraging survival (PFS and OS) with a clinically acceptable toxicity profile that does not worsen health related quality of life and appears to be better than that experienced with chemotherapy. Responses in this patient population are important because of accompanying potential improvement in distressing symptoms such as bone disease, ascites and liver dysfunction, skin disease, and improvement in performance status. Prolonged response rates have the potential to translate into survival benefit, given the currently high mortality of these patients. Patients with advanced SM have limited treatment options and effective therapies with improved toxicity are urgently needed in this disease setting.

In their feedback to the pERC Initial Recommendation, the sponsor noted a need for a new mechanism to support access to treatments for patients with rare diseases. Furthermore, the sponsor suggested that midostaurin for advSM could be used as a demonstration of a risk sharing agreement with the public payers while the sponsor would collect further data for a subsequent

submission to CADTH. In response to the sponsor's feedback the CGP supported a form of managed access program for ultra-rare diseases. Furthermore, the CGP expressed concern that a negative pERC recommendation could prevent patients from receiving midostaurin on an exceptional access basis. Drawing on their own clinical experience, the CGP reiterated the need for treatment options in this setting in which patients may neither show a good response to nor tolerate chemotherapy well. In addition, some treatment centres have no access to clinical trials, and it is not always feasible to send patients to another province to enrol in a study.
In their feedback on the pERC Initial Recommendation, the registered clinician noted that cytoreductive therapy is readily available and an alternative treatment option in this patient population. Further, it was noted that there is substantial uncertainly in the therapeutic benefit of midostaurin due to the limitations in the evidence from non-comparative phase II trials. In response to the registered clinician's feedback, the CGP reiterated that, while cytoreductive therapies (such as hydroxyurea, interferon-alpha and cladribine) are readily available these treatments appear to be less effective (e.g., ORR about 20% for hydroxyurea) or have a shorter duration of response (e.g., 11-12 months median duration of response for interferon-alpha and cladribine) compared with the results seen with midostaurin (e.g., study 2201 showed a response rate of 60% for advSM and median duration of response was 31.4 months [95% CI: 10.8; NE]). In addition, the CGP reiterated that midostaurin is likely to have a favourable toxicity profile compared to chemotherapy/cytoreductive therapy. Overall, the CGP emphasized that despite the limitations of the present phase II evidence, midostaurin appears to be a biologically active treatment, with relatively high efficacy and low toxicity which makes it an attractive new treatment option in the present space. The CGP reiterated that due to advSM being an ultra-rare disease high quality RCTs are likely not feasible in this disease setting.

In making this conclusion, the CGP also considered that:

- The data supporting this conclusion are from non-randomized studies. Hence, there is no reliable estimate of the comparative efficacy or effectiveness of midostaurin to chemotherapy. There are currently no ongoing trials comparing midostaurin vs other therapies, possibly given the rarity of the disease and it would be a difficult study to recruit for.

- The follow-up of trials of midostaurin usage in other indications such as AML, does not show any significant long-term side effects and these include phase III studies.

- Patient advocacy group input stated that the majority of these patients with experience with midostaurin (n=5) spoke highly favourable of midostaurin as it was reported to result in a significant improvement in their quality of life by helping them control their symptoms and enabling them to gradually return to their activities; two patients reported that they had to discontinue the therapy with midostaurin due to side effects.

- Being an oral medication, midostaurin will likely save the cost of outpatient admission for chemotherapy and also significant pharmacy and nursing time. CGP noted that patients typically do not require additional resources. The frequency of clinic visits is typically not more than they would need otherwise; in fact, patients would likely require less resources than patients on cytoreductive therapies.

- Midostaurin is indicated regardless of the KIT D816 mutation status. In first line, it is an appropriate option for patients who are KIT D816V mutation negative (approximately 10% of patients). In some patients, clinicians may consider giving

imatinib first, as is may be better tolerated than midostaurin. The treatment selection, however, should be left to the discretion of the treating physician.

- While there is no clear consensus on sequencing of therapies, midostaurin would be the preferred first line option, particularly in MCL patients, as it appears to be the most effective therapy and well tolerated. Midostaurin is also appropriate as salvage treatment in patients progressing after interferon (IFN) – α, cladribine, or other cytoreductive therapy. However, there are insufficient data to generalize the results to patients who relapsed after ≥ 3 prior SM therapies and who have not previously received midostaurin. Upon failure of midostaurin, treatment options are limited and include the previously noted cytoreductive therapies, which have more myelosuppressive and other toxicities. Allogeneic stem cell transplantation might be an option for eligible patients.

- Indication creep: The prevalence of indolent SM is likely much higher than advanced SM and provides some concern about indication creep. For example, in the Danish epidemiological study[38], the prevalence of indolent SM (including cutaneous mastocytosis) was 8.24/100,000 compared to 0.4/100,000 for ASM. This ratio of approximately 15-20 cases of indolent SM for every one case of ASM fits with clinical experience in Canada as well. However, the criteria for ASM are objective clinical, pathological and radiological findings, so it should be straightforward for clinicians to distinguish ASM patients, who would be eligible for midostaurin, from ISM/cutaneous mastocytosis patients, who would not.

- The CGP reiterated that there is no standard of care and a high need for treatment options in the present small patient population under review. Midostaurin was approved by the U.S. Food and Drug Administration (FDA) for the treatment of adult patients with advanced SM in April 2017. Current consensus guidelines (i.e., NCCN) also recommend using midostaurin for this indication. Given the overall good and durable responses, and tolerable toxicity profile, midostaurin should be made available to these patients. Although some patients will have a response to other treatments, almost all of them will relapse again. Midostaurin could also act as salvage treatment in patients progressing after interferon (IFN)-α, cladribine, or other cytoreductive therapy.

Provincial Advisory Group's (PAG) Related Implementation Questions:

- CGP agreed that patients who currently receive cytoreductive therapies would need to be addressed on a time-limited basis.
- With respect to the concern regarding the pill burden, CGP noted that given the pills come in 2 divided dosages, midostaurin is typically given 4 pills at a time, patients have not particularly complained about this in their practice. In addition, given that the other alternatives are chemotherapy which is an injection and more cumbersome to administer (additional patient's time and cost for travelling to clinic and chair time), an oral treatment such as midostaurin, is still a favoured option.
- With respect to PAG seeking guidance on treatment duration and definition of clinical benefit, the CGP noted that there is no defined treatment duration. As long as the treatment is effective with no unacceptable toxicity, patients will continue on the drug. With regards to a definition of clinical benefit, it varies from patient to patient and would typically mean resolution of symptoms, as defined in

the study as complete resolution of 1 or more C-findings or partial response defined as >50% improvement of one or more than 1 C- findings. Also, some clinicians may measure serial serum tryptase levels.

- cKIT mutation testing turn-around time can be slow (up to three weeks). The University Health Network (UHN) provides the test in Ontario. British Columbia (BC) Children's Hospital and Vancouver General Hospital both offer the test in BC. Some patients with very aggressive SM/mast cell leukemia have a packed marrow and it is not possible to get a bone marrow aspirate. In these patients it is not possible to complete cKIT mutation testing right now because the current generation of cKIT mutation assays are not sensitive enough to pick up the mutation in the peripheral blood, thus a bone marrow sample is required. There are new assays coming down the pipeline (and in use in the United States) which have markedly higher sensitivity and enable cKIT mutation testing on the peripheral blood. As per the WHO diagnostic criteria a bone marrow will still be required to evaluate other diagnostic criteria.

2 BACKGOUND CLINICAL INFORMATION

This section was prepared by the pCODR Hematology Clinical Guidance Panel. It is not based on a systematic review of the relevant literature.

2.1 Description of the Condition

Mastocytosis is divided into cutaneous mastocytosis (CM) and systemic mastocytosis (SM), see Table 2.1. Diagnosis of SM requires demonstration of pathologic mast cell infiltration in extracutaneous organs, with or without skin involvement. In the pediatric population, mastocytosis is typically limited to the skin and most cases will improve or resolve by adolescence.[54]

Table 2.1: WHO classification of mastocytosis

WHO mastocytosis classification
1. Cutaneous mastocytosis (CM)
2. Systemic mastocytosis
a. Indolent systemic mastocytosis (ISM)*
b. Smoldering systemic mastocytosis (SSM)*
c. Systemic mastocytosis with an associated hematological neoplasm (SM-AHN)†
d. Aggressive systemic mastocytosis (ASM)*
e. Mast cell leukemia (MCL)
3. Mast cell sarcoma (MCS)

*These subtypes require information regarding B and C findings for complete diagnosis,[20] all of which may not be available at the time of initial tissue diagnosis.

†This category is equivalent to the previously described "systemic mastocytosis with an associated clonal hematological non-mast cell lineage disease (SM-AHNMD)." AHNMD and AHN can be used synonymously.

Source: EPAR[18]

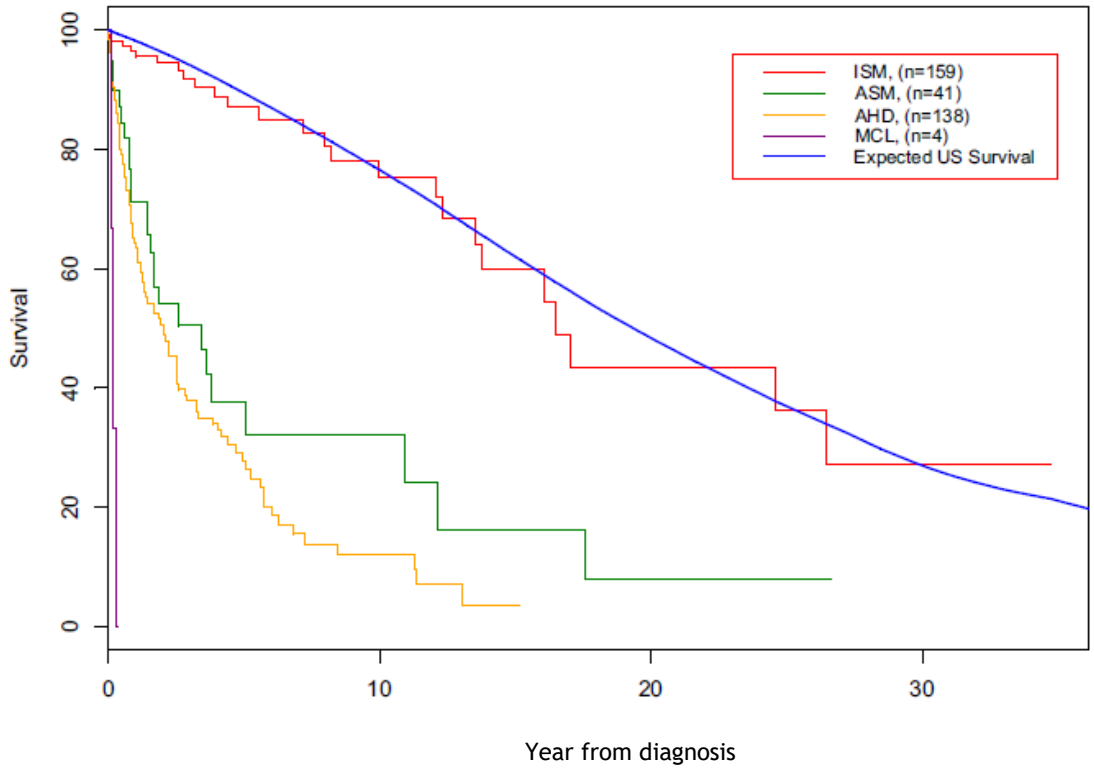
Adults who develop mastocytosis more often have SM, which tends to be a chronic condition. Over 95% of adults with SM have a c-KIT D816V mutation or other exon 17 KIT mutations.[55] Indolent and smouldering SM typically do not require systemic therapy, and have survival comparable to age-matched controls as illustrated in a Mayo clinic cohort. Patients with advanced SM have inferior survival and require systemic therapy to treat symptoms and reverse or prevent end organ damage, see Figure 2.1.

1) Aggressive systemic mastocytosis (ASM): ASM is SM with "C" findings such as cytopenias due to mast cell infiltration of bone marrow, palpable hepatomegaly, liver dysfunction or portal hypertension, skeletal involvement with osteolytic lesions, palpable splenomegaly with hypersplenism, or malabsorption and weight loss due to gastrointestinal mast cell infiltration.[56] Median survival in a large Mayo clinic cohort of 41 patients was 41 months.[39]

2) Systemic mastocytosis with an associated hematologic neoplasm (SM-AHN): SM can be associated with myeloid neoplasms such as myeloproliferative neoplasms (MPNs), chronic myelomonocytic leukemia (CMMol) and myelodysplastic syndromes. One type of myeloid neoplasm associated with prominent eosinophilia, increased mast cells, and PDGFRa or PDGFRb mutations and responsive to imatinib, is now classified as a subtype of chronic eosinophilic leukemia (CEL) rather than SM. SM may also be associated with lymphoid neoplasms such as lymphoma and myeloma. Median survival in a Mayo clinic cohort of 138 patients with SM-AHN was 24 months.

3) Mast cell leukemia (MCL): This is a rare and very aggressive form of SM characterized by a dense infiltration of mast cells in the bone marrow accounting for > 20% of cells in the aspirate. Median survival in the Mayo cohort of 4 patients was only 2 months.

Figure 2.1: Observed Kaplan-Meier Curve for Patients Classified According to the WHO Mastocytosis Classification Compared with Expected US Survival (Age-and Sex -Matched cohort)



Source: EPAR[18]

2.2 Accepted Clinical Practice

The management of indolent and smouldering SM, as well as symptom control, are reviewed in detail elsewhere.[56,57] This section will focus on accepted systemic treatment of advanced SM, including ASM, SM-AHN, and MCL. Current treatment options for advSM are very limited.

Response to treatment is typically measured according to the Valent criteria, wherein a major response is defined as complete resolution of ≥ 1 C finding, a good partial response is > 50% improvement in ≥ 1 C finding, and a minor partial response is a > 20% to ≤ 50% improvement in ≥ 1 C finding.[5,58]

Historically, a number of cytoreductive agents have been used to treat SM, but response rates, and in particular major response rates, are low. A retrospective study of 108 patients with SM from the Mayo Clinic examining interferon-alpha (n=40), hydroxyurea (n=26), imatinib mesylate (n=22) or 2-chlorodeoxyadenosine (a.k.a. cladribine, n=22) demonstrated response rates as follows:[47]

- Interferon-alpha (n=40): Overall response 53%, major response 18%. Median duration of response was 12 months (range, 1-67 months).
- Hydroxyurea (n=26): Overall response 19%, major response 0%. Median duration of response was 31.5 months (range, 5-50 months).
- Imatinib mesylate (n=22): overall response 18%, major response 8%. Median duration of response 19.6 months (range 9-69 months).
- Cladribine (n=22): overall response 55%, major response 37%. Median duration of response was 11 months (range, 3-74 months).

Imatinib is approved by Health Canada (HC) for treatment of adult patients with aggressive sub-types of SM (ASM and SM with associated hematological clonal non-mast cell lineage disease [AHNMD]) without the D816V c-Kit mutation. If c-Kit mutational status in patients with ASM or SM-AHNMD is not known or unavailable, treatment with imatinib may be considered if there is no satisfactorily response to other therapies.[48] Testing for the c-KIT D816V mutation is part of the general workup for suspected SM. Patients who have the D816V c-Kit mutation are not considered sensitive to imatinib. The HC approval for imatinib is based on a phase II clinical study (Study B2225) that enrolled a diverse population of patients suffering from life-threatening diseases associated with Abl, Kit or PDGFR protein tyrosine kinases. Additional information came from published case reports/series. It appears that imatinib is effective in the management of patients with eosinophilia-associated myeloid neoplasms characterized by the FIP1L1-PDGFRA fusion tyrosine kinase. Of note, historic reports of patients responding to imatinib were likely patients who would now be classified as having chronic eosinophilic leukemia (CEL) with PDGFR alpha or beta mutations and increased mast cells, rather than SM per se. Rare cases of transmembrane KIT mutation such as F522C or K509I rendering sensitivity to imatinib therapy have been reported, although testing for these rare, variant KIT mutations is not routinely available.[59,60] In current Canadian clinical practice, it is estimated that the HC indication for imatinib is applicable to approximately 10% of patients with advanced SM.[49,50]

Cladribine appears to be the most effective and rapidly acting option among traditional cytoreductive agents, and a large French retrospective study reported response rates as follows:[31]

- ASM (n=14): overall response 43%, major response 36%
- ASM-AHN (n=11): overall response 45%, major response 27%
- MCL (n=1): no response.

The median duration of response for ASM patients was 2.47 years (range 0.5-8.6 years). The most significant grade 3 and 4 toxicities included neutropenia (47%) and infectious complications or febrile neutropenia (22%). Cladribine is typically given at a dose of 5mg/m^2 or 0.13-0.17mg/kg IV or subcutaneously 5 days per month. The median number of cycles given in the Mayo study was 3 and in the French study was 3.7.[31,47]

Cladribine is favored for patients in need of rapid de-bulking of disease.[56,61] Interferon alpha, particularly the pegylated forms (which are better tolerated than conventional interferon) are options for patients with more indolent disease. Interferon is often started with corticosteroids in some centers, and the steroids are gradually tapered. According to the CGP, if interferon is deemed effective after 3-4 months of treatment it is continued as long as clinical benefit is achieved. Hydroxyurea is rarely used first line in modern practice due to lack of efficacy.

In this context, midostaurin, an oral multiple tyrosine kinase inhibitor, has emerged as a biologically active therapy for patients with ASM, SM-AHN or MCL irrespective of KIT D816V mutation status in two prospective single arm studies[3,4]. Although there has not been a head to head comparison to date of cladribine and midostaurin, or imatinib and midostaurin in patients who are KIT D816V negative, the relatively high efficacy and low toxicity of midostaurin make it an attractive option for many patients with ASM, regardless of their KIT D816V mutation status.

The American National Cancer Care Network (NCCN) treatment guidelines for advSM recommend clinical trial or midostaurin, or other cytoreductive therapies as the first line treatments for advSM.

The CGP noted that the pERC Initial Recommendation for midostaurin does not appear to align with the NCCN guidelines which recommends clinical trials, midostaurin, or other cytoreductive therapies in the first line treatments for advSM.

2.3 Evidence-Based Considerations for a Funding Population

The true incidence and prevalence of the disease is unknown as population-based studies are lacking. One population-based study from Denmark[38] of adult (age ≥ 15 years) SM reported an incidence of 0.89/100,000/year and prevalence 9.59/100,000.[38] Approximately 50% of the cases included in this study were patients with indolent SM, including urticaria pigmentosa. The incidence rates of ASM, SM-AHN, and MCL were much lower, 0.01, 0.04 and 0.01 per 100,000 respectively. The mean age of all patients with ASM was 60.3 years in this study (range 32-89 years)

Extrapolating this to a total incidence of advanced SM of 0.06 per 100,000, it is estimated that in Canada's population of 37 million, approximately 20 new cases per year would arise. One caveat is that other confirmatory population-based studies are lacking, and this is likely an under-estimate as SM is increasingly recognized.

2.4 Other Patient Populations in Whom the Drug May Be Used

The largest group of patients where midostaurin may be considered are patients with cutaneous mastocytosis or indolent SM (ISM).

A search of clinicaltrials.gov yields several ongoing trials of midostaurin in these conditions:

NCT01920204[62] (closed, not recruiting): To study in a pilot phase II trial the efficacy of midostaurin administered at an oral dose of 100 mg twice daily in patients with indolent or smoldering systemic mastocytosis on mediator symptom reduction, documented by the Mastocytosis Symptom Assessment Questionnaire, measured at 3 months.

NCT00831974[63] (completed Dec 2018): Phase IIa, open-label, randomized study of oral AB1010 in patients with systemic indolent mastocytosis with handicap and not bearing activating point mutations in the phosphotransferase domain of c-Kit such as the main mutation Asp-816-Val (D816V).

Preliminary results of the phase II trial above[62] have been published as a letter and indicate improvement in the MASF symptom score.[64] The Valent response criteria used for 2201 and 2213 are not applicable to this population as they do not have "C" criteria.

The Danish epidemiological study[38] indicates that the prevalence of ISM is much higher than advanced SM, at 8.24 per 100 000 compared to 0.4 per 100 000 (ASM, SM-AHN and MCL combined). Thus, if midostaurin were eventually approved for ISM, that would potentially increase the eligible patient population by over 20-fold.

The difficulty in predicting whether ISM will meet the bar for approval lay in the survival data. While robust data showing a survival advantage in patients with advanced SM treated with midostaurin over standard of care is lacking, the real-world experience of clinicians indicates that this biologically active agent likely improves quantity and quality of life in patients suffering from ASM. However, demonstrating improved survival in ISM patients will be challenging as their survival at present is very similar to age matched controls (Figure 2.1).

3 SUMMARY OF PATIENT GROUP INPUT

One patient group, Mastocytosis Society Canada (MSC), with support of the Canadian Organization for Rare Disorders (CORD) provided input on midostaurin (Rydapt) for systemic mastocytosis (SM).

Participants for this patient survey were recruited through two sources. MSC conducted a survey which was distributed via their newsletter to their member subscribers. The link to the survey and information was also made available on their website from July 27 to August 26, 2019.

A total of 97 survey respondents provided input to MSC with 10% of the respondents being caregivers. MSC noted that while the introduction of their survey specified that it was about SM, there was no restriction on who could take part. Please see Table 3.1 below for a breakdown of survey respondents by their status (i.e., caregiver vs. patient with self-identified diagnosis, etc.).

About three-fourths of the patients represented in the survey identified as females (73%) and one-fourth (24%) as males, with the remaining choosing not to respond. For patients who provided their demographic information (83/97), 92% live in Canada, 5% in the USA, and the reminder elsewhere (Australia, Belgium and France). Among Canadian respondents, more than half (56%) reside in Ontario, 18% live in Alberta, 16% in Quebec and the remainder in Manitoba (5%), Saskatchewan (4%), and New Brunswick (2%).

Table 3.1: Survey Respondents by Responder Category

Survey Responder Categories	% of Survey Respondents n (%)
Total number of survey respondents	97 100%
Self-identified as diagnosed with SM	52 (54%)
Caregivers for someone with SM (family member or professional caregiver)	10 (10%)
Self-identified as diagnosed with other type of mastocytosis (not systemic)	12 (13%)
Self-identified as *not diagnosed* with SM but symptoms consistent with SM	11 (11%)
Self-identified as living with a related condition* (sometimes in addition to SM)	10 (10%)
Professional Working with SM patients	1 (1%)
No Answer	1 (1%)
Notes: * Including mast cell activation syndrome (MCAS), cutaneous mastocytosis or mast cell leukemia; SM = Systemic mastocytosis.	

MSC and CORD noted that, from a patient's perspective, SM is a very aggressive and debilitating condition with limited treatment options for patients. Patients considered symptom control to be their biggest concern, as the disease has significantly impacted their ability to carry on their daily activities. Some of the most debilitating symptoms reported by patients include fatigue, headaches, lightheadedness, gastro-intestinal problems and skin-related issues such as lesions, hives, rashes and itching and allergic reactions. Patients reported that these symptoms have

caused a significant amount of physical and psychological distress to not only themselves but also their caregivers and loved ones.

MSC and CORD commented that overall, current therapies do not appear to halt the progression of disease or control bouts of symptoms. Some of the most common therapies that have been used by patients to control symptoms included antihistamines (for skin and abdominal reactions), allergen immunotherapy or epinephrine for allergic reactions, steroids and chemotherapy. The survey results revealed very little patient awareness of midostaurin, as almost three-fourths (73%) of survey respondents reported that they had never heard of midostaurin and only 10% knew about the drug and how it was used. Overall, approximately five patients had indicated that they had experience with midostaurin. While some patients spoke highly favourable of midostaurin as it was reported to result in a significant improvement in their quality of life (i.e., helps with symptom control and gradual return to activities) others spoke of its benefits but were also challenged by the drug regimen and its side effects. Two patients reported that they had to discontinue the therapy with midostaurin due to side effects. MSC and CORD however cautioned against the generalizability of these reactions to the larger population due to the very small number of patients who have experience with midostaurin. When presented with the drug profile of midostaurin, the majority of patients (93%) responded favourably and said that it should be made available through drug plans. An overarching theme in patient responses was the ability to maintain a level of independence to be able to carry on their daily tasks. Patients value new therapies that would provide better symptom management, improve quality of life and survival, and would have minimal or manageable side effects.

Of note, quotes are reproduced as they appeared in the survey, with no modifications made for spelling, punctuation or grammar. The statistical data that are reported have also been reproduced as is according to the submission, without modification. Please see below for a summary of specific input received from the patient group.

3.1 Condition and Current Therapy Information

3.1.1 Experiences patients have with systemic mastocytosis

For patient respondents who identified themselves as being diagnosed with SM (52 patients), the majority were between the ages of 30 to 49 at diagnosis (44%); with 17% <30 at the age at diagnosis, 23% between 50-59, 9% >60, and 7% did not answer. Overall, 31% were diagnosed between 2 and 5 years ago, 20% <2 years ago, 19% from 5-10 years ago, and 29% >10 years ago. These respondents were further prompted to identify their SM subtype as shown in Table 3.2 below.

Table 3.2: Survey respondents who identified themselves as being diagnosed with SM (total = 52) listed by SM subtype

SM subtypes:	% of respondents (total = 52)
Indolent SM	51%
Smouldering SM	15%
Aggressive SM	12%
Advanced MS with unknown subtype	4%
Not known	9%
Other*	11%
Note: * Including patients who explained having potential changes in	

diagnosis (e.g., “recently found more mast cells”, “awaiting results from last biopsy”, “was told I have CMML as well as SM”)

MSC and CORD commented that given the rarity of the condition and the non-specificity of many symptoms, persons with SM are often misdiagnosed. MSC and CORD highlighted that of the present survey respondents, only 15% said that they had not been misdiagnosed prior to getting diagnosed with SM. Furthermore, 15% said they had received just one misdiagnosis, 21% had received two to three misdiagnoses, 20% had received four to five misdiagnoses, 5% had received five to nine misdiagnoses and 5% reported that they had received more than ten wrong diagnoses.

The survey respondents reported that most of the clinical (physical) symptoms common to SM were experienced frequently and with severe impact. The cognitive and psychological symptoms were slightly less frequent or severe but did affect most respondents at least some of the time.

Experience of living with SM was solicited in two ways: an open-ended question and a fixed-choice rating scale. Respondents were presented with a list of physical, cognitive, and psychological effects of SM and asked to rate the degree to which they experienced difficulties or problems with each, on a five-interval scale identified as “*no problem, never”, “minor, infrequent”, “moderate, sometimes”, “serious, frequent”*, and “*incapacitating, regularly*.” MSC and CORD indicated that while indolent and smouldering SM are, by definition, less “severe” subtypes of mastocytosis than aggressive SM, the types of symptoms reported, and their experienced severity, were more or less same across all subtypes.

Symptoms rated as most difficult across all subtypes were ‘fatigue, headaches, lightheadedness’ and ‘skin lesions, red-brown spots’ experienced as ‘severe/frequent’ or ‘incapacitating/life-threatening’ by 57%. Patients with aggressive SM rated gastro-intestinal problems such as “nausea, vomiting, diarrhea,” as most difficult, with more than 70% of respondents rating these as “severe/frequent” or “incapacitating/life-threatening.” Skin-related symptoms were “severe/frequent” for more than half of all respondents, specifically “hives, rash, itching” for 52% of the total pool and 67% of the ASM respondents and “skin lesions, red-brown spots” for 57% of all respondents.

Respondents reported severe problems related to “abdominal pain, stomach ulcers” (43%) or “liver, spleen, GI tract, respiratory problems” (41%). About one-third (35%) also reported experiences of severe “bone pain”. In terms of cognitive issues, about one-third (31%) said they had severe problems with “confusion, memory loss” while a similar number (35%) said these were “minor” or “no problem”. In terms of psychological impact, about two-fifths (40%) said the experience of “anxiety, depression, or panic attacks” was severe but 29% said that these were “minor” or “no problem”.

Below are some key comments by survey respondents regarding experience of living with or caring for someone with SM, as well as the impact on family and others.

“SM has affected my ability to work, exercise, travel and socialize. I have to think about everything I do and plan every day to make sure that I don’t not have a reaction. There is not a moment that I am not aware of my condition. I am fortunate to have health benefits and drug coverage while my husband is working. I do worry about the day he retires and I have to pay out of pocket.”

“I have frequent anaphylactic reactions [that] leave me unable to leave the house except when necessary for medical appointments... I have dozens of anaphylaxis triggers, including sunlight, heat, stress (positive or negative), friction, vibration, chemicals, scents, being startled, any kind of physical exertion, foods, and on and on… I have to remain in a temperature-controlled

environment… I don't get to do any typical "mom" things - outings, school conferences, travel, even grocery shopping."

3.1.2 Patients' Experiences with Current Therapy for Systemic Mastocytosis

MSC and CORD noted that up to now, there have been no specific therapies for treating SM. Most patients have received some type of therapy to suppress allergic or immune reactions or to address skin spots or lesions. Overall, 83% of the survey respondents said that they were either currently receiving or had received in the past one or more types of treatments related to SM. The remainder had not received treatment or were not sure. MSC and CORD commented that the ratio of having received treatment versus no treatment is about the same for those diagnosed with ASM. They suggested that it is possible that patients may have passed away prior to treatment.

Survey respondents were presented with a list of treatments and asked to indicate whether they were using these therapies in the past or currently, with an option for "not sure". The most common treatment currently used by patients are antihistamines, which is used by more than four-fifths of the patients to manage skin reactions (84%) and abdominal reactions (81%). Approximately 7% of patients reported that they had never used antihistamines. Overall, 51% reported that they were currently using some form of allergen immunotherapy or epinephrine for allergic reactions and 35% reported that they have used it in the past.

The use of steroids among the patients was not common - 32% of patients reported having taken corticosteroids in the past and 17% were currently taking them. MSC and CORD noted that fewer respondents had accessed more intensive therapies, although the use might be higher among the ASM group than the overall group of patients. Approximately 17% of all respondents reported having exposure to ultraviolet light for urticaria spots or itching while 33% of the ASM cohort had used this therapy. Similarly, about 9% of all respondent patients had received surgery for skin lesions but 17% of ASM respondents reported currently receiving this type of surgery. Regarding chemotherapy, 17% of the ASM respondents reported having experience with 2-CDA (Cladribine) compared to 7% of the whole group. Similarly, 33% of ASM patients reported having used or currently using tyrosine kinase inhibitors (TKIs), compared to 12% of the rest of the group.

MSC and CORD also asked survey respondents to rate the effectiveness of each therapy in managing SM symptoms or progression, on a five-interval scale anchored by "not at all", "little or poorly", "somewhat", "well" and "very well." Overall, in terms of antihistamines, most respondents felt that they were at least moderately effective, with an even split between those who said it was working "well" or "very well" (40%) and those rating these as "moderately effective." The ASM patients were considerably less positive in their ratings of antihistamine effectiveness.

Among survey respondents who had used allergen immunotherapies or epinephrine, there were three times as many respondents who felt positive about their effectiveness than those who gave negative ratings. Responses regarding steroids were not as positive with responses being evenly split: one-third of users rated they worked "well" or "very well", one-third rated "poorly" or "not at all", and one-third stated "moderate" about their effectiveness. In terms of chemotherapy, the number of those who had experience was very small but there was a 3:2 ratio in terms of those who said "not at all effective" relative to those who felt it had been "effective." The reflections were very similar for TKIs, with slightly fewer users who felt they had benefited than those who felt it had worked.

Additionally, MSC and CORD asked survey respondents to rate the overall effectiveness of all their current therapies, including non-prescription medicines, foods, and dietary management, but not including midostaurin. Overall, almost half said therapies were "effective" or "very effective" and about one-third said they were "not at all" or only "somewhat ineffective." These ratings were also true of the ASM group.

However, MSC and CORD commented that when these responses are taken in the context of their unscripted descriptions of living with SM, a picture emerged of a disease with few treatment options and a high degree of unmet need. Patients are unable to live a 'normal life' with a level of self-sufficiency or independence that allows them to take care of themselves and to participate in the activities of daily living. While these treatments do work to manage recurring symptoms, most patients must remain highly vigilant of their day-to-day exposure to allergy triggers and to feelings of physical or mental fatigue and emotional distress. They speak of the need to rely heavily on family support. MSC and CORD highlighted that none of the therapies appear to prevent bouts of symptomology, nor do they halt disease progression.

When MSC and CORD asked survey respondents to express their primary expectations for a new therapy, patients expressed hope for a cure but stressed that they would value a new therapy that would provide better symptom management, improve quality of life (daily functioning) and survival, and would have minimal or manageable side effects.

Below is a key comment by one respondent regarding expectations for a new therapy:
"Let me have peace of mind so that I can enjoy my life with my kids. Hopefully prevent anaphylactic reactions."

3.1.3 Impact of Systemic Mastocytosis and Current Therapy on Caregivers

The MSC and CORD survey did not ask specific questions regarding caregiver experience.

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for and Experiences To Date with Midostaurin

MSC and CORD noted that almost three-fourths (73%) of survey respondents said that they had never heard of midostaurin; only 10% knew about the drug and how it was used. The percentage was much higher among the ASM group, where 57% knew about the drug and how it was used and 43% did not.

Overall, there were five patients who indicated experience with midostaurin and two that reported they were unsure. MSC and CORD indicated that their responses reflected both the benefits of the therapy as well as the difficulties. According to MSC and CORD, two patients who had experience with midostaurin felt overall very positive, primarily because they felt that the therapy reduced the burden of disease and perhaps, most importantly, allowed them to return to "normal, daily life." Several patients who had experience with midostaurin spoke of the benefits and hope for future disease management but were also challenged by the drug regimen and side effects. As reported by MSC and CORD, in one case, the patient adapted the drug schedule and, in another situation, the patient said that issues were resolved with pre-treatment or concomitant therapy. Two patients chose not to continue the therapy with midostaurin because of the side effects. MSC and CORD cautioned that because the number of patients who have experience with midostaurin is small, it may be difficult to generalize their reactions to a larger patient population.

Below are key comments by patient respondents regarding their experience with midostaurin:

"I am only 6 months into my treatment and am gradually having the dose of Rydapt increased. I am excited to see for the first time in 20 years, my tryptase levels drop! I felt (before Rydapt) helpless as I watched my tryptase levels climb and my symptoms worsen, my liver and spleen swell and the only treatment was to help with the symptoms I was told there was no cure for this disease. My quality of life lessening as I participated less and less. It can be very depressing if you let it get to you."

"Benefits: 1. Severe reduction of bone and muscle pain. 2. Increased mobility - able to get out and socialize. 3. Dramatically reduced effect of Mast cell proliferation (results from bone marrow samples, reduced / eliminated skin blotches (very discolored spots on arms, legs and truck).4. Increased social activities.
Symptoms and Progression: 1. Reduced many critically blood parameters back to acceptable levels. 2. It has reduced SM effects significantly.
Rydapt Effects: 1. Allows patient to sleep better without pain (pain reduced by 70%) 2. More emotional 3. Overall major increase in quality of life."

"I found the drugs side effects outweighed the benefits in MY situation but someone with a less aggressive form of SM and better prognosis may benefit. We never had a cure for AIDS without people having free access to treatment ?? I have not had a follow up bone marrow since the transplant or short term midostaurin treatment so I'm only going by symptoms ... not on medical test results."

MSC and CORD further noted that patients had realistic expectations in terms of reviewing the drug profile and other patients' experiences to decide (with their physician) whether midostaurin would be right for them personally. MSC and CORD provided patients with a summary of the drug profile of midostaurin and asked about the importance of having midostaurin available as an option to treat ASM, SM-AHN, and MCL. The majority of patients (93%) responded that it should be made available through drug plans.

Below are key comments by patient respondents regarding making midostaurin available to other patients:

"Individuals who are affected by SM and whose symptoms are not well controlled by other treatments should definitely have access to Rydapt. It is in the patient's best interest but also in the best interest of the family and our Canadian society for each person who is affected by SM to be able to live a full and productive life. The associated costs of burn out, treating depression and anxiety in the patient and caregivers are costly for our health care system and the money is better spent treating the patient with Rydapt."

"It would change their entire life. People who do not have the disease do not understand how total debilitating it can be. To have a medication that could ease some symptoms would be incredible."

3.3 Companion Diagnostic Testing

None.

3.4 Additional Information

None.

4 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The Provincial Advisory Group includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website (www.cadth.ca/pcodr). PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

Overall Summary

Input was obtained from **all nine** provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation:

Clinical factors:

- No standard of care in this setting

Economic factors:

- High cost of midostaurin
- Additional pharmacy resources and clinic visits may be required

Please see below for more details.

4.1 Currently Funded Treatments

PAG noted that there is no standard of care for the treatment of adult patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated hematological neoplasm (SM-AHN), or mast cell leukemia (MCL). Patients may receive cytoreductive therapies (e.g., imatinib, cladrabine, cytarabine, azacitidine, hydroxyurea and fludarabine) plus mast cell stabilizers or inhibitors of release (e.g., antihistamines).

4.2 Eligible Patient Population

The pivotal trial of midostaurin in patients with ASM or MCL excluded patients who had ASM with eosinophilia. PAG is seeking guidance on whether these patients would be eligible for midostaurin.

If recommended for reimbursement, PAG noted that patients who are currently receiving cytoreductive therapies would need to be addressed on a time-limited basis.

There is a low potential for indication creep given the small number of patients with ASM, SM-AHN, or MCL.

4.3 Implementation Factors

The high cost and affordability of midostaurin may be a barrier to implementation and would need to be addressed.

The recommended dose of midostaurin is 100 mg twice daily. Dose modifications with the 25mg capsule strengths is an enabler to implementation. However, there is a potential for pill burden with a total of 8 capsules daily along with concomitant medications.

PAG is seeking guidance on treatment duration and definition of clinical benefit as the discontinuation criteria is “treatment should continue as long as clinical benefit is observed or until unacceptable toxicity occurs”.

As midostaurin is administered orally, PAG identified that chemotherapy units and chair

time would not be required *compared to cytoreductive therapies*. Dispensing midostaurin would require *additional* pharmacy resources. *Additional health care resources (e.g., frequent clinic visits while patients are on therapy)* are required for monitoring adverse effects and tolerability with midostaurin.

Midostaurin is an oral drug that can be delivered to patients more easily than intravenous therapy in both rural and urban settings, where patients can take oral drugs at home. PAG identified the oral route of administration is an enabler to implementation. However, in some jurisdictions, oral medications are not funded in the same mechanism as intravenous cancer medications. This may limit accessibility of treatment for patients in these jurisdictions as they would first require an application to their pharmacare program and these programs can be associated with co-payments and deductibles, which may cause financial burden on patients and their families. The other coverage options in those jurisdictions which fund oral and intravenous cancer medications differently are: private insurance coverage or full out-of-pocket expenses.

4.4 Sequencing and Priority of Treatments

PAG is seeking guidance on optimal treatment sequencing and preference of midostaurin compared with cytoreductive therapies as well as what treatment options would be available to patients upon progression of midostaurin in this setting.

4.5 Companion Diagnostic Testing

KIT D816V mutation status testing is required as it is required for the diagnosis of systemic mastocytosis. PAG noted that the requirement for mutation testing would add additional costs to treatment. Some jurisdictions do not have mutation testing available in their provinces and other options, such as sending tissue samples out of province, would need to be explored. PAG noted that additional information on KIT D816V mutation testing would be helpful, including the costs and accessibility of the test.

4.6 Additional Information

None.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

One individual clinician input was provided by a hematologist/oncologist from Cancer Care Ontario Hematology DAC for the review of midostaurin (Rydapt) 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 clinician asserted an unmet medical need considering that systemic mastocytosis is a very symptomatic disease with poor outcomes. Midostaurin was recommended as a first-line treatment as it appears to have better responses than other treatments and seems to be tolerable.

Please see below for a summary of specific input received from the registered clinician.

5.1 Current Treatment(s) for systemic mastocytosis

The clinician indicated that there is currently no standard of care for the target patient population of this review. Patients may receive cytoreductive therapies (e.g., imatinib, cladrabine, cytarabine, azacitidine, hydroxyurea and fludarabine) plus mast cell stabilizers or inhibitors of release (e.g., antihistamines). The clinician noted that azacitidine would not be covered for this indication in Ontario.

5.2 Eligible Patient Population

The clinician stated that the patient population in the reimbursement request aligns with the Health Canada indication and the main pivotal trial population. Furthermore, the clinician noted that there is an unmet need given this indication is for a rare clinical scenario with poor outcomes and very symptomatic patients. The inclusion and exclusion criteria of the pivotal trial can be applied to Canadian clinical practice.

The clinician mentioned that the trial included patients that were KIT D816V mutation status positive and negative with the majority being mutation positive. Therefore, midostaurin would likely be used in all cases as first line therapy irrespective of KIT D816V mutation status.

5.3 Relevance to Clinical Practice

The clinician noted to have experience with midostaurin for a patient with ASM on a compassionate supply protocol and that other clinicians at their practice centre have also occasionally used midostaurin. The clinician stated that midostaurin would be the preferred first line therapy for ASM as it appears to be tolerable with a toxicity that is similar to other commonly used drugs for blood diseases. The response rate and duration of response with midostaurin appears to be better than with other available treatments. Some of the other available treatments are chemotherapeutic which could have higher toxicity than midostaurin particularly in more susceptible patients. The clinician responded that there are no obvious contraindications to using midostaurin.

5.4 Sequencing and Priority of Treatments with Midostaurin

The clinician indicated that midostaurin would be the preferred first line option as it appears to be the most effective therapy and well tolerated. Upon its failure, treatment options are limited and include the previously noted cytoreductive therapies, which are more myelosuppressive and have other toxicities. The clinician further noted that allogeneic stem cell transplantation might be an option for eligible patients but would likely be used rarely.

5.5 Companion Diagnostic Testing

The clinician noted that testing is done on bone marrow samples. The University Health Network (UHN) provides the test in Ontario, with a turnaround time of approximately 2 weeks which is acceptable for most situations. The clinician mentioned that in some review articles it is suggested to use the KIT D816V mutation status in deciding between midostaurin and other therapies (e.g., imatinib). However, the clinician highlighted that the pivotal trial of midostaurin included patients irrespective of their KIT D816V mutation status, and therefore, the preference would be to use midostaurin for everyone as first line treatment regardless of their KIT D816V mutation status.

5.6 Implementation Questions

5.6.1 The recommended treatment with midostaurin is that "treatment should continue as long as clinical benefit is observed or until unacceptable toxicity occurs". In clinical practice, what definition of clinical benefit is used? What discontinuation criteria would be used?

The clinician noted that clinical benefit could include improvement in blood counts, reduction in liver/spleen size, improvement in constitutional symptoms and/or quality of life. The clinician mentioned that some of these improvements are measurable (i.e., blood counts, transfusion frequency, organomegaly), while others are more subjective. These clinical benefits would also likely correlate with biochemical markers, such as tryptase. According to the clinician, the discontinuation criteria can be based on a lack of improvement in lab values or transfusion needs. The clinician suspects that once the disease progresses it would be quite obvious and midostaurin would be stopped. Other treatments would be tried since the disease is aggressive.

5.7 Additional Information

Not applicable.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the efficacy and safety of midostaurin for the treatment of adult patients with ASM, SM-AHN, and MCL.

Supplemental questions relevant to the pCODR review were identified while developing the review protocol and are outlined in section 7. The pCODR Clinical Guidance Panel (CGP) and the pCODR Methods Team did not identify other relevant literature providing supporting information for this review.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the CGP and the pCODR Methods Team. Studies were chosen for inclusion in the review based on the criteria in the table below. Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold. The literature search strategy and detailed methodology used by the pCODR Methods Team are provided in Appendix A.

Table 6.1: Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published or unpublished RCTs In the absence of RCT data, fully published clinical trials investigating safety and efficacy of midostaurin for advanced systemic mastocytosis (i.e., ASM, SM-AHN, or MCL) should be included. **	Adult patients (≥ 18 years of age) with ASM, SM-AHN, or MCL <u>Subgroups of interest</u>: • Prior anti-neoplastic therapy (yes vs. no) • *KIT* mutation (yes vs. no) • RBC or platelet transfusion dependent (yes vs. no) • Disease sub-type (ASM vs. SM-AHN vs. MCL)	Midostaurin	Cladribine Imatinib Interferon-alpha ± prednisone Allogeneic HCT Cytarabine Hydroxyurea Fludarabine	<u>Efficacy</u> • **OS** • PFS • ORR • DOR • DCR • **PRO and HRQoL** • Tryptase levels • Bone marrow mast cell burden <u>Safety</u> • **AEs** • SAEs • WDAEs • AESI (e.g., GI, hematologic) • Dose modifications
Abbreviations: AE = adverse event; AESI = adverse event of special interest; ASM = aggressive systemic mastocytosis; DCR = disease control rate; DOR = duration of response; GI = gastrointestinal; HCT = hematopoietic cell transplantation; HRQoL = health-related quality of life; MCL = mast cell leukemia; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PRO = patient-reported outcome; RBC = red blood cells; RCT = randomized controlled trial; SAE = serious adverse event; SM-AHN = systemic mastocytosis with associated hematological neoplasm; WDAE = withdrawal due to adverse event				

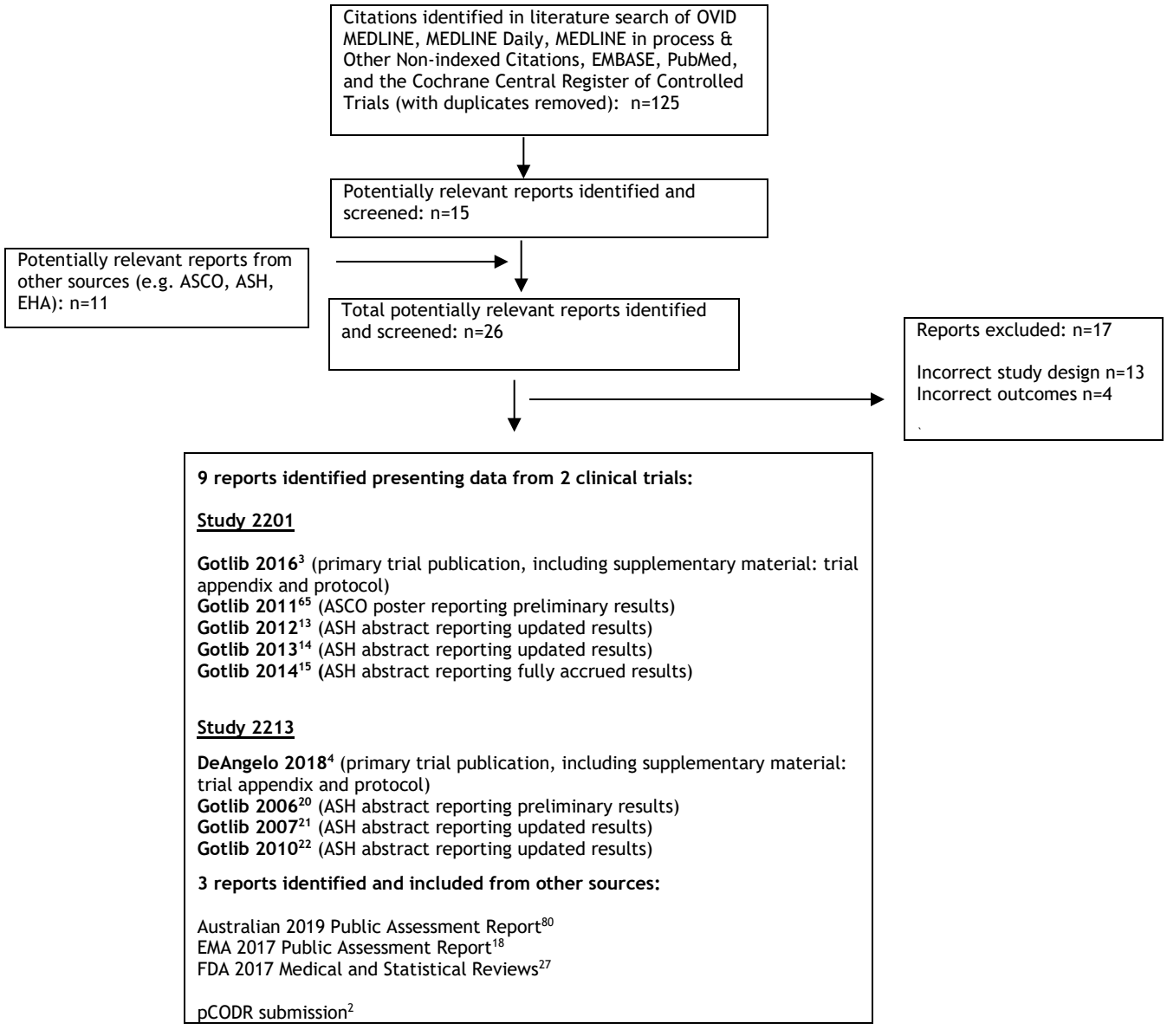
** Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)*
***Single-arm non-randomized trials were included in the absence of RCT data*

6.3 Results

6.3.1 Literature Search Results

Of the 26 potentially relevant reports identified, nine reports[3,4,13-15,20-22,65] were included in the pCODR systematic review and 17 reports were excluded.[28,29,34,66-79] Studies were excluded because they were of incorrect study design including a prospective survey and comparison with historical controls,[28,29,66] an incremental quality-adjusted survival analysis,[67] a pooled survival analysis,[34] case reports,[71,72,76] reviews,[73-75] a description of an analytical method,[78] or were studies that reported on outcomes not of interest to this review (e.g., potential molecular markers).[68-70,77,79]

Figure 6.1. QUOROM Flow Diagram for Inclusion and Exclusion of Studies



Note: Additional data related to Study 2213 and 2201were also obtained through requests to the Submitter by pCODR.

6.3.2 Summary of Included Studies

Two single-arm, open-label, multicentre, non-randomized trials, Study 2213 and Study 2201, were identified that met the eligibility criteria for this review. Characteristics of the trials are summarized in Table 6.2 and specific aspects of trial quality are summarized in Table 6.3.

6.3.3 Detailed Trial Characteristics

Table 6.2: Summary of Trial Characteristics of Study 2201 and Study 2213

Study 2201[2,3]			
Trial Design	**Inclusion Criteria**	**Intervention and Comparator**	**Trial Outcomes**
Other Identifiers: NCT00782067 PKC412D2201 Characteristics: Phase II, single-arm, open-label, international, multicentre, non-randomized trial Sample size: FAS: 116; PEP: 89 Locations: 29 sites in 12 countries including Australia, Europe, Canada (2 sites), UK and USA Patient Enrolment Dates: January 2009 to July 2012 Prespecified interim analysis data cut-off: March 15, 2012 Updated data cut-off: December 1, 2014[b] Study completion date (last patient last visit): August 24, 2017 Funding: Novartis Pharmaceuticals	<u>Key Inclusion Criteria:</u> Adult patients ≥ 18 years with diagnosis of ASM, SM-AHN or MCL, ECOG performance status 0-3, life expectancy > 12 weeks, ECG with QTcF ≤ 450 msec, ≥1 C-findings, adequate hepatic and renal function. Patients with MCL were to have BM aspirate smears with ≥ 20% immature mast cells.[18] <u>Key Exclusion Criteria:</u> CVD including CHF Class III or IV as per NYHA, LVEF < 50%, MI within the previous 6 months or poorly controlled hypertension, heart block (Canada only), patients who relapsed after ≥ 3 prior SM treatments, receipt of investigational, targeted therapy, chemotherapy, interferon-α or cladribine within 30 days, receipt of midostaurin prior to study entry,[81] patients with ASM with eosinophilia and known positivity for FIP1L1-PDGFRα fusion unless relapse or disease progression on imatinib, HIV infection or active viral hepatitis, HGF support within 14 days, surgery, and patients with pulmonary infiltrate	Midostaurin 100 mg orally twice daily as continuous 4-week cycles for up to 6 cycles after which patients entered an extension phase There was no comparator arm Treatment continued until disease progression, unacceptable toxicity, or withdrawal due to any cause.	<u>Primary:</u> ORR by SSC[a] <u>Secondary:</u> DOR TTR PFS OS Safety and tolerability Histopathologic response based on mast cell infiltration in BM and changes in serum tryptase levels. Exploratory outcomes: patient-reported outcomes (MSAS and SF-12), disease control rate, and characterization of KIT mutational status

Study 2201[2,3]			
Trial Design	**Inclusion Criteria**	**Intervention and Comparator**	**Trial Outcomes**
	including suspected infectious origin.[18]		
Study 2213[2,4]			
Trial Design	**Inclusion Criteria**	**Intervention and Comparator**	**Trial Outcomes**
Other Identifiers: NCT00233454 PKC412A2213 Characteristics: Phase II, single-arm, open-label, multicentre, non-randomized trial Sample size: Non-randomized and treated: 26 Locations: 3 sites in USA Patient Enrolment Dates: July 2005 to April 2010 Interim analysis data cut-off date: June 1, 2007. The data cut of date, June 1, 2007, was estimated by the sponsor. Because Study 2213 was initially an investigator-sponsored trial and abstracts and study publications were controlled strictly by the study investigators, the sponsor was unable to confirm the exact data cut-off date for the interim analysis.[17] Updated data cut-offs: December 3, 2012 and March 1, 2017[d] Final Analysis Date: could not be confirmed by sponsor.[23] Funding: Investigator-initiated trial sponsored by Stanford University and Novartis	<u>Key Inclusion Criteria:</u> Adult patients ≥ 18 years with histologically documented ASM, SM-AHN or MCL irrespective of *KIT* D816V mutation status, ≥ 1 C-findings, Karnofsky PS ≥ 30% (equivalent to ECOG performance status 0-3), SCr ≤ 2.0 mg/dL, normal liver enzymes or if elevated due to ASM/MCL then ALT, AST, and/or bilirubin ≤ 4 x ULN, absence of active pulmonary disease unless related to SM.[4] <u>Key Exclusion Criteria:</u> Use of any investigational agent, chemotherapy, cladribine, or interferon-α within 30 days, HGF support within 14 days, HIV infection, active viral hepatitis, or any other concurrent severe or uncontrolled medical condition or disease involving the CNS.[4]	Midostaurin 100 mg orally twice daily as continuous 28-day cycles for up to 12 cycles after which patients entered an extension phase There was no comparator arm Treatment continued until unacceptable toxicity, unsatisfactory therapeutic effect, or withdrawal due to specified causes. If a patient did not achieve a MR or PR in the first 2 months, then treatment was to be discontinued.	<u>Primary:</u> ORR by INV[c] <u>Secondary:</u> Safety and tolerability Pharmacokinetics *KIT* mutation status OS PFS
Abbreviations: ALT = alanine transaminase; ASM = aggressive systemic mastocytosis; AST = aspartate transaminase; BM = bone marrow; CHF = congestive heart failure; CNS = central nervous system; CVD = cardiovascular disease; DOR = duration of response; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FAS = full analysis set; HGF = hematopoietic growth factor; HIV = human immunodeficiency virus; LVEF = left ventricular			

Study 2201[2,3]			
Trial Design	**Inclusion Criteria**	**Intervention and Comparator**	**Trial Outcomes**
ejection fraction; MCL = mast cell leukemia; MI = myocardial infarction; MR = major response; MSAS = Memorial Symptom Assessment Scale; NYHA = New York Heart Association; ORR by INV = overall response rate by investigator assessment; ORR by SSC = overall response rate by study steering committee; OS = overall survival; PEP = primary efficacy population; PFS = progression-free survival; PR = partial response; PS = performance score; Scr = serum creatinine; SF-12 = Medical Outcomes Study 12-Item Short-Form Health Survey; SM = systemic mastocytosis; SM-AHN = systemic mastocytosis with associated hematologic neoplasm; TTR = time to response; ULN = upper limit of normal			
Notes: [a] ORR was defined as the proportion of patients classified as confirmed responders (i.e., those with a major response [MR] or a partial response [PR]) during the first six cycles of midostaurin treatment adjudicated by the study steering committee (SSC) according to modified Valent[5] and Cheson[6,7] criteria and confirmed for ≥ 8 weeks [b] The cut-off date of December 1, 2014 was designated [redacted][52] *(Non-Disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the manufacturer that it can be publicly disclosed).* [c] ORR was defined as the proportion of patients who had a best overall response of MR or PR by investigator assessment over the first two cycles according to Valent criteria[11] and confirmed for ≥ 8 weeks [d] The cut-off date of December 3,2012 [redacted]. The reason for the cut-off date of March 1, 2017 was not specified[4] *(Non-Disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the manufacturer that it can be publicly disclosed).*			

Table 6.3: Select Quality Characteristics of Included Study 2201 and Study 2213

Study	2201[2,3]	2213[2,4]
Treatment vs. Comparator	Midostaurin (no comparator)	Midostaurin (no comparator)
Primary outcomes	ORR by SSC	ORR by INV
Required sample size	The study used an adapted Fleming two-stage design[82] with planned sample size for Stage 1 of 40 patients. If efficacy was declared (ORR [MR or PR]) in ≥ 19 of the 40 patients), an extension phase would be initiated with enrollment of an additional 80 patients. If intermediate efficacy declared (ORR in 15 to 18 of the 40 patients) at the end of Stage 1, then an additional 20 patients would be enrolled in Stage 2. If efficacy declared (ORR in ≥ 27 of the 60 patients), then an extension phase would be initiated with enrollment of an additional 80 patients.[3] The null hypothesis was that ORR ≤ 30% whereas the alternative hypothesis was that ORR ≥ 50% among enrolled patients, using an exact binomial test at a	The study was designed with an accrual goal of 25 patients[4] using a Simon two-stage design.[83] According to the design, n=10 patients were enrolled in Stage 1 and if ≥ 1 patients responded (i.e., achieved ORR [MR or PR]) then n=15 patients were enrolled in Stage 2. If ≥ 5 of 25 patients achieved ORR, then further investigation was warranted. [redacted][2] and the probability of accepting the treatment when the true response rate is ≤ 10% was 9.4% and the probability of rejecting the treatment when the true response rate is ≥ 30% was 10.4%.[4] *(Non-Disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of*

Study	2201[2,3]	2213[2,4]
	one-sided overall nominal type 1 error rate of 0.025. The overall power was 84% for rejecting the null at the end of Stage 1 or 2 and 68% for rejecting the null at the end of Stage 1.[3]	*Information Guidelines. This information will remain redacted until notification by the manufacturer that it can be publicly disclosed).*
Sample size	116 (FAS); 89 (PEP)	26
Randomization method	NA (single-arm)	NA (single-arm)
Allocation concealment	NA	NA
Blinding	Open-label	Open label
ITT Analysis	No (PEP)[a]	Yes
Final analysis	Yes	Yes
Early termination	No	No
Ethics Approval	Yes	Yes
Abbreviations: FAS = full analysis set; NA = not applicable; ORR by INV = overall response rate by investigator; ORR by SSC = overall response rate by study steering committee; PEP = primary efficacy population		
Notes: [a] The primary efficacy outcome was measured in the PEP which was defined as patients in the FAS who met diagnostic criteria for ASM or MCL and presented with at least one measurable C-finding at study entry and/or patients with transfusion-dependent anemia due to their underlying disease at study entry as confirmed by the SSC.		

a) Trials

Two trials met the inclusion criteria for this review: Study 2201 (N=116) and Study 2213 (N=26).

Study 2201

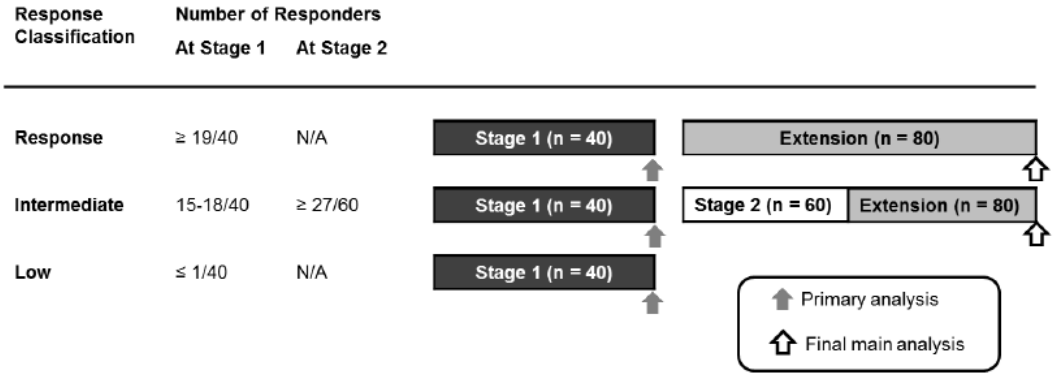
Study 2201 was a phase II, single-arm, open-label, international, multicentre, non-randomized trial that evaluated the efficacy and safety of midostaurin in patients with ASM, SM-AHN, or MCL regardless of *KIT* D816V mutation status.[3] The study was conducted at 29 sites in Australia, Europe, UK, Turkey, USA and Canada (2 sites).[81] The trial was sponsored by Novartis Pharmaceuticals who collected and analyzed the data in conjunction with the authors who had full access to the data. A SSC evaluated patient eligibility and performed post-hoc adjudication of responses for each of the first 12 cycles of midostaurin treatment and every third cycle thereafter.[3] Histopathologic results were reviewed centrally and *KIT* genotyping was performed by a third party.[3] Study 2201 has now been completed.

Trial phases

The study design of Study 2201 is depicted in Figure 6.2. The study used an adapted Fleming two-stage design.[82] The planned sample size for Stage 1 was 40 patients and if ≥ 19 of the 40 patients exhibited a response (ORR defined as a MR or PR), then an additional 80 patients would be enrolled in an extension phase.[3] If the rate of response was intermediate at the end of Stage 1 (15 to 18 of the 40 patients

exhibiting a response), then an additional 20 patients would be enrolled in Stage 2 and in turn, if ≥ 27 of the 60 patients exhibited a response, then an additional 80 patients would be enrolled in the extension phase.[3]

Figure 6.2: Study design of Study 2201



N/A denotes not applicable.

Source: N Engl J Med, Gotlib J, Kluin-Nelemans HC, George TI, et al., Efficacy and safety of midostaurin in advanced systemic mastocytosis, 374:2530-41. Copyright © 2016 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[3]

Eligibility Criteria

Patients enrolled in Study 2201 met the key inclusion criteria detailed in Table 6.2.[3] The diagnosis of SM sub-type (i.e., ASM, SM-AHN, or MCL) was based on World Health Organization (WHO) criteria.

Patients with the C-finding of anemia or thrombocytopenia who were receiving red blood cell (RBC) or platelet transfusions were required to have another C-finding at study entry unless these patients presented with transfusion-dependent anemia (defined as ≥ four units of RBCs within 56 days of study start). These patients could enroll in the study even if they did not have any measurable C-findings, including hemoglobin < 10 g/dL. Patients with any other known concurrent severe and/or uncontrolled medical condition, CVD, heart block (Canada only), HIV infection or viral hepatitis, or who relapsed after ≥ 3 regimens of SM treatment, or who had received any investigational agent, chemotherapy, cladribine, or interferon-α within 30 days, or HGF support within 14 days of initiating midostaurin were not eligible. Patients with eosinophilia who were positive for the FIP1L1-PDGFRA fusion were not eligible unless they relapsed or had progressed on imatinib.[3] For more details on the key exclusion criteria for Study 2201, please refer to Table 6.2.

Analysis Populations

The analysis populations[18] in Study 2201 of interest to this review are as follows:

- **Final Analysis Set (FAS)** was defined as per the intention-to-treat (ITT) principle and comprised all patients to whom study drug was assigned.
- **Primary efficacy population (PEP)** consisted of patients in the FAS who met diagnostic criteria for ASM or MCL and presented with at least one measurable C-finding at study entry and/or patients with transfusion-dependent anemia due to their underlying disease at study entry as

confirmed by the SSC. The primary outcome of ORR by SSC was analyzed in the PEP.

- **Safety analysis set** included all patients who received at least one dose of study drug and was used for all safety analyses.
- **Per protocol set (PPS)** consisted of all patients from the PEP who did not have any major protocol deviations.

Outcomes

The primary outcome in Study 2201 was the proportion of patients with ORR as adjudicated by the SSC (ORR by SCC) occurring in the first six 4-week treatment cycles and maintained for ≥ eight weeks in the PEP.[3] The SSC adjudicated ORR according to modified Valent response criteria[5] and Cheson criteria[6,7] for transfusions.[3] An ORR comprised a MR defined as complete normalization of ≥ 1 C-finding(s) and no confirmed progression in other C-findings or a PR defined as > 50% improvement in ≥ 1 C-finding(s) and no progression or occurrence of new C-findings (good PR) or a > 20% to ≤ 50% improvement in ≥ 1 C-finding(s) and no progression or occurrence of new C-findings (minor PR).[3] For patients with transfusion-dependent anemia or thrombocytopenia as sole clinical C-finding, responses were assessed using modified Cheson response criteria (i.e., a MR was defined as no transfusions for eight weeks and PR was defined as ≥ 50% decrease in transfusions over eight weeks).[3]

Various sensitivity analyses were conducted on the primary outcome of ORR by SSC to support the primary analysis.[18]

Secondary outcomes included evaluation of DOR, TTR, PFS, OS, safety and tolerability of midostaurin, and histopathologic response based on mast cell infiltration in the bone marrow and changes in serum tryptase levels. Exploratory outcomes of interest to this review were patient-reported outcomes (PROs) and HRQoL measurements, clinical benefit or disease control rate (DCR), and characterization of *KIT* mutational status.[18]

DOR was defined as the time from start of first documented and confirmed response to first documented and confirmed SM-related progression or death.[3] TTR was defined as the time from date of start of treatment to the date of onset of first confirmed MR or PR. PFS was defined as the time from treatment start to the first confirmed disease progression sustained for ≥ four weeks, development of secondary acute myeloid leukemia, or death from any cause.[3] For DOR and PFS, patients were censored at the last adequate assessment in the event of ≥ two missing assessments or at the start of a new antineoplastic therapy. OS was defined as the time from treatment start to death from any cause and was censored at the time of the last contact date prior to the time of the analysis cut-off date for patients who were known to be alive or lost to follow-up. Histopathologic response was determined based on changes from baseline in bone marrow mast cell burden and serum tryptase levels.[3]

Safety assessments consisted of collecting data on AEs, serious AEs, and changes from baseline in vital signs and laboratory results (hematology, blood chemistry) Assessment was done according to the Common Toxicity Criteria for Adverse Events

(CTCAE) version 3.0. All safety analyses were conducted in the Safety Analysis Set (SAS) defined as all patients who received at least one dose of study drug.[18]

Exploratory outcomes included the assessment of patient-reported outcomes using the MSAS[8] and the SF-12.[9,10] The MSAS is a questionnaire to assess the frequency, severity, and associated distress of 32 common symptoms.[3] A decreased score indicates an improvement (i.e., a reduction in symptoms). The total MSAS score (TMSAS) is an average of all 32 symptoms, with a range of 0-4 and a minimal important difference of 0.20 to 0.45.[3] The physical symptom (PHYS) subscale is the average score of six physical symptoms (constipation, dry mouth, feeling drowsy, lack of appetite, lack of energy, and pain), with a range of 0-4 and a minimal important difference of 0.31-0.42.[3] The psychological symptom (PSYCH) subscale is the average of four psychological symptoms (feeling irritable, feeling nervous, feeling sad, and worrying), with a range of 0-4 and a minimal important difference of 0.45-0.66.[3] The global distress index (GDI) incorporates the frequency for the 10 symptoms on the PHYS and PSYCH subscales, with a range of 0-4 and a minimal important difference of 0.36-0.59.[3] MSAS scores were summarized by comparing the frequency of symptoms reported at baseline and at the time of best (lowest) TMSAS score. In addition, the MSAS subscores were evaluated at baseline and at the time of best TMSAS score for each patient.

The SF-12 questionnaire evaluates 12 measures, providing two scales of the patient's HRQoL: the physical composite score (PCS) and the mental composite score (MCS).[3] An increased scale score indicates improvement (better HRQoL). The PCS includes questions regarding general health, physical function, physical role functioning (e.g., being physically able to perform work and other activities), and bodily pain. The MCS includes questions regarding vitality, emotional role functioning, mental health, and social functioning. SF-12 scores were summarized by comparing the baseline values with the best (highest) value reported for each patient during the study. Change in HRQoL was based on the difference of these two values. Both the MCS and PCS score of the SF-12 have a range of 0-100 and a minimal important difference of 4 points.[3]

An additional exploratory outcome included DCR, which was defined as the proportion of patients with a best overall response of MR, PR, or stable disease (SD), which was reported for the PEP.[84]

Analyses:

The results of Study 2201 have been analyzed, presented or published using data from five different data extraction dates: March 15, 2012,[13] December 1, 2012,[14] July 9, 2013,[3,15] December 1, 2014,[2] and August 24, 2017 (final OS analysis only).[16] The sponsor confirmed that the only planned interim analysis was the first data cut-off date of March 15, 2012[13] which reported the results of 62 patients enrolled in Stage 1.[85] The clinical data presented in this report for Study 2201 corresponds with a data cut-off date of December 1, 2014 as reported in the CSR for Study 2201 and is in alignment with the data cut-off date in the economic evaluation submitted by the sponsor.[2] The median duration of follow-up as of December 1, 2014 was 43 months (range: 29 to 70) and 21 (18.1%) patients in the FAS and 15 (16.9%) patients in the PEP remained on treatment.

Protocol Amendments

The original protocol for Study 2201 was amended as below.[18] The CADTH Methods Team concluded that in general the amendments were minor and administrative in nature. It is not expected that the protocol amendments will have had any significant impact on the observed study outcomes.

- Amendment 1: Changes to inclusion and exclusion criteria and schedule of examinations to optimize capturing disease evolution and reduce patient burden and to refine and clarify language (November 25, 2008).[18]
- Amendment 2: Revisions to ensure only patients with measurable C-findings due to mastocytosis were enrolled included the addition of a patient enrollment approval process by SSC, the addition of histopathologic response as secondary objective, addition of PEP definition and additional sub-analyses, the implementation of an extension phase,[18] and mandating the administration of prophylactic antiemetics.[1](November 23, 2010)
- Amendment 3: Exclusion of patients with heart block as requested by Canadian health authorities (December 6, 2010).[18]
- Amendment 4: Clarify follow-up of patients who discontinued study treatment in absence of disease progression, and an updated definition of disease progression (February 8, 2012).[18]
- Amendment 5: Included language to allow patients to continue to receive midostaurin in accordance with local regulations (August 20, 2012).[18]
- Amendments 6: Revision of definition of end of study to allow for extended data collection in patients with ASM or MCL (i.e., five years after last patient first treatment or when all patients had discontinued study treatment whichever occurred first) (May 27, 2014).[18]

Statistical Analyses

Details on the quality of the study characteristics and sample size calculation of Study 2201 are provided in Table 6.3.

The primary efficacy outcome (ORR by SCC) in Study 2201 was analyzed in the PEP and reported as the proportion of patients with confirmed responses in the first six cycles, along with the two-sided P-value and Clopper-Pearson 95% CIs.[2]

Subcategories of the proportions of patients with MR or PR were also summarized with frequency counts and percentages. For DOR, TTR, OS, and PFS, Kaplan-Meier estimates and associated 95% CIs were derived in the PEP.[3] The number of patients with a best decrease of >50% in mast cell infiltrates relative to baseline and the number of patients with a best decrease of > 50% in serum tryptase levels relative to baseline (and lasting at least 56 days) were summarized.[3] Descriptive and summary statistics were also used to summarize patient responses for the MSAS and SF-12 using the PEP and the FAS.[84] DCR was summarized for the PEP along with 95% CIs.[84]

Subgroups pre-specified by the sponsor[b] that are of interest to this review for evaluation of ORR by SCC and OS were as follows:

[b] The sponsor defined the SM sub-type subgroups differently from the WHO classification in their analyses. The sponsor identified the SM sub-types as 1) ASM (which includes ASM and SM-AHN), 2) MCL

- ASM vs. MCL patients
- Associated hematological clonal non-mast cell lineage disease (AHNMD) (yes vs. no)
- Prior antineoplastic treatment regimen for SM and AHNMD (yes vs. no)
- Baseline *KIT* D816V mutation (positive, negative/unknown)

No subgroup analyses by baseline RBC or platelet transfusion dependence were conducted.

Study 2213

Study 2213 was a phase II, single-arm, open-label, multicentre, non-randomized trial that evaluated the efficacy and safety of midostaurin in patients with ASM, SM-AHN, or MCL regardless of *KIT* D816V mutation status.[4] The study was conducted at three sites in the USA.[86] The trial was an investigator-initiated trial [redacted].[86] *(Non-Disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the manufacturer that it can be publicly disclosed).*

Trial phases

A Simon two-stage design was used for Study 2213.[83] According to this design, in Stage 1, 10 patients were initially accrued and if ≥ 1 patient(s) responded by investigator assessment (i.e., achieved ORR [MR or PR]) then n=15 patients were to be enrolled in Stage 2. If ≥ 5 of the 25 patients responded, then further investigation of midostaurin was warranted.[4] If none of the first 10 patients had a response, then the study was to be closed.

Each patient could receive up to 12 cycles of midostaurin treatment. If a patient did not achieve a documented MR or PR during the first two cycles, they were to be discontinued from the study. Any patient with a continued response beyond 12 cycles and without a requirement for any other chemotherapy could continue to receive midostaurin through an extension phase. All patients continued midostaurin until confirmed disease progression or discontinuation for any other reasons in either of the study stages or extension phase. Other reasons included AEs, abnormal laboratory value[s], abnormal test procedure[s], unsatisfactory therapeutic effect, patient's condition no longer required study treatment, protocol violation, withdrawal of consent, lost to follow-up, administrative problems, or death.

and 3) ASM or MCL with associated hematological clonal non-mast cell lineage disease (AHNMD). As a result, the sponsor's pre-specified subgroup analyses are reported by these subgroups in this report. The European Medicines Agency (EMA) public assessment report; however, did include SM sub-type sub-group analyses according to the WHO classification (i.e., ASM, SM-AHN, and MCL) and so whenever possible, the results from the EMA report for the SM sub-type sub-group analyses are reported in this report.

Eligibility Criteria

Patients enrolled in Study 2213 met the key inclusion criteria detailed in Table 6.2.[4]

Patients who had received any investigational agent, chemotherapy, cladribine, or interferon-α within 30 days, or hematopoietic growth factor (HGF) support within 14 days of initiating midostaurin were not eligible.[4] For more details on the key exclusion criteria for Study 2213, please refer to Table 6.2.

Analysis Populations

The analysis populations in Study 2213 of interest to this review are as follows:[12]

Full analysis set (FAS) was defined as per the intention-to-treat principle (ITT) and comprised all patients to whom study drug was assigned.

- **Safety analysis set** included all patients who received at least one dose of study drug and was used for all safety analyses.
- **Primary efficacy population (PEP)** comprised all patients in the FAS who had received at least 14 days of midostaurin treatment and who did not have any major protocol deviations. The primary outcome of ORR by INV was summarized using the PEP (which was identical to the FAS).

Outcomes

The primary outcome was the proportion of patients with overall response by investigator assessment (ORR by INV) defined as a MR or a PR according to Valent response criteria[11] and confirmed for ≥ eight weeks during the first two cycles of midostaurin treatment.[2,4] A MR was defined as complete resolution of ≥ 1 C-finding(s) and no progression in other C-findings.[4] C-findings included cytopenias, osteolysis with or without pathological fractures, hepatosplenomegaly and/or with impaired liver function and/or ascites, and malabsorption.[4] A PR was defined as incomplete regression of ≥ 1 C-findings without complete regression and without progression in other C-findings.[4] Responses were assessed at the completion of each cycle and if patients did not achieve a MR or PR by the end of two cycles, they were discontinued from the trial. As the Valent criteria do not address red blood cell (RBC) or platelet transfusion requirements, RBC and platelet transfusion independence was defined as freedom from RBC or platelet transfusions for ≥ eight weeks in patients requiring ≥ four units of RBCs or platelets in the eight weeks prior to study entry.[4,11]

Secondary outcomes included evaluation of safety and tolerability, *KIT* mutation status, OS, and PFS.[4] [redacted].[12] *(Non-Disclosable information was used in this pCODR Guidance Report and the manufacturer requested this safety information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the manufacturer that it can be publicly disclosed).* OS was calculated as the time from the first treatment dose of midostaurin until the date of death or data cut-off.[4] PFS was calculated from the first day of midostaurin treatment to the date of disease progression (SM or AHN component) or death.[4] [redacted].[12] *(Non-Disclosable information was used in this pCODR*

Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the manufacturer that it can be publicly disclosed).

[redacted].[12] *(Non-Disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the manufacturer that it can be publicly disclosed).*

Analyses:

The results of Study 2213 have been analyzed, presented or published using data from five different data extraction dates: June 1, 2006,[20] June 1, 2007,[21] and June 1, 2010[22] (the first three data cuts mentioned are estimated by the sponsor)[17], December 3, 2012[2] and March 1, 2017.[4] As Study 2213 was an investigator-sponsored trial (whereby all abstracts and study publications were controlled strictly by the study investigators)[23], the sponsor was unable to confirm which of the data cut-off dates were pre-specified[85] as well as the final analysis cut off date.[23] The clinical data presented in this report for Study 2213 corresponds with a data cut-off of December 3, 2012 as reported in the CSR[2] and March 1, 2017,[4] the data cut-off for the main publication for Study 2213. The data cut-off date of March 1, 2017 is in alignment with the data cut-off date in the sponsor's economic evaluation.[85] The median duration of follow-up as of March 1, 2017 was 124 months (range: 82 to 140) and two (7.7%) patients remained on treatment.[4]

Statistical Analyses

Details on the quality of the study characteristics of Study 2213 are provided in Table 6.3. A sample size calculation was not undertaken for this trial; rather, a Simon two-stage design was used.[83]

The primary efficacy outcome (ORR by INV) was analyzed in the FAS and reported as the proportion of patients who had a confirmed best overall response of MR or PR along with 95% Clopper-Pearson confidence intervals (CIs).[4] Subcategories of the proportions of patients with MR or PR were also summarized with frequency counts and percentages. For OS, PFS, and DOR, Kaplan-Meier estimates and associated 95% CIs were derived in the FAS.[4]

Pre-specified subgroups[c] of interest to this review for evaluation of the primary outcome of ORR by INV were as follows:

- ASM vs. MCL patients
- AHNMD (yes vs. no)

[c] The sponsor defined the SM sub-type subgroups differently from the WHO classification in their analyses. The sponsor identified the SM sub-types as 1) ASM (which includes ASM and SM-AHN), 2) MCL and 3) ASM or MCL with associated hematological clonal non-mast cell lineage disease (AHNMD). As a result, the sponsor's pre-specified subgroup analyses are reported by these subgroups in this report. The European Medicines Agency (EMA) public assessment report; however, did include SM sub-type sub-group analyses according to the WHO classification (i.e., ASM, SM-AHN, and MCL) and so whenever possible, the results from the EMA report for the SM sub-type sub-group analyses are reported in this report.

- Prior antineoplastic treatment regimen for SM and AHNMD (yes vs. no)
- Baseline *KIT* D816V mutation (positive, negative/unknown)

b) Populations

Study 2201

Patient enrollment took place between January 2009 to July 2012. A total of 116 patients entered the study and were included in the FAS. Details of patient baseline demographic and disease characteristics are provided in Table 6.4. In the FAS, median age was 63 years (range: 25 to 82), 66% of patients were male, and 34% of patients had an ECOG performance score of 2 to 3.[3] In the PEP (n= 89), the corresponding results were 64 years (range: 25 to 82), 64% of patients were male, and 36% had ECOG performance status of 2 to 3. More than 50% of patients had not received any prior therapies and most (84% in the FAS and 87% in the PEP) were positive for a *KIT* D816 mutation. Of the 89 patients in the PEP, 16 patients (18%) were diagnosed with ASM, 57 patients (64%) with SM-AHN, and 16 patients (18%) with MCL (of which six [7%] had MCL associated with AHN). All patients had at least one sign of organ damage with the largest category of patients (33% in the FAS and 43% in the PEP) having three or more C-findings. Baseline median tryptase levels were 200 µg/mL (range: 2 to 12,069) in the FAS and 236 µg/mL (range: 27 to 12,069) in the PEP. Median bone marrow mast cell burden was 40% (range: 3 to 98) in the FAS and 50% (range: 8 to 98) in the PEP.

Study 2213

Patient enrollment took place between July 2005 and April 2010. A total of 26 patients entered the study and were included in the FAS. Details of patient baseline demographic and disease characteristics are provided in Table 6.5. Median age was 64.5 years (range: 24 to 79), 58% of patients were male, and 54% of patients had an ECOG performance score of 2 to 3. Most patients (>80%) had received prior therapies and were positive (77%) for a *KIT* D816 mutation. Of the 26 enrolled patients, three patients (12%) were diagnosed with ASM, 17 patients (65%) with SM-AHN, and six patients (23%) with MCL. All patients had at least one sign of organ damage with the largest category of patients (39%) having at least two C-findings.[4] Baseline median tryptase levels were 323 ng/mL (range: 22 to 1255) and median bone marrow mast cell burden was 50% (range: 5 to 95).[4]

Table 6.4: Study 2201 Baseline Patient Characteristics

Characteristics		Intent-to-Treat Population (n = 116)	Primary Efficacy Population (n = 89)
Median age (range), y		63 (25-82)	64 (25-82)
Male, n (%)		76 (66)	57 (64)
ECOG performance status, n (%)	0-1	77 (66)	57 (64)
	2-3	39 (34)	32 (36)
Number of prior therapies, n (%)	None	64 (55)	52 (58)
	1	29 (25)	21 (24)
	2	15 (13)	12 (13)
	≥ 3	8 (7)*	4 (4)*
Types of prior therapies, n (%)†	Cladribine	17 (15)	12 (13)
	Imatinib	11 (9)	10 (11)
	Hydroxycarbamide	12 (10)	9 (10)
	Interferon α/PEG-interferon-α	11 (9)	7 (8)
	Dasatinib	6 (5)	5 (6)
	Prednisolone/prednisone	8 (7)	5 (6)
	Cytarabine	5 (4)	4 (4)
	Decitabine	2 (2)	2 (2)
	Other	14 (12)	6 (7)
Histopathology review, n (%)			
SM subtype	Non-MCL	95 (82)	73 (82)
	ASM	ND	16 (18)
	SM-AHN	ND	57 (64)
	MCL	21 (18)	16 (18)
	MCL with AHN	10 (9)	6 (7)
AHN	Any	83 (72)	63 (71)
	CMML	32 (28)	25 (28)
	MDS/MPN-U	30 (26)	22 (25)
	MDS	10 (9)	7 (8)
	CEL	4 (3)	4 (4)
	Other	5 (4)	5 (6)
KIT D816 mutation status, n (%)	Positive	98 (84)	77 (87)‡
	Negative	13 (11)	10 (11)
	Unknown	5 (4)	2 (2)
Median bone marrow mast cell burden (range), %		40 (3-98)	50 (8-98)
Median serum tryptase level (range), µg/L		200 (2-12,069)	236 (27-12,069)
Organomegaly, n (%)	Spleen	104 (90)	82 (92)
	Liver	73 (63)	63 (71)
Ascites, n (%)		58 (50)	51 (57)

Measurable C-findings, n (%)			
Hematologic[§,¶]	Anemia	28 (24)	28 (32)
	Not transfusion-dependent	8 (7)	8 (9)
	Transfusion-dependent	20 (17)	20 (22)
	Thrombocytopenia	55 (47)	55 (62)
	Not transfusion-dependent	51 (44)	51 (57)
	Transfusion-dependent	4 (3)	4 (5)
	Neutropenia	7 (6)	7 (8)
Nonhematologic	Hypoalbuminemia	48 (41)	48 (54)
	Increased total bilirubin	25 (22)	25 (28)
	Weight loss[‖]	12 (10)	12 (13)
	Increased ALT	6 (5)	6 (6)
	Increased AST	2 (2)	2 (2)
Number of C-findings per patient, n (%)	1	31 (27)	31 (35)
	2	20 (17)	20 (22)
	≥ 3	38 (33)	38 (43)

Abbreviations: AHN = associated hematologic neoplasm; ALT = alanine transaminase; ASM = aggressive systemic mastocytosis; AST = aspartate transaminase; CEL = chronic eosinophilic leukemia; CMML = chronic myelomonocytic leukemia; ECOG = Eastern Cooperative Oncology Group; MCL = mast cell leukemia; MDS/MPN-U = myelodysplastic/myeloproliferative neoplasm – unclassifiable; ND = not determined; PEG = pegylated; SM = systemic mastocytosis

Note: Intention-to-treat population is identical to the FAS

Source: N Engl J Med, Gotlib J, Kluin-Nelemans HC, George TI, et al., Efficacy and safety of midostaurin in advanced systemic mastocytosis, 374:2530-41. Copyright © 2016 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society[3]

Table 6.5: Study 2213 Baseline Patient Characteristics

Characteristics	(n = *26*)
Median age, years (range)	64.5 (24–79)
Male, *n* (%)	15 (58)
ECOG performance status, n *(%)*	
0–1	12 (46)
2–3	14 (54)
Time from SM diagnosis (by bone marrow biopsy) to start of study treatment, days (range)	241 (12–1756)
Number of prior therapies, n *(%)*	
None	5 (19)
1	8 (31)
2	6 (23)
⩾3	7 (27)
Types of prior therapies, n *(%)*	
Corticosteroids	14 (54)
Imatinib	10 (39)
2-Chlorodeoxyadenosine	5 (19)
Hydroxycarbamide	4 (15)
Dasatinib	4 (15)
(PEG)-interferon-α	3 (12)
Other[a]	3 (12)
Denileukin difitox	2 (8)
Histopathology review, n *(%)*	
SM subtype	
ASM	3 (12)
SM-AHN	17 (65)
CMML	12 (46)
MDS/MPN-U	3 (12)
MDS	2 (8)
MCL[b]	6 (23)
KIT D816 mutation[c,d], *n* (%)	20 (77)
Other *KIT* mutation[e]	1 (4)
KIT mutation negative[f]	5 (19)
Median tryptase level, ng/ml (range)	323 (22–1255)
Median bone marrow mast cell burden, % (range)	50 (5–95)
Karyotype, n *(%) (denominator*, n = *25)*	
Normal	19 (73)
Abnormal[g]	6 (23)
Organomegaly, n *(%)*	
Liver	18 (69)
Spleen	20 (77)

Abbreviations: AHN, associated hematologic neoplasm; ASM, aggressive systemic mastocytosis; CMML, chronic myelomonocytic leukemia; ECOG, Eastern Cooperative Oncology Group; MCL, mast cell leukemia; MDS/MPN-U, myelodysplastic syndrome/myeloproliferative neoplasm-unclassifiable; PEG, pegylated; SM, systemic mastocytosis. [a]Other therapies: daclizumab (*n* = 1); acute myeloid leukemia (AML)-type chemotherapy (3+7) (*n* = 1); CHOP (*n* = 1). [b]Two MCL patients had CMML-1 as an AHN. [c]*KIT* D816V = 19, *KIT* D816Y = 1. [d]One patient also had a *FLT3* internal tandem duplication mutation. [e]*KIT* S451C = 1. [f]One patient had a *MPL* 2 amino acid insertion mutation. [g]One patient had a t(5;12) constitutional karyotype abnormality.

Source: Reprinted by permission from Macmillan Publishers Limited: Springer Nature, Leukemia. Efficacy and safety of midostaurin in patients with advanced systemic mastocytosis: 10-year median follow-up of a phase II trial, DeAngelo DJ et al., 32:470–478. COPYRIGHT 2018[4]

c) Interventions

Study 2201

Study 2201 was a single-arm trial. The intervention was oral midostaurin 100 mg twice daily with meals (provided as 4 x 25 mg capsules) in 4-week continuous cycles.[3,18] Patients were advised to swallow capsules whole and to space doses approximately 12 hours apart. Patients continued treatment until disease progression, intolerable toxicity, or withdrawal due to any cause. Patients who discontinued study treatment were monitored regularly at approximately three-month intervals until the end of study. Patients who remained on treatment at the end of the study could continue to receive midostaurin in a compassionate use program or through local supply processes.[84]

Dose adjustments and interruptions were permitted for pre-specified hematologic and non-hematologic toxicities according to a detailed algorithm.[3] Patients experiencing toxicity had treatment interrupted until recovery to ≤ grade 2 severity or for a maximum of 21 days. Patients could be re-challenged at a dose of midostaurin 50 mg twice daily. Any patient requiring dose interruption for more than 21 days or who was unable to tolerate midostaurin 50 mg twice daily was discontinued. For patients with non-hematologic toxicities only, a dose increase back to 100 mg twice daily could be attempted in the subsequent cycle if the toxicities occurred in the first two months of treatment. Patients who tolerated the resumption of dose remained at 100 mg twice daily and those who did not remained at a modified dose of 50 mg twice daily and were discontinued if toxicities recurred at the lower dose.[84]

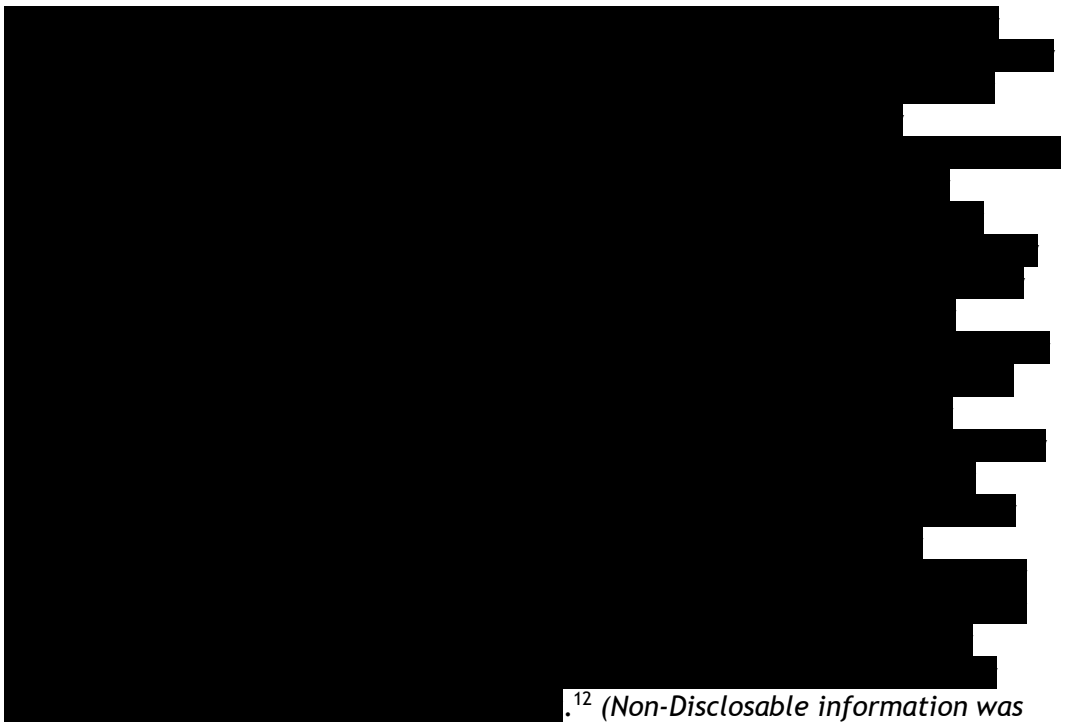
Permitted concomitant medications included glucocorticoids and histamine receptor antagonists for severe mediator-related symptoms or anaphylaxis. Otherwise, glucocorticoids were to be used sparingly, tapered, and stopped within 14 days of midostaurin treatment. Prophylactic anti-emetics for prevention of nausea and vomiting were administered to all patients. Other anticancer agents (e.g., chemotherapy, radiation therapy, or biologic response modifiers), investigational drugs, and HGFs were not permitted. Use of CYP3A4/5 inducers or inhibitors was discouraged. [84]

Based on a data cut-off of December 1, 2014 in the safety set (N=116), the median duration of treatment with midostaurin was 11.4 months (range: 0.3 to 68.3) and the median daily dose was 198.7 mg (range: 66.9 to 271.4). Overall, 57 patients (49.1%) had at least one dose interruption and 70 patients (60.3%) required at least one dose reduction. The main reason for both dose interruptions and reductions were due to adverse events (AEs).

Study 2213

Study 2213 was also a single-arm trial. The intervention was oral midostaurin 100 mg twice daily with meals (provided as 4 x 25 mg capsules) administered as continuous 28-day cycles for up to 12 cycles.[4] Patients with an on-going response of

MR or PR and without unacceptable toxicity could continue to receive midostaurin through an extension protocol beyond the 12 cycles. During the first cycle of treatment, patients were hospitalized from Day 1-3 to monitor for signs and symptoms of mast cell degranulation. Following treatment discontinuation, patients were followed up for one year.



.[12] *(Non-Disclosable information was used in this pCODR Guidance Report and the manufacturer requested this safety information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the manufacturer that it can be publicly disclosed).*

Use of concomitant therapies necessary for supportive care and safety were generally permitted (e.g., prophylactic anti-emetics). During treatment with midostaurin, medications used for symptoms of SM (e.g., glucocorticoids) were also allowed. Prohibited concomitant therapies during midostaurin treatment included use of chemotherapies, radiation therapy, or biologic response modifiers, investigational drugs, HGFs, and use of CYP3A4/5 inducers or inhibitors.

Based on a data cut-off of December 3, 2012, the median duration of midostaurin treatment was 9.8 months (range: 0.8 to 80.1). Median dose intensity was 1398.4 mg/week. Overall, 13 patients (50%) required at least one dose interruption and one dose reduction, respectively. The main reasons for both dose interruptions and reductions were due to AEs.

Based on a data cut-off of March 1, 2017, the median duration of treatment was 19 months (range: 2 to 132).[4] Based on information in the publication, dose reductions occurred in six patients (23%) due to grade 1 or 2 nausea or vomiting (n=2), grade 1 headache (n=1), grade 2 diarrhea (n=1), grade 3 thrombocytopenia (n=1), and grade 3 hyperlipasemia (n=1). Re-escalation of dose to 100 mg twice daily was possible in two patients (33%).[4]

d) Patient Disposition

Details of patient disposition for Study 2201 and Study 2213 are detailed in Table 6.7.

Study 2201

In Study 2201, of the 116 patients enrolled, 27 were considered unevaluable for response as adjudicated by the SSC, resulting in 89 patients being included in the PEP. Patients were considered unevaluable due to the absence of measurable C-findings (n=14 patients) or measurable C-findings that were unrelated to mastocytosis (n=13 patients).

[redacted].[52] *(Non-Disclosable information was used in this pCODR Guidance Report and the manufacturer requested this safety information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the manufacturer that it can be publicly disclosed).* Death was the primary reason for discontinuation in eight patients (6.9%) in the FAS (n=2 deaths due to disease progression and n=6 deaths due to AEs) and in seven patients (7.9%) in the PEP (n=1 due to disease progression and n=6 due to AEs).

All patients continued study drug until confirmed disease progression, unacceptable toxicity, or discontinuation/withdrawal for any other reason.[3] Patients who discontinued before completing the study were scheduled for a visit at which time all end of treatment assessments were performed. If patients declined to return for a visit, at a minimum they were contacted for a safety evaluation 28 days after the last dose of study drug. The survival status of all discontinued patients was monitored regularly at 3-month intervals until the end of study.[84]

Patients who discontinued midostaurin could go on to additional therapies at the investigator's discretion. Overall, 35 (39.3%) patients in the PEP received antineoplastic therapies following discontinuation of midostaurin as detailed in Table 6.6. Antineoplastics included mainly purine analogs (22.5%; primarily cladribine), pyrimidine analogs (13.5%; primarily azacytidine and cytarabine), and protein kinase inhibitors (13.5%; primarily midostaurin with eight patients receiving midostaurin in a compassionate use program outside of the study protocol).

Table 6.6: [redacted]

(Non-Disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the manufacturer that it can be publicly disclosed)
Source: Sponsor's submission[2]

Study 2213

Based on the data cut-off of December 3, 2012, 19 patients (73.1%) had discontinued and seven patients (26.9%) continued on-treatment,[12] whereas the corresponding proportions at the March 1, 2017 cut-off were 24 patients (92.3%) and two patients (7.7%), respectively.[4] The main reasons for discontinuation of study treatment were due to disease progression and unsatisfactory therapeutic effect for both data cut-offs. All patients who discontinued were followed for survival for one year.[12]

Table 6.7: Patient Disposition in Study 2201 and Study 2213

	Study 2201		Study 2213	
Analysis population	**FAS (N=116)**	**PEP[a] (N=89)**	**FAS (N=26)**	**FAS (N=26)**
Data cut-off	**Dec 1, 2014**		**Dec 3, 2012**	**Mar 1, 2017**
Patients treated, n (%):	116 (100)	89 (100)	26 (100)	26 (100)
Treatment on-going	21 (18.1)	15 (16.9)	7 (26.9)	2 (7.7)
End of treatment	95 (81.9)	74 (83.1)	19 (73.1)	24 (92.3)
Primary reason for DC, n (%):				
Disease progression	44 (37.9)	35 (39.3)	6 (23.1)	7 (26.9)
Adverse event(s)	28 (24.1)	22 (24.7)	4 (15.4)	6 (23.1)
Unsatisfactory therapeutic effect	0 (0)	0 (0)	5 (19.2)	8 (30.8)
Withdrawal of consent	10 (8.6)	8 (9.0)	3 (11.5)	3 (11.5)
Death	8 (6.9)	7 (7.9)	1 (3.8)	0 (0)
Protocol deviation	2 (1.7)	1 (1.1)	0 (0)	0 (0)
Lost to follow-up	1 (0.9)	0 (0)	0 (0)	0 (0)
Administrative problems	1 (0.9)	0 (0)	0 (0)	0 (0)
Abnormal test procedure results	1 (0.9)	1 (1.1)	0 (0)	0 (0)

Abbreviations: DC = discontinuation; FAS = full analysis set; PEP = primary efficacy population; SM = systemic mastocytosis

Notes:
[a] The PEP comprised patients in the FAS who met diagnostic criteria for aggressive mastocytosis (ASM) or mast cell leukemia (MCL) and presented with at least one measurable C-finding at study entry and/or patients with transfusion-dependent anemia due to their underlying disease at study entry as confirmed by the study steering committee (SSC).

Source: EPAR[18], DeAngelo et al., 2018[4], and Sponsor's submission[2]

e) Limitations/Sources of Bias

- Both Study 2201 and Study 2213 were non-randomized, single-arm, phase II trials. The non-randomized and non-comparative design of the trials complicates the interpretation of the efficacy and safety data for midostaurin because all patients received the same treatment. The lack of comparison with an active comparator or standard of care/placebo precludes the ability to assess the relative therapeutic benefit or safety of midostaurin against a relevant comparator. This is true in terms of both the clinical significance and statistical significance of study outcomes.

- Both Study 2201 and Study 2213 were open-label trials which potentially increases the risk of performance and detection bias because study personnel and patients were aware of the treatment allocation. For example, the efficacy results may have been biased in favour of midostaurin if the study personnel or patients believed that the drug would have a therapeutic benefit. Furthermore, if study personnel and patients knew that the treatment was

midostaurin (which has previously been available for the treatment of acute myeloid leukemia and is known to cause gastrointestinal and other AEs), this could have influenced the reporting of harms outcomes. The lack of blinding is expected to have the largest impact on the reporting of subjective outcomes such as PROs and AEs.

- Sample sizes in both Study 2201 (N=116) and Study 2213 (N=26) were small which is not unexpected given the rarity of advSM. Although many subgroup and sensitivity analyses were pre-specified in both trials, the results of these analyses are associated with significant uncertainty as the resultant sample sizes for the subgroup and sensitivity analyses are even smaller and associated with wide CIs. The lack of statistical interaction testing and adjustments for multiple comparisons adds to the uncertainty associated with the results. Therefore, the results of any subgroup or sensitivity analyses are considered as exploratory.

- In Study 2201, there is a risk of selection bias because the SSC adjudicated patient entry into the trial in an unblinded manner which may have led to a selected population. In this regard, not all patients who would potentially be eligible for midostaurin participated in the trial, but rather, only those patients adjudicated by the SSC according to information in patient listings were able to participate. According to the sponsor, 182 patients were screened for entry into Study 2201 and 116 (63.7%) patients were adjudicated by the SSC to be eligible for study entry.[87] As a result, more than a third (36.3%) of the patients were screening failures.[87] The most common reason for screening failures was that the patient did not meet diagnostic/severity criteria. Another frequently mentioned reason was an unacceptable test procedure result.[25] A selected population could affect the generalizability of the study results to all patients with advanced SM.

- In Study 2201, the primary efficacy and secondary analyses were conducted in the PEP (N=89) which excluded 27 patients who were unevaluable for response by the SSC. The patients were considered unevaluable due to absence of measurable C-findings (n=14) or measurable C-findings that were unrelated to mastocytosis (n=13). As a result, the PEP is a modified ITT population in which almost a quarter (23.3%) of patients who had been adjudicated for entry into the study by the SSC were excluded from the primary efficacy analyses. The sponsor did conduct sensitivity analyses in the FAS which comprises the ITT population and the results were generally supportive of those in the PEP.

- The appropriateness of ORR as a primary outcome in both Study 2201 and Study 2213 is unclear. Given the limitations associated with the OS analyses in both trials (e.g., lack of power calculation for OS, only one-year survival follow-up in Study 2213, and potential confounding by patients who received subsequent therapies in Study 2201), it is unclear whether ORR can be considered to be an appropriate surrogate for OS.

- Both Study 2201 and Study 2213 were not powered to adequately assess OS and PFS. In addition, the interpretation of OS and PFS results is challenging in single-arm trials as it is unclear to what extent the outcomes can be attributed to the treatment effect of the drug.[27] Further, in Study 2213 patients were only followed up for survival for one year, therefore long-term survival beyond one

year cannot be determined in this trial. The analysis of OS and PFS in Study 2201 could also have been affected by the large number of patients censored at the data cut-offs for these analyses (e.g., 39.3% for the OS analysis and 49.4% for the PFS analysis in the PEP). In the PEP, 13 (14.6%) patients were censored from the PFS analysis for starting new antineoplastic therapy; however, for the OS analysis, patients were censored only for on-going without an event (25 [28.1%] patients) or no updated survival data within two weeks of the survival analysis cut-off (10 [11.2%] patients). As 35 (39.3%) patients in the PEP went on to receive subsequent antineoplastic therapies after discontinuation of midostaurin, this could have confounded the OS analysis as it is unknown if survival was prolonged due to treatment with midostaurin or the subsequent antineoplastic therapy, or the combination/sequential use of the therapies.

- All primary and secondary efficacy and safety analyses in Studies 2201 and 2203 were assessed regardless of SM sub-type. Although the primary and key secondary outcomes (e.g., ORR, OS) were also reported by SM sub-type, there is significant uncertainty in these results owing to the small sample sizes of the subgroups. Combining all advanced SM patients into one group, regardless of SM sub-type, discounts the potential for clinical heterogeneity in disease processes or the potential for differences in prognostic heterogeneity depending upon the specific SM sub-type.[26] Furthermore, in the SM-AHN sub-type, the type of hematologic neoplasm may impart clinical and prognostic differences.[26]

- PROs were only reported in Study 2201 as exploratory outcomes. No statistical analyses were planned and according to the statistical analysis plan, only descriptive and summary statistics were to be conducted. The PRO results are further limited by missing data. For the proportion of patients with improvement in the total MSAS score and in SF-12 subscales, only about 60% of patients were considered evaluable based on having baseline scores > 0 and assessments for at least 168 days/six cycles. The number of patients for whom PRO data were available steadily declined over the course of the study ([redacted]).[52] *(Non-Disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the manufacturer that it can be publicly disclosed).* This is reflected in the compliance rate as well. [redacted].[52] *(Non-Disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the manufacturer that it can be publicly disclosed).* There is also a lack of validation of the PRO instruments and minimally important differences in patients with advSM. Additionally, the trial was non-randomized and the impact of midostaurin on PRO in relation to other therapies is unknown. As a result, no firm conclusions regarding the clinical significance of the PRO outcomes could be drawn although it appears that midostaurin does not negatively impact patients' quality of life.

- In Study 2201, the ORR was adjudicated by the SSC according to modified Valent[5] and Cheson criteria.[6,7] During the US FDA review[1] of midostaurin for advanced SM, it was requested that the sponsor provide an analysis of treatment response (ORR) according to the International Working Group on Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis consensus criteria (IWG criteria).[37] The IWG criteria are more stringent, primarily because they require 12-week confirmation of response and a minimum range of improvement for most C-findings compared to the modified Valent[5] and Cheson criteria.[6,7] According to the IWG criteria, the ORR (N=115) was 16.5% (95% 10.3; 24.6) if defined as complete response + PR; however, as the IWG criteria are not directly comparable to the modified Valent[5] and Cheson criteria,[6,7] it is not appropriate to test the results against the null ORR rate of 30% for interpretation of treatment efficacy.[1]

- For Study 2201, according to the sponsor, only one interim analysis was pre-specified which corresponds with a data cut-off date of July 19, 2012.[13,17] For Study 2213, because it was initially an investigator-sponsored trial, the sponsor was unable to confirm which, if any, of the data cut-off dates were pre-specified.[17] Therefore, the analyses conducted at the data cut-off times reported in this report (i.e., December 1, 2014 for Study 2201 and December 3, 2012 and March 1, 2017 for Study 2213) were not pre-specified and planned analyses. The main publication for Study 2201 (Gotlib et al., 2016)[3] has a data cut-off of July 9, 2013 whereas the CSR has a data cut-off of December 1, 2014. In addition, Study 2213 (DeAngelo et al., 2018)[4] has a data cut-off of March 1, 2017 whereas the CSR has a data cut-off of December 3, 2012. This is a limitation of the trials because it is not clear what informed the decision to look at the data at multiple time points. Although statistical comparisons were not conducted in the included trials, undertaking unplanned interim analyses increases the risk of type 1 error and may lead to overestimation of the treatment effect.

6.3.4 Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

The median duration of follow-up in Study 2201 (i.e., difference between treatment start date and the cut-off date of December 1, 2014) was 43 months (range: 29 to 70 months) for the reported efficacy outcomes unless otherwise specified. For the final OS analysis (August 24, 2017) in Study 2201, the median duration of follow-up was 76 months[24] ([redacted])[52].*(Non-Disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the manufacturer that it can be publicly disclosed).* The median duration of follow-up in Study 2213 for the data cut-off of December 3, 2012 was 73 months (range: 31 to 89 months)[18] and for the data cut-off of March 1, 2017, was 124 months (range: 82 to 140 months).[4]
The sponsor defined the SM sub-type subgroups differently from the WHO classification in their analyses. The sponsor identified the SM sub-types as 1) ASM

(which includes ASM and SM-AHN), 2) MCL and 3) ASM or MCL with associated hematological clonal non-mast cell lineage disease (AHNMD). As a result, the sponsor's pre-specified subgroup analyses are reported by these subgroups in this report. The European Medicines Agency (EMA) public assessment report; however, did include SM sub-type sub-group analyses according to the WHO classification (i.e., ASM, SM-AHN, and MCL) and so whenever possible, the results from the EMA report for the SM sub-type sub-group analyses are reported in this report.[4]

Due to the methodological limitations of the subgroup analyses (e.g., small sample sizes, lack of adjustment for multiplicity, and lack of statistical interaction testing) conducted in Study 2201 and Study 2213, only results of the subgroup analyses of the key outcomes of OS and ORR will be presented in this report.

A summary of the results of the primary and secondary efficacy outcomes from Study 2201 and Study 2213 is presented in Table 6.8.

Table 6.8: Summary of Efficacy Outcomes in Study 2201 and Study 2213

Efficacy Outcomes	Study 2201		Study 2213	
Data cut-off	**December 1, 2014**		**December 3, 2012**	**March 1, 2017**
Median follow-up (range)	43 months (range: 29 to 70)		73 months (range: 31 to 89)	124 months (82 to 140)
Analysis population, N	**PEP (N=89)**	**FAS (N=116)**	**FAS (N=26)**	**FAS (N=26)**
Overall survival				
No. deaths, n (%)	54 (60.7)	67 (57.4)	[redacted]	22 (84.6)
Median OS, months (95% CI)	26.8 (17.6; 34.7)	28.7 (20.3; 38.0)	[redacted]	40.0 (27.3; 52.7)
Progression-free survival				
No. PFS events, n (%)	45 (50.6)	45 (38.8)	8 (30.8)	10 (38.5)
Median PFS, months (95% CI)	17.0 (10.2; 24.8)	17.0 (10.2; 24.8)	38.6 (11.3; NE)	41.0 (4.4; 77.6)
Overall response rate[a]				
ORR, n (%) (95% CI)	53 (59.6) (48.6; 69.8)	53 (45.7) (36.4; 55.2)	19 (73.1) (52.2; 88.4)	18 (69) (50; 88)
Major response, n (%)	40 (44.9)	40 (34.5)	13 (50.0)	13 (50)
Partial response, n (%)	13 (14.6)	13 (11.2)	6 (23.1)	5 (19)
Stable disease, n (%)	11 (12.4)	11 (9.5)	6 (23.1)	5 (19)
Progressive disease, n (%)	10 (11.2)	10 (8.6)	1 (3.8)	3 (12)
Not evaluable, n (%)	15 (16.9)	42 (36.2)	0 (0)	0 (0)
Duration of Response				
Median DOR, months (95% CI)	31.4 (10.8; NE)	NR	Not reached	132 (NR)
Disease Control Rate[b]				
n (%) (95% CI)	64 (71.9) (61.4; 80.9)	64 (55.2) (45.7; 64.4)	NR	NR
Patient-reported and HRQoL outcomes				
TMSAS scores				
≥50% decrease from BL, n (%)	20 (22.5)	NR	NA	NA
SF-12 scores				
≥50% increase from BL in PCS, n (%)	10 (11.2)	NR	NA	NA
≥50% increase from BL in MCS, n (%)	3 (3.4)	NR	NA	NA
Serum tryptase level				
Median BL, µg/L (range)	236 (26.6 to 12,069.0)	236 (26.6 to 12,069.0)	323 (22.2 to 1255.0)	323 (22.2 to 1,255.0)
≥50% decrease from BL, n (%)	34 (38.2)	46 (39.7)	13 (50.0)	12 (46)
BM mast cell burden				
Median BL % (range), n	50 (8 to 98)	50 (8 to 98)	50 (5.0 to 95.0)	50 (5.0 to 95.0)
≥50% decrease from BL, n	[redacted]	NR	12 (46.1)	17 (68) (n=25)

Abbreviations: BL = baseline; BM = bone marrow; CI = confidence interval; DOR = duration of response; FAS = full analysis set; HRQoL = health-related quality of life; MCS = mental component score of the SF-12; NA = not applicable; NE = not estimable; NR = not reported; ORR = overall response rate; OS = overall survival; PCS = physical component score of the SF-12; PFS = progression-free survival; PEP = primary efficacy population; SF-12 = Short form health survey-12; TMSAS = Total Memorial Symptom Assessment Score

Notes:

[a] The primary efficacy outcome in Study 2201 was ORR (MR + PR) by study steering committee adjudication and in Study 2213 was ORR (MR + PR) by investigator assessment

[b] Defined as the sum of MR + PR + SD

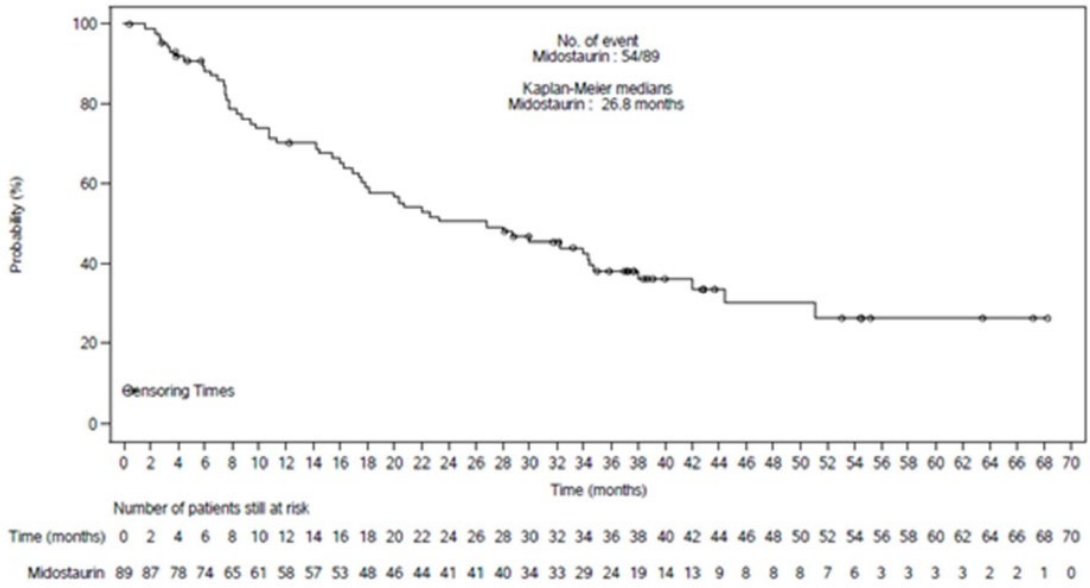
(Non-Disclosable information was used in this pCODR Guidance Report and the manufacturer requested this efficacy information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the manufacturer that it can be publicly disclosed).

Overall Survival

Study 2201

The Kaplan-Meier plot of OS for all patients in the PEP with data cut-off of December 1, 2014 is depicted in Figure 6.3. OS was a secondary outcome in Study 2201.

Figure 6.3: Study 2201: Kaplan-Meier Plot of Overall Survival (PEP) Data cut-off: December 1, 2014



Source: Sponsor's submission[88]

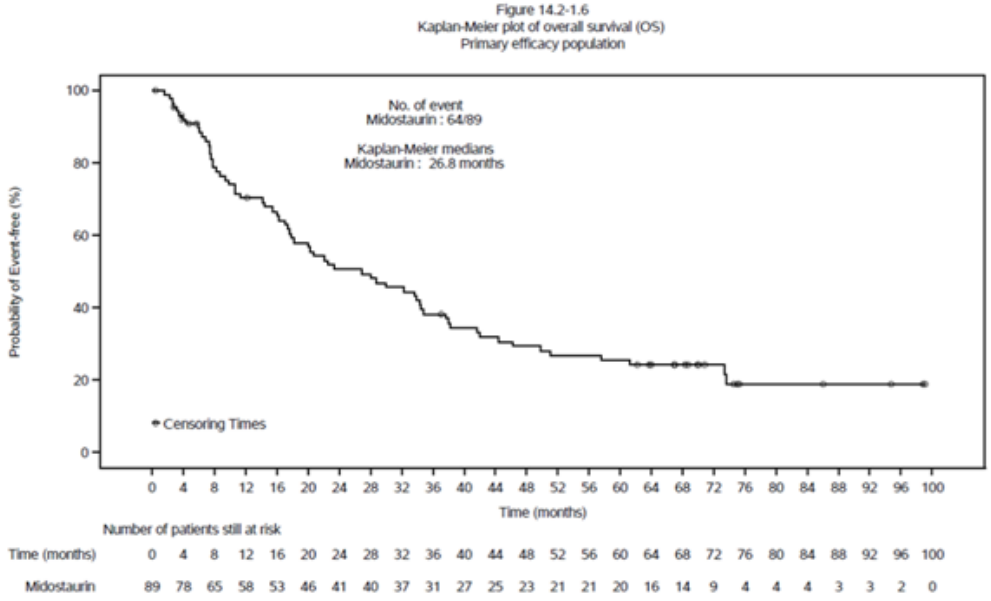
At the time of data cut-off (December 1, 2014), 54 patients (60.7%) in the PEP had died[88] and median OS was 26.8 months (95% CI: 17.6; 34.7), see Table 6.9.[1] The median time to censoring was 37 months[18] and 35 patients (39.3%) in the PEP were censored due to on-going without an event (n=25) and to lost to follow-up for analysis purposes (i.e., no updated survival information available to determine vital status within 2 weeks of the cut-off date; n=10).[52] An analysis by the US Food and Drug Administration (FDA) corroborated the OS estimates in the PEP at one and two years (i.e., probability of OS was 70% [95% CI: 59; 79] and 51% [95% CI: 39; 61], respectively, as per the FDA).[27]

In the FAS (data cut-off date of December 14, 2014), 67 patients (57.7%) had died[88] and median OS was 28.7 months (95% CI: 20.3; 38.0).[1] The median time to censoring was 38 months[18] and 49 patients (42.2%) were censored due to on-going without an event (n=35) and lost to follow-up for analysis purposes (n=14).[52]

In the final OS analysis (data cut-off of August 24, 2017), there were 10 additional deaths in the PEP following the primary analysis (data cut-off of December 1, 2014). The Kaplan-Meier plot for OS in the PEP with data cut-off of August 24, 2017 is depicted in Figure 6.4. The median OS remained similar (i.e., 26.8 months [95% CI: 17.6; 34.4]). The median time to censoring was 67 months and there were 25 patients who were censored due to on-going without an event (n=4), lost to follow-

up early during study (n=9), and alive in the 5 months before the data cut-off (n=12).[24]

Figure 6.4: Study 2201: Kaplan-Meier Plot of Overall Survival (PEP) Data cut-off: August 24, 2017



Source: Checkpoint Response November 13, 2019[73]

In the final OS analysis (data cut-off of August 24, 2017), there were 13 additional deaths in the FAS following the primary analysis (data cut-off of December 1, 2014) and median OS was 28.7 months (95% CI: 20.3; 38.0) which was similar to the primary analysis (data cut-off of December 14, 2014).[24] The median time to censoring was 67 months[24] [redacted].[19] *(Non-Disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the manufacturer that it can be publicly disclosed).*

The median duration between treatment start date and data cut-off date was 76 months ([redacted]).[19] *(Non-Disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the manufacturer that it can be publicly disclosed).*

According to the one pre-specified interim analysis of Study 2201 (N=62) with data cut-off of July 19, 2012 and median follow-up of 27 months, the median OS had not yet been reached.[13] In seven patients with MCL; however, the OS was reported to be 22.6 months.[13]

Tables 6.9 reports the OS results for all patients in the PEP and for patients by SM disease sub-type as defined by the WHO classification (i.e., ASM, SM-AHN, and MCL).[18]

Table 6.9: Study 2201: Summary of Overall Survival for All Patients and by SM Disease Subtype as defined by the WHO classification (PEP): Data cut-off: December 1, 2014

	All Patients evaluated N=89	ASM N=16	SM-AHN N=57	MCL N=16	Subtype unknown N=0
n/N (%)	54/89 (60.7)	5/16 (31.3)	39/57 (68.4)	10/16 (62.5)	0
Median time to censoring (months)	37	38	37	37	NA
Percentiles (95% C.I) (months)					
25%	9.8 [7.5 , 16.0]	34.7 [9.8 , .]	10.7 [6.0 , 16.3]	7.5 [3.4 , 8.7]	. [. , .]
Median	26.8 [17.6, 34.7]	51.1 [28.7, .]	20.7 [16.3, 33.9]	9.4 [7.5 , .]	. [. , .]
75%	. [42.0, .]	. [51.1, .]	42.0 [32.2, .]	. [9.4 , .]	. [. , .]
% Event-free probability estimate [95% C.I]:					
6 months	89.6 [81.0 , 94.5]	100.0 [,]	87.3 [75.1 , 93.7]	87.5 [58.6 , 96.7]	. [. , .]
12 months	70.2 [59.2 , 78.8]	93.3 [61.3 , 99.0]	70.2 [56.0 , 80.6]	47.1 [21.6 , 69.1]	. [. , .]
18 months	59.1 [47.8 , 68.8]	93.3 [61.3 , 99.0]	55.0 [40.8 , 67.2]	40.4 [16.7 , 63.1]	. [. , .]
24 months	50.5 [39.3 , 60.7]	86.2 [55.0 , 96.4]	45.5 [31.9 , 58.2]	33.7 [12.3 , 56.8]	. [. , .]
36 months	38.2 [27.5 , 48.8]	69.6 [37.4 , 87.5]	31.0 [18.9 , 43.9]	33.7 [12.3 , 56.8]	. [. , .]
48 months	29.8 [18.4 , 42.2]	69.6 [37.4 , 87.5]	19.9 [8.6 , 34.5]	33.7 [12.3 , 56.8]	. [. , .]
60 months	26.1 [14.6 , 39.2]	34.8 [1.7 , 76.2]	19.9 [8.6 , 34.5]	33.7 [12.3 , 56.8]	. [. , .]

- Percentiles with 95% CIs are calculated from PROC LIFETEST output using method of Brookmeyer and Crowley (1982).
- % Event-free probability estimates are the estimated probabilities that a patient will remain event-free up to the specified time point
- % Event-free probability estimates are obtained from the Kaplan-Meier survival estimates; Greenwood formula is used for CIs of KM estimates.
- n : Total number of OS events included in the analysis.
- N : Total number of subjects included in the analysis.

Source: EPAR Report[18]

Tables 6.10 reports the OS results for all patients in the FAS and for patients by SM disease sub-type as defined by the WHO classification (i.e., ASM, SM-AHN, and MCL). The probability of OS in the FAS was 74.1% (95% CI, 64.7 – 81.3) at 1 year, 53.2% (95% CI, 43,3 – 62.2) at 2 years, 42.2% (95% CI, 32.6 - 51.8) at 3 years, and 31.8% (95% CI, 21.3 – 42.9) at 5 years.[18]

Table 6.10: Study 2201: Summary of Overall Survival for All Patients and by SM Disease Subtype as defined by the WHO classification (FAS) Data cut-off: December 1, 2014

OS	PEP	FAS				
	ALL (N=89)	ALL (N=116)	ASM (N=16)	SM-AHN (N=73)	MCL (N=21)	Type unknown (N=9)
Median OS, months						
Estimated median	26.8	28.7	51.1	21.1	22.6	NR
(95% CI)	(17.6, 34.7)	(20.3, 38.0)	(28.7, -)	(16.8, 32.2)	(8.3, -)	-

Source: FDA Reviewer Report[1]

Additional pre-specified subgroup analyses of OS in the PEP that are of interest to this review (i.e., by prior therapies, *KIT* mutation status, and SM sub-type according to the sponsor's classification) are presented in Table 6.11. As previously explained, the sponsor defined the SM sub-type subgroups differently from the WHO classification in their analyses. The sponsor identified the SM disease sub-types as 1) ASM (which includes ASM and SM-AHN), 2) MCL and 3) ASM or MCL with associated hematological clonal non-mast cell lineage disease (AHNMD). [redacted].[52] *(Non-Disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the manufacturer that it can be publicly disclosed)*

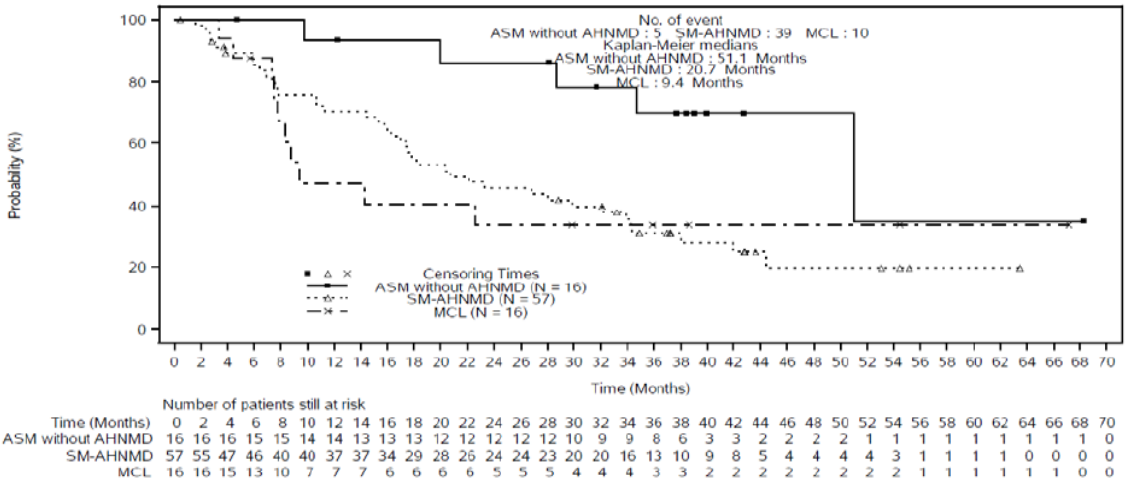
Table 6.11: [redacted]

(Non-Disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the manufacturer that it can be publicly disclosed)

Source: Sponsor's submission[52]

The Kaplan-Meier plot for OS in the PEP by SM sub-type according to the sponsor's classification is shown in Figure 6.5.

Figure 6.5: Study 2201: Kaplan-Meier Plot of Overall Survival by SM sub-type (according to sponsor's classification) (PEP) Data cut-off December 1, 2014



ASM without AHNMD are all patient who have MCL diagnosis = 'No or missing' and AHNMD = 'No or missing' at baseline as per Central histopathologist review.
SM-AHNMD are all patient who have MCL diagnosis = 'No or missing' and AHNMD = 'Yes' at baseline as per Central histopathologist review.
MCL are all patient who have MCL diagnosis = 'Yes' at baseline as per Central histopathologist review.

Source: EPAR report[18]

Study 2213

[redacted]*.(Non-Disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the manufacturer that it can be publicly disclosed)*

Table 6.12: Study 2213: [redacted]

(Non-Disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the manufacturer that it can be publicly disclosed)

Source: Sponsor's submission[12]

Figure 6.6: Study 2213: [redacted]

(Non-Disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the manufacturer that it can be publicly disclosed)

Source: Sponsor's submission[12]

[redacted].[12] *(Non-Disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the manufacturer that it can be publicly disclosed)*

Based on a data cut-off of March 1, 2017, 22 patients (84.6%) had died and median OS was 40.0 (95% CI: 27.3; 52.7).[4] Results of the subgroup analysis of median OS by SM sub-type were similar to those at the December 3, 2012 data cut-off.[4]

Progression-free Survival

Study 2201

PFS by SSC assessment was defined as the time from start of treatment to the date of first confirmed progression or death due to any cause and was a secondary outcome in Study 2201. Based on a data cut-off of December 1, 2014, 45 (50.6%) patients in the PEP experienced an event (Table 6.13). Median PFS was 17.0 months (95% CI: 10.2; 24.8) with a median time to censoring of nine months (Figure 6.7). Overall, 44 (49.4%) patients in the PEP were censored due to on-going without an event (n=14), start of new cancer therapy (n=13), adequate assessment no longer available (n=10), withdrew consent (n=4) and event documented after ≥ two or more missing response assessments (n=3).[12]

Table 6.13: Study 2201: Progression-free Survival per SSC Adjudication (PEP) Data cut-off December 1, 2014

	Midostaurin N=89
n/N (%)	45/89 (50.6)
Median time to censoring (months)	9
Percentiles (95% CI) (months)	
25%	5.6 [3.7, 9.3]
Median	17.0 [10.2, 24.8]
75%	NR [28.7, NE]
% progression-free probability estimate [95% CI]	
6 months	73.9% [62.4, 82.3]
12 months	55.0% [42.5, 65.9]
18 Months	46.6% [34.2, 58.1]
24 months	39.5% [27.5, 51.3]

Percentiles with 95% CIs are calculated from PROC LIFETEST using Brookmeyer and Crowley (1982).

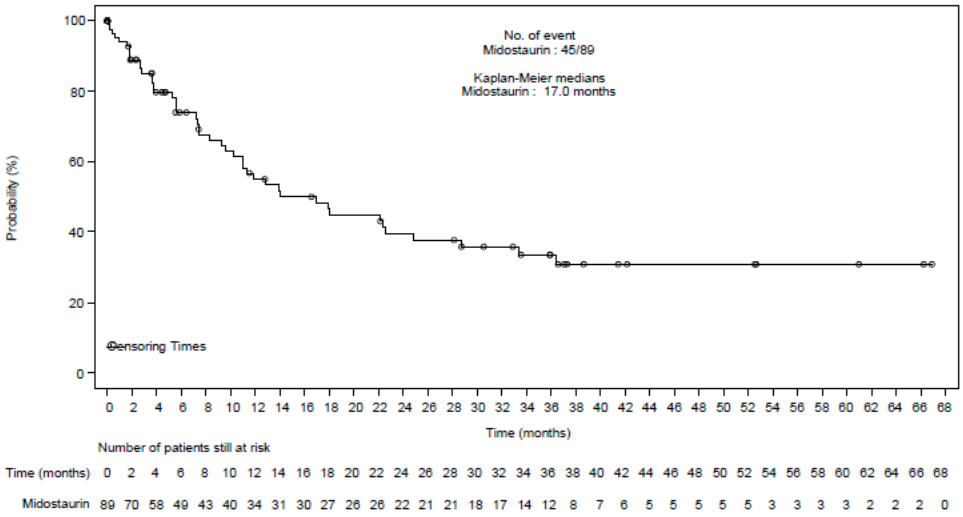
% Event-free probability estimates are estimated probabilities that a patient will remain event-free up to the specified time point, obtained from the KM survival estimates; Greenwood formula is used for CIs of KM estimates.

n: Total number of patients with disease progression or deaths included in the analysis.

N: Total number of patients included in the analysis.

Source: Sponsor's submission[2]

Figure 6.7: Study 2201 Kaplan-Meier Plot of Progression-free Survival per SSC Adjudication (PEP) Data cut-off December 1, 2014



Source: Sponsor's submission[85]

Based on the data cut-off of December 1, 2014 in the FAS, 45 patients (38.8%) experienced a PFS event corresponding with a median PFS of 17.0 months (95% CI: 10.2; 24.8). Overall, 71 patients in the FAS were censored, mainly for no baseline C-finding (n=27) followed by on-going without an event (n=14).[52]

Study 2213

In Study 2213, at the data cut-off of December 3, 2012, eight patients (30.8%) experienced either disease progression or death (Table 6.14). Median PFS was 38.6 months (95% CI: 11.3; NE) and the median time to censoring was eight months (Figure 6.8).

Table 6.14: Study 2213: Progression-free Survival (FAS) Data cut-off December 3, 2012

	All Patients N=26
n/N (%)	8/26 (30.8)
Median time to censoring (months)	8
Percentiles (95% CI) (months)	
25%	11.3 (1.8, 38.6)
Median	38.6 (11.3, NE)
75%	NR (38.6, NE)
%Progression-free probability estimates (95% CI)	
6 months	82.6 (59.0, 93.3)
12 months	69.3 (42.4, 85.5)
18 months	62.4 (35.3, 80.7)
24 months	62.4 (35.3, 80.7)

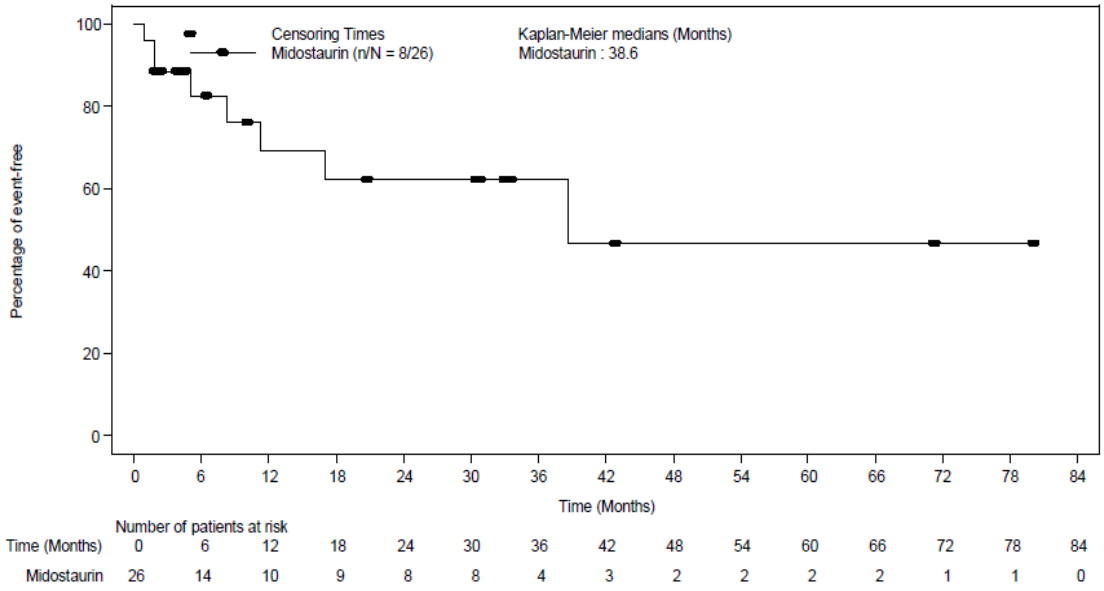
% Event-free probability estimates are the estimated probabilities that a patient will remain event-free up to the specified time point

% Event-free probability estimates are obtained from the Kaplan-Meier survival estimates; Greenwood formula is used for CIs of Kaplan-Meier estimates.

NR= not reached; NE= not estimable

Source: Sponsor's submission[12]

Figure 6.8: Study 2213: Kaplan-Meier Plot of Progression-free Survival (FAS) Data cut-off December 3, 2012



n represents the number of patients in the population with an event

Source: N Engl J Med, Gotlib J, Kluin-Nelemans HC, George TI, et al., Efficacy and safety of midostaurin in advanced systemic mastocytosis, 374:2530-41. Copyright © 2016 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society[12]

Based on a data cut-off of March 1, 2017, 10 patients (38.5%) experienced a PFS event and median PFS was 41.0 months (95% CI: 4.4; 77.6).[4]

Overall Response Rate

Study 2201

The ORR by SSC in the PEP was the primary efficacy outcome in Study 2201. As detailed in Table 6.15 for the data cut-off of December 1, 2014, 53 patients in the PEP had a confirmed best response of MR (n=40) or PR (n=13) by the SSC. The ORR was 59.6% (95% CI: 48.6; 69.8) with a two-sided P-value <0.001 for rejecting the null hypothesis of ORR ≤ 30%.

Table 6.15: Study 2201: Best Overall Response per SSC Adjudication (PEP) Data cut-off December 1, 2014

Best overall response	Midostaurin N=89 n (%)
Major Response (MR)	40 (44.9)
Complete Remission (CR)	0
Incomplete Remission (IR)	19 (21.3)
Pure Clinical Response (PCR)	15 (16.9)
Unspecified	6 (6.7)
Partial Response (PR)	13 (14.6)
Good Partial Response (GPR)	11 (12.4)
Minor Response (MinR)	2 (2.2)
Unspecified (U)	0
Stable Disease (SD)	11 (12.4)
Progressive Disease (PD)	10 (11.2)
Not Evaluable	15 (16.9)
Overall Response Rate (ORR=MR+PR)*	53 (59.6)
95% CI for ORR**	[48.6,69.8]
Two sided p-value***	<0.001
Disease control rate (DCR=MR+PR+SD)#	64 (71.9)
95% CI for DCR**	[61.4,80.9]

*Overall response rate (ORR) was defined as the proportion of patients in the PEP with a confirmed best response of MR or PR in the first 6 cycles of treatment (confirmed at least 56 days apart) as assessed by the SSC using modified Valent/Cheson criteria.

Disease control rate (DCR) was defined as the proportion of patients with a confirmed best overall response of MR or PR or SD in the first 6 cycles of treatment as assessed by the SSC using modified Valent/Cheson criteria.

**Exact (Clopper-Pearson) confidence interval

***Exact two sided p-value, null hypothesis, ORR ≤ 30%

Source: EPAR[18]

A sensitivity analysis was conducted that included an analysis of ORR for the FAS and the PPS. For these analyses, all patients who were deemed to be ineligible for the PEP were assessed as being 'non-evaluable' and were classified as subtype 'non-responders'. Based on these analyses, the ORR was 45.7% (95% CI: 36.4; 55.2) in the FAS (N=116) and 58.1% (95% CI: 47.0; 68.7) in the PPS (N=86).

Subgroup analyses by SM sub-type were also reported as categorized at baseline by SSC adjudication as presented in Table 6.16.

Table 6.16: Study 2201: Best Overall Response by SM Sub-type (PEP) Data cut-off December 1, 2014

Best overall response, n (%)	ASM Subgroup (n=16)	SM-AHN (n=57)	MCL (n=16)
Major response (MR)	10 (62.5)	23 (40.4)	7 (43.8)
Complete remission	0 (0)	0 (0)	0 (0)
Incomplete remission	6 (37.5)	9 (15.8)	4 (25.0)
Pure clinical response	4 (25.0)	9 (15.8)	2 (12.5)
Unspecified	0 (0)	5 (8.8)	1 (6.3)
Partial response (PR)	2 (12.5)	10 (17.5)	1 (6.3)
Good partial response	1 (6.3)	10 (17.5)	0 (0)
Minor response	1 (6.3)	0 (0)	1 (6.3)
Unspecified	0 (0)	0 (0)	0 (0)
Stable disease	1 (6.3)	7 (12.3)	3 (18.8)
Progressive disease	1 (6.3)	6 (10.5)	3 (18)
Not evaluable	2 (12.5)	11 (19.3)	2 (12.5)
ORR (MR + PR) [95% CI]	12 (75.0) [47.6; 92.7]	33 (57.9) [44.1; 70.9]	8 (50.0) [24.7; 75.3]

Source: EPAR[18]

Pre-specified subgroup analyses of interest to this review (i.e., prior therapies, *KIT* mutation status, and disease sub-type) in the PEP are presented in Table 6.17. In patients with ASM (categorized below as ASM plus SM-AHN) ORR was 61.6% (95% CI: 49.5; 72.8) and 50.0% (95% CI: 24.7; 75.3) in patients with MCL. Patients who were positive for the *KIT* D816V mutation had ORR of 63.0% (95% CI: 50.9; 74.0) compared to 43.8% (95% CI: 19.8; 70.1) in patients who were negative for the mutation. Prior therapy did not appear to affect the ORR (i.e., ORR was 62.2% [95% CI: 44.8; 77.5] in patients with prior therapies and 57.7% [95% CI: 43.2; 71.3] in patients without prior therapies).

Table 6.17: Study 2201: Subgroup analysis of ORR by SSC adjudication (PEP) Data cut-off December 1, 2014

Subgroups	ORR (95% CI)
Overall (n=89)	59.6 (48.6, 69.8)
ASM or MCL	
ASM (n=73)	61.6 (49.5, 72.8)
MCL (n=16)	50.0 (24.7, 75.3)
ASM or MCL with or without AHNMD	
With AHNMD (n=63)	57.1 (44.0, 69.5)
Without AHNMD (n=15)	73.3 (44.9, 92.2)
Age	
<65 years (46)	58.7 (43.2, 73.0)
≥ 65 years (43)	60.5 (44.4, 75.0)
Gender	
Male (n=57)	54.4 (40.7, 67.6)
Female (n=32)	68.8 (50.0, 83.9)
Race	
Caucasian (n=86)	59.3 (48.2, 69.8)
Other (n=3)	66.7 (9.4, 99.2)
***KIT* D816V mutation in SM component**	
KIT D816V positive (n=73)	63.0 (50.9, 74.0)
KIT D816V negative/unknown (n=16)	43.8 (19.8, 70.1)
Prior therapies for SM or AHNMD	
Prior therapies (n=37)	62.2 (44.8, 77.5)
No prior therapies (n=52)	57.7 (43.2, 71.3)

Source: Sponsor's submission[52]

According to the one pre-specified interim analysis of Study 2201 with data cut-off July 19, 2012 and median follow-up of 27 months, of 62 patients enrolled in Stage 1, 40 (65%) patients were considered eligible for efficacy.[13] There were 24 patients that had a best overall response of MR or PR, corresponding with an ORR of 60% (95% CI: 43.4; 75.1) which is consistent with the results reported for the data cut-off of December 1, 2014. Overall, 52.5% of patients had a MR, 7.5% had a PR, 20% had SD, 7.5% had PD, and 12.5% were not evaluable.[13]

Study 2213

In Study 2213, ORR by INV was the primary efficacy outcome which was defined as the proportion of patients with a best overall response of MR or PR occurring during the first two cycles of midostaurin treatment. Based on a data cut-off date of December 3, 2012, 13 patients (50.0%) had a MR and six patients (23.1%) had a PR corresponding with an ORR by INV of 73.1% (95% CI: 52.2; 88.4) as detailed in Table 6.18.

Table 6.18: Study 2213: Overall Response Rate by INV (FAS) Data cut-off December 3, 2012

	All Patients N=26 n (%)
Best overall response	
Major Response (MR)	13 (50.0)
Complete Remission (CR)	0
Incomplete Remission (IR)	5 (19.2)
Pure Clinical Response (PCR)	8 (30.8)
Partial Response (PR)	6 (23.1)
Good Partial Response (GPR)	4 (15.4)
Minor Response (MinR)	2 (7.7)
No Response	7 (26.9)
Stable Disease (SD)	6 (23.1)
Progressive Disease (PD)	1 (3.8)
Not Evaluable	0
Overall Response Rate (ORR=MR+PR)*	19 (73.1)
95% CI for ORR	[52.2, 88.4]

*Overall response rate (ORR) was defined as the proportion of patients in FAS with an overall best response of major response (MR) or partial response (PR) in the first 2 cycles of treatment as assessed by Investigator using Valent criteria.

The 95% CI for ORR was computed using an exact binomial confidence interval

Source: EPAR[18]

In Study 2213, subgroup analyses of ORR in patients with ASM versus MCL were conducted. The ORR was 75.0% (95% CI: 50.9, 91.3) in patients with ASM (n=20) and 66.7% (95% CI: 22.3, 95.7) in patients with MCL (n=6). In patients who were positive for a *KIT* D816V mutation (n=14), the ORR was 78.6% (95% CI: 49.2, 95.3) and 66.7% (95% CI: 34.9, 90.1) in patients with negative or unknown mutations (n=12). In patients with prior treatment (n=20), the ORR was 70.0% (95% CI: 45.7; 88.1) compared to 83.3% (95% CI: 35.9; 99.6) in patients without prior therapy (n=6).[12]

Based on a data cut-off of date of March 1, 2017, the confirmed ORR within the first 12 cycles in the FAS (N=26) was 69% (95% CI: 50; 88).[4] Of the 18 patients with either a MR or PR (as per the ORR definition), one patient was categorized as having ASM, 13 patients as SM-AHN, and four patients as MCL.[4]

Duration of Response

Study 2201

In Study 2201, DOR was a secondary outcome and was based on the proportion of patients with a confirmed MR or PR during the first six cycles of midostaurin treatment (N=53). At the December 1, 2014 data cut-off date, the median DOR by SSC adjudication for all patients in the PEP (N=89) was 31.4 months (95% CI: 10.8; NE).[89] [redacted].[51] [redacted].[2] *(Non-Disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information*

Guidelines. This information will remain redacted until notification by the manufacturer that it can be publicly disclosed)

Study 2213

In Study 2213, DOR was also a secondary outcome and was defined as the time from start of the first documented response as per investigator assessment until the date of first documented disease progression or death due to ASM or MCL. The DOR analysis included only patients in the FAS with a documented MR or PR during the first two cycles. At the data cut-off date of December 3, 2012, 4 out of 19 responders (21.1%) had an event and the median DOR had not been reached. The estimated probability of being in response at 12 months was 77.0% (95% CI: 43.5; 92.1). Based on a data cut-off date of March 1, 2017, median DOR was formally reached at 132 months when a patient with SM- chronic myelomonocytic leukemia (CMML) who had been on midostaurin therapy for 11 years progressed to acute myeloid leukemia.[4]

Disease Control Rate

Study 2201

DCR was an exploratory outcome in Study 2201 only and is defined as the sum of MR + PR + Stable Disease (SD) in the first six cycles of treatment as per the SSC. Based on a data cut-off date of December 1, 2014, 64 patients had either a MR, PR, or SD corresponding with a DCR of 71.9% (95% CI: 61.4; 80.9).

Patient-Reported Outcomes

Study 2201

PROs were reported in Study 2201 as an exploratory outcome. PROs were not collected in study 2213. Questionnaires were administered prior to patients being scanned or informed about their disease status. Results were analysed and summarized using descriptive statistics.[84] The questionnaires were administered every cycle during the first 12 cycles, and every 3 cycles thereafter until disease progression, development of unacceptable toxic effects, or the end of the study, whichever occurred first.[3] A decreased MSAS score indicates an improvement or reduction in symptoms. The Total MSAS (TMSAS) score is the average of all the symptom scores of all the 32 symptoms in the MSAS instrument whereas the GDI, PHYS, and PSYCH subscales measure global distress, physical, and psychological symptoms, respectively. The number of patients providing QoL scores declined substantially over the course of the first year. [redacted].[52] *(Non-Disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the manufacturer that it can be publicly disclosed).* Of the 89 patients in the PEP, 80 patients had non-missing baseline values, 78 patients had a TMSAS score > 0, and 52 patients were evaluable for ≥ 168 days/5 cycles/5.5 months.[52] Overall, 20/52 patients (38.5%) had ≥ 50% decrease in TMSAS

score relative to baseline for at least 168 days. A summary of patients with TMSAS and other MSAS subscales scores that improved for ≥ 168 days is provided in Table 6.19.

Table 6.19: Study 201: Summary of Patients with MSAS Scores Improved for ≥ 168 Days (PEP) Data cut-off December 1, 2014

	Midostaurin
	N =89
Categories	**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.

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

Source: EPAR[18]

A decrease of ≥ 50% in TMSAS score or MSAS subscales scores was more frequently observed in patients who achieved an ORR than in those who did not achieve an ORR, see Table 6.20 below.

Table 6.20: Overall response rate by PRO response category (MSAS) in Study 2201 (PEP)

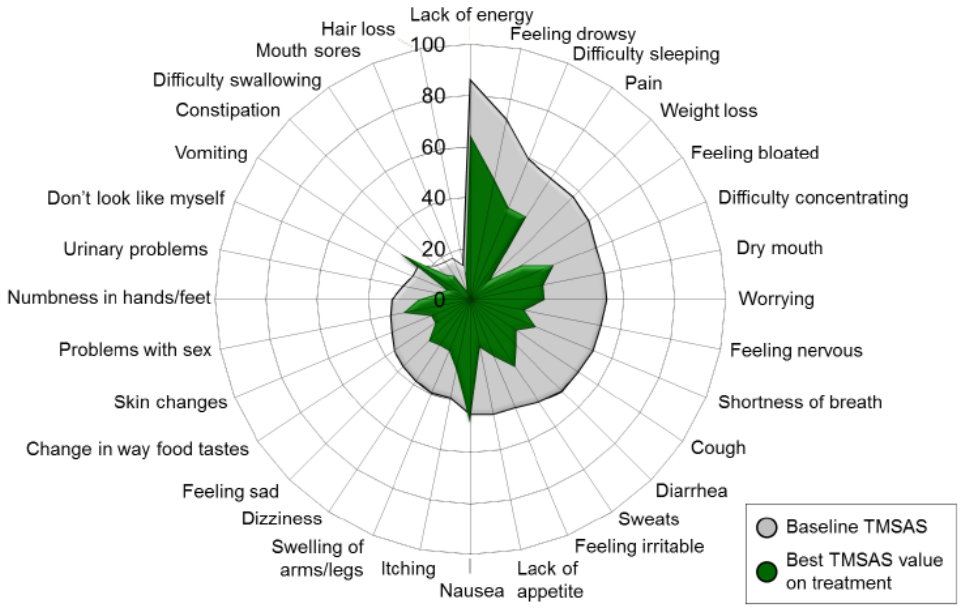
	ORR in patients with at least 50% reduction in PRO score	ORR in patients with less than 50% reduction in PRO score	p-value [1]
PRO instrument and subscales	**n/N (%)**	**n/N (%)**	
TMSAS	15/20 (75.0)	31/57 (54.4)	0.1211
MSAS-GDI	17/25 (68.0)	27/48 (56.3)	0.4505
MSAS-PHYS	17/19 (89.5)	29/57 (50.9)	0.0028
MSAS-PSYCH	14/21 (66.7)	27/46 (58.7)	0.5976
P-value based on a Fisher exact test.			

Source: EPAR[18]

Furthermore, symptoms improvement was examined by assessing the prevalence of MSAS symptoms at baseline and post-baseline ([redacted][53], and best TMASA score on study).[3] *(Non-Disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the manufacturer that it can be publicly disclosed).* Results show a decline in the prevalence of all MSAS symptoms except of nausea and vomiting, which are adverse events associated with midostaurin. Figure 6.8 (spider plot) shows baseline symptoms for 79 evaluable patients in decreasing prevalence in a clockwise direction (grey shading). The symptom prevalence at the time of the best total MSAS score value on treatment is shown in green. [redacted].[53] *(Non-Disclosable information was used in this pCODR Guidance Report and*

the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the manufacturer that it can be publicly disclosed).

Figure 6.8: Symptoms (MSAS) at baseline for 79 evaluable patients in decreasing prevalence (grey shading) and symptoms for each patient at the time of the best total MSAS score value on treatment (green shading)



Source: N Engl J Med, Gotlib J, Kluin-Nelemans HC, George TI, et al., Efficacy and safety of midostaurin in advanced systemic mastocytosis, 374:2530-41. Copyright © 2016 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society[3]

The SF-12, a general health status instrument, was used to measure change from baseline in HRQoL in the PEP. An increased score on the SF-12 indicates improvement (better HRQoL). The eight domains of the SF-12 can be combined into a summary PCS and MCS. The number of patients providing QoL scores declined substantially over the course of the first year. [redacted].[52] *(Non-Disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the manufacturer that it can be publicly disclosed).*
Of the 89 patients in the PEP, 53 patients (with non-missing baseline values or baseline scores > 0) were evaluable for at least 168 days. Of the 53 evaluable patients, 10 patients (18.9%) and three patients (5.7%) had a ≥ 50% increase in PCS and MCS scores, respectively, relative to baseline.[52]
The results of patients who experienced ≥ 50% increase (improvement) in PCS and MCS scores for at least 168 days in the PEP are provided in Table 6.21.

Table 6.21: Study 2201: Summary of Patients with SF-12 Scores Improved for ≥ 168 days (PEP) Data cut-off December 1, 2014

Categories	Midostaurin N =89 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)

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

Source: pCODR Submission Material[52]

The sponsor was requested to clarify if the changes from baseline for the TMSAS and PCS and MCS of the SF-12 were clinically meaningful (i.e., whether the minimal clinically important difference was met or not). In response[16], the sponsor advised that in a post-hoc analysis of the median best percentage change from baseline in the total and subscale scores of the MSAS and PCS and MCS scores of the SF-12, the minimally important differences for the instruments had been met.[16] The thresholds for the minimally important differences identified by the sponsor were based on a study of the MSAS in patients with cancer pain[90] and from a systematic review of minimal important differences for the most frequently used PROs[30] and were not validated specifically in patients with advSM.[16]

The decline in the number of eligible patients over the first 12 treatment cycles leads to uncertainty in the PRO results beyond cycle 12 and possibly in earlier cycles. Patient reported outcomes estimates up to cycle 12 may not represent an accurate picture of the patients' experiences with midostaurin for a longer period of time. Additionally, the trial was non-randomized and the impact of midostaurin on PRO in relation to other therapies is unknown. PRO data were reported based on descriptive exploratory analyses. As per study protocol, no statistical analyses were planned to confirm PRO results. Due to above limitations, no firm conclusions can be drawn based on the PRO results.

Serum Tryptase Levels

Study 2201

At baseline, the median serum tryptase level in the PEP (N=89) was 236 µg/L (range: 26.6 to 12,069.0).[18] A summary of serum tryptase levels in patients in the PEP over the first 12 cycles of midostaurin treatment (based on a data cut-off of December 1, 2014) is provided in Table 6.22. There were 34 patients (38.2%) in the PEP that experienced a ≥ 50% reduction in serum tryptase levels relative to baseline that were sustained for ≥ 56 days. In the FAS, there were 46 patients (39.7%) who had a sustained serum tryptase response.[73]

Table 6.22: Study 2201: Summary of Serum Tryptase Levels (µg/L) over 12 cycles (PEP) Data cut-off December 1, 2014

Time point	Statistics	n	Value	Change from baseline	% change from baseline
Baseline	Mean (SD)	89	570.62 (1362.23)	-	-
	Median		236	-	-
	Q1;Q3		174; 436	NA	NA
	Min; Max		26.6; 12069.0		
C1D28	Mean (SD)	81	322.49 (463.450)	-267.3 (1246.33)	-12.94 (91.405)
	Median		197	-71	-36
	Q1;Q3		91; 298	−218; 0	−61; 0
	Min; Max		10.9; 2890.0	-10845.0; 1034	-98.7; 587.5
C2D28	Mean (SD)	75	289.93 (441.466)	-294.4 (1244.38)	-16.80 (91.504)
	Median		189	-69	-31
	Q1;Q3		105; 284	−251; 0	−63; −0.2
	Min; Max		12.2; 3530.0	-10671.0; 328.0	-92.1; 636.8
C3D28	Mean (SD)	72	303.63 (398.260)	-287.1 (1244.60)	-22.27 (50.305)
	Median		193	-62	-37
	Q1;Q3		93; 373	−291; 3	−58; 5
	Min; Max		12.5; 2660.0	-10375.0; 326.0	-95.5; 115.7
C6D28	Mean (SD)	60	273.68 (278.125)	-269.7 (1361.55)	-15.04 (77.046)
	Median		200	-83	-41
	Q1;Q3		98; 349	−260; 13.5	−64; −7
	Min; Max		12.7; 1599.0	-10470.0; 648.0	-95.5; 257.1
C12D28	Mean (SD)	46	231.32 (233.369)	-119.5 (279.024)	-20.61 (82.527)
	Median		155	-109	-49
	Q1;Q3		66; 290	−250; 25	−71; −14.5
	Min; Max		11.0; 1050.0	-925.2; 672.0	-94.9; 266.7
NA=not applicable					

Source: EPAR[18]

In the one pre-specified interim analysis (N= 62; data cut-off July 19, 2012 and median duration of follow-up of 27 months), the median change in serum tryptase level in the 40 evaluable patients was -61% (range: -97% to 16%), with 16 (40%) patients exhibiting ≥ 50% reduction lasting for eight weeks or more.[13]

Study 2213

At baseline, median serum tryptase levels in the FAS were 323.0 µg/L (range: 22.2 to 1255.0). Based on the data cut-off of December 3, 2012, 13 patients (50%) had a decrease in serum tryptase levels of > 50% compared to baseline.[12] Based on a data cut-off of March 1, 2017, 12 patients (46%) exhibited a decrease of ≥ 50% in serum trypase levels and eight patients (31%) maintained this reduction for at least two cycles.[4]

Bone Marrow Mast Cell Burden

Study 2201

At baseline, median mast cell infiltration in the PEP (N=89) was 50% (range: 8 to 98). A summary of mast cell infiltration (%) over the first 12 cycles of midostaurin treatment is provided in Table 6.23. [redacted].[52] *(Non-Disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the manufacturer that it can be publicly disclosed).*

Table 6.23: Study 2201: Summary of Mast Cell Infiltration (%) over 12 cycles (PEP) Data cut-off December 1, 2014

Time point	Statistics	n	Value	Change from baseline	% change from baseline
Baseline	Mean (SD)	89	48.7 (23.74)		
	Median		50		
	Q1;Q3		30; 65	NA	NA
	Min; Max		8; 98		
C3D28	Mean (SD)	59	37.6 (21.82)	-14.9 (21.77)	-23.28 (45.729)
	Median		30	-10	-25
	Q1;Q3		20; 50	−30; 0	−53; 0
	Min; Max		5; 80	-70; 40	-90.9; 160.0
C6D28	Mean (SD)	53	34.2 (23.54)	-18.4 (25.51)	-27.42 (54.186)
	Median		30	-20	-33
	Q1;Q3		15; 50	−35; 0	−67; 0
	Min; Max		2; 95	-85; 40	-90.9; 160.0
C12D28	Mean (SD)	41	30.5 (24.97)	-25.3 (31.50)	-37.31 (59.475)
	Median		20	-25	-53
	Q1;Q3		15; 40	−45; −5	−75; −7.7
	Min; Max		5; 90	-90; 55	-94.7; 220.0
NA=not applicable					

Source: EPAR[18]

In the one pre-specified interim analysis (N = 62; data cut-off July 19, 2012 and median duration of follow-up of 27 months), the median change in mast cell burden in 32 evaluable patients was - 41% (range: - 92% to 83%), with 15 (47%) exhibit a ≥ 50% reduction.[13]

Study 2213

At baseline, median mast cell infiltrates in bone marrow biopsy (FAS) was 50.0% (range: 5.0 to 95.0). Based on the data cut-off of December 3, 2012, 12 patients (46.1%) had a decrease in bone marrow mast cell infiltration of > 50% compared to baseline.[12] Based on the cut-off date of March 1, 2017, of 25 evaluable patients, 17 (68%) had at least ≥ 50% reduction in bone marrow mast cell burden and of these, 10 patients (59%) exhibited this decrease for at least two consecutive bone marrow biopsies.[4]

Harms Outcomes

The evaluation of the safety of midostaurin in advanced systemic mastocytosis was primarily based on pooled safety data from the safety analysis sets (i.e., patients who received at least one dose of midostaurin in Study 2201 (N=116) and Study 2213 (N=26) for a pooled data set of N=142 patients.[2] As a result, harms data for the individual trials as well as the pooled safety data are presented corresponding with a data cut-off of December 1, 2014 for Study 2201 and December 3, 2012 for Study 2213. In the pooled analysis set, the median duration of exposure to midostaurin was 11.4 months (range: 0 to 81) and 48.6% of patients had received at least 12 months of midostaurin.[18]

A summary of the frequency of AEs by individual trial and the pooled analysis is provided in Table 6.24.

Overall, all patients (100%) in both trials experienced an AE and of these, 93.1% (Study 2201) and 96.2% (Study 2213) were suspected to be drug-related.[18] The most frequent AEs suspected to be drug-related were gastrointestinal (GI)-related (e.g., nausea, vomiting, diarrhea), the majority of which were of grade 1 or 2 severity.[18] Furthermore, 88.8% (Study 2201) and 61.5% (Study 2213) of patients experienced AEs of grade 3-4 severity.[18] The most frequent grade 3-4 AEs were due to myelosuppression (e.g., anemia, thrombocytopenia, and neutropenia).[18]

Table 6.24: Summary of Overall Adverse Events in Study 2201 and Study 2213 (Safety Analysis Sets)

	D2201 N=116	A2213 N=26	AdSM pool N=142
Category	**n (%)**	**n (%)**	**n (%)**
On-treatment deaths	22 (19.0)	4 (15.4)	26 (18.3)
Adverse events (AEs)	116 (100)	26 (100)	142 (100)
Suspected to be drug-related	108 (93.1)	25 (96.2)	133 (93.7)
Grade 3-4 AEs	103 (88.8)	16 (61.5)	119 (83.8)
Suspected to be drug-related	51 (44.0)	8 (30.8)	59 (41.5)
Clinically notable AEs	116 (100)	26 (100)	142 (100)
Suspected to be drug-related	106 (91.4)	25 (96.2)	131 (92.3)
Serious adverse events (SAEs)	85 (73.3)	12 (46.2)	97 (68.3)
Suspected to be drug-related	27 (23.3)	4 (15.4)	31 (21.8)
AEs leading to discontinuation	30 (25.9)	4 (15.4)	34 (23.9)
Suspected to be drug-related	15 (12.9)	1 (3.8)	16 (11.3)
AEs requiring dose interruption and / or reduction	67 (57.8)	13 (50.0)	80 (56.3)
AEs requiring additional therapy	116 (100)	25 (96.2)	141 (99.3)

Source: [SCS Appendix 1-Table 5-19.1], [SCS Appendix 1-Table 5-20.1], [SCS Appendix 1-Table 5-21.1], [SCS Appendix 1-Table 5-22.1], [SCS Appendix 1-Table 5-23], [SCS Appendix 1-Table 5-24.1], [SCS Appendix 1-Table 5-25.1], [SCS Appendix 1-Table 5-26.1], [SCS Appendix 1-Table 5-27.1], [SCS Appendix 1-Listing 5.4], [SCS Appendix 1-Listing 5-6].

Source: EPAR[18]

A summary of the most frequently reported AEs (> 10% in the pooled dataset) by individual trials and by pooled data is provided in Table 6.25. The most frequently reported AEs across both trials and in the pooled data set were GI-related toxicity (e.g., nausea, vomiting, diarrhea), infections, and myelosuppression.

Table 6.25: Summary of Frequent AEs (> 10% in Pooled Dataset) in Study 2201 and Study 2213 (Safety Analysis Sets)

	D2201		A2213		Advanced SM pool	
	N=116		N=26		N=142	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Any preferred term	116 (100)	103 (88.8)	26 (100)	16 (61.5)	142 (100)	119 (83.8)
Nausea	93 (80.2)	8 (6.9)	24 (92.3)	0	117 (82.4)	8 (5.6)
Vomiting	77 (66.4)	8 (6.9)	19 (73.1)	0	96 (67.6)	8 (5.6)
Diarrhoea	65 (56.0)	9 (7.8)	8 (30.8)	0	73 (51.4)	9 (6.3)
Oedema peripheral	40 (34.5)	5 (4.3)	10 (38.5)	0	50 (35.2)	5 (3.5)
Anaemia	38 (32.8)	29 (25.0)	9 (34.6)	4 (15.4)	47 (33.1)	33 (23.2)
Fatigue	31 (26.7)	10 (8.6)	13 (50.0)	2 (7.7)	44 (31.0)	12 (8.5)
Constipation	29 (25.0)	1 (0.9)	12 (46.2)	0	41 (28.9)	1 (0.7)
Pyrexia	33 (28.4)	6 (5.2)	5 (19.2)	0	38 (26.8)	6 (4.2)
Abdominal pain	34 (29.3)	5 (4.3)	3 (11.5)	0	37 (26.1)	5 (3.5)
Headache	28 (24.1)	2 (1.7)	9 (34.6)	0	37 (26.1)	2 (1.4)
Thrombocytopenia	22 (19.0)	14 (12.1)	8 (30.8)	3 (11.5)	30 (21.1)	17 (12.0)
Pruritus	25 (21.6)	4 (3.4)	4 (15.4)	0	29 (20.4)	4 (2.8)
Arthralgia	23 (19.8)	3 (2.6)	4 (15.4)	0	27 (19.0)	3 (2.1)
Back pain	25 (21.6)	2 (1.7)	2 (7.7)	0	27 (19.0)	2 (1.4)
Dyspnoea	19 (16.4)	6 (5.2)	7 (26.9)	2 (7.7)	26 (18.3)	8 (5.6)
Cough	21 (18.1)	1 (0.9)	2 (7.7)	0	23 (16.2)	1 (0.7)
Neutropenia	17 (14.7)	13 (11.2)	2 (7.7)	2 (7.7)	19 (13.4)	15 (10.6)
Nasopharyngitis	18 (15.5)	0	1 (3.8)	0	19 (13.4)	0
Urinary tract infection	15 (12.9)	3 (2.6)	4 (15.4)	1 (3.8)	19 (13.4)	4 (2.8)
Dizziness	15 (12.9)	0	4 (15.4)	0	19 (13.4)	0
Musculoskeletal pain	18 (15.5)	1 (0.9)	0	0	18 (12.7)	1 (0.7)
Pleural effusion	14 (12.1)	5 (4.3)	4 (15.4)	1 (3.8)	18 (12.7)	6 (4.2)
Epistaxis	15 (12.9)	4 (3.4)	2 (7.7)	0	17 (12.0)	4 (2.8)
Upper respiratory tract infection	10 (8.6)	2 (1.7)	6 (23.1)	0	16 (11.3)	2 (1.4)
Hypokalaemia	12 (10.3)	5 (4.3)	4 (15.4)	1 (3.8)	16 (11.3)	6 (4.2)
Electrocardiogram QT prolonged	13 (11.2)	1 (0.9)	2 (7.7)	0	15 (10.6)	1 (0.7)
Insomnia	12 (10.3)	0	3 (11.5)	0	15 (10.6)	0
SM=systemic mastocytosis						

Source: EPAR[18]

Deaths

There was a total of 26 (18.3%) on-treatment deaths (i.e., deaths occurring on treatment and up to 28 days after the last dose of study drug) across both trials. Ten deaths were directly attributed to disease progression whereas other frequent primary causes were sepsis (n=5), cardiac disorders (n=5), and multi-organ failure (n=3).[73] In addition, seven additional on-treatment deaths were reported after the cut-off dates of the individual studies up to April 30, 2016 (i.e., four deaths in

Study 2201 and three deaths in Study 2213, of which four were due to disease progression).[18] None of the deaths were judged to be related to study drug by investigators.

Serious Adverse Events

Serious AEs occurred in 68.3% of patients in the pooled dataset and common reasons included [redacted] ([redacted])[53], primarily pneumonia 7.0%, sepsis, 7.0%, and urinary tract infection, 4.2%). *(Non-Disclosable information was used in this pCODR Guidance Report and the manufacturer requested this safety information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the manufacturer that it can be publicly disclosed).* The most frequent hematologic AEs reported as serious AEs were febrile neutropenia (4.9%) and anemia (4.2%).

Withdrawals due to Adverse Events

AEs leading to discontinuation were reported by 34 (23.9%) of patients in the pooled dataset. The most frequent reasons were nausea (2.1%), ascites (2.1%), and ECG QT interval prolonged (2.1%) where all other AEs leading to discontinuation were reported in no more than two patients each.[73]

Dose interruptions were reported for 67 patients (47.2%) in the pooled safety set: 29 patients (20.4%) had 1 dose interruption and 38 patients (26.8%) had more than 1 dose interruption. Dose reductions were reported for 84 patients (59.2%) in the pooled safety set: 38 patients (26.8%) had 1 dose reduction and 46 patients (32.4%) had more than 1 dose reduction. AEs were the most frequent reason for dose interruptions (59 of 67 interruptions) and dose reductions (63 of 84 reductions), followed by dosing error. AEs leading to dose interruption/adjustment were most commonly related to GI events: nausea (n=12, 12.0%), vomiting (n=13, 9.2%) and diarrhoea (n=7, 4.9%); ECG QT prolonged events (n=10, 7.0%); haematological events: neutropenia (n=8, 5.6% patients), thrombocytopenia (n=6, 4.2% patients) and anaemia (n=4, 2.8% patients); pyrexia (n=6 4.2%), and fatigue (n=5 3.5%).[73]

Adverse Events of Special Interest

The most frequent AEs (94.4%) in the pooled dataset were GI-related comprising nausea (82.4%), vomiting (67.6%), and diarrhea (51.4%). The majority were grade 1 to 2 severity. GI-related AEs of grade 3-4 severity occurred in 14.8% of all patients (i.e., diarrhea, 6.3%, nausea and vomiting, 5.6% each). Only four patients (2.8%) discontinued treatment due to nausea, vomiting, or diarrhea.[53]Of note, both Study 2201 and Study 2213 permitted use of anti-emetics concomitantly with midostaurin.

Hematologic AEs were frequent in both Study 2201 and Study 2213 and grouped terms for AEs of anemia, leukopenia, and thrombocytopenia were used in the pooled safety analysis. Anemia-related AEs occurred in 33.1% of patients, of which 23.2% were of grade 3-4 severity and 4.2% were serious AEs. Leukopenia-related AEs (i.e., neutropenia, febrile neutropenia, and leukopenia) occurred in 22.5% of patients, of which 17.6% were grade 3-4 and 6.3% were serious AEs.[53] Thrombocytopenia-related AEs (i.e., thrombocytopenia, platelet count decreased) occurred in 21.8% of patients, of which 12.0% were grade 3-4 and 1.4% were serious AEs.[53]

In terms of safety updates, the FDA requested a safety update which corresponded with a cut-off date of July 1, 2016. The update mainly consisted of updated data from Study 2201 (300 patient-months) and additional follow-up on seven patients

from Study 2213. The FDA determined that the updated safety data did not reveal new safety concerns.[1] [redacted].[19] *(Non-Disclosable information was used in this pCODR Guidance Report and the manufacturer requested this safety information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the manufacturer that it can be publicly disclosed).*

6.4 Ongoing Trials

No on-going and/or unreported trials for midostaurin in the treatment of advanced systemic mastocytosis were identified for inclusion in this section.

7 SUPPLEMENTAL QUESTIONS

The following supplemental questions were identified during development of the review protocol as relevant to the pCODR review of midostaurin for the treatment of adult patients with ASM, SM-AHN, and MCL:

- Critical appraisal of the sponsor's submitted naïve treatment comparison of midostaurin and SOC for the treatment of ASM, SM-AHN, and MCL
- Critical appraisal of the sponsor's submitted pooled survival analysis of midostaurin clinical study data from Study 2201 and Study 2213 in patients with advSM compared with historical controls

Topics considered in this section are provided as supporting information. The information has not been systematically reviewed.

7.1 Critical appraisal of the sponsor's submitted naïve treatment comparison

7.1.1 Objective

The objective of this section is to summarize and critically appraise the methodology and results of the sponsor's submitted naïve treatment comparison of midostaurin with SOC for the treatment of advanced SM.[2] The purpose of the critical appraisal is to inform the CADTH review of the economic evaluation submitted by the sponsor.

7.1.2 Findings

There is no standard of care for the treatment of adult patients with ASM, SM-AHN, or MCL.. The sponsor assumed SOC to be a combination of available therapies (i.e., interferon, hydroxyurea, cladribine, and cytarabine) weighted by respective market share estimates, that are used off-label in Canada for the treatment of adult patients with advanced SM.[2] Detailed methodology for the naïve treatment comparisons was not provided by the sponsor or in the source publications.

According to the sponsor, the OS estimate for SOC was derived through hazard mapping using a published hazard ratio (HR) of 2.2 (95% CI: 1.08; 4.47)[28] for OS favoring midostaurin over control. The published HR was used to generate an estimated OS curve for SOC. The published HR was based on a naïve comparison of survival data from 28 patients who received midostaurin through a compassionate-use program with that of 44 historical controls who did not receive midostaurin; all of whom were registered in the French CEREMAST database.[28,29] A comparison of the demographic and disease characteristics of patients included in Study 2201 and Study 2213 (included in the systematic review for this report) with those of the midostaurin-treated patients and historical controls used in the naïve treatment comparison is provided in Table 7.1.

Data for the midostaurin-treated patients in the treatment comparison was obtained via a prospective survey of patients receiving midostaurin in a compassionate-use program who were registered in the CEREMAST database whereas data for historical controls who did not receive midostaurin was retrospectively extracted from the same database.[28,29] According to the publication, patients were matched only on the basis of age at diagnosis and SM sub-type.[28,29] The OS rate for the 28 midostaurin-treated patients was 42.7% (95% CI: 18.0; 1.0) compared with 14.9% (95% CI: 6.0; 36.0) for the 44 historical controls who did not receive midostaurin; P = 0.03.[28,29] The corresponding HR was 2.2 (95% CI: 1.08; 4.47); P = 0.02.[28]

For the ORR estimate for SOC (52.2%) used in the economic model, a weighted average (by sample size) was calculated from the ORR of 50% (n=32) for cladribine reported in a retrospective cohort analysis by Barete et al., 2015[31] and an average ORR of 57.1% (n=14) for interferon that was calculated in a review paper by Valent et al., 2003.[5] For cladribine, while the retrospective analysis included 68 patients, only 32 patients had aggressive mastocytosis and the other 36 patients had indolent mastocytosis. For interferon, an average ORR was calculated by the authors of the review based on the response rates of 14 patients who used interferon with or without prednisone based on information reported from seven separate case reports.[5,31] The sponsor's choice of cladribine and interferon for the SOC ORR was based on expert opinion and the assumption that together these agents make up 90% of the market share (60% interferon and 30% cladribine) for advanced SM therapy in Canada.[2] The CGP broadly supported that assumption, however, noted that imatinib is also currently a relevant comparator in this setting for patients without the D816V c-KIT mutation. Further, the CGP noted that fludarabine, cytarabine, and hydroxyurea are rarely used.

Table 7.1: Comparison of Demographic and Disease Characteristics of Patients with Mastocytosis Treated with Midostaurin in Study 2201 and Study 2213 and a French Compassionate Use Program with a Historical Cohort of Patients with Mastocytosis Not Treated with Midostaurin

Characteristics (clinical/biological)	CPKC412D2213[51]	CPKC412D2201[29]	French TUA compassionate cohort[31,a]	French historical control group[a]
Number of patients	26	89	28	44
Male sex, n (%)	15 (57)	57 (64)	24 (85)	27 (61)
Age, median (range)	62 (24–79)	64 (25–82)	67 (29–85)	–
Age at diagnosis, median (range)	na	na	65 (12–84)	66 (14–87)
SM subtype according to the WHO, n (%)				
ASM	4 (15)	16 (18)	4 (14)	5 (11)
SM-AHNMD	20 (77)	57 (64)	18 (64)	33 (75)
MCL	2 (8)	16 (18)	3 (11)	2 (5)
MCS	–	–	1 (4)	2 (5)
Progressive SSM	–	–	2 (7)	2 (5)
C-findings, median (range)	All patients had 1 or	2 (1 to ≥3)	2.5 (0–4)	2 (0–4)
C-findings excluding cytopenia	more C-findings	na	2 (0–3)	1 (0–3)
Hematopoietic organ enlargement,[b] n (%)	na	82 (92)	27 (96)	38 (86)
Urticaria pigmentosa, n (%)	na	na	13 (46)	na
Mast cell mediator symptoms,[c] (%)	na	na	13 (46)	26 (59)
Bone marrow mast cell burden, % (range)	na	50 (8–98)	35 (10–80)	na
Tryptase, median (range)	na	236 (27–12,069)	200 (85–2000)	103 (4–900)
Gene mutations, %				
WT c-*KIT*	na	11	3.5	16
D816V c-*KIT*	69	87	96.5	84
ASXL1	na	na	30 (75% of SM-AHNMD)	19 (85% of SM-AHNMD)
TET2	na	na	43 (83% of SM-AHNMD)	29 (70% of SM-AHNMD)
Number of previous therapies – median (range)	1.5 (0–4)	0 (0 to ≥3)	1.5 (1–3)	2 (1–4)
Steroids, %	na	6	21	41
2-CdA, %	na	13	21	49
Interferon, %	na	8	11	8
TKI other than midostaurin, %	na	17	0	13
Thalidomid, %	na	na	0	18
mTOR inhibitor, %	na	na	11	5
Other, %	na	na	0	5
ORR[d], %	69	60	71	NA
Major response	38	45	57	
Partial response	30	15	14	
Stable disease	15	12	11	
Progressive disease	15	11	18	
RR%[d] according to WHO-SM subtype				
ASM	na	75	75	NA
SM-AHNMD	na	58	72	
MCL	na	50	66	
MCS	–	–	0	
Progressive SSM	–	–	100	
Median treatment duration, months (range)	na	11.4 (0.3–51.5)	10.5 (2–32)	NA
Median follow-up, months (range)	na	26 (12–54)	18.5 (3–36)	NA
Median response duration, months (range)	na	24.1 (18.1-not estimated)	17 (5–32)	NA

Safety/adverse events Any grade % is available (grade 3 and/or 4. % or number if percentage not available)	Decreasing frequency: nausea/vomiting (G3. n=2) Diarrhea Fatigue (G3. n=2) Anemia (G3. n=1) Thrombocytopenia (G3. n=1) Hyperlipasemia (G3. n=1)	Nausea 79% (6%) Vomiting 66% (6%) Diarrhea 54% (8%) Peripheral edema 34% (4%) Abdominal pain 28% (3%) Fatigue 28% (9%) Constipation 24% (1%) Headache 23% (2%) Arthralgia 20% (2%) Cough 19% (1%) Dizziness 13% QT interval prolongation (12%) Neutropenia 48% (24%) Anemia 63% (41%) Thrombocytopenia 52% (29%)	Nausea 89% (39%) Vomiting 25% (3.5%) Photosensitivity 25% Fatigue 14% (3.5%) Diarrhea 10.5% Drug-induced toxidermia 3.5% (3.5%) Peripheral edema 3.5% Lymphopenia 67% Cytolytic hepatitis 7%	NA
Discontinuation due to adverse events	na	22%	10%	NA

Abbreviations: AHNMD = associated clonal hematological non-mast cell lineage disease; ASM = aggressive systemic mastocytosis; C = clinical; G = grade; MCL = mast cell leukemia; MCS = mast cell sarcoma; mTOR = mammalian target of rapamycin; na = not available; NA = not applicable; ORR = overall response rate; RR = response rate; SM = systemic mastocytosis; SSM = smoldering systemic mastocytosis; TKI = tyrosine kinase inhibitor; TUA = transitory use authorization; WHO = World Health Organization; WT = wild type; 2-CdA = 2-chloro-deoxy-adenosine; MCAS = mast cell activation syndrome.

Source: Republished with permission of Dove Medical Press Ltd., from Clinical potential of midostaurin in advanced systemic mastocytosis, Chandesris MO et al., 2017:7 Pages 25—35, copyright2017; permission conveyed through Copyright Clearance Center, Inc. [29]

7.1.3 Limitations and Critical Appraisal

The data upon which the clinical inputs for OS and ORR for SOC are based in the economic evaluation were not prospectively derived, nor from a clinical trial setting. The OS estimate for SOC is based upon a naïve treatment comparison between midostaurin-treated patients for whom data was prospectively collected through a survey, thus allowing for specific data elements to be collected. In contrast, data for historical controls were retrospectively extracted from the CEREMAST database and thus subject to the limitations associated with retrospective data collection (e.g., reliance on what was reported in the past and important missing data elements). No information on the respective follow-up times for OS (i.e., time from start of treatment to assessment of OS) or on the absolute differences in OS between midostaurin-treated patients and historical controls was available. Furthermore, there are no data for ORR or ORR by SM sub-type for the historical control group as detailed in Table 7.1. The ORR estimate for SOC was based upon the weighted average of the ORR for cladribine from a retrospective analysis that included 32 patients with aggressive mastocytosis and an average ORR for interferon calculated by the authors of a review paper based on the response rates of 14 patients derived from information reported in seven separate case reports.

For the SOC OS estimate, the 28 midostaurin-treated patients and 44 historical controls in the treatment comparison were matched only for age at diagnosis and the WHO-defined sub-type of mastocytosis.[28,29] The sponsor was requested to confirm if a propensity score matching method was used to match patients which they were not able to do due to limited information available in the publication.[30] Although Chandesris et al., state that there were no significant differences between the groups based on demographic or disease characteristics, the two groups were not matched based on prior treatments as the historical control group received more treatment lines than the midostaurin-treated patients, most notably steroids (41% versus 21%) and cladribine (49% versus 21%), respectively. Historical control patients also received other therapies that were not considered to be SOC as defined by the sponsor (e.g., 13% of patients received tyrosine kinase inhibitors other than midostaurin [which may have included imatinib] and 18% of patients received thalidomide compared to no patients receiving either type of therapy in the midostaurin-treated group). Given that the historical control group was more heavily pre-treated than the midostaurin-treated patients it is possible that these

patients were more refractory to treatment and therefore predisposed to worse survival outcomes than the midostaurin-treated patients. In addition to patients in the treatment

comparison receiving prior therapies that were not included in the sponsor's definition of SOC, they also did not receive certain therapies (e.g., hydroxyurea and cytarabine) that were identified by the sponsor as being SOC. It is unknown what effect the specific prior therapies, or lack thereof, may have had on OS.

Both the midostaurin-treated and historical control groups in the treatment comparison included patients with mast cell sarcoma (i.e., 1 patient [4%] and 2 patients [5%]) and progressive smouldering SM (2 patients [7%] and 2 patients [5%]), respectively. It is unclear if the inclusion of patients with these diagnoses introduced any confounding factors in the estimation of OS which should be reflective of patients in the target population (i.e., patients with ASM, SM-AHN, or MCL)

In the midostaurin-treated patients, the median duration of treatment was 10.5 months (range: 2 to 32), median duration of follow-up was 18.5 months (range: 3 to 36), and median DOR was 24.1 months (range: 18.1 to not estimated), whereas there was no information available for any of these parameters for the historical control group. While the ORR in the midostaurin-treated patients was reported to be 71% (of which 57% of patients had a MR, 14% had a PR, 11% had stable disease, and 18% had progressive disease), these data were not available for the historical control group. The missing information in the historical control group compromises the comparison of the two groups as it is not known if patients were matched based on these important parameters. Further, the lack of information on ORR in the historical control group precludes the ability to compare ORR between the two groups to discern if the results are in line with, and corroborate those of, the OS comparison.

The ORR estimate for SOC was derived from the weighted average of ORR values previously reported in the literature for cladribine and interferon. For cladribine, the ORR estimate was based on a retrospective cohort study of 68 adult patients with mastocytosis registered in the French CEREMAST database.[31] Of the 68 patients treated with cladribine, 36 (53%) had indolent mastocytosis and 32 (47%) had advanced mastocytosis.[31] Of the 32 patients, 14 (21%) had ASM, 17 (25%) had SM-AHNMD, and one patient (1.4%) had MCL.[31] The median age of patients at treatment initiation was 54 years (range: 17 to 83), 49% were male and 81% had a KIT D816V mutation.[31] Previous treatments used by patients included interferon (19%), tyrosine kinase inhibitors (e.g., imatinib, masitinib, dasatinib, and imatinib then masitinib) (6%/6%/1%/3%), thalidomide (7%), and hydroxyurea (4%). The ORR (n=32) was 50% which corresponded with 37.5% of patients experiencing a MR and 12.5% a PR. For interferon, the ORR estimate of 57.1% was obtained from a review paper and appears to have been calculated from the sum of the responses of 14 patients based on information reported from seven case reports identified by the authors. Of these, three patients (21.4%) had achieved a MR and five patients (35.7%) had achieved a PR.[5] Only limited information on patient characteristics (e.g., diagnosis and organs affected) was available for the interferon-treated patients.

7.1.4 Summary

To derive estimates for OS and ORR for SOC in the economic evaluation, the sponsor relied on naïve treatment comparisons. A major limitation of a naïve treatment comparison is that it is not possible to determine if any observed differences in efficacy or safety between therapies is solely due to the treatment or rather due to bias or confounding factors such as differences in study populations, definitions of outcomes, or study designs.[32] The opposite may also occur in a naïve comparison where a finding of similar efficacy between treatments may be incorrect because differences in the included trials may have masked true treatment differences.[32] It would have been preferable for the sponsor to have conducted a matching-adjusted indirect

comparison (MAIC) which uses individual patient level data to match baseline summary statistics of patients to compare treatment outcomes across balanced trial populations.[33] Although the sponsor indicated that conducting an indirect treatment comparison, naïve/unanchored comparison, or MAIC was not feasible because Study 2201 was a single arm trial[25] and lack of data, the sponsor did not conduct a systematic literature review, conduct a risk of bias assessment on the included studies, or compared patient-reported outcomes or safety between the treatments in their comparison. The studies from which the SOC comparator data were obtained are associated with numerous methodological limitations (e.g., small sample sizes, limited data reporting, retrospective analyses, missing data elements) which adds further uncertainty to the interpretation of any apparent treatment differences in OS and ORR between midostaurin and SOC. Due to the above limitations, the comparative efficacy estimates obtained for OS and ORR should be interpreted with caution and are likely biased. It is difficult to quantify or identify the direction of the bias. As a result, the estimates may over- or underestimate the true treatment effect associated with midostaurin.

7.2 Critical appraisal of the sponsor's submitted pooled survival analysis

7.2.1 Objective

The objective of this section is to summarize and critically appraise the methodology and results of an unpublished pooled survival analysis by Reiter et al., 2017[34] submitted by the sponsor. This analysis compared pooled OS data for midostaurin-treated patients with a known date of diagnosis from Study 2201 and Study 2213 with OS data from patients enrolled in a German registry who were not treated with midostaurin. The purpose of the critical appraisal is to inform the CADTH review of the economic evaluation which included a supportive analysis by Reiter et al., 2017.[34]

7.2.2 Findings

Information on the Reiter et al., 2017 analysis was only available from the slides of an oral presentation that was submitted by the sponsor, thus details on the methodology are limited. The authors pooled OS data for midostaurin-treated patients with a known date of diagnosis from Study 2201 (n=63) and Study 2213 (n=26) and compared the pooled dataset (n=89) with OS data from historical controls (n=42) who were not treated with midostaurin. The historical controls were identified from a German registry (i.e., University Medical Centre, Mannheim, Germany). The date of diagnosis was known for 63 (71%) patients from Study 2201 and for 100% of patients from Study 2213 and the historical controls. Of the patients with a known date of diagnosis, most (52 [83%] patients from Study 2201, 29 [69%] historical controls, and five [19%] of patients from Study 2213) were diagnosed from ≥ 2009 to < 2015, whereas 14%, 24%, and 77% of patients, respectively, were diagnosed from ≥ 2005 to < 2009. Across all three data sources, ≤ 5% of patients were diagnosed prior to 2005 and only 2% (historical controls only) were diagnosed ≥ 2015. Baseline characteristics were comparable between the pooled midostaurin-treated patients and historical controls, except for age at diagnosis and time from diagnosis to start of last therapy, as detailed in Table 7.2.

Table 7.2: Baseline characteristics of pooled patients from Study 2201 and Study 2213 and historical controls

Characteristic	Midostaurin-treated patients (n=89)	Historical controls (n=42)
Age at diagnosis, n (%) > 65 years	 37 (42)	 30 (71)
Sex, n (%) Male	 58 (65)	 29 (69)
KIT D816 mutation status, n (%) Mutated Unknown	 73 (82) 1 (1)	 39 (93) 0 (0)
SM sub-type, n (%) ASM SM-AHN MCL	 16 (18) 59 (66) 14 (16)	 9 (21) 28 (67) 5 (12)
Time from diagnosis to start of last therapy, median (IQR), months	2.2 (0.5 to 7.8)	7.3 (1.0 to 26.1)
Number of therapies, median (range)	2 (1 to 5)	2 (0 to 5)
Serum tryptase levels (range), µg/L At diagnosis Prior to last treatment	 NA 267 (22.2 to 12069.0)	 195 (14.0 to 1675.0) NA
Abbreviations: ASM = aggressive systemic mastocytosis; IQR = interquartile range; MCL = mast cell leukemia; NA = not applicable; SM-AHN = systemic mastocytosis with associated hematologic neoplasm;		

Source: Reiter et al., 2017[91]

The primary analysis in Reiter et al., 2017[34] was a comparison of OS between non-matched patients in the pooled midostaurin-treated patient group (n=89) and historical controls (n=42) to determine if baseline characteristics and subgroup analyses affected OS and the HR. A supportive analysis was conducted in which propensity scoring was used to match midostaurin-treated patients (n=42) from the pooled dataset with historical controls (n=42). Matching was based on a propensity score using age at diagnosis, WHO-defined SM sub-type (i.e., ASM, SM-AHN, and MCL), prior lines of treatment, and sex as factors. Midostaurin-treated patients and historical controls were matched 1:1 based on their assigned propensity score and a stratified Cox regression model using the matched pairs as strata was used to analyze the matched dataset. A sensitivity analysis was also conducted in the non-matched dataset in which OS was compared from the date of the last treatment received to death. As the key OS analysis for purposes of the EGP reanalysis for the economic evaluation was the matched pairs analysis using propensity scoring, this will be the focus of this summary and critical appraisal.

Median exposure to midostaurin in the pooled dataset was 12.9 months. Median follow-up in the pooled midostaurin-treated patients was 79.5 months (range: 51.4 to 234.0) and in historical controls was 84.2 months (range: 22.3 to 176.3). The data cut-off for the midostaurin-treated patients was July 1, 2016 and for the historical controls was May 9, 2017.

For the matched pairs analysis based on propensity scoring, there were 31 events in the pooled midostaurin-treated patients and 36 events in the historical controls. Median OS was 27.8 months (95% CI; 19.3; 44.6) in the pooled midostaurin-treated patients and 19.5 months (95% CI: 13.0; 35.3) in the historical controls, corresponding with a 36% lower risk of death in midostaurin-treated patients or a HR for death of 0.636 (95% CI: 0.326; 1.244).

7.2.3 Limitations and Critical Appraisal

The Reiter et al., 2017[34] analysis is unpublished and the only source of information on the analysis were slides from an oral presentation, hence details on the methodology and study results are limited. As with the Chandesris study,[28,29] the OS data for the historical controls in

the Reiter analysis were not prospectively derived, nor were they from a clinical trial setting. Nonetheless, the Reiter analysis did provide more details on the methodology employed than the Chandesris study. The Reiter analysis included only patients with a known date of diagnosis which comprised all (100%) patients in Study 2213 and the historical controls, but only 63 (71%) patients from Study 2201. Therefore, 26 (29%) of patients in Study 2201 were excluded from the analysis. In a supportive analysis, Reiter et al., used propensity scoring to match midostaurin-treated patients and historical controls 1:1 on four factors: age at diagnosis, WHO-defined SM sub-type, prior treatments, and sex. Although the Chandesris study stated that patients were matched on two factors (i.e., age at diagnosis and WHO-defined SM sub-type), it could not be confirmed whether propensity score matching was done.[30] Of note, while patients were matched on prior treatments in the Reiter analysis, they were not in the Chandesris study and the CADTH methods team identified that patients in the historical control cohort were more heavily pre-treated than those in the compassionate use program.

In the Reiter analysis, matching was also done to a more contemporary group of patients as most patients (~95%) were diagnosed after 2005. In Study 2201, patients were enrolled from January 2009 to July 2012 and in Study 2213, patients were enrolled from July 2005 to April 2010. Given that the registry data are contemporary with the data from the midostaurin clinical trials, there is less likelihood that potential confounding factors related to timing, such as availability of treatments and clinical practice patterns, would have differed between the patient groups. In the Reiter analysis, the median duration of follow-up in midostaurin-treated patients was more than four times longer than that in the Chandesris trial. Median follow-up in the pooled midostaurin dataset in the Reiter analysis was 79.5 months (range: 51.4 to 234.0) whereas in the Chandesris study, the median duration of follow-up was 18.5 months (range: 3 to 36). For historical controls, median follow-up in the Reiter analysis was 84.2 months (range: 22.3 to 176.3) and was unknown in the Chandesris study.

There was no information in the Reiter analysis pertaining to SOC or the specific treatments that the historical controls received. All that was reported was the median number of prior therapies received at baseline which was two for both the pooled midostaurin dataset (range: 1 to 5 prior therapies) and historical controls (range: 0 to 5 prior therapies). As the registry data is contemporary with the midostaurin trials, it can be speculated that similar treatments were available to patients who entered Study 2201 and Study 2213 as well as the historical controls.

In the Reiter analysis, OS data for patients from Study 2201 and Study 2213 were pooled into one dataset. The CADTH Methods team noted in the systematic review that the trials differed in various design features (e.g., inclusion of patients without a C-finding but who were transfusion-dependent in Study 2201, differences in response and discontinuation criteria). A key difference between the trials is the duration of survival follow-up. In Study 2201, the duration of OS follow-up was until the end of the study (i.e., five years after last patient last visit or when all patients discontinued the study) whereas in Study 2213 patients were only followed up for OS for one year post-treatment. As a result, the reported median follow-up of 79.5 months (range: 51.4 to 234.0) in the pooled midostaurin dataset may be somewhat misleading because for patients in Study 2213, the maximum follow-up duration for OS data would have been only one year. It is not known if these potential sources of heterogeneity had any effect on the outcomes of the pooled analyses.

7.2.4 Summary

An alternate source for the HR for OS which was derived from an unpublished pooled survival analysis by Reiter et al., 2017 was provided in the economic evaluation.[34] The alternate HR estimate was derived from an unpublished study by Reiter et al., 2017[34] submitted by the

sponsor. In a supportive analysis, Reiter et al., used propensity score matching to match pooled midostaurin-treated patients (N=42) from Study 2201 and Study 2213 with a known date of diagnosis 1:1 with a historical cohort of patients (N=42) from a German registry who did not receive midostaurin. The Reiter analysis may be a better source for the HR estimate compared to the Chandesris study, from which the sponsor derived the HR estimate for the submitted economic evaluation. The Reiter analysis matched patients on more factors (i.e., age at diagnosis, WHO-defined SM sub-type, prior treatments, and sex), matched to a more contemporary group of patients (~95% of patients were diagnosed after 2005), had longer median follow-up for the pooled midostaurin-treated patients and historical controls, and provided a more conservative HR estimate (i.e., HR = 1.57 [95% CI: 0.80; 3.07]). Key limitations identified with the Reiter analysis were lack of information on SOC or the specific treatments received by the historical controls and the pooling of data from Study 2201 and Study 2213 due to differences in study design such as the different length of follow-up for survival data. As with the Chandesris study, Reiter et al., did not conduct a systematic literature review to identify all potential studies, conduct a risk of bias assessment, or consider patient-reported outcomes or safety outcomes in their analysis. Due to the above limitations, the comparative efficacy estimates obtained for OS should be interpreted with caution and are likely biased.

8 COMPARISON WITH OTHER LITERATURE

The pCODR CGP and the pCODR Methods Team did not identify other relevant literature providing supporting information for this review.

9 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR Systemic Mastocytosis Clinical Guidance Panel and supported by the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on midostaurin for advanced systemic mastocytosis. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant pCODR Economic Guidance Report. Details of the pCODR review process can be found on the CADTH website (www.cadth.ca/pcodr).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines. The manufacturer, as the primary data owner, did not agree to the disclosure of some clinical information which was provided to pERC for their deliberations, and this information has been redacted in this publicly posted Guidance Report.

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report.

The Systemic Mastocytosis Clinical Guidance Panel is comprised of three clinical oncologists. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the CADTH website (www.cadth.ca/pcodr). Final selection of the Clinical Guidance Panels was made by the pERC Chair in consultation with the pCODR Executive Director. The Panel and the pCODR Methods Team are editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

APPENDIX A: LITERATURE SEARCH STRATEGY AND DETAILED METHODOLOGY

1. Literature search via Ovid platform

Database(s): **EBM Reviews - Cochrane Central Register of Controlled Trials** July 2019**, Embase** 1974 to 2019 September 04**, Ovid MEDLINE(R) ALL** 1946 to September 04, 2019

#	Searches	Results
1	(rydapt* or midostaurin* or benzoylstaurosporine* or CGP 41251 or CGP41251 or CGP 41 251 or PKC 412* or PKC412* or NVP PKC 412* or NVPPKC 412* or NVPPKC412* or ID912S5VON).ti,ab,ot,kf,kw,hw,nm,rn.	2914
2	exp Mastocytosis, Systemic/ or Leukemia, Basophilic, Acute/	5436
3	((systemic* or disseminated* or leukemia* or leukaemia* or leucemia* or leucamia* or disease*) adj5 (mastocytos* or mast cell* or basophilic*)).ti,ab,kf,kw.	12366
4	(ASM or SM AHN or SMAHN or MCL or adv SM or advSM).ti,ab,kf,kw.	34956
5	or/2-4	47962
6	1 and 5	434
7	6 use medall	98
8	6 use cctr	11
9	*midostaurin/	380
10	(rydapt* or midostaurin* or benzoylstaurosporine* or CGP 41251 or CGP41251 or CGP 41 251 or PKC 412* or PKC412* or NVP PKC 412* or NVPPKC 412* or NVPPKC412*).ti,ab,kw,dq.	1624
11	or/9-10	1659
12	exp systemic mastocytosis/ or mast cell leukemia/	4742
13	((systemic* or disseminated* or leukemia* or leukaemia* or leucemia* or leucamia* or disease*) adj5 (mastocytos* or mast cell* or basophilic*)).ti,ab,kw,dq.	12348
14	(ASM or SM AHN or SMAHN or MCL or adv SM or advSM).ti,ab,kw,dq.	35019
15	or/12-14	47794
16	11 and 15	310

17	16 use oemezd	207
18	17 not conference abstract.pt.	106
19	17 and conference abstract.pt.	101
20	limit 19 to yr=2014-current	65
21	7 or 8 or 18	215
22	remove duplicates from 21	126
23	20 or 22	191
24	limit 23 to english	187

2. Literature search via PubMed

A limited PubMed search was performed to retrieve citations not found in the MEDLINE search.

Search	Query	Items Found
#18	Search **(#16 AND publisher[sb])** Filters: **English**	5
#17	Search **(#16 AND publisher[sb])**	5
#16	Search **(#4 AND #15)**	104
#15	Search **(#11 OR #13 OR #14)**	27702
#14	Search **(ASM[tiab] OR SM AHN[tiab] OR SMAHN[tiab] OR MCL[tiab] OR adv SM[tiab] OR advSM[tiab])**	12898
#13	Search **((systemic*[tiab] OR disseminated*[tiab] OR leukemia*[tiab] OR leukaemia*[tiab] OR leucemia*[tiab] OR leucamia*[tiab] OR disease*[tiab]) AND (mastocytos*[tiab] OR mast cell*[tiab] OR basophilic*[tiab]))**	14621
#11	Search **"Mastocytosis, Systemic"[Mesh] OR "Leukemia, Basophilic, Acute"[Mesh]**	1698
#4	Search **(#2 OR #3)**	12476
#3	Search **(rydapt*[tiab] OR midostaurin*[tiab] OR benzoylstaurosporine*[tiab] OR CGP 41251[tiab] OR CGP41251[tiab] OR CGP 41 251[tiab] OR PKC 412*[tiab] OR PKC412*[tiab] OR NVP PKC 412*[tiab] OR NVPPKC 412*[tiab] OR NVPPKC412*[tiab] OR ID912S5VON[rn])**	12476
#2	Search **"midostaurin" [Supplementary Concept]**	330

3. Cochrane Central Register of Controlled Trials (CENTRAL)

(searched via Ovid)

4. Grey literature search via**:**

Clinical trial registries:

US National Library of Medicine. ClinicalTrials.gov
https://clinicaltrials.gov/

Canadian Partnership Against Cancer Corporation. Canadian Cancer Trials
http://www.canadiancancertrials.ca/

Search: Rydapt/midostaurin, aggressive systemic mastocytosis

Select international agencies including:

US Food and Drug Administration (FDA)
https://www.fda.gov/

European Medicines Agency (EMA)
https://www.ema.europa.eu/

Search: Rydapt/midostaurin, aggressive systemic mastocytosis

Conference abstracts:

American Society of Clinical Oncology (ASCO)
https://www.asco.org/

European Society for Medical Oncology (ESMO)
https://www.esmo.org/

American Society of Hematology (ASH)
http://www.hematology.org/

Search: Rydapt/midostaurin, aggressive systemic mastocytosis — last five years

Detailed Methodology

The literature search for clinical studies was performed by an information specialist from the pCODR Methods Team using the abovementioned search strategy, which was peer-reviewed according to the *PRESS Peer Review of Electronic Search Strategies* checklist (https://www.cadth.ca/resources/finding-evidence/press).[92]

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid, Embase (1974–) via Ovid, the Cochrane Central Register of Controlled Trials (CENTRAL) via Ovid; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Nubeqa/darolutamide and aggressive systemic mastocytosis.

No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English-language documents but not limited by publication year.

The search is considered up to date as of December 12, 2019.

Grey literature (literature that is not commercially published) was identified by searching websites from relevant sections of the *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* checklist (https://www.cadth.ca/grey-matters).[93] Included in this search were the websites of regulatory agencies (US Food and Drug Administration and European Medicines Agency), clinical trial

registries (US National Institutes of Health's clinicaltrials.gov and Canadian Partnership Against Cancer Corporation's Canadian Cancer Trials), and relevant conference abstracts. Conference abstracts were retrieved through a search of the Embase database limited to the last five years. Abstracts from the American Society of Clinical Oncology (ASCO), the European Society for Medical Oncology (ESMO), and the American Society of Hematology (ASH) were searched manually for conference years not available in Embase. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the CADTH Clinical Guidance Panel. As well, the sponsor of the drug was contacted for additional information, as required by the pCODR Review Team.

Study Selection

One member of the pCODR Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. One member of the pCODR Methods Team independently made the final selection of studies to be included in the review and differences were resolved through discussion.

Included and excluded studies (with reasons for exclusion) are identified in section 6.3.1.

Quality Assessment

Assessment of study bias was performed by one member of the pCODR Methods Team with input provided by the Clinical Guidance Panel and other members of the pCODR Review Team. SIGN-50 Checklists were applied as a minimum standard. Additional limitations and sources of bias were identified by the pCODR Review Team.

Data Analysis

No additional data analyses were conducted as part of the pCODR review.

Writing of the Review Report

This report was written by the Methods Team, the Clinical Guidance Panel and the pCODR Secretariat:

- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions on the net clinical benefit of the drug.
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups, by the Provincial Advisory Group (PAG), and by Registered Clinicians.

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