NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Midostaurin for treating advanced systemic mastocytosis [ID1573]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Midostaurin for treating advanced systemic mastocytosis [ID1573]

Contents:

The following documents are made available to consultees and commentators:

The **final scope** and **final stakeholder list** are available on the NICE website.

1. **Company submission** from Novartis

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submissions** from:
   a. UK Mastocytosis Support Group

4. **Expert personal perspectives** from:
   a. Dr Steven Knapper, Clinical Reader in Haematology / Consultant Haematologist – clinical expert, nominated by Novartis, UK Mastocytosis Support Group and Leukaemia Care
   b. Dr Deepti Radia, Consultant Haematologist – clinical expert, nominated by Novartis, UK Mastocytosis Support Group and Leukaemia Care

5. **Evidence Review Group report** prepared by Liverpool Reviews and Implementation Group

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   a. Dr Steven Knapper, Clinical Reader in Haematology / Consultant Haematologist – clinical expert, nominated by Novartis, UK Mastocytosis Support Group and Leukaemia Care

10. **Technical engagement response from consultees and commentators:**
    a. Leukaemia Care and UK Mastocytosis Support Group

11. **Evidence Review Group critique of company response to technical engagement** prepared by Liverpool Reviews and Implementation Group

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Midostaurin for treating advanced systemic mastocytosis [ID1573]

Document B

Company evidence submission

Novartis Pharmaceuticals UK Ltd

March 2020

File name	Version	Contains confidential information	Date
FINAL Novartis_ID1573_Midostaurin Advanced SM_Document B REDACTED	Final	Yes	04th March 2020

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List of abbreviations

AE	Adverse event
AESI	Adverse event of special interest
AIC	Akaike information criterion
ALT	Alanine aminotransferase
AML	Acute myeloid leukaemia
ANC	Absolute neutrophil count
APAR	Australian Public Assessment Report
ASH	American Society of Hematology
ASM	Aggressive systemic mastocytosis
AST	Aspartate aminotransferase
AUD	Australian dollar
BIC	Bayesian information criterion
BNF	British National Formulary
CD	Cluster of differentiation
CI	Confidence interval
CSR	Clinical study report
CUP	Compassionate use programme
CYP3A4	Cytochrome P450 3A4
HiDAC	High-dose cytarabine consolidation
dL	Decilitre
DoR	Duration of response
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
ECG	Electrocardiogram
ECNM	European Competence Network on Mastocytosis
ECOG	Eastern Cooperative Oncology Group
ED	Emergency department
EMA	European Medicines Agency
eMIT	Electronic market information tool
EPAR	European Public Assessment Report
EQ-5D-3L	EuroQol 5 Dimensions 3 Levels
ERG	Evidence Review Group
FAS	Final analysis set
FDA	Food and Drug Administration
FLAG-IDA	Fludarabine, high-dose cytarabine with granulocyte-colony stimulating factor
FLT3	fms-like tyrosine kinase 3
GDI	Global distress index
GEE	Generalised estimating equation
GP	General practitioner
Hb	Haemoglobin
HCL	Hairy cell leukaemia
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRG	Healthcare resource group
HRQoL	Health-related quality of life
HSCT	Haematopoietic stem cell transplant
HST	Highly specialised technology
HU	Hydroxyurea
HUI	Health Utilities Index

ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
IFN	Interferon
IPD	Individual patient-level data
IQR	Interquartile range
ISM	Indolent SM
ITT	Intention-to-treat
IWG-MRT	International Working Group-Myeloproliferative Neoplasms Research and Treatment
JAK	Janus kinase
KM	Kaplan-Meier
LCI	Lower confidence interval
llog	Loglogistic
lnorm	Lognormal
LYG	Life years gained
MAPK	Mitogen-activated protein kinase
MCL	Mast cell leukaemia
MCS	Mental composite score
mL	Millilitre
MR	Major response
MRI	Magnetic resonance imaging
MSAS	Memorial Symptom Assessment Scale
MU	Million units
NA	Not applicable
NB-UVB	Narrowband ultraviolet B light
NCCN	National Comprehensive Cancer Network
NE	Not estimated
NHS	National Health Service
NICE	The National Institute for Health and Care Excellence
NR	Not reported
NSAID	Non-steroidal anti-inflammatory drugs
ONS	Office for National Statistics
ORR	Overall response rate
OS	Overall survival
PAS	Patient access scheme
PBAC	Pharmaceutical Benefits Advisory Committee
PCS	Physical composite score
PD	Progressed disease
PDGFR	Platelet-derived growth factor receptor
PEP	Primary efficacy population
PFS	Progression-free survival
PH	Proportional hazards
PHYS	Physical symptom subscale
PI3K	Phosphoinositide 3-kinase
PKC	Protein kinase C
PLT	Platelet count
PPS	Per protocol set
PR	Partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic sensitivity analysis
PSM	Partitioned survival model

PSS	Personal and Social Services
PSSRU	Personal Social Services Research Unit
PSYCH	Psychological symptom subscale
PUVA	Psoralen plus ultraviolet A
QALY	Quality-adjusted life year
QC	Quality control
QTcF	Corrected QT interval by Fridericia
RCT	Randomised controlled trial
RDI	Relative dose intensity
RFS	Relapse-free survival
SAE	Serious adverse event
SCF	Stem-cell factor
SCFR	Stem-cell growth factor receptor
SD	Standard deviation
SE	Standard error
SES	Safety evaluation set
SF-12	Short-form 12
SLR	Systematic literature review
SM	Systemic mastocytosis
SM-MDS	Systemic mastocytosis-myelodysplastic syndrome
SM-AHN	Systemic mastocytosis with an associated haematological neoplasm
SM-AL	Systemic mastocytosis with acute leukaemia
SM-CMML	Systemic mastocytosis with chronic myelomonocytic leukaemia
SM-MDS	Systemic mastocytosis with myelodysplastic syndrome
SM-MPN	Systemic mastocytosis with myeloproliferative neoplasm
SmPC	Summary of Product Characteristics
SoC	Standard of care
SSM	Smouldering systemic mastocytosis
STA	Single technology appraisal
STAT	Signal transducer and activator of transcription
TA	Technology appraisal
TKI	Tyrosine kinase inhibitor
TMSAS	Total Memorial Symptom Assessment Scale
TSD	Technical Support Document
TTD	Time-to-treatment discontinuation
TTO	Time trade-off
TTR	Time to response
UCI	Upper confidence interval
UK	United Kingdom
ULN	Upper limit of normal
US	United States
VEGFR	Vascular endothelial growth factor receptor 2
VPAS	Voluntary Scheme for Branded Medicines Pricing and Access
weib	Weibull
WHO	World Health Organization
WTP	Willingness-to-pay

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 *Decision problem*

This submission covers the full marketing authorisation of midostaurin for the treatment of adult patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated haematological neoplasm (SM-AHN) and mast cell leukaemia (MCL), collectively described as advanced systemic mastocytosis (advanced SM).

The decision problem addressed within this submission is consistent with the NICE final scope for this appraisal as outlined in Table 1.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated haematological neoplasm (SM-AHN) or mast cell leukaemia (MCL)	Adults with ASM, SM-AHN or MCL, collectively described as advanced systemic mastocytosis (advanced SM)	In line with the final NICE scope
Intervention	Midostaurin	Midostaurin	In line with the final NICE scope
Comparator(s)	Current clinical management including but not limited to: • Interferon alpha • Cladribine • Imatinib • Nilotinib • Dasatinib (These treatments do not currently have a marketing authorisation in the UK for this indication)	Current clinical management including: • Interferon alpha • Cladribine • Imatinib • Pegylated interferon alpha (peg-interferon alpha) • "AML-like" treatments	UK clinical experts indicated that nilotinib and dasatinib are very rarely used in UK clinical practice[1], and as such these therapies are excluded from the base case economic analysis. However, the economic model retains the flexibility for these comparators to be explored in scenario analyses, to reflect all of the treatments listed in the final NICE scope. The base case economic analysis also includes pegylated interferon alpha and "AML-like" treatments, which UK clinical experts described as additional treatment options for patients with advanced SM. The clinical experts indicated that: • Interferon alpha (Roferon-A and IntronA) has been relatively discontinued, with peg-interferon alpha more commonly used in UK clinical practice[1]

			• "AML-like" treatments comprise non-intensive chemotherapy such as azacitidine in addition to more intensive chemotherapies[1]
Outcomes	The outcome measures to be considered include: • Overall survival (OS) • Progression-free survival (PFS) • Overall response rate (ORR) • Adverse events (AEs) of treatment • Health-related quality of life (HRQoL)	The outcome measures considered include: • OS • PFS • ORR • AEs of treatment • HRQoL	In line with the final NICE scope
Economic analysis	• The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year (QALY) • The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared • Costs will be considered from a National Health Service (NHS) and Personal Social Services (PSS) perspective • The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account	• The cost-effectiveness of the treatments evaluated in this appraisal has been expressed in terms of incremental cost per QALY • A lifetime time horizon has been adopted to capture all relevant costs and health-related utilities • Costs have been considered from an NHS and PSS perspective • Commercial arrangements for the intervention, comparator and subsequent treatment technologies have been taken into account	In line with the final NICE scope

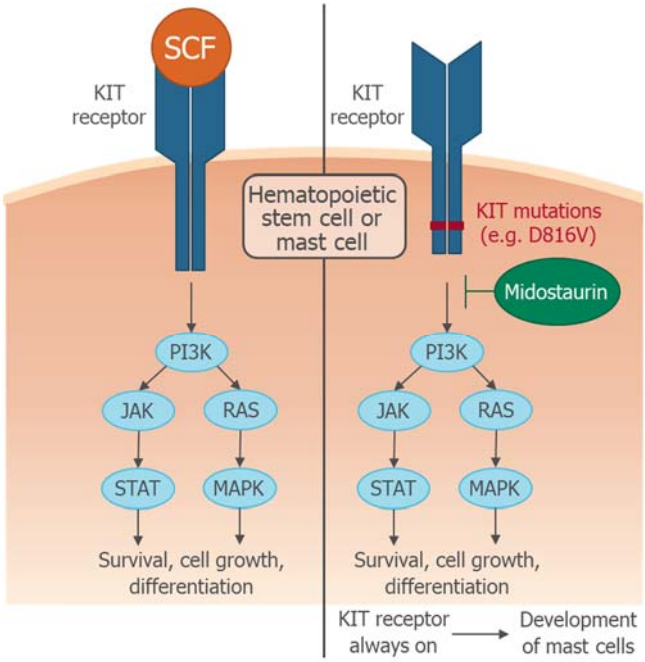
Subgroups to be considered	If evidence allows, subgroup analysis by disease type to include: • ASM • SM-AHN • MCL	One exploratory economic subgroup analysis has been considered: • Patients with SM-AHN + MCL	• This submission covers the full marketing authorisation of midostaurin for the treatment of adult patients with ASM, SM-AHN and MCL (collectively described as advanced SM). • Given the extremely heterogeneous nature of the disease, clinical activity and prognoses (life expectancy of 41 months to 11 years, 24 months to 4.4 years, and 2 months to 9.2 months for ASM, SM-AHN, and MCL, respectively), economic subgroup analyses by individual subtype of advanced SM were initially considered for this submission; however, the results of these analyses would be associated with considerable uncertainty since the key trial for midostaurin (D2201) is a single-arm, phase II open-label study (n=89) in an extremely heterogeneous patient population with very limited patient numbers for each subgroup (n=16, n=57 and n=16) for the ASM, SM-AHN and MCL subgroups, respectively) • An exploratory economic subgroup analysis was conducted for the pooled subgroup of SM-AHN or MCL patients since these populations have a much shorter life expectancy compared with the ASM subgroup. This approach was considered reasonable by UK clinical experts, with acknowledgement that this analysis is solely based on the much shorter life expectancy of this population and the available evidence

Abbreviations: Advanced SM: advanced systemic mastocytosis; AEs: adverse events; AML: acute myeloid leukaemia; ASM: aggressive systemic mastocytosis; D816V: substitution of aspartic acid in position 816 to valine; FDA: Food and Drug Administration; HRQoL: health-related quality of life; MCL: mast cell leukaemia; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; PSS: Personal Social Services; QALY: quality-adjusted life year; SM-AHN: systemic mastocytosis with associated haematological neoplasm; UK: United Kingdom.
Source: NICE Appraising life-extending, end of life treatments;[2] NICE Final Scope [ID1573].[3]

B.1.2 *Description of the technology being appraised*

A summary of the mechanism of action, marketing authorisation status, costs and administration requirements of midostaurin for the treatment of advanced SM is presented in Table 2.

Table 2: Technology being appraised

UK approved name and brand name	Midostaurin (Rydapt®)
Mechanism of action	Midostaurin is a small-molecule drug, which acts as a multi kinase inhibitor.[4] Kinases are a class of enzymes responsible for the phosphorylation (activation) of several proteins via signal transduction cascades. Midostaurin is a competitive inhibitor to several receptor tyrosine kinases, including mast/stem cell growth factor receptor (SCFR) (also known as KIT or CD1117), fms-like tyrosine kinase 3 (FLT3), platelet-derived growth factor receptor (PDGRF) and vascular endothelial growth factor receptor 2 (VEGFR2), as well as members of the serine/threonine kinase family such as protein kinase C (PKC).[4] Receptor tyrosine kinases such as FLT3 and KIT play important roles in the regulation of cell growth and survival in normal haematopoiesis (blood cell production) and disease (Figure 1).[5] **Figure 1: Mechanism of action of midostaurin at the KIT receptor signal transduction cascade in advanced SM**  **Abbreviations:** JAK: janus kinase; MAPK: mitogen-activated protein kinase; PI3K: phosphoinositide 3-kinase; SM: systemic mastocytosis; SCF: stem-cell factor; STAT: signal transducer and activator of transcription. **Source:** Adapted from Verstovsek *et al.* (2013).[6] Although the exact disease mechanism remains unknown, an activating mutation in the *KIT* gene, such as D816V, is present in up to 96% of patients with advanced SM and is associated with constitutively active KIT signalling resulting in abnormal mast cell growth and proliferation.[7] Midostaurin acts to inhibit aberrant cell signalling mediated through the KIT receptor, to decrease abnormal mast cell proliferation, survival and histamine release.[8] Importantly, midostaurin inhibits both wild-type and D816V-mutant *KIT*, and is the first targeted therapy available for the treatment of advanced SM patients.[4] More broadly, midostaurin also interacts with PKC, PDGRF and VEGFR2 to inhibit the

	mitogenic signalling of the respective growth factors in cells, resulting in cell growth arrest (Figure 1).[4]
Marketing authorisation/ CE mark status	Midostaurin (Rydapt®) was granted a marketing authorisation by the EMA as a monotherapy for the treatment of adult patients with advanced SM (ASM, SM-AHN and MCL) on 18th September 2017.[9] Midostaurin has also been granted orphan designation by the EMA for this indication.[10]
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	• In addition to its licence for advanced SM, midostaurin was also granted a marketing authorisation by the EMA in combination with standard daunorubicin and cytarabine induction and high-dose cytarabine consolidation chemotherapy, and for patients in complete response followed by single agent maintenance therapy for adult patients with newly diagnosed AML who are FLT3 mutation-positive on 18th September 2017[9] • The SmPC and EPAR for midostaurin are provided within the reference pack for this submission • Midostaurin is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients listed in section 6.1 of the SmPC[4] • Concomitant administration of potent CYP3A4 inducers, e.g. rifampicin, St. John's Wort (*Hypericum perforatum*), carbamazepine, enzalutamide, phenytoin and others is also contraindicated[4]
Method of administration and dosage	• Midostaurin should be taken orally twice daily at approximately 12-hour intervals with food[4] • The recommended starting dose for the treatment of advanced SM is 100 mg twice daily[4] • Treatment should be continued as long as clinical benefit is observed or until unacceptable toxicity occurs[4] • As an oral therapy, there are no special administration requirements for midostaurin and patients or their carers may simply administer treatment at home • Full details of any dose modifications required for midostaurin are reported in the SmPC[4]
Additional tests or investigations	No additional tests or investigations are required in order to initiate treatment with midostaurin in advanced SM.
List price and average cost of a course of treatment	• The list price of midostaurin 25 mg (56 capsules) is £5,609.94[11] • Treatment is carried out in cycles of 28 days[4] • A 28-day cycle requires 4 packs. The cost of a 28-day cycle is £22,439.76 (4 x £5,609.94)
Patient access scheme	A confidential simple patient access scheme (PAS) exists for midostaurin in the AML indication, in which the NHS is able to procure midostaurin at a net price lower than the current list price. Midostaurin is provided to the NHS with a [redacted] discount off the list price, and this PAS price has been included in the economic analysis of this submission. It should be noted that [redacted].

Abbreviations: AML: acute myeloid leukaemia; ASM: aggressive systemic mastocytosis; CYP3A4: cytochrome P450 3A4; EMA: European Medicines Agency; EPAR: European public assessment report; FLT3: fms-like tyrosine kinase 3; MCL: mast cell leukaemia; PAS: patient access scheme; PDGFR: platelet-derived growth factor receptor; PKC: protein kinase C; SM: systemic mastocytosis; SM-AHN: systemic mastocytosis with associated haematological neoplasm; SmPC: summary of product characteristics; VEGFR2: vascular endothelial growth factor receptor 2.
Source: European Public Assessment Report for Midostaurin (2017),[9] Gotlib *et al.* (2016),[12] Midostaurin BNF (2019),[11] Midostaurin SmPC (2017),[4] Ustun *et al.* (2016).[13]

B.1.3 *Health condition and position of the technology in the treatment pathway*

Disease overview

- Mastocytosis encompasses a heterogenous group of rare diseases characterised by the increased proliferation, accumulation and activity of mast cells[14, 15]
- In systemic mastocytosis (SM), abnormal mast cells infiltrate various tissues and organ systems, such as the bone marrow, the spleen, the liver, lymph nodes, and/or the gastrointestinal tract[15]
- Advanced SM is the most severe form of the disease and comprises ASM, SM-AHN and MCL[14, 15]

Epidemiology

- The exact prevalence of advanced SM in England is unknown; however, a study from Denmark indicates the incidence of advanced SM to be 0.06/100,000,[16] and as such, it is estimated that approximately 40 new patients are diagnosed with advanced SM in the UK each year (with 34 patients in England).[1, 16] Given the rare nature of the disease, midostaurin has been granted orphan designation by the EMA for the advanced SM indication[10, 17]

Morbidity and mortality

- Mastocytosis is associated with a wide range of debilitating symptoms caused by extensive mast cell proliferation, tissue infiltration and release of inflammatory mediators.[15, 18, 19] Advanced SM is associated with increased organ infiltration, leading to organ dysfunction such as organomegaly, organopathy or organ failure.[13] Symptoms can include fatigue, itching, bone or muscle pain, osteoporosis, fractures, systemic symptoms related to histamine and leukotriene release and anaphylaxis, which can be severe[15, 18-20]
- The wide spectrum of varied and severe symptoms confer a substantial negative impact on patient HRQoL, as well as a considerable burden on carers[21, 22]
- Advanced SM has a significant impact on life expectancy with median survival times from diagnosis of <24 months[23] in the overall advanced SM population, 41 months[18] to 11 years[24] for patients with ASM, 24 months[18] to 4.4 years[16] for patients with SM-AHN and <2 months[18] to 9.2 months[25] for patients with MCL[18] These broad and varying estimates reflect the heterogenous nature of systemic mastocytosis and the different populations included the different studies.

Clinical pathway of care

- Due to the rare nature of the disease, management of advanced SM is highly specialised and limited to only 5 centres cross the UK, including 3 in England
- There is no established treatment pathway for advanced SM in the UK and treatment is highly individualised and based primarily on the patient's symptoms.
- No curative treatments are available for advanced SM and current clinical management consists of symptom control coupled with cytoreductive therapy to delay disease progression. Local UK-specific guidelines are expected to be published in 2021[26]
- Cytoreductive therapy options may include interferon alpha, cladribine, imatinib, nilotinib and dasatinib; however, none of these therapies are licensed for the treatment of advanced SM in Europe.[27] The evidence base for the comparators is often only available in a mixed population of patients with advanced and non-advanced disease but suggests that these therapies are associated with unfavourable treatment profiles including limited efficacy and poor tolerability[28-36]
- Midostaurin is the first and only medicine to hold a marketing authorisation in this indication in the EU and the only targeted therapy which has demonstrated significant disease-modifying activity in advanced SM[4, 8, 37] As such, midostaurin has the potential to fulfil the unmet need for effective therapies in this disease area.

B.1.3.1 Disease overview

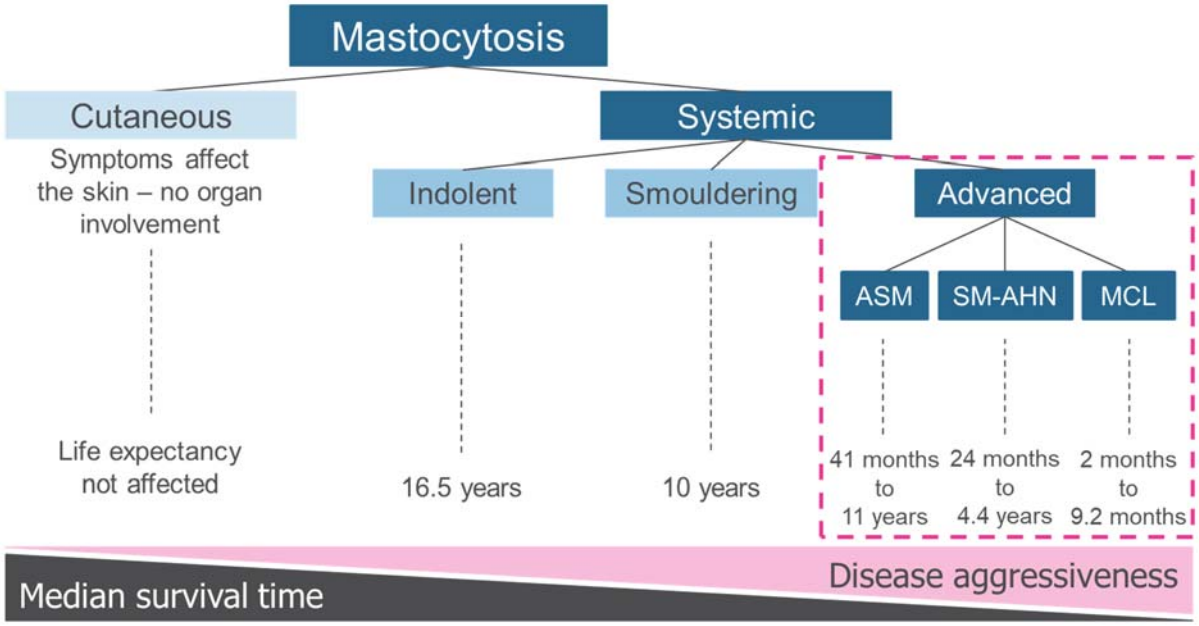
Mastocytosis encompasses a heterogenous group of rare diseases characterised by the increased proliferation, accumulation and activity of mast cells.[14, 15] Mast cells are a type of white blood cell, which mediate local immune response and inflammation by releasing mediator compounds such as histamines.[38, 39] In normal physiology, mast cells arise from haematopoietic stem cells in the bone marrow and migrate to colonise peripheral tissues of the respiratory and the gastrointestinal tracts, the nervous system and the skin.[38]

In mastocytosis, mast cells become neoplastic, which is characterised by uncoordinated clonal expansion and growth.[15] This aberrant increase in numbers causes abnormal mast cells to accumulate and form clusters or aggregates. When the mast cells are confined to the skin, patients are diagnosed with cutaneous mastocytosis. When the abnormal mast cells infiltrate various organ systems, such as the bone marrow, the spleen, the liver, and/or the gastrointestinal tract, patients are diagnosed with systemic mastocytosis (SM).[14, 15]

There are three types of SM: indolent, smouldering and advanced, with decreasing life expectancy (Figure 2).

- Indolent SM (ISM) is the least severe form of the disease, where neoplastic mast cells have infiltrated some organs without causing any dysfunction.[40]
- Smouldering SM (SSM), previously classified as a subtype of ISM,[15, 41] is associated with increased mast cell infiltration and burden, despite the absence of organ dysfunction.[29]
- Advanced SM, the subject of this appraisal is the most severe form of the disease, and is associated with a poor prognosis due to extensive and aggressive mast cell infiltration causing organopathy and bone marrow insufficiency.[40] Patients with advanced SM are classified into three distinct groups of systemic mastocytosis: ASM, SM-AHN and MCL.[14, 15]

Figure 2: Mastocytosis classification and survival



Abbreviations: ASM: aggressive systemic mastocytosis; MCL: mast cell leukaemia; SM-AHN: systemic mastocytosis with associated haematologic neoplasm.
Source: Arber *et al.* (2016),[42] Budnik *et al.* (2019),[25] Cohen *et al.* (2014),[16] Jawhar *et al.* (2019),[24] Lim *et al.* (2009a),[18] Pardanani (2016).[41]

Although the exact disease mechanism remains unknown, SM is typically associated with an activating gain-of-function point mutation in the *KIT* gene. This gene encodes the transmembrane receptor tyrosine kinase, KIT, which interacts with stem cell factor (SCF) in mast cells to regulate cell proliferation, differentiation, adhesion, histamine release and survival.[41, 43] Up to 96% of patients with advanced SM carry a *KIT* mutation in their mast cells identified in the bone marrow.[7] KIT mutations have also been detected in CD34+ haematopoietic progenitor cells, eosinophils, monocytes, neutrophils and lymphocytes, suggesting that it may first arise in haematopoietic stem cells.[7] The single most common mutation identified is a substitution of aspartic acid in position 816 to valine (*KIT* D816V), present in approximately 81% of advanced SM patients, although other somatic and germline mutations can also be present.[6]

Disease diagnosis and classification criteria

Due to the rare nature of SM and the fact that patients may exhibit non-specific symptoms, the diagnosis of systemic disease is especially challenging in the absence of skin involvement.[29] Significant clinical experience with advanced SM in the UK is largely limited to 5 key specialist centres (Guy's and St Thomas' London, Royal Liverpool Hospital, Beatson West of Scotland Cancer Centre Glasgow, Cardiff University Hospital and Oxford University Hospital), and despite improvements in diagnosis, UK clinical experts have highlighted that advanced SM remains under-recognised.[1]

Diagnostic criteria for SM were defined by the World Health Organisation (WHO) in 2001, and updates to the criteria were published in 2008 and 2016, but these updates do not impact the classification of patients with advanced SM subtypes. As of the 2016 update, mastocytosis is no longer considered a subgroup of myeloproliferative neoplasms (MPN), but is instead considered a distinct disease category.

Consistent with the WHO (2001) diagnostic criteria, the 2016 update recognises five subtypes of SM (ISM, SSM, SM-AHN, ASM, and MCL)(Table 3), which are diagnosed when 1 major and 1 minor criterion or ≥3 minor criteria are present (Table 4).[29]

- If the diagnostic criteria for SM are met as well as the criteria for an associated clonal haematological non-mast cell lineage disease, then SM-AHN is diagnosed.[29] AHN is a novel abbreviation and can be used instead of (or synonymously to) the previous term “associated hematologic non-mast cell-lineage disease (AHNMD).”[14] SM-AHN can be further categorised according to the type of AHN, including an associated myeloid neoplasm (such as SM-myeloid proliferative neoplasm [SM-MPN], SM-chronic myelomonocytic leukaemia [SM-CMML] and SM-myelodysplastic syndrome [SM-MDS]), lymphoma, myeloma, chronic lymphocytic leukaemia or primary amyloidosis.[29] Similarly, SM-AHN can also be further categorised according to the subtype of SM, including ISM-AHN, ASM-AHN and MCL-AHN.
- If there is no evidence of an associated haematological neoplasm but bone marrow smears show ≥20% mast cells, patients are diagnosed with MCL.[29]
- Additional diagnostic criteria are focused on “B” findings and “C” findings, which indicate organ dysfunction and/or bone marrow insufficiency (Table 4).[29] A diagnosis of ASM is made when ≥1 “C” finding(s) is present. If there are no “C” findings, patients are diagnosed with either SSM (if they have ≥2 “B” findings) or ISM. In the original WHO (2001) diagnostic criteria, SSM was classified as a subvariant of ISM.

Patients with advanced SM belong to the most aggressive classifications of systemic mastocytosis: ASM, SM-AHN and MCL (Figure 2).[14, 15] However, it is important to note that the population of

interest for this submission does not include patients with ISM-AHN, in line with the clinical trials for midostaurin in this indication (the midostaurin trials included patients with 'C' findings and thus advanced disease). Despite belonging to the SM-AHN classification according the WHO (2016) diagnostic criteria, these patients are not considered to have "advanced" disease, due to the indolent nature of the SM component of the disease.

It should also be noted that the treatment implications of the presence and number of "B" or "C" findings may not be consistent across the literature. Some studies consider "B" findings to mean "Borderline Benign" and "C" findings to mean "require Cytoreduction therapy" or "consider cytoreduction", whereas others may not link these diagnostic criteria to treatment decisions.[44, 45]

Table 3: WHO (2016) classifications of systemic mastocytosis

Classification of mastocytosis	Criteria
Indolent systemic mastocytosis (ISM)	• Meets criteria for SM[a] • No "C" findings[a] • No evidence of associated haematological neoplasm • Isolated bone marrow mastocytosis[b] • As above (ISM), but with bone marrow involvement and no skin involvement, generally low-burden of mas cells
Smouldering systemic mastocytosis (SSM)	• As above (ISM), but with 2 or more "B" findings, and no "C" findings,[a] generally high-burden of MC
Systemic mastocytosis with an associated haematological neoplasm (SM-AHN)	• Meets criteria for SM and criteria for AHN as a distinct entity per the WHO classification
Aggressive systemic mastocytosis (ASM)	• Meets criteria for SM • One or more "C" findings[a] • No evidence of MCL
Mast cell leukaemia (MCL)	• Meets criteria for SM • Bone marrow biopsy shows diffuse infiltration, usually dense, by atypical, immature mast cells • Bone marrow aspirate smears show ≥20% mast cells • In classic cases, mast cells account for ≥10% of peripheral blood white cells. Aleukemic MCL variant (<10% circulating mast cells)

Blue shading indicates the classifications that are collectively described as advanced SM and are of relevance for this submission. [a] See Table 4 for diagnostic criteria for systemic mastocytosis and definitions of "B" and "C" findings. [b] Provisional categories.
Abbreviations: ASM: aggressive systemic mastocytosis; ISM: indolent systemic mastocytosis; MCL: mast cell leukaemia; SM: systemic mastocytosis; SM-AHN: systemic mastocytosis with associated haematological neoplasm; WHO: World Health Organization.
Source: Adapted from Pardanani *et al.* (2019).[29]

Table 4: WHO (2016) diagnostic criteria for systemic mastocytosis

Major criterion	Minor criteria
Multifocal, dense infiltrates of mast cells (≥15 mast cells in aggregates) in sections of bone marrow and/or other extracutaneous organs	In biopsy >25% of mast cells are spindle-/atypically shaped in bone marrow or other extracutaneous organs or >25% of mast cells in bone marrow aspirate are immature or atypical
	KIT point mutation at codon 816 in bone marrow, blood, or other extracutaneous organs
	Mast cells express CD25 with/without CD2 in bone marrow, blood, or other extracutaneous organs

	Serum tryptase level persistently >20 ng/mL[a]
"B" findings:	
• High mast cell burden shown on bone marrow biopsy: >30% infiltration of cellularity by mast cells (focal, dense aggregates) and serum total tryptase level >200 ng/mL	
• Signs of dysplasia or myeloproliferation, in non-mast cell lineage(s), but insufficient criteria for definitive diagnosis of an AHN, with normal or only slightly abnormal blood counts	
• Hepatomegaly without impairment of liver function, palpable splenomegaly without hypersplenism, and/or lymphadenopathy on palpation or imaging	
"C" findings:	
• Cytopaenia(s): ANC <1,000/µL or Hb <10 g/dL or PLT <100,000/µL	
• Palpable hepatomegaly with impairment of liver function, ascites and/or portal hypertension	
• Palpable splenomegaly with associated hypersplenism	
• Malabsorption with hypoalbuminemia and weight loss	
• Skeletal lesions: large-sized osteolyses with/without pathologic fractures	

[a]Not valid as a SM criterion in SM-AHN.
Abbreviations: AHN: associated haematological neoplasm; ANC: absolute neutrophil count; CD: cluster of differentiation; dL: decilitre; Hb: haemoglobin; MC: mast cell; PLT: platelet count; SM: systemic mastocytosis; WHO: World Health Organisation.
Source: Pardanani (2019).[29]

Epidemiology

Given the rare disease status of advanced SM, the exact incidence is unknown.[46] The disease is most common in adult Caucasians over the age of 60 and there is no gender predominance.[17]

A retrospective cohort analysis of 547 patients diagnosed with SM between 1997 and 2010 in Denmark estimates the incidence of advanced SM to be 0.06/100,000 and the prevalence to be 0.4 per 100,00016 (Table 5). In recognition of this rare condition, midostaurin has been granted orphan designation by the EMA for this indication.[10, 17]

Based on the above European data and the latest UK population estimates, it is estimated that approximately 40 new patients are diagnosed with advanced SM in the UK each year, of which 34 patients are estimated to be diagnosed annually with advanced SM in England (Table 5). This estimate is consistent with those provided by UK clinical experts who estimated that approximately 40–50 new patients are diagnosed with advanced SM each year in the UK.[1]

Table 5: Estimated prevalence of advanced SM subtypes in Europe

Disease subtype	Incidence estimates per 100,000	Prevalence estimates per 100,000	Source
SM-AHN	0.04 (0.03 – 0.06)	0.31 (0.18–0.50)	Cohen et al. (2014)[16]
ASM	0.01 (0.006 – 0.03)	0.09 (0.03–0.21)	Cohen et al. (2014)[16]
MCL	0.01 (0.003 – 0.02)	0.00	Cohen et al. (2014)[16]

Abbreviations: Advanced SM: advanced systemic mastocytosis; ASM: aggressive systemic mastocytosis; MCL: mast cell leukaemia; SM-AHN: systemic mastocytosis with associated haematologic neoplasm.

Table 6: Assumptions and calculation of the patient population with advanced SM eligible for treatment with midostaurin

Assumption		Value	Reference
Incidence			
1	Incidence of ASM	0.01/100,000	Epidemiology of SM in Denmark[16]
	Incidence of SM-AHN	0.04/100,000	
	Incidence MCL	0.01/100,000	
	Incidence of advanced SM	**0.06/100,000**	
2	England population (2018)	55,977,000	ONS[47]
3	**England incidence advanced SM (2018)**	**34**	**Calculation (assumption 1 x assumption 2)**
Prevalence			
4	Prevalence of ASM	0.09/100,000	Epidemiology of advanced SM in Denmark[16]
	Prevalence of SM-AHN	0.31/100,000	
	Prevalence MCL	0.00/100,000	
	Prevalence of advanced SM	**0.4/100,000**	
5	**England Prevalence advanced SM (2018)**	**224**	**Calculation (assumption 2 x assumption 4)**
Total Advanced SM population, eligible for treatment			
6	**Advanced SM in England**	**258**	**Calculation (assumption 3 + assumption 5)**
7	Proportion of patients eligible for cytoreductive therapy (e.g. midostaurin)	67%	Clinical opinion (Proportion of patients *ineligible* for cytoreductive therapy = 33%)[1]
8	**Patients in England eligible for midostaurin**	**174**	**Calculation (assumption 7 x assumption 8)**

Abbreviations: Advanced SM: advanced systemic mastocytosis; ASM: aggressive systemic mastocytosis; MCL: mast cell leukaemia; ONS: Office for National Statistics; SM-AHN: systemic mastocytosis with associated haematologic neoplasm.

Disease burden

Mastocytosis is also associated with a wide range of debilitating symptoms caused by mast cell infiltration and activity, which can be severe and are grouped into 4 categories: constitutional, cutaneous, musculoskeletal and mediator-related systemic symptoms.[15, 18-20] Constitutional symptoms include fatigue, weight loss, diaphoresis and chills. Cutaneous symptoms relate to mast cell invasion and activity in the skin, causing urticaria, severe itching and lesions. Musculoskeletal symptoms include joint, bone or muscle pain, as well as osteoporosis and fractures due to the invasion and osteolytic activity of mast cells from the bone marrow. Upon exposure to potential triggers of mast cell activation, patients can also experience systemic symptoms, related to the release of inflammatory mediators, such as histamines and leukotrienes. These symptoms can vary from abdominal pain, nausea, vomiting, headache, hypotension and tachycardia to systemic acute reactions such as anaphylaxis, which can be life-threatening.[15, 18, 19]

In addition, patients with advanced SM may also present with organ dysfunction such as organomegaly, organopathy or even organ failure, due to mast cell accumulation.[18] The most commonly affected organs include the bone marrow, the liver, the bones, the spleen and the

gastrointestinal tract. In the bone marrow, organopathy is usually associated with marked cytopaenia, whereas liver organopathy presents as hepatomegaly, ascites and/or increased liver enzymes.[45]

This wide spectrum of varied and severe symptoms is highly distressing for individual patients, with over half of advanced SM patients reporting extended impact of the disease resulting in depression (54%), anxiety (62%), difficulty sleeping (69%) and difficulty concentrating (85%).[21] Over 90% of patients also reported the disease to interfere substantially with family life and social interactions, as well as work, daily activities and leisure time.[21]

Collectively these symptoms can confer a substantial reduction in the HRQoL of patients, which further exacerbates the significant disease burden associated with reduced life expectancy.[22] There may also be a considerable burden on carers, as SM patients become progressively more dependent on their assistance and support. This caregiver burden is not captured within the economic analysis for this submission.

Mortality

The available epidemiological data indicate that the most common disease subtype within the overall population of advanced SM is the SM-AHN subtype, with the ASM and MCL subtypes being less common (Table 5). Median survival from diagnosis differs substantially between the different subtypes of advanced SM and is estimated to be between 41 months[18] to 11 years[24] for ASM, 24 months[18] to 4.4 years[16] for SM-AHN, and 2 months[18] to 9.2 months[25] for MCL patients, demonstrating the heterogeneous nature of the disease, and the need for further clinically effective therapies to prolong survival.

The median survival estimates of 24 months to 4.4 years reported in the literature for patients with SM-AHN includes patients that were classified with advanced disease according to the pivotal trials for midostaurin (measurable C-findings, i.e. ASM-AHN) as well as those with indolent disease (i.e ISM-AHN). Consequently, given the heterogeneous patient population included in these studies, it is unclear how many patients classed as SM-AHN “truly” have advanced disease (ASM-AHN) versus indolent disease (ISM-AHN), thus the “true” survival for patients defined as SM-AHN (ASM-AHN) as per the pivotal D2201 and A2213 trials is unknown. Consequently, the survival estimates from the literature for SM-AHN provide a very optimistic upper bound estimate of survival given the better prognosis of patients with ISM, and survival in patients with SM-AHN is likely to be lower than that reported in the literature. Survival data from a pooled analysis comparing patients treated with midostaurin in D2201 and A2213 with a contemporary German registry of patients with advanced SM (similar to that of the midostaurin trials i.e. patients with ASM or MCL ± AHN), showed median survival from diagnosis to be 19.5 months (95% CI: 13.0–35.3) in patients who had not received midostaurin in the registry. This data shows that the median survival for the overall advanced SM population (patients with ASM or MCL ± AHN) is less than 24 months and that the median survival for patients with ASM-AHN or MCL (who have the shortest life expectancy) is likely to be lower than 24 months. Midostaurin is therefore likely to meet the NICE criteria for an end of life medicine.

B.1.3.2 Clinical pathway of care

There is no established treatment pathway for advanced SM in the UK and there are currently no UK-specific clinical guidelines. Treatment approach is highly individualised and options are considered separately for each patient.[48, 49] The only available clinical guidelines in this disease area are those of the National Comprehensive Cancer Network (NCCN) in the US, which were

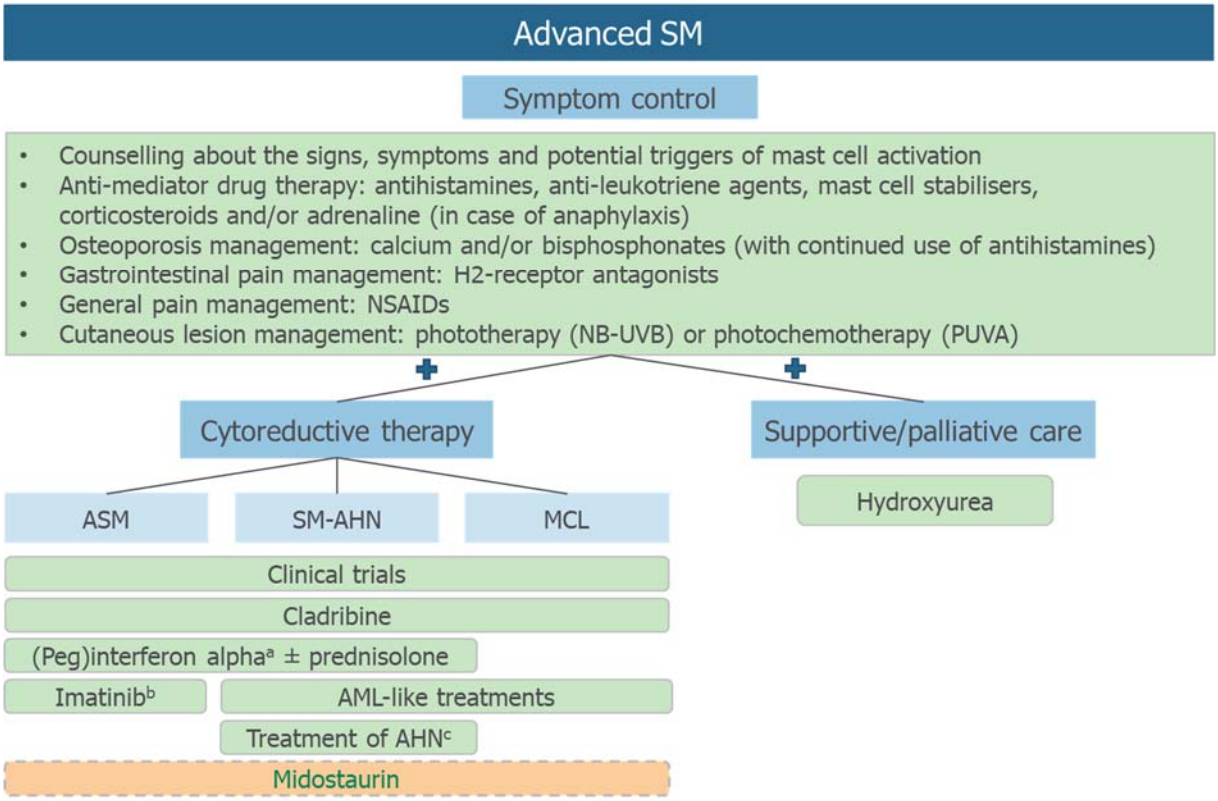
published in 2019.[48] These guidelines were the first international treatment guidelines to be published for SM. The first local UK guidelines are not expected until 2021.[26]

The only curative therapy for advanced SM is allogeneic haematopoietic stem cell transplant (allo-HSCT). However, this is only suitable for a very small proportion of patients who are sufficiently fit for transplant and for whom a suitable donor can be found. In addition, treatment failure after an initial response has been observed in 17.5% of patients with advanced SM, with rates as high as 33.3% observed in MCL patients specifically.[29, 50] Feedback from UK clinical experts suggests that very few patients with advanced SM would be eligible for allo-HSCT and, should midostaurin be available to the NHS, midostaurin would not displace allo-HSCT, but be used alongside it as a debulking agent and/or bridge to transplant.[51] As such, allo-HSCT is very rarely used in UK clinical practice and, in accordance with the NICE final scope, it has not been considered as a comparator in this appraisal.

Further feedback from UK clinical experts suggests that approximately one third of patients are too frail or at too high a risk of cytopaenia to receive currently available cytoreductive therapies and thus receive only supportive/palliative care.[1] Consequently, the goal of clinical management for the vast majority of patients with advanced SM is symptom control and delay of disease progression with cytoreductive therapy aimed at modifying the underlying pathology of the disease. No cytoreductive therapies have been recommended by NICE for the treatment of advanced SM and, with the exception of midostaurin, no therapies hold a marketing authorisation for this indication in the UK.[27]

The US NCCN guidelines recommend that treatments for symptom control are administered concurrently with cytoreductive therapy.[48] In the case of SM-AHN, the associated haematological neoplasm is treated separately and may be prioritised over treatment for the SM component of the disease, dependent on the individual presentation and which disease requires treatment. This approach is consistent with current treatment practice in the UK, as confirmed by UK clinical experts.[51] Although the NCCN guidelines present cytoreductive therapy options for each disease subtype (ASM, SM-AHN and MCL), UK clinical experts have indicated that disease management is largely patient-specific. A summary of the anticipated UK clinical pathway of care for patients with advanced SM is presented in Figure 3, which has been adapted from the NCCN guidelines based on feedback from UK clinical experts.

Figure 3: Anticipated pathway of care for patients with advanced SM in the UK



[a]Pegylated or un-pegylated interferon alpha with or without prednisolone.
[b]Only if KIT D816V mutation negative or if eosinophilia is present with FIP1L1-PDGFRA fusion gene.
[c]In patients with SM-AHN, only if SM component treatment takes precedence over AHN component treatment.
Whist nilotinib and dasatinib are included in the NICE final scope, these treatments have limited use in UK clinical practice, so have not been considered here. Allo-HSCT is very rarely used in UK clinical practice and, in accordance with the NICE final scope, it has also not been considered here.
Abbreviations: Advanced SM: advanced systemic mastocytosis; AML: acute myeloid leukaemia; ASM: aggressive systemic mastocytosis; HSCT: haematopoietic stem cell transplant; MCL: mast cell leukaemia; NB-UVB: narrowband ultraviolet B; NSAIDs: non-steroidal anti-inflammatory drugs; PUVA: psoralen plus ultraviolet A; SM-AHN: systemic mastocytosis with associated haematologic neoplasm; UK: United Kingdom.
Source: NHS (2019),[27] Sadasivam *et al.* (2010),[52] Novartis Advance SM Advisory Board (29th January 2020).[1]

Symptom control

As described in Section B.1.3.1, patients can experience a range of debilitating symptoms caused by mast cell infiltration and activity, therefore, treatments for symptom control are taken concomitantly with cytoreductive therapy (Figure 3). Some patients experience systemic symptoms, including anaphylaxis, due to increased mast cell activity and the release of inflammatory mediators such as histamines and leukotrienes. In order to control or prevent these symptoms, anti-mediator drug therapy including antihistamines, anti-leukotriene agents (e.g. montelukast), mast cell stabilisers (e.g. sodium cromoglicate) and oral or topical corticosteroids are often used.[27, 52] In cases of anaphylaxis, adrenaline autoinjectors may also be used, and for patients who develop osteoporosis, calcium and bisphosphonates can be administered to stimulate an increase in bone density.[27, 52] For SM patients who experience stomach ulcers and pain, H2-receptor antagonists can be used to counteract the effects of histamine on the stomach,[27] with non-steroidal anti-inflammatory drugs (NSAIDs) used for general pain management.[53] Phototherapy with narrowband ultraviolet B light (NB-UVB) or photochemotherapy with psoralen plus ultraviolet A light (PUVA) may be used to prevent the release of histamine by mast cells in the skin and alleviate the associated cutaneous lesions, [27] however specific treatment combinations

are dependent on individual patient symptoms with symptom control continuously reassessed to address the progressive nature of advanced SM.[27, 52]

Cytoreductive therapy

Cytoreductive therapy is used to reduce the high underlying mast cell burden and ameliorate disease-related organ dysfunction in advanced SM.[29] There is no clear standard therapy and treatments are considered on an individual basis.[48, 49] Upon treatment failure (lack of response or disease progression), disease stage is reassessed and patients may receive alternate cytoreductive therapy.

As indicated in the NICE final scope, current treatment options for advanced SM may include interferon alpha, cladribine, imatinib, nilotinib and dasatinib (Figure 3).[3] However, since midostaurin is the only cytoreductive therapy licensed for use in advanced SM in Europe, the use of other cytoreductive therapies in this indication is off-label. Moreover, these therapies have been shown to be associated with limited efficacy and considerably poor tolerability, with many patients exhibiting short-lived responses due to the development of resistance.[14, 28-36]

- Despite clinical evidence for cladribine showing it to be associated with significant toxicity (up to 82% of patients experiencing Grade 3/4 adverse events), and many patients developing resistance,[14, 30] cladribine is the most commonly used therapy for patients with advanced SM in UK clinical practice (54%), particularly if rapid mast cell debulking is required.[1]
- Pegylated or un-pegylated interferon alpha may be used for some patients (26%), but generally only partial and minor responses have been observed, with a time to best response of up to a year or longer. It has similarly shown poor tolerability, with up to 75% of patients suffering from toxicities which result in a high dropout rate from treatment.[14, 28, 29] UK clinical experts noted that interferon alpha (Roferon-A and IntronA) has been discontinued, and thus peg-interferon alpha is more commonly used in clinical practice (24% versus 2% receiving interferon alpha).[1]
- The tyrosine kinase inhibitors (TKIs) imatinib, nilotinib and dasatinib are possible treatment options but are not commonly used in UK clinical practice due to very limited clinical evidence:
    - Imatinib is licensed by the FDA for the treatment of only one disease subpopulation – ASM,[31] with its use further restricted to patients who *do not* have the *KIT* D816V mutation. Up to 96% of advanced SM patients have a *KIT* D816 mutation and the D816V mutation is present in approximately 81% of patients.[6, 7] Moreover, imatinib has shown extremely limited clinical activity in *KIT* D816V positive patients.[32-34] UK clinical experts consulted at an advisory board meeting suggested that the use of imatinib may be limited to 5% of patients in clinical practice.[1]
    - Both nilotinib and dasatinib are not included in the NCCN guidelines as treatments for advanced SM. The *KIT* D816V mutation confers partial resistance against nilotinib, and dasatinib has a short half-life *in vivo*;[14] as such, nilotinib and dasatinib have shown limited clinical efficacy, with pivotal phase II trials demonstrating ORRs or 21.6% and 33%, respectively.[35, 36] The lack of clear clinical evidence for these treatments was also highlighted by UK clinical experts, and suggested that their use in clinical practice is negligible.[1]

UK clinical experts also highlighted that some patients may receive “AML-like” treatments (16%) for advanced SM, including intensive chemotherapies for patients fit for high-dose chemotherapy (e.g. DA [cytarabine plus daunorubicin] induction followed by high-dose cytarabine consolidation [HiDAC], or FLAG-IDA [fludarabine, high-dose cytarabine with granulocyte-colony stimulating factor] for adverse risk) and for patients deemed unfit for high--dose chemotherapy (e.g. low-dose

cytarabine, or hypomethylating agents [azacitidine]).[1] However, there is limited evidence of the efficacy and safety of "AML-like" treatments in advanced SM beyond case reports on the treatment of the AHN component in patients with SM-AHN[54, 55] and molecular studies, which have explored the effect of "AML-like" treatments on neoplastic mast cells with view to co-treatment with midostaurin.[56, 57]

Finally, midostaurin, a multi-kinase inhibitor, is already recommended for the treatment of ASM, SM-AHN and MCL in the NCCN guidelines, and has already been used in some patients in UK clinical practice via a company compassionate use programme.[48]

Supportive/palliative care

Supportive/palliative care is a treatment option reserved for those patients that are considered too frail or are at too high a risk of cytopaenia to receive cytoreductive therapies.[1] This category may include therapies such as hydroxyurea to reduce mast cell burden alongside standard palliative treatments.

Since patients receiving supportive/palliative care would not receive midostaurin or other active treatments in clinical practice, supportive/palliative care has not been considered a comparator in this submission.[1]

Positioning of midostaurin in the treatment pathway for advanced SM in the UK

As described previously in Section B.1.3.1, patients with advanced SM have a poor prognosis with short life expectancy. There is no generally accepted standard therapy for advanced SM patients[27] and the response rates associated with current treatment options such as (peg)interferon alpha and cladribine may be variable and short-lived with patients developing resistance.[14, 58-60] Consequently, there is a need for well-tolerated and effective therapy to reduce disease burden and improve survival rates and HRQoL. Midostaurin is the first and only medicine to hold a marketing authorisation in this indication in the UK[37] and it is the only targeted therapy available for the treatment of advanced SM, having demonstrated significant disease-modifying activity by a substantial decrease in the bone marrow mast cell burden, serum tryptase level and *KIT* D816V allele burden.[8]

In this submission, midostaurin is positioned for the treatment of adult patients with advanced SM (ASM, SM-AHN or MCL), in line with the population stated within the marketing authorisation, the pivotal phase II trial D2201[12] and the supportive phase II trial A2213.[61] Based on feedback from UK clinical experts, the vast majority of patients receive cladribine, (peg)interferon alpha with or without prednisolone or "AML-like" treatments in the UK, whilst a small proportion of patients receive imatinib. These therapies therefore constitute the comparators to midostaurin in the context of this submission and have been included within the treatment mix for the comparator of current clinical management within the base case economic analysis. Clinical expert feedback indicates that nilotinib and dasatinib are very rarely used, however, these therapies have also been included as optional comparators within the economic model (Section B.3.2.3), in line with the NICE final scope.

B.1.4 *Equality considerations*

In relation to NICE's equality scheme, no equality issues related to the use of midostaurin are foreseen. However, it is important to note that the ultra-rare nature of advanced SM and the assessment of this indication via the single technology appraisal (STA) route rather than the highly

specialised technology (HST) route could ultimately disadvantage patients with this disease given that:

- The availability and quality of evidence for this appraisal (due to the rarity of the disease) is not what is typically considered the gold standard in terms of evidence generation and is, therefore, associated with a higher degree of uncertainty than that of more common conditions where more robust evidence including randomised controlled trials (RCTs) may be available. The study design of the pivotal trial underpinning the evidence base and marketing authorisation for midostaurin was considered acceptable by various regulatory bodies, [9, 79] given the rare nature of the disease and lack of effective treatment options. This is important when considering that the evidence base for the comparator therapies (none of which are licensed in Europe for this indication) predominantly consists of a small number of observational studies and is much less robust. The pivotal trial represents the largest ever study of advanced SM patients.
- Midostaurin for advanced SM was not deemed eligible for assessment via the HST process, a process specifically designed for the evaluation of technologies for ultra-rare diseases. It is therefore important to note that the attitudes, methods and decision-making criteria differ between the HST and STA processes, with the HST process taking into consideration broader decision-making criteria in comparison to the conventional STA process and allowing for an inherently higher level of clinical uncertainty. Furthermore, the cost-effectiveness thresholds for the two evaluation processes are substantially different. As such, it is possible that a decision based on the HST process may be different to that resulting from the STA process, potentially disadvantaging patients with rare diseases that are assessed via the STA process.

B.2 Clinical effectiveness

Study identification

- A systematic literature review (SLR) identified two clinical trials of midostaurin in patients with advanced SM (D2201[12, 62] and A2213[61, 63]) and two historical control studies comparing patients receiving midostaurin in a clinical trial or compassionate use programme with historical control data from European registries (Reiter *et al.* [2017][23] and CEREMAST[64, 65])
  - D2201 is an international, multicentre, single-arm, open-label phase II study that included 116 patients with advanced SM and represents the pivotal clinical trial for midostaurin in this indication.[12] A2213 is a multicentre, single-arm, open-label investigator initiated phase II study that included 26 patients with advanced SM[61]
  - Reiter *et al.* (2017)[23] reports on a pooled analysis of D2201 and A2213 compared with historical control data from a German registry and CEREMAST[64, 65] provides a comparison of patients receiving midostaurin as part of a French compassionate use programme with historical control data from a French registry
  - In addition, four more records reporting on the use of midostaurin met the inclusion criteria for the SLR.[66-69] Two of these studies provided secondary reports of data from D2201 in case series (Jawhar *et al.* [2017a])[66] or pooled analyses (Jawhar *et al.* [2017b][67]). The remaining two studies provided individual patient data only (Jain *et al.* [2017][68] and Carvalhosa *et al.* [2015][69]). Since these four studies only provide secondary reports of case studies or do not report summary data, these data were not included in this submission and do not inform the economic model
- The SLR identified 8 studies that report summary efficacy data for comparator therapies (Barete *et al.* [2015],[30] Hauswirth *et al.* [2004],[60] Hochaus *et al.* [2015],[35] Jawhar *et al.* [2017a],[66] Lim *et al.* [2009],[18, 70] Pagano *et al.* [2008],[71] Pardanani *et al.* [2009][72] and Verstovsek *et al.* [2008][36]). All studies were single-arm trials or observational studies
- No direct evidence of midostaurin compared with the comparators of interest was identified. The two historical control studies (Reiter *et al.* [2017][23] and CEREMAST[64, 65]) are the only available evidence of the comparative efficacy of midostaurin versus standard of care (SoC)

Efficacy

- At the time of the data cut-off of 9th July 2013 for the D2201 study:[12]
  - The overall response rate was, 60% (95% confidence interval [CI]: 49–70), with 45% and 15% of patients achieving major and partial responses, respectively
  - Median OS was 28.7 months (95% CI: 18.1–not estimated)
  - Median PFS was 14.1 months (95% CI: 10.2–24.8)
- At the time of the final analysis for OS (data cut-off: 24th August 2017) for the D2201 study,[73] median OS was [redacted]
- At the time of the data cut-off of 1st March 2017 for the A2213 study:[61]
  - The best overall response rate was 69% (95% CI: 50–88), with 50% of patients achieving a major response and 19% having a partial response
  - Median OS was 40.0 months (95% CI: 27.3–52.7)
  - Median PFS was 41.0 months (95% CI: 4.4–77.6)
- Response rates were similar regardless of the subtype of advanced SM across both D2201 and A2213

B.2.1 *Identification and selection of relevant studies*

A clinical SLR was conducted to identify relevant clinical evidence (in the form of randomised controlled trials [RCTs], interventional non-RCTs and observational studies) for the efficacy and safety of midostaurin and the relevant comparators for the treatment of advanced SM. The SLR was performed and reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and the methodological principles of conduct for systematic reviews from the University of York Centre for Reviews and Dissemination's "Guidance for Undertaking Reviews in Health Care".[74, 75]

The searches were conducted on 30th October 2019 and a total of 798 unique records were suitable for review; of these, 29 records fulfilled the eligibility criteria for inclusion in the SLR. Supplementary searches of conferences, SLR bibliographies and clinical trials registries yielded 273 records; of these, five records fulfilling the eligibility criteria were identified. Full details of the SLR search strategy, study selection process and results can be found in Appendix D.

A total of 29 unique studies were included in the SLR, reported in 34 records (30 full-text publications, 2 clinical trial records and 2 abstracts). Of these 29 unique studies:

- 6 studies (10 records) reported evidence for midostaurin,
- 22 studies (23 records) reported evidence for comparator therapies, and
- 1 study (1 record) reported evidence for both midostaurin and the comparator therapies.

B.2.2 *List of relevant clinical effectiveness evidence*

Details of the clinical effectiveness evidence identified for midostaurin are presented in Section B.2.2.1 and details of the clinical effectiveness evidence identified for the comparators are presented in Section B.2.2.2.

B.2.2.1 Clinical effectiveness evidence for midostaurin

As described previously, 6 studies (10 records) included in the SLR reported evidence for midostaurin, and 1 study (1 record) reported evidence for both midostaurin and the comparator therapies.

An overview of these 7 studies (11 records) is presented in Table 6, and, whilst there are 8 studies in Table 7, it is important to note that Reiter *et al.* (2017)[23] (a pooled analysis of D2201 and A2213 versus historical control data from a German registry) is not considered a "unique study", but was still included in the SLR since it included data from D2201 and A2213 studies.

The clinical evidence identified for midostaurin comprises clinical trial evidence, historical comparison evidence and further evidence as described below.

Clinical trial evidence

Two non-randomised trials: D2201 and A2213[12, 61, 62, 63]

- D2201: an international, multicentre, single-arm, open-label, phase II study of 116 patients with advanced SM (the pivotal clinical trial for midostaurin in this indication)
- A2213: a supportive investigator-initiated multicentre, single-arm, open-label phase II study of 26 patients with advanced SM

Historical comparison evidence

Two historical control comparisons that compared midostaurin with historical data from European registries.

- Reiter *et al.* (2017)[23]: a pooled analysis of D2201 and A2213 versus historical control data from a German registry. As described previously, this study was included within the SLR but not considered a "unique study" since it included data from D2201 and A2213
- CEREMAST[64, 65]: a comparison of a prospective observational survey of 28 patients with mastocytosis treated with midostaurin in France, compared with 44 historical controls

Full details of these historical control studies are reported in Section B.2.9.1 since these studies are the only available evidence of the comparative efficacy of midostaurin with SoC in the absence of any head-to-head RCTs. It should also be noted that the data from these studies were used to inform the economic analysis.

Further identified evidence

Four additional studies reporting data for patients treated with midostaurin either provided secondary reports of data from D2201 in case series or pooled analyses (Jawhar *et al.* [2017a][66] and Jawhar *et al.* [2017b][67]) or did not present summary data (Jain *et al.* [2017][68] and Carvalhosa *et al.* [2015][69]).

Given the availability of evidence from the larger D2201 and A2213 trials and the fact that the same data used to inform the Jawhar *et al.* (2017a[66] and 2017b[67]) studies, these were not used to inform the efficacy of midostaurin in the economic model. Note that, since Jawhar *et al.* (2017a)[66] also presented data for patients treated with cladribine, one of the relevant comparators for this submission, a summary of this study has been provided in Section B.2.9.2. Since Jain *et al.* (2017)[68] and Carvalhosa *et al.* (2015)[69] only reported individual patient data, and therefore do not provide meaningful estimates of efficacy, these two studies have not been discussed any further in this submission and were not used to inform the economic model. These studies have been summarised by citation in Table D.4.1.3 of Appendix D.

Table 6: Evidence identified in the SLR for patients treated with midostaurin

Study name	Study design	Record	Included in the SLR	Data presented in submission	
Clinical trials					
D2201	Clinical trial	Gotlib *et al.* (2016)[12]	Yes	Yes	Section B.2
		ClinicalTrials.gov (2018)[62]	Yes	Yes	
A2213	Clinical trial	DeAngelo *et al.* (2018)[61]	Yes	Yes	Section B.2
		ClinicalTrials.gov (2018)[63]	Yes	Yes	
Historical control comparisons					
D2201 and A2213[a]	Pooled analysis and historical control comparison	Reiter *et al.* (2017)[23]	Yes	Yes	Section B.2.9.1

CEREMAST	Prospective survey and historical control comparison	Chandesris *et al.* (2016)[64]	Yes	Yes	Section B.2.9.1
		Chandesris *et al.* (2017)[65]	Yes	Yes	
Additional records					
Jawhar *et al.* (2017a)[66]	Case series including patients from D2201 and CUP	Jawhar *et al.* (2017a)[66]	Yes	No	N/A
Jawhar *et al.* (2017b)[67]	Pooled analysis of D2201 and CUP	Jawhar *et al.* (2017b)[67]	Yes	No	N/A
Jain *et al.* (2017)[68]	Retrospective analysis	Jain *et al.* (2017)[68]	Yes	No (IPD)	N/A
Carvalhosa *et al.* (2015)[69]	Retrospective analysis	Carvalhosa *et al.* (2015)[69]	Yes	No (IPD)	N/A

[a]Note the Reiter *et al.* (2017) publication is included in the SLR, but as a pooled analysis of two existing trials, for the purposes of the SLR and the PRISMA diagram it was not considered a "unique" study.
Abbreviations: CUP: compassionate use programme; IPD: individual patient data; N/A: not applicable.

In conclusion, four key studies provide relevant evidence for midostaurin in advanced SM and have therefore been summarised further in Table 7 below. Whilst the supportive A2213 study has been included in the SLR, data from this study has only been used to inform the economic analysis in the context of the pooled D2201/A2213 historical control analyses.

Table 7: Clinical effectiveness evidence for midostaurin

Study	Clinical trial evidence		Historical comparison evidence	
	D2201 (NCT00782067)[12]	A2213 (NCT00233454)[61]	Reiter *et al.* (2017)[23]	CEREMAST[64, 65]
Study design	An international, multicentre, single-group, open-label, phase II study (N=116)	An investigator-initiated multicentre, open-label, phase II study (N=26)	A pooled analysis of patients included in D2201 (n=63) and A2213 (n=26) compared with historical control data (n=42)	A prospective observational survey of patients with mastocytosis treated with midostaurin under a transitory use authorisation programme (n=28) compared with historical control data (n=44)
Population	Adults over the age of 18 with ASM, SM-AHN or MCL according to WHO criteria		Adults over the age of 18 with ASM, SM-AHN or MCL according to WHO criteria	Patients with mastocytosis, including SSM, advanced SM (ASM, SM-AHN, MCL) and mast cell sarcoma (N=28)
Intervention	Midostaurin 100 mg twice daily in continuous cycles of 28 days	Midostaurin 100 mg twice daily in continuous cycles of 28 days for up to 12 cycles	Midostaurin 100 mg twice daily in continuous cycles of 28 days	Midostaurin 100 mg twice daily, cycle length unclear
Comparator	N/A – single-arm study design		42 patients from a German patient registry contemporary with both trials	Patients matched for the age at diagnosis and subtype of mastocytosis who did not receive midostaurin (N=44)
Indicate if trial supports application for marketing authorisation	Yes		No	No
Indicate if trial used in the economic model	Yes	No	Yes	Yes
Rationale for use/non-use in the model	• Pivotal registration trial for midostaurin in the advanced SM indication • Largest prospective trial to date in patients with advanced SM	• Investigator-initiated study and therefore individual patient level data not available • Treatment and study not reflective of UK clinical	• Data used to inform survival for the comparator arm in the model as part of base case analyses	• Data used to inform survival of comparator arm in the model as part of scenario analyses

	• Individual patient level data available • Treatment and study reflective of the SmPC and UK clinical practice in that patients continued treatment until no clinical benefit was observed or until unacceptable toxicity occurred	practice in that per study protocol, treatment was discontinued for non-responders		
Reported endpoints specified in the decision problem[a]	• **OS** • **PFS** • **ORR** • Adverse effects of treatment • HRQoL	• OS • PFS • ORR • Adverse effects of treatment	• **OS**	• **OS** • ORR • Adverse effects of treatment
All other reported endpoints[a]	• DoR • TTR • Patient-reported symptoms (by the Memorial Symptom Assessment Scale)	• DoR • TTR • PK	• No other endpoints	• DoR

[a]Reported endpoints from each study included in the model are presented in bold.
Abbreviations: ASM: aggressive systemic mastocytosis; CUP: compassionate use programme; DoR: duration of response; HRQoL: health-related quality of life; MCL: mast cell leukaemia; NHS: National Health Service; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; PK: pharmacokinetics; SM: systemic mastocytosis; SM-AHN: systemic mastocytosis with associated haematologic neoplasm; SSM: smouldering systemic mastocytosis; TTR: time to response; WHO: World Health Organisation.
Source: Chandesris *et al.* (2016),[64] Chandesris *et al.* (2017),[65] DeAngelo *et al.* (2018),[61] Gotlib *et al.* (2016),[12] Reiter *et al.* (2017).[23]

B.2.2.2 Clinical effectiveness evidence for comparator therapies

As described previously, 22 unique studies (23 records) reporting evidence for comparator therapies and 1 additional study (1 record) reporting evidence for both midostaurin and the comparators were identified in the SLR. Of these 22 unique studies:

- 15 unique studies (15 records) did not present summary data and presented individual patient data and therefore could not provide meaningful estimates of efficacy to inform the comparator arm in the model. Consequently, these studies have been summarised by citation in Table D.4.1.3 of Appendix D.
- 8 unique studies (9 records) were extracted (Barete *et al.* (2015),[30] Hauswirth *et al.* (2004),[60] Hochaus *et al.* (2015),[35] Jawhar *et al.* (2017a),[66] Lim *et al.* (2009),[18, 70] Pagano *et al.* (2008),[71] Pardanani *et al.* (2009)[72] and Verstovsek *et al.* (2008)[36]) and of these 8 studies:
    - 2 studies were single-arm trials
    - 6 studies reported observational data only.

An overview of these 8 studies is provided in Table 8 below with further details of the patient populations, study design and outcomes for these studies presented in Section B.2.9.2.

Finally, given the paucity of data identified for the comparator therapies, additional targeted searches were carried out with view to identifying any databases or registries containing patients with SM. A total of 7 databases were identified; however, no relevant published records were eligible for inclusion in the SLR. A full list of databases and records excluded from the SLR is presented in Table D.4.2.2 of Appendix D, along with a brief rationale for exclusion.

Table 8: Clinical effectiveness evidence for comparator therapies

Study ID	Full reference
Comparator therapies	
Barete *et al.* (2015)	Barete S, Lortholary O, Damaj G, et al. Long-term efficacy and safety of cladribine (2-CdA) in adult patients with mastocytosis. Blood 2015;126:1009-1016.
Hauswirth *et al.* (2004)	Hauswirth AW, Simonitsch-Klupp I, Uffmann M, et al. Response to therapy with interferon alpha-2b and prednisolone in aggressive systemic mastocytosis: report of five cases and review of the literature. Leukemia Research 2004;28:249-257.
Jawhar *et al.* (2017a)	Jawhar M, Schwaab J, Meggendorfer M, et al. The clinical and molecular diversity of mast cell leukemia with or without associated hematologic neoplasm. Haematologica 2017;102:1035-1043.
Lim *et al.* (2009)	Lim KH, Pardanani A, Butterfield JH, et al. Cytoreductive therapy in 108 adults with systemic mastocytosis: Outcome analysis and response prediction during treatment with interferon-alpha, hydroxyurea, imatinib mesylate or 2-chlorodeoxyadenosine. American Journal of Hematology 2009;84:790-4.
	Lim KH, Tefferi A, Lasho TL, et al. Systemic mastocytosis in 342 consecutive adults: Survival studies and prognostic factors. Blood 2009;113:5727-5736.
Hochhaus *et al. (2015)*	Hochhaus A, Baccarani M, Giles FJ, et al. Nilotinib in patients with systemic mastocytosis: analysis of the phase 2, open-label, single-arm nilotinib registration study. Journal of Cancer Research & Clinical Oncology 2015;141:2047-60.
Pagano *et al.* (2008)	Pagano L, Valentini CG, Caira M, et al. Advanced mast cell disease: An Italian Hematological Multicenter experience. International Journal of Hematology 2008;88:483-488.
Pardanani *et al.* (2009)	Pardanani A, Elliott M, Reeder T, et al. Imatinib for systemic mast-cell disease. Lancet 2003;362:535-6.

Verstovsek *et al.* (2008)	Verstovsek S, Tefferi A, Cortes J, et al. Phase II study of dasatinib in Philadelphia chromosome-negative acute and chronic myeloid diseases, including systemic mastocytosis. Clinical Cancer Research 2008;14:3906-15.

Abbreviations: SLR: systematic literature review.

B.2.3 *Summary of methodology of the relevant clinical effectiveness evidence*

D2201, an international, multicentre, single-group, open-label, phase II trial, represents the pivotal clinical trial for midostaurin in this indication, and the data presented from this trial are reported in the primary publication by Gotlib *et al.* (2016),[12] supplemented by data from the clinical study report (CSR).[73]

Supportive evidence for the efficacy and safety of midostaurin in the patient population of interest for this appraisal is from A2213, an investigator-initiated, multicentre, single-group, open-label, phase II trial. The data for A2213 presented in this submission are from the published manuscript by DeAngelo *et al.* (2018),[61] and, since this study is not a Novartis-sponsored trial, it should be noted that the only data available to Novartis are those in the public domain.

The methodology and results of the historical comparison studies (Reiter *et al.* [2017][23] and CEREMAST[64, 65]) are presented in Section B.2.9.1, since these studies provide evidence of the overall survival benefit of midostaurin over the current SoC.

B.2.3.1 Trial design and methodology

D2201 and A2213 are two completed multicentre, single-group, open-label, phase II studies in adults with advanced SM (ASM, SM-AHN or MCL) who were treated with midostaurin orally at 100 mg twice daily as continuous 4-week cycles.[12, 61] This treatment regimen aligns with the licensed dose of midostaurin in this indication.[4] A summary of the methodology of D2201 and A2213 is presented in Table 9, and an overview of the study design of each trial is presented in Figure 4. The full inclusion and exclusion criteria of the two trials are presented in the study protocols, which have been provided alongside this submission.

Table 9: Summary of trial methodology of relevant clinical trials

	D2201 (N=116)	A2213 (N=26)
Locations	• International: 29 centres in 12 countries worldwide (Australia, Austria, Belgium, Canada, France, Germany, Netherlands, Norway, Poland, Turkey, UK, US) • UK enrolled 4 patients in 3 centres (Glasgow, London & Liverpool)	• US-based: 3 centres
Trial design	• An international, multicentre, single-group, open-label, phase II study • Adapted Fleming two-stage design	• A multicentre, single-group, open-label, phase II study • Simon two-stage design
Eligibility criteria for participants	A summary of the key inclusion and exclusion criteria is provided below: **Key inclusion criteria** • Adults (≥18 years of age)	A summary of the key inclusion and exclusion criteria is provided below: **Key inclusion criteria** • Adults (>18 years of age)

	• Diagnosed with ASM, SM-AHN or MCL according to WHO criteria • ECOG performance status 0–3 • Serum creatinine ≤2.0 mg/dl • ALT/AST within 2.5x ULN and serum bilirubin within 1.5x ULN or, if the cause of liver enzyme elevation was considered related to ASM/MCL, ALT/AST within 5x ULN and serum bilirubin within 3x ULN • Life expectancy ≥12 weeks • QTcF interval ≤450 ms **Key exclusion criteria** • Previous treatments for mastocytosis ≥3 • SM treatment with investigational or approved agent within 30 days before day 1 of midostaurin • Cardiac ejection fraction <50% • Known diagnosis of impaired cardiovascular disease, HIV infection or active viral hepatitis • Pregnancy or breastfeeding • AHN requiring immediate cytoreductive therapy or targeted drugs • Eosinophilia and positive result for the *FIP1L1-PDGFRA* fusion, unless relapsed or progressed on prior imatinib treatment • Hematopoietic growth factor support and surgical procedures other than central venous catheter placement and other minor procedures within 14 days before day 1 of midostaurin • Pulmonary infiltrate on chest X-ray, particularly residual infiltrate following resolved clinical symptoms of pulmonary infection, unless the infiltrate was due to disease-related pleural effusion • Prior treatment with midostaurin	• Diagnosed with ASM, SM-AHN or MCL according to WHO criteria • ECOG performance status 0–3 • Serum creatinine ≤2.0 mg/dl • Liver enzyme values within normal limits or, if the cause of liver enzyme elevation was considered related to ASM/MCL, ALT, AST and/or total bilirubin within 4x ULN • Absence of active pulmonary disease unless considered related to SM **Key exclusion criteria** • Pregnancy or breastfeeding • SM treatment with investigational agent, chemotherapy (including cladribine) or interferon alpha within 30 days before day 1 of midostaurin • Hematopoietic growth factor support within 14 days before day 1 of midostaurin • Known diagnosis of HIV infection, or active viral hepatitis, any other concurrent severe or uncontrolled medical condition or disease involving the central nervous system
Method of study drug administration	Midostaurin was administered orally at 100 mg twice daily as continuous 28-day/4-week cycles	
Trial protocol	• Patients received treatment with midostaurin until disease progression, death, development of unacceptable toxic effects or withdrawal of consent • No cycle limit was established in	• Patients received treatment with midostaurin for up to 12 cycles in the main trial protocol and treatment was discontinued in patients who had not achieved a MR or a PR within the first 2

	the main trial protocol • At the start of treatment (days 1–3), patients were hospitalised for monitoring of initial mast cell degranulation symptoms	treatment cycles • An extension trial protocol was available for patients with an ongoing response and without unacceptable toxicity after the initial 12 cycles of treatment • At the start of treatment (days 1–3), patients were hospitalised for monitoring of initial mast cell degranulation symptoms
Permitted and disallowed concomitant medication	**Permitted treatments** • Antiemetics **Prohibited treatments** • Concurrent antineoplastic therapy • Glucocorticoid therapy (prednisone at a dose of >10 mg daily or the equivalent for ≥1 treatment cycle) – patients were classified as unable to be evaluated for response	**Permitted treatments** • Antiemetics **Prohibited treatments** • Not specified
Primary endpoint[a]	• Best Response defined as the percentage of participants who classified as confirmed responders (MR or PR within the first 6 treatment cycles and maintained for ≥8 weeks) based on modified Valent and Cheson criteria as adjudicated by the study steering committee	• Best Response defined as the percentage of participants who classified as confirmed responders (MR or PR within the first 2 treatment cycles and maintained for ≥8 weeks) based on published Valent and Cheson criteria
Secondary and other endpoints	• OS • PFS • DoR • TTR • Safety and tolerability • Patient-reported symptoms (by the MSAS) • HRQoL (SF-12) • Response assessment based on all C-findings combined, including non-measurable ones • Histopathologic response based on mast cell infiltration and serum tryptase levels	• OS • PFS • DoR • TTR • Safety and tolerability • Pharmacokinetics • Histopathologic response based on mast cell infiltration and serum tryptase levels
Endpoint assessment	Treatment responses and patient-reported outcomes were assessed after every cycle during the first 12 cycles and every 3 cycles thereafter until end of treatment or end of the study, whichever occurred first.	
Pre-planned subgroups	• Disease subtype (ASM, SM-AHN and MCL) • Number of prior therapies (0 and ≥1) • KIT D816V mutation status (positive and negative or unknown)	• Disease subtype (ASM, SM-AHN and MCL) • C-findings present at baseline (anaemia, thrombocytopaenia, neutropenia and non-haematologic C-findings) • KIT D816V mutation status

		(positive and negative)
Duration of study and follow-up	• Median duration of follow-up: 26 months (range 12–54) • The study was initiated on 6th January 2009 and completed on 24th August 2017	• Median duration of follow-up: 124 months (range 82–140) • The study was initiated on 7th July 2005 and completed on 29th December 2017

[a]In D2201, response assessment was based on measurable C-findings only, as adjudicated by the steering committee. Ascites and osteolytic lesions were not considered as measurable C-findings. In A2213, response assessment was based on measurable and non-measurable C-findings.
Abbreviations: ALT: alanine aminotransferase; ASM: aggressive systemic mastocytosis; AST: aspartate aminotransferase; DoR: duration of response; ECOG: Eastern Cooperative Oncology Group; HIV: human immunodeficiency virus; HRQoL: health-related quality of life; MCL: mast cell leukaemia; MR: major response; MSAS: Memorial Symptom Assessment Scale; OS: overall survival; PFS: progression-free survival; PR: partial response; QTcF: corrected QT interval by Fridericia; SF-12: Medical Outcomes Study 12-Item Short-Form Health Survey; SM: systemic mastocytosis; SM-AHN: systemic mastocytosis with associated haematologic neoplasm; TTR: time to response; ULN: upper limit of normal; WHO: World Health Organisation.
Source: ClinicalTrials.gov (2018),[62] ClinicalTrials.gov (2018),[63] D2201 CSR (data cut-off: 24th August 2017),[73] DeAngelo *et al.* (2018),[61] European Public Assessment Report of Midostaurin (2017),[9] Gotlib *et al.* (2016).[12]

The main differences in trial design were observed in the eligibility criteria, the trial protocol and the primary endpoint assessment:

Eligibility criteria

- D2201 had more stringent exclusion criteria compared to A2213, particularly with regards to AHN requiring immediate cytoreductive therapy, eosinophilia and pulmonary infiltrates in patients.[12, 61, 73]

Duration of treatment

- In D2201, patients received treatment with midostaurin until disease progression, death, development of unacceptable toxic effects or withdrawal of consent and no cycle limit was established in the main trial protocol. In A2213, patients received treatment with midostaurin for up to 12 cycles in the main trial protocol and treatment was discontinued in patients who had not achieved a MR or a PR within the first 2 treatment cycles. An extension trial protocol was available for patients with an ongoing response and without unacceptable toxicity after the initial 12 cycles of treatment.

Adjudication of response

- In D2201, best response defined as the percentage of participants who classified as confirmed responders (major response [MR] or partial response [PR] within the first 6 treatment cycles and maintained for ≥8 weeks) based on modified Valent and Cheson criteria as adjudicated by the study steering committee. In A2213, best response was defined within the first 2 treatment cycles and was not adjudicated by the study steering committee.

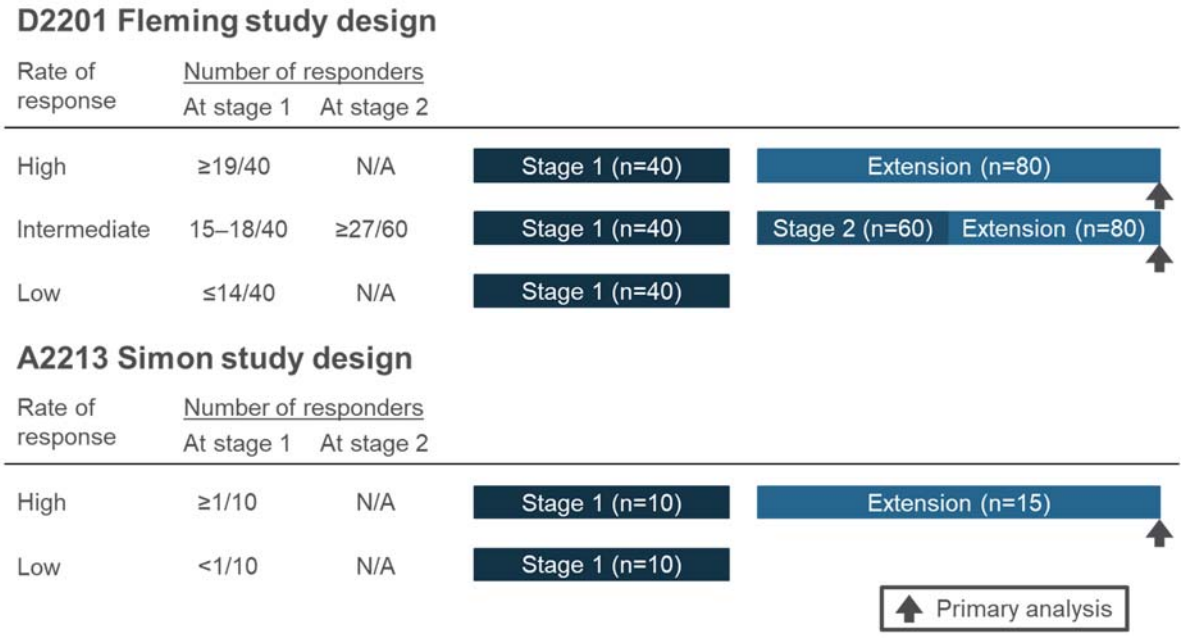
Study design

- D2201 employed a Fleming two-stage design, where the preliminary efficacy of midostaurin was first assessed in a smaller population of 40 patients enrolled in Stage 1 (Figure 4).[12, 73] After all patients still in the study had received 6 cycles of treatment, best overall response was assessed. In accordance with the Fleming study design, if a treatment response was observed in ≤14 patients enrolled in Stage 1, the treatment would be declared ineffective and the trial would be completed. If 15 responders were identified at Stage 1, enrolment of an additional 20 patients into Stage 2 would begin. A supportive analysis would be performed on the Stage 1 and Stage 2 patients when all Stage 2 patients have had 12 cycles of treatment or else have

shown progression, intolerable toxicity or withdrawn due to any cause. If ≥19 responders were identified amongst the first 40 eligible patients enrolled at Stage 1 or ≥27 responders were identified amongst the first 60 eligible patients enrolled up to Stage 2, an extension phase would be initiated and additional patients would be enrolled. Treatment protocols were consistent between stages. Among the 40 patients determined to be eligible and adjudicated for best overall response by the study steering committee at the end of Stage 1, 24 patients were responders.[73] Therefore, the null hypothesis was rejected and an extension phase was initiated. A total of 116 patients were enrolled: 63 patients in Stage 1, and 53 patients in the extension phase.

- A2213 employed a Simon two-stage design, where the preliminary efficacy of midostaurin was first assessed in a smaller patient population of 10 patients enrolled in Stage 1 (Figure 4).[61] In accordance with the Simon study design, if treatment response was observed in <1 patient enrolled in Stage 1, the treatment would be declared ineffective and the trial would be completed. If ≥1 responder was identified at Stage 1, an extension phase would be initiated and additional patients would be enrolled. Treatment protocols were consistent between the two stages. Among the 9 patients determined to be evaluable for efficacy at the end of Stage 1, 6 patients were classified as responders.[76] Therefore, the null hypothesis was rejected and an extension phase was initiated. A total of 26 patients were enrolled: 11 patients in Stage 1, and 15 patients in the extension phase.[61, 76]

Figure 4: Two-stage study designs of D2201 and A2213



The duration of stage 1 was ≥6 cycles of treatment for D2201.
Abbreviations: N/A: not applicable
Source: D2201 CSR (data cut-off: 24th August 2017),[73] DeAngelo et al. (2018),[61] Gotlib et al. (2016).[12]

Endpoint definitions

- The primary endpoint of both D2201 and A2213 was best overall response.
    - In D2201, a confirmed response was defined as any MR (defined as complete resolution of ≥1 C-finding) or PR (defined as >50% improvement in ≥1 C-finding [good partial response] or as >20% to ≤50% improvement in ≥1 C-finding [minor partial response]) within the first 6 treatment cycles and maintained for ≥8 weeks by the adjudication of the study steering committee based on modified Valent and Cheson

criteria.[12, 77] Modified Valent criteria were applied to measurable C-findings, excluding ascites and osteolytic lesions. Response in patients presenting with transfusion-dependent anaemia or thrombocytopaenia as the sole C-finding was assessed using modified Cheson response criteria, where MR was defined as no transfusions for 8 weeks, and PR was defined as ≥50% decrease in transfusions over 8 weeks.[12] In addition, a post-hoc analysis of D2201 data was conducted using the more stringent response criteria published by the International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) and European Competence Network on Mastocytosis (ECNM), referred to as IWG criteria, and the results of this post-hoc analysis are presented in Appendix E.1.

- In A2213, a confirmed response was defined as any MR (defined as complete resolution of ≥1 C-finding) or PR (defined as >50% improvement in ≥1 C-finding [good partial response] or as ≤50% improvement in ≥1 C-finding [minor partial response]) within the first 2 treatment cycles maintained for ≥8 based on published Valent criteria.[61, 78] Published Valent criteria were applied to all C-findings, including ascites and osteolytic lesions. Response in patients presenting with transfusion-dependent anaemia or thrombocytopaenia requiring ≥4 units of red blood cells or platelets in the 8 weeks before study entry was assessed using Cheson response criteria, where transfusion independence was defined as freedom from transfusions for ≥8 weeks.

A summary of Valent response criteria applied in D2201 and A2213 is presented in Appendix D.

B.2.3.2 Baseline characteristics

An overview of the baseline characteristics of patients in the D2201 and A2213 trials is presented in Table 10.[12, 61] Overall, patient baseline characteristics were comparable between the two trials. Patients enrolled in D2201 were between the ages of 25 and 82 years old (mean 63 years), over half were male (66%) and the majority were white (96%). Patients enrolled in A2213 were between the ages of 24 and 79 years old (mean 64.5 years), over half were male (58%) and the majority were white (81%).

In both D2201 and A2213, the advanced SM subtype was determined according to the WHO diagnostic criteria (2001).[12, 61] Distribution of patients between disease subtypes was similar across both trials with 19% and 12% of patients diagnosed with ASM, 63% and 65% of patients diagnosed with SM-AHN and 18% and 23% of patients diagnosed with MCL in D2201 and A2213, respectively.

The majority of patients were positive for a KIT D816 mutation, with rates of 84% in D2201 and 77% in A2213. Additionally, a high mast cell burden was present in both patient populations. In the bone marrow, a median mast cell infiltration of 40% to 50% was observed in D2201 and A2213, respectively. Systemically, high mast cell activity was indicated by a serum tryptase level at or above the diagnostic threshold of 200 µg/L,[29] with median values of 200 µg/L in D2201 and 323 µg/L in A2213.

Key differences between the patient populations in D2201 and A2213 were primarily related to disease severity, as evidenced by ECOG performance status, number of previous therapies and number of C-findings per patient. An ECOG performance status of 2 or 3, indicative of increased symptom impact on patient mobility and self-care,[79] was recorded in over half of all patients in A2213 (54%), compared to a third of patients in D2201 (34%). With regards to previous therapies, over half of patients enrolled in D2201 (55%) and under a third of patients in A2213 (19%) had not

received any prior treatment. Finally, 50% of patients treated as part of A2213 presented with 3 or more C-findings in contrast to 33% of patients enrolled in D2201. These characteristics suggest that the disease burden of the patient population of A2213 may be higher than that for the patients enrolled in D2201, although similarities in mast cell burden and serum tryptase levels do not indicate this. This has been discussed further in Section B.2.8.

Table 10: Baseline characteristics of patients in D2201 (FAS) and A2213 (FAS)

	D2201 (N=116)	A2213 (N=26)
Age (years)		
Median (range)	63.0 (25–82)	64.5 (24–79)
Age category (years) – n (%)		
<65	[redacted]	-
65–74	[redacted]	-
≥75	[redacted]	-
Sex – n (%)		
Male	76 (66)	15 (58)
Female	40 (34)	11 (42)
Race – n (%)		
Caucasian	[redacted]	21 (81)[e]
Black	[redacted]	-
Other	[redacted]	-
Missing	[redacted]	-
Ethnicity – n (%)		
Hispanic/Latino	[redacted]	-
Other	[redacted]	-
Missing	[redacted]	-
ECOG performance status – n (%)		
0	[redacted]	12 (46)
1	[redacted]	
2	[redacted]	14 (54)
3	[redacted]	
Number of previous therapies – n patients (%)		
0	64 (55)	5 (19)
1	29 (25)	8 (31)
2	15 (13)	6 (23)
≥3	8 (7)[a]	7 (27)
Subtype of advanced SM – n (%)		
ASM	22 (19)[b]	3 (12)
SM-AHN	73 (63)[b]	17 (65)
MCL	21 (18)	6 (23)[f]
***KIT* D816 mutation status – n (%)**		
Positive	98 (84)[c]	20 (77)[g]
Negative	13 (11)	5 (19)

Other	5 (4)[d]	1 (4)[h]
Bone marrow mast-cell burden – %		
Median (range)	40 (3–98)	50 (5–95)
Serum tryptase level – µg/L		
Median (range)	200 (2–12,069)	323 (22–1,255)
Number of C-findings per patient – n patients (%)		
1	31 (27)	3 (12)
2	20 (17)	10 (38)
≥3	38 (33)	13 (50)
Time from diagnosis – days		
Median	86	-

[a]Therapy in some of these cases was directed toward the AHN component of SM-AHN.
[b]These numbers were derived from the EPAR and calculated by subtracting the known number of patients in each category from the total number of patients in the trial.
[c]A total of 73 patients were positive for the KIT D816V mutation, 3 were positive for the KIT D816Y mutation, and 1 was positive for the KIT D816L mutation.
[d]*KIT* D816 mutation status unknown.
[e]This number was calculated by subtracting the proportion of Caucasians in D2201 from the pooled analysis of D2201 and A2213 presented in the APAR.
[f]Two MCL patients had chronic myelomonocytic leukemia-1 as an AHN.
[g]A total of 19 patients were positive for the KIT D816V mutation and 1 was positive for the KIT D816Y mutation.
[h]The patient was positive for the KIT S451C mutation.
Abbreviations: APAR: Australian Public Assessment Report; ASM: aggressive systemic mastocytosis; D816: mutation in codon for aspartic acid in position 816; ECOG: Eastern Cooperative Oncology Group; EPAR: European Public Assessment Report; FAS: full analysis set; MCL: mast cell leukaemia; SM: systemic mastocytosis; SM-AHN: systemic mastocytosis with associated haematologic neoplasm; FAS: final analysis set.
Source: Australian Public Assessment Report of Midostaurin (2019),[80] D2201 CSR (data cut-off: 24th August 2017),[73] DeAngelo *et al.* (2018),[61] European Public Assessment Report of Midostaurin (2017),[9] Gotlib *et al.* (2016).[12]

B.2.4 *Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence*

The analysis sets used in the analysis of D2201 and A2213 are presented in Table 11 below.

Table 11: Trial populations used for the analysis of endpoints of D2201 and A2213

	D2201 (N=116)	A2213 (N=26)
Full analysis set (FAS)	All patients to whom study treatment has been assigned according to the intention-to-treat (ITT) principle (n=116)	All patients to whom study treatment has been assigned according to the intention-to-treat (ITT) principle (n=26)
Primary efficacy population (PEP)	All patients who had measurable C-findings considered related to SM[a] (n=89) The PEP population is used to inform the economic evaluation	All patients who had measurable and non-measurable C-findings (n=26)
Safety evaluation set (SES)	All patients who received ≥1 dose of midostaurin (n=116)	All patients who received ≥1 dose of midostaurin (n=26)
Per protocol set (PPS)	All patients from the PEP who did not have any major protocol deviations which could affect the evaluation of the primary endpoint (n=86)	-

[a]Ascites and osteolytic lesions were not considered as measurable C-findings. C-findings related to SM were adjudicated by the steering committee of D2201.
Abbreviations: FAS: full analysis set; ITT: intention-to-treat; PEP: primary efficacy population; PPS: per protocol set; SES: safety evaluation set; SM: systemic mastocytosis.
Source: DeAngelo *et al.* (2018),[61] Gotlib *et al.* (2016).[12]

Analysis of primary endpoint

The primary endpoint of D2201 and A2213 was best overall response. Full details of the statistical methods used for the analyses of D2201 and A2213 are presented in Table 12.

Table 12: Statistical methods for the analysis of D2201 and A2213

	D2201 (N=116)	A2213 (N=26)
Hypothesis objective	• The primary efficacy analysis was performed by testing the null hypotheses that the overall response rate among enrolled patients would be ≤30%, against the alternative hypothesis that the response rate at the end of stage 1 would be ≥50%, at a one-sided overall nominal type I error rate of 0.025 • At the end of stage 1: o The null hypothesis would be rejected if 19 or more of the 40 patients enrolled were responders o The alternative hypothesis would be rejected if 14 or fewer of the 40 patients enrolled were responders • Stage 2 must be done if the number of observed responses lay between 15 to 18 inclusive • At the end of stage 2: o The null hypothesis would be rejected if 27 or more of the 60 patients enrolled were responders	• The primary efficacy analysis was performed by testing the null hypotheses that the true response rate among enrolled patients would be ≤10%, against the alternative hypothesis that the true response rate would be ≥30% • At the end of stage 1: o The null hypothesis would be rejected if 1 or more of the 10 patients enrolled were responders o The alternative hypothesis would be rejected if none of the 10 patients enrolled were responders
Statistical analysis	• Statistical analysis of the primary endpoint was carried out using an exact binomial test • The primary endpoint was expressed as the frequency of confirmed responses occurring in the first 6 cycles, along with the exact two-sided p-value and the Clopper–Pearson 95% CI • Secondary endpoints, such as OS, PFS and DoR were summarised using Kaplan–Meier estimates and associated 95% CI	• The Cox proportional hazards model and log-rank test were used to calculate the HR for responders relative to non-responders with 95% CI and p-value, respectively • Fisher's exact test was used for comparison of response rates among subgroups • The primary endpoint was expressed as the frequency of confirmed responses during the first 12 cycles along with the 95% CI • Secondary endpoints, such as OS, PFS and DoR were summarised using Kaplan–Meier estimates and associated 95% CI

Sample size, power calculation	• A Fleming two-stage design was employed • A total of 120 patients were planned to be enrolled, with 40 patients enrolled at stage 1 and up to 80 patients enrolled in the extension phase • The associated power to reject the null hypothesis was 84% overall and 68% at the end of stage 1	• A Simon two-stage design was employed • A total of 25 patients were planned to be enrolled, with 10 patients enrolled at stage 1 and up to 15 patients enrolled in the extension phase • The associated chance of falsely rejecting the null hypothesis is 9.4%, and the likelihood of falsely rejecting the alternative hypothesis is 10.4%
Data management, patient withdrawals	• Patients for whom no assessment was available or who discontinued the study before the end of the 6th cycle without having obtained a MR or PR before discontinuation were considered non-responders	• Patients with missing tumour assessment or who died or discontinued the study before having their first assessment were considered non-responders

Abbreviations: CI: confidence intervals; DoR: duration of response; HR: hazard ratio; MR: major response; OS: overall survival; PFS: progression-free survival; PR: partial response.
Source: A2213 Clinical Trial Protocol (2004),[78] D2201 Clinical Trial Protocol (2008),[77] DeAngelo *et al.* (2018),[61] Gotlib *et al.* (2016).[12]

Analysis of secondary endpoints

Secondary endpoints of D2201 were OS, PFS, DoR and TTR. Additional exploratory endpoints were patient-reported symptoms, HRQoL and response assessment based on all C-findings combined, including non-measurable ones. Secondary endpoints of A2213 were OS, PFS, DoR, TTR and pharmacokinetics. All secondary endpoints were analysed using descriptive summary statistics with further details presented in Table 12.

Analysis of safety endpoints

All safety endpoints were analysed for the SES using descriptive summary statistics.

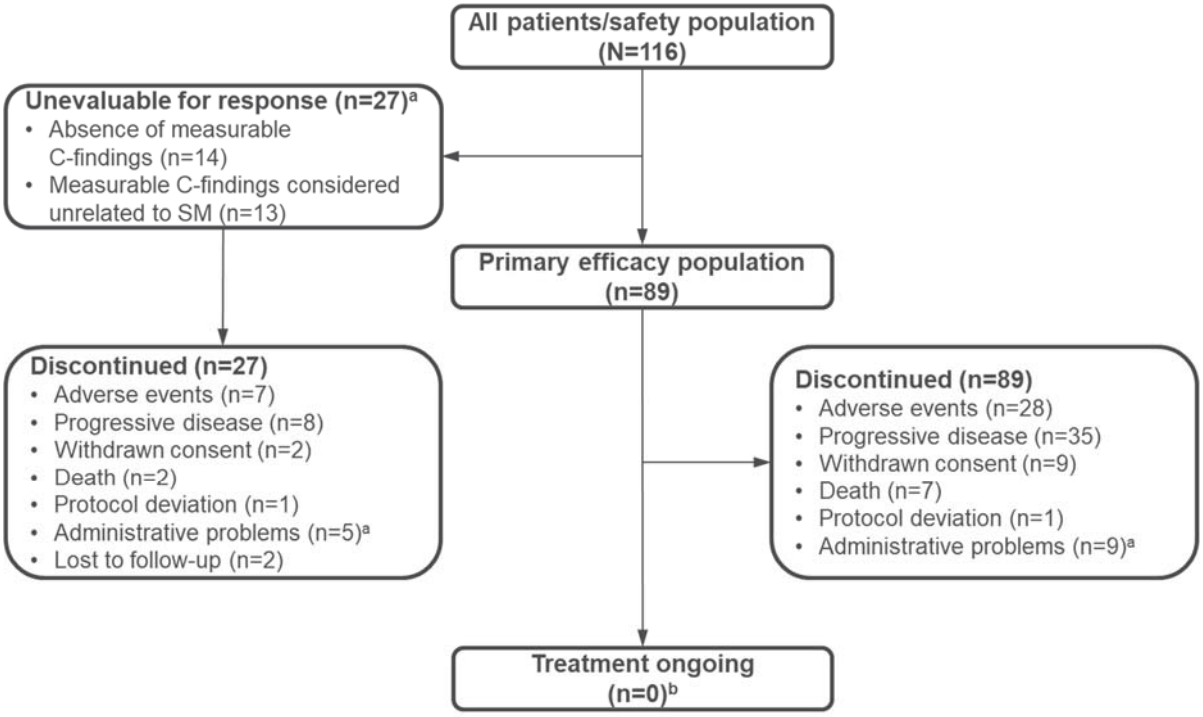
B.2.4.1 Participant disposition

D2201 (NCT00782067)

A total of 116 patients with advanced SM were enrolled and received treatment with midostaurin in the D2201 trial.[12, 73] Of these, 27 patients were considered unevaluable for response as adjudicated by the study steering committee. All 116 patients were included in the FAS and SES, and 89 eligible patients were included in the PEP.

As of the data cut-off of 24th August 2017, all 116 patients discontinued the study (PEP n=89, unevaluable for response n=27).[12, 73] Lack of efficacy, as evidenced by progressive disease, was the most common reason for discontinuation (PEP n=35, unevaluable for response n=8). A consort diagram of patient disposition is presented below (Figure 5).

Figure 5: Consort diagram of D2201



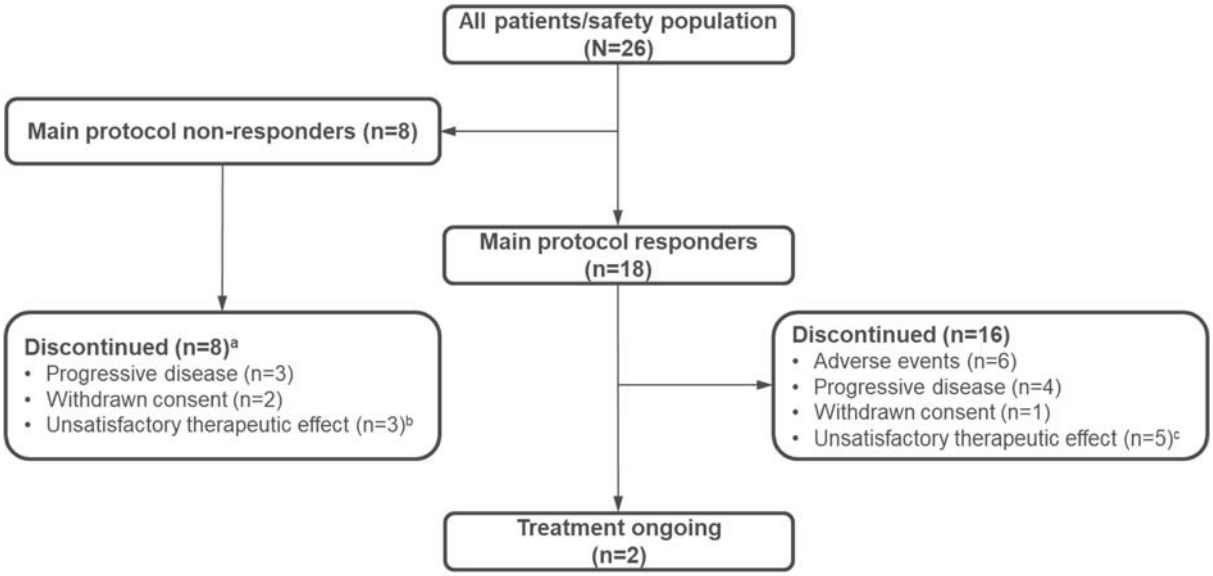
[a]Data for the 'unevaluable for response' group were calculated based on the difference between the figures reported for the PEP and the figures reported for the FAS in the CSR.
[b]Thirteen of the fourteen patients with reason administrative problems were patients who were receiving study treatment at the end of study cut-off date and transitioned from study supplied drug to commercial drug or compassionate access at study close.
Final analysis data cut-off: 24th August 2017; FAS.
Abbreviations: SM: systemic mastocytosis.
Source: D2201 CSR Report (data cut-off: 24th August 2017).[73]

A2213 (NCT00233454)

In A2213, a total of 26 patients with systemic mastocytosis were enrolled in the trial and received treatment with midostaurin.[61] All 26 patients were eligible for efficacy evaluation and all were included in the FAS and SES.

As of the data cut-off of 1st March 2017, 24 patients (92.3%) had discontinued the study (main protocol responders n=16, main protocol non-responders n=8).[61] Lack of efficacy, as evidenced by unsatisfactory therapeutic effect and/or progressive disease, was the most common reason for discontinuation (main protocol responders n=9, main protocol non-responders n=8). A consort diagram of patient disposition is presented below (Figure 6).

Figure 6: Consort diagram of A2213



Analysis data cut-off: 1st March 2017; FAS.
[a]These figures were calculated by subtracting the number of main protocol responder discontinuations from the total number of discontinuations reported for all patients.
[b]Per protocol, patients not achieving an initial response by the end of two cycles were discontinued from the study.
[c]Patients with unsatisfactory therapeutic effect were discontinued per investigator discretion.
Source: DeAngelo *et al.* (2018).[61]

B.2.5 *Quality assessment of the relevant clinical effectiveness evidence*

A summary of the quality assessment conducted for the D2201 and A2213 trials using the Downs and Black checklist is presented below in Table 13.[81] Full details of the quality assessment are presented in Appendix D for all of the trials identified in the SLR.

Table 13: Quality assessment of D2201 and A2213

Study	D2201	A2213
1. Is the hypothesis/aim/objective of the study clearly described?	Yes–To measure the efficacy, safety and patient-reported outcomes of midostaurin-treated patients with advanced SM	Yes–To evaluate the long-term safety and efficacy of midostaurin in patients with advanced SM
2. Are the main outcomes to be measured clearly described in the Introduction or Methods section?	Yes–Primary, secondary and exploratory endpoints pre-specified	Yes–Primary and secondary endpoints clearly described
3. Are the characteristics of the patients included in the study clearly described?	Yes–Baseline characteristics of all patients that entered the trial are given	Yes–Inclusion/exclusion criteria given
4. Are the intervention(s) of interest clearly described?	Yes–Clearly described	Yes–Clearly described
5. Are the distributions of principal confounders in each group of subjects to be compared clearly described?	Yes–Detailed breakdown of patient characteristics given	Yes–Detailed breakdown of patient characteristics given
6. Are the main findings of the	Yes–Clearly described	Yes–Clearly described

study clearly described?		
7. Does the study provide estimates of the random variability in the data for the main outcomes?	Yes–Ranges and 95% confidence intervals given	Yes–Ranges and 95% confidence intervals given
8. Have all important adverse events that may be a consequence of the intervention been reported?	Yes–Adverse events that occurred in at least 10% of patients reported, and other adverse events reported on the CT.gov record	Yes–Adverse events that occurred in at least 10% of patients reported, and other adverse events reported on the CT.gov record
9. Have the characteristics of patients lost to follow-up been described?	No–No details provided of patients lost to follow-up	No–No details provided of patients lost to follow-up
10. Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?	Yes–p-values reported to an appropriate significance level	Yes–p-values reported to an appropriate significance level
11. Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	Unclear–Number of patients screened prior to study entry unclear	Unclear–Number of patients screened prior to study entry unclear
12. Were those subjects who were prepared to participate representative of the entire population from which they were recruited?	Unclear–The study has not demonstrated that the distribution of the main confounding factors was the same in the study sample and the source population	Unclear–Proportion of patients screened that then gave consent not reported
13. Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?	Unclear–No details provided	Yes–Patients treated at cancer institutes or an academic centre
14. Was an attempt made to blind study subjects to the intervention they have received?	No–Open-label study	No–Open-label study
15. Was an attempt made to blind those measuring the main outcomes of the intervention?	No–Open-label study	No–Open-label study
16. If any of the results of the study were based on "data dredging", was this made clear?	No–Subgroup analysis performed that was not mentioned in methods	No–Extensive subgroup analyses in the supplementary that were not described in the methods
17. In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?	Unclear–No details provided	Unclear–No details provided

18. Were the statistical tests used to assess the main outcomes appropriate?	Yes–Statistical analyses used appropriate	Yes–Statistical analyses used appropriate
19. Was compliance with the intervention/s reliable?	Unclear–No details provided	Unclear–No details provided
20. Were the main outcome measures used accurate (valid and reliable)?	Yes–Full details/definitions of outcomes provided	Yes–Full details/definitions of outcomes provided
21. Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	N/A–Single-arm study	N/A–Single-arm study
22. Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?	N/A–Single-arm study	N/A–Single-arm study
23. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	Yes–Outcomes were adjusted as part of a multivariate analysis	No–No adjustments reported
24. Were losses of patients to follow-up taken into account?	Unclear–It is unclear how patients lost to follow-up were taken into account	Unclear–Study used best value measured whilst on treatment; it is unclear how patients lost to follow-up were taken into account
25. Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?	Yes–The null hypothesis that the overall response rate among enrolled patients would be no more than 30% was tested with the use of an exact binomial test at a one-sided overall nominal type I error rate of 0.025. The associated power to reject the null hypothesis was 84% overall and 68% at the end of stage 1 when a response rate of at least 50% was considered as the fixed alternative hypothesis	Unclear–No details provided

Abbreviations: N/A: not applicable; SM: systemic mastocytosis.
Source: Downs and Black (1998).[81]

B.2.6 *Clinical effectiveness results of the relevant trials*

The clinical effectiveness results for the D2201 and A2213 studies are described below with the results from the historical control studies reported in Section B.2.9, since the historical control data are the only data that provides evidence of the overall survival benefit of midostaurin over the current SoC.

B.2.6.1 D2201 (NCT00782067)

D2201 was an international, multicentre, single-group, open-label, phase II trial, which enrolled 116 patients from January 2009 to July 2012. Clinical data for the different outcomes were identified from 3 data cut-off points, with data from the most recent data cut-off used to inform the economic model. The data cut-off points and outcomes assessed are as follows:

- **Data cut-off: 9th July 2013**
    - This analysis includes the analysis of overall response, overall survival (OS), progression-free survival (PFS), duration of response (DoR), time to response (TTR), safety and tolerability, patient-reported symptoms and HRQoL[12]
    - Data from this analysis are reported from the published manuscript by Gotlib *et al.* (2016)[12]
- **Data cut-off: 1st December 2014**
    - This analysis includes the analysis of overall response, OS, PFS, DoR, TTR, safety and tolerability, and patient-reported symptoms
    - Data from this analysis are reported from the European Public Assessment Report (EPAR) and the Australian Public Assessment Report (APAR)[9, 80]
- **Data cut-off: 24th August 2017**
    - This data cut-off corresponds to a final analysis of OS and safety
    - Data from this analysis are reported from the D2201 CSR[73]

Efficacy data for both the primary efficacy population (PEP) and full analysis set (FAS) are reported below, however only the PEP was used to inform the economic evaluation.

Primary endpoint: best overall response (data cut-off: 9th July 2013)

The primary endpoint of D2201 was best overall response. A confirmed response was defined as any MR or PR within the first 6 treatment cycles and maintained for ≥8 weeks by the adjudication of the study steering committee based on modified Valent and Cheson criteria.

At the end of stage 1 (40 patients), the response rate was 60% (n=24/40 patients; 95% CI: 43–75), which was significantly greater than the prespecified 30% threshold for rejection of the null hypothesis (p<0.001).[12]

At the time of the analysis (data cut-off: 9th July 2013), the best overall response rate for the PEP was 60% (n=53/89 patients; 95% CI: 49–70; p<0.001), with 45% having a MR (n=40/89 patients) and 15% having a PR (n=13/89 patients).[12] Details of the types of response observed in the PEP are presented in Table 14. The overall response rate for the FAS was 46% (n=53/116 patients).[12] The median follow-up time in this analysis was 26 months (range 12–54 months) and the median duration of treatment was 11.4 months (range 0.3–51.5 months).

Table 14: Types of response in D2201

Type of response	Number of responders (n)	Proportion (%)
Overall response	**53**	**60**
Major response	40	45
Complete remission	0	0

Incomplete remission	19	21
Pure clinical response	15	17
Unspecified	6	7
Partial response	13	15
Good partial response	11	12
Minor partial response	2	2
Stable disease	**11**	**12**
Progressive disease	**10**	**11**
Patient could not be evaluated for response[a]	**15**	**17**

[a]Reasons that patients could not be evaluated for response were concurrent use of high-dose glucocorticoids (n=9 patients), not enough time receiving treatment (n=3 patients), death (n=1 patient), red-cell transfusion (n=1 patient), and neutropenia (n=1 patient). Patients who could be evaluated for response had an assessment at baseline and at least one post-baseline assessment during the first 6 cycles of treatment.
Analysis data cut-off: 9th July 2013; PEP.
Source: Gotlib *et al.* (2016).[12]

Primary endpoint: best overall response (data cut-off: 1st December 2014)

Data for best overall response at the time of the 1st December 2014 data cut-off, remained the same as that of the earlier cut-off of the 9th July 2013 and therefore ORR data from this most recent data cut-off were used to inform the economic analysis in Section B.3.3.4.

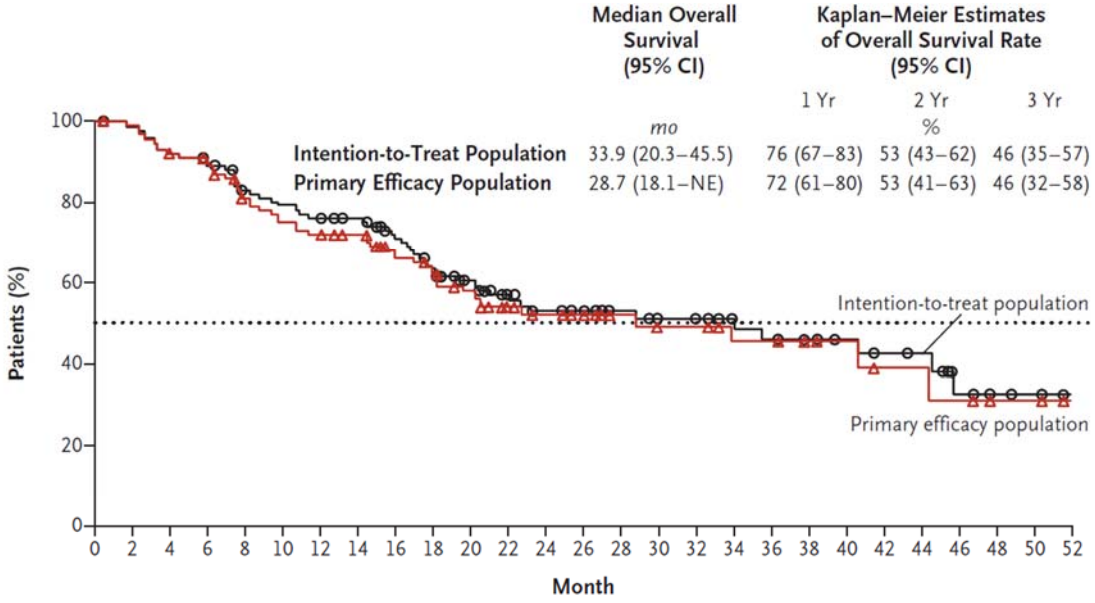
Secondary endpoints

Overall survival (OS) (data cut-off: 9th July 2013)

In D2201, OS was defined as the time from start of study treatment to the date of death due to any cause, with data censored at the last contact date for patients who were still alive or lost to follow-up at the time of the analysis cut-off date.

At the time of the analysis (data cut-off: 9th July 2013), median OS was 28.7 months (95% CI: 18.1–not estimated) for the PEP (Figure 7).[12] The event-free probability estimate of survival at 3 years was 46% (95% CI: 32–58). For the FAS, median OS was 33.9 months (95% CI: 20.3–45.5). The event-free probability estimate of survival at 3 years was 46% (95% CI: 35–57). At the time of data cut-off, 48 patients were alive.

Figure 7: Kaplan-Meier plot of OS in D2201



Analysis data cut-off: 9th July 2013; PEP and FAS (represented by the 'intention-to-treat' population).
Abbreviations: CI: confidence intervals; NE: not estimated; Yr: year.
Source: Gotlib *et al.* (2016).[12]

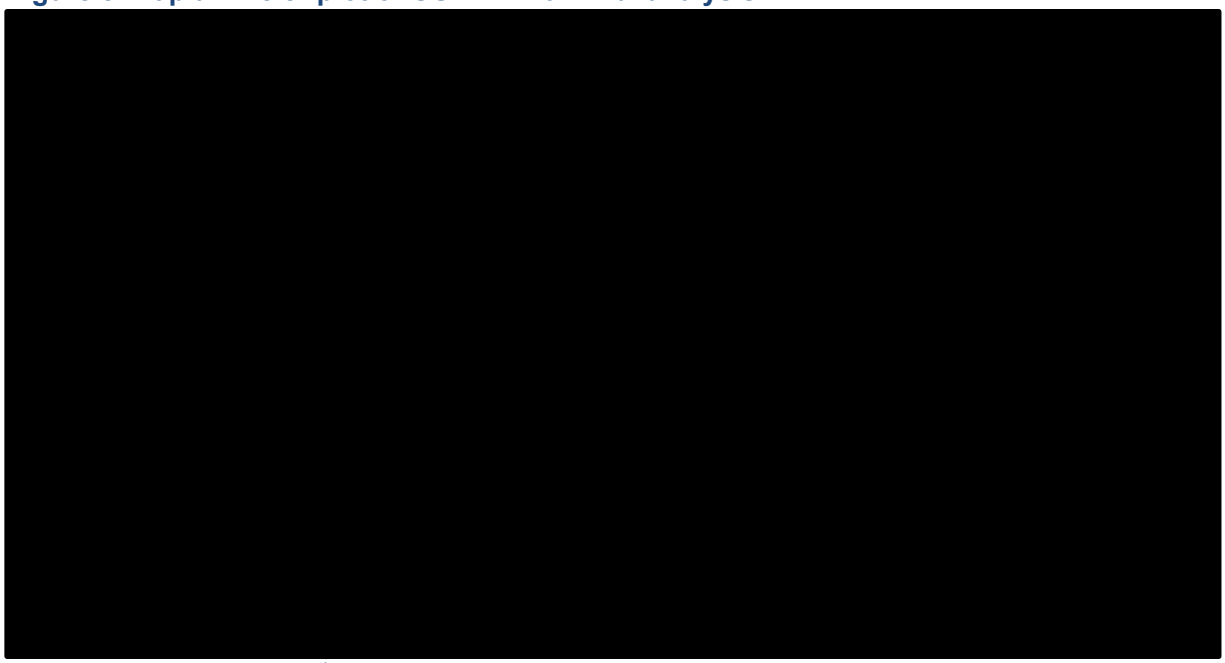
Overall survival (OS) (data cut-off: 1st December 2014)

At the time of the analysis (data cut-off: 1st December 2014), median OS was 26.8 months (95% CI: 17.6–34.7) for the PEP.[9, 80] The event-free probability estimate of survival at 3 years was 38.2% (95% CI: 27.5–48.8). For the FAS, median OS was 29.9 months (95% CI: 20.3–42.0). The event-free probability estimate of survival at 3 years was 42.4% (95% CI: 32.6–51.8). At the time of data cut-off, 35 patients were alive.

Overall survival (OS) (final analysis of OS and safety data cut-off: 24th August 2017)

At the time of the final OS analysis (data cut-off: 24th August 2017), median OS remained similar to that of the 1st December 2014 data cut-off and was [redacted] for the PEP (Figure 8).[73] The event-free probability estimate of survival at 5 years was [redacted]. The median time to censoring was [redacted], the median duration between treatment start date and cut-off date was [redacted] and the median follow-up time for OS was [redacted]. At the time of data cut-off, [redacted] patients were censored as follows: ongoing without event ([redacted]), lost to follow-up early during the study ([redacted]) and lost to follow-up, but alive in the 5 months before the data cut-off ([redacted]).

Figure 8: Kaplan-Meier plot of OS in D2201 final analysis



Final analysis data cut-off: 24th August 2017; PEP.
Source: D2201 CSR (data cut-off: 24th August 2017).[73]

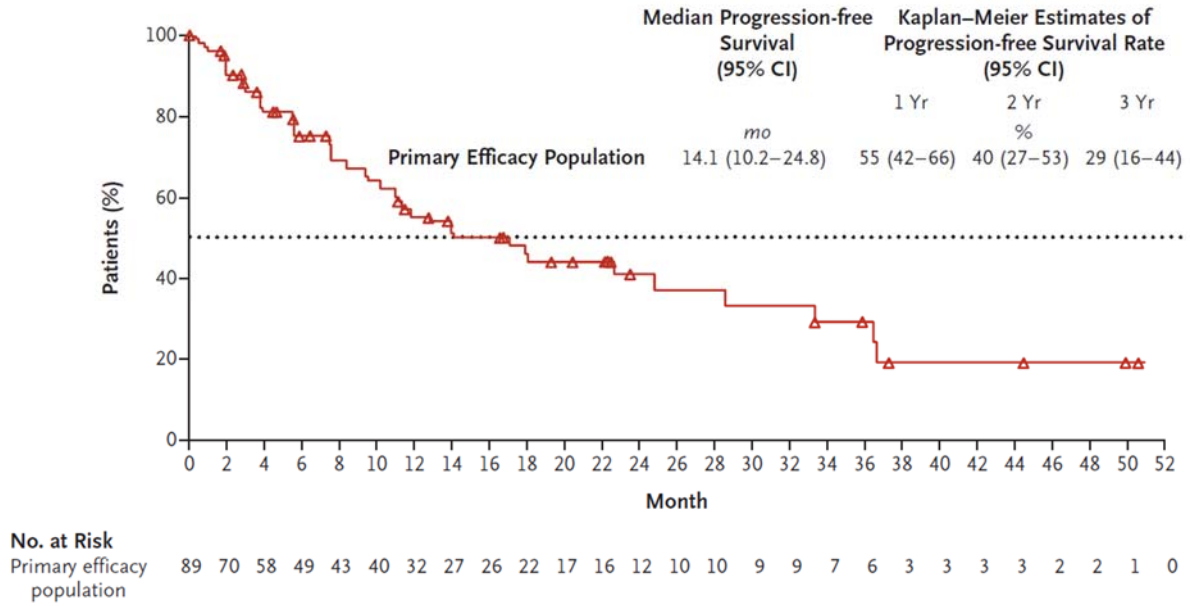
For the FAS, median OS was [redacted].[73] The event-free probability estimate of survival at 5 years was [redacted] and the median time to censoring was [redacted]. At the time of data cut-off, [redacted] patients were censored as follows: ongoing without event ([redacted]), lost to follow-up early during the study ([redacted]) and lost to follow-up, but alive in the 5 months before the data cut-off ([redacted]). OS data from this data cut-off were used to inform the economic analysis in Section B.3.3.2.

Progression-free survival (PFS) (data cut-off: 9th July 2013)

In D2201, PFS was defined as time from treatment start to the first confirmed disease progression sustained for ≥4 weeks, development of secondary AML or death from any cause, with data censored at the last adequate assessment in case of ≥2 missing assessments or at the start of a new antineoplastic therapy.

Median PFS was 14.1 months (95% CI: 10.2–24.8) for the PEP (Figure 9).[12] The estimated probability of being progression free at 12 months was 55.0% (95% CI: 42–66).

Figure 9: Kaplan-Meier plot of PFS in D2201



Analysis data cut-off: 9th July 2013; PEP.
Abbreviations: CI: confidence interval.
Source: Gotlib *et al.* (2016).[12]

Progression-free survival (PFS) (data cut-off: 1st December 2014)

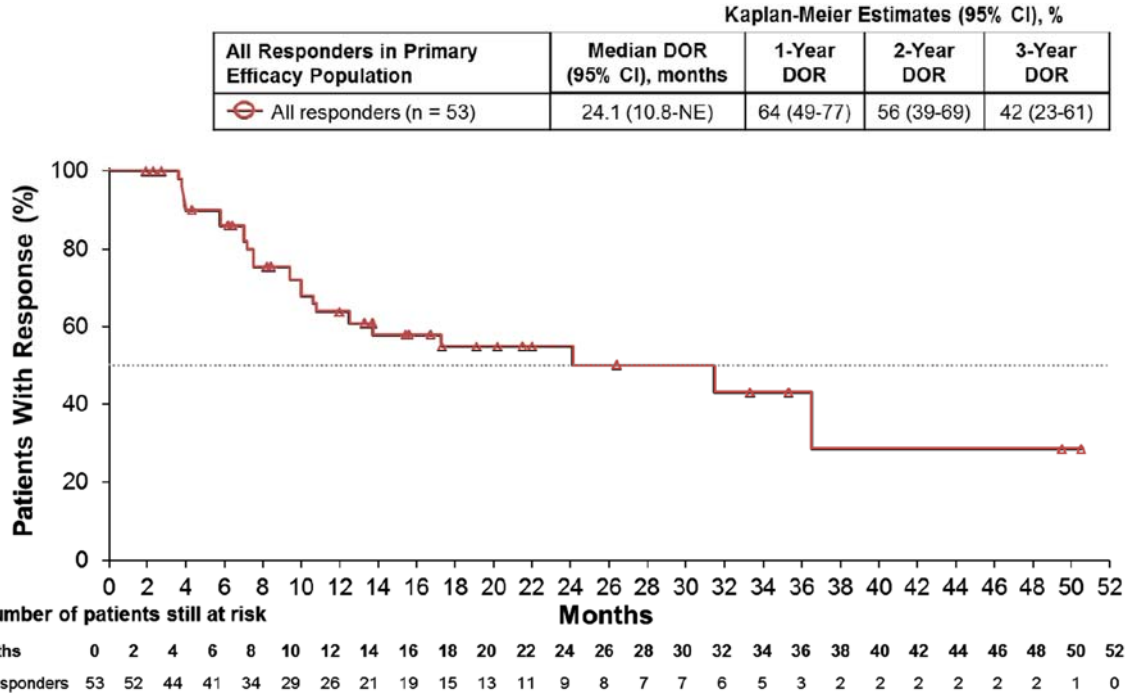
Median PFS was 17.0 months (95% CI: 10.2–24.8) for the PEP.[9, 80] The estimated probability of being progression free at 12 months was 55.0% (95% CI: 42.5–65.9). PFS data from this data cut-off were used to inform the economic analysis in Section B.3.3.3 (Figure 32).

Duration of response (DoR) (data cut-off: 9th July 2013)

In D2201, DoR was defined as the time from start of first documented and confirmed response to first documented and confirmed SM-related progression or death, with data censored at the last adequate assessment in case of ≥2 missing assessments or at the start of a new antineoplastic therapy.

Median DoR among the 53 patients who had a response in the PEP was 24.1 months (95% CI: 10.8–not estimated; Figure 10).[12] The estimated probability of sustained response at 12 months was 64% (95% CI: 49–77).

Figure 10: Kaplan-Meier plot of DoR in D2201



Analysis data cut-off: 9th July 2013; n=53 patients with documented response.
Abbreviations: CI: confidence interval; DoR: duration of response.
Source: Gotlib *et al.* (2016).[12]

Duration of response (DoR) (data cut-off: 1st December 2014)

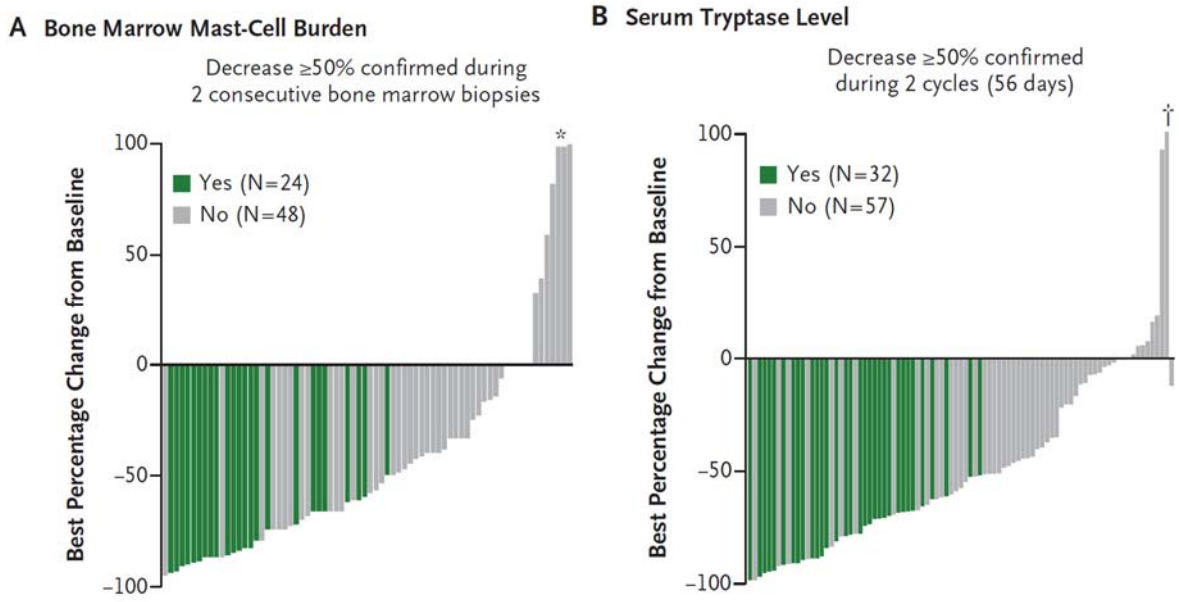
Median DoR among the 53 patients who had a response in the PEP was 31.4 months (95% CI: 10.8–not evaluable).[80] DoR data from this data cut-off were used to inform the economic analysis in Section B.3.3.4 (Figure 34).

Histopathologic response (data cut-off: 9th July 2013)

In D2201, histopathologic response was defined as change from baseline of percentages of mast cell infiltrates in the bone marrow at each assessment. Change of serum tryptase levels from baseline at the respective assessments was also evaluated as a surrogate marker for histopathologic response.[77]

Median best percentage change in bone marrow mast-cell burden among the 72 evaluable patients was -59% (range -96% to 160%)(Figure 11.A).[12] A decrease in bone marrow mast cell burden of ≥50% was observed in 57% of patients (n=41/72), with 33% of patients (n=24/72) maintaining a response for at least two consecutive biopsies. Median best percentage change in serum tryptase level among all 89 patients was -58% (range -99% to 185%)(Figure 11.B). A decrease in serum tryptase level of ≥50% was observed in 60% of patients (n=53/89), with 36% of patients (n=32/89) maintaining a response for at least 56 days. Decreases in both marrow mast cell burden and serum tryptase level were observed in 78% of the patients.

Figure 11: Histopathologic response in D2201



Panel A shows best percentage change in bone marrow mast cell burden with midostaurin therapy in 72 patients who had a baseline evaluation and at least one postbaseline evaluation. One patient had a best percentage change of more than 100% (160%; asterisk). Panel B shows best percentage change in serum tryptase level in all 89 patients in the PEP. Two patients had a best percentage change of more than 100% (118% and 185%; dagger). Analysis data cut-off: 9th July 2013; PEP.
Source: Gotlib *et al.* (2016).[12]

Histopathologic response (data cut-off: 1st December 2014)

Data for histopathologic response at the time of the 1st December 2014 data cut-off, remained the same as that of the earlier cut-off of the 9th July 2013.[9, 80]

Patient-reported outcomes

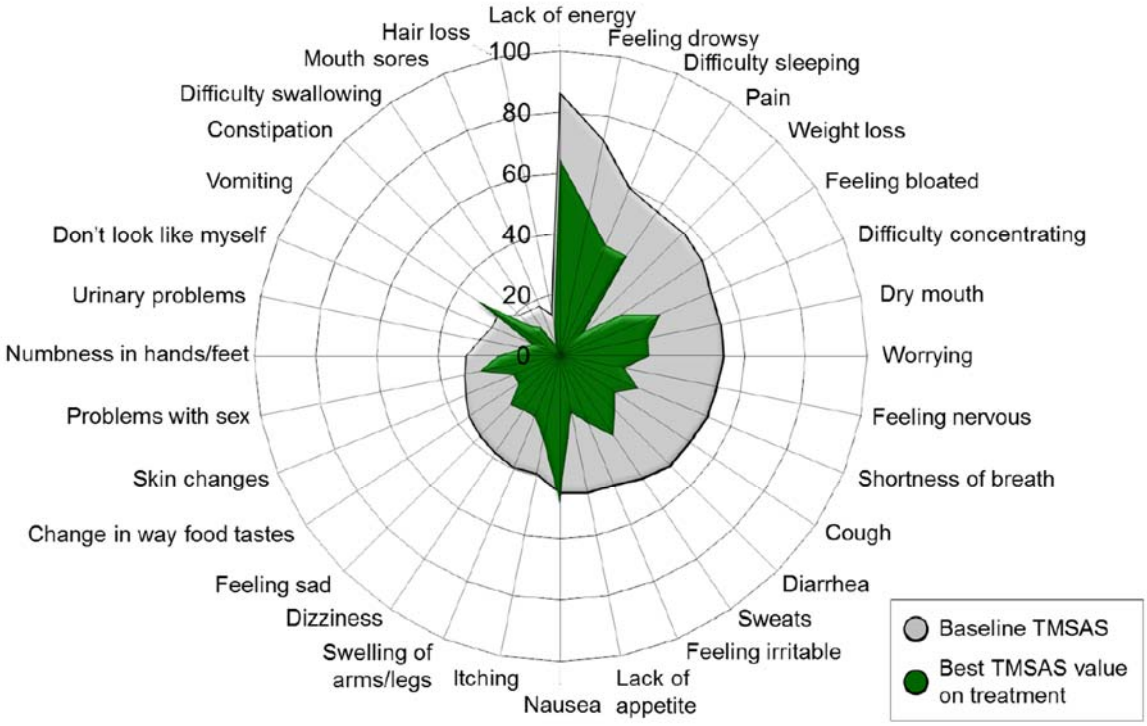
Patient-reported symptoms (data cut-off: 9th July 2013)

In D2201, patient-reported symptoms were assessed using the Memorial Symptom Assessment Scale (MSAS), with patients reporting on the frequency, severity and associated distress of 32 symptoms.[82, 83] The total MSAS score (TMSAS) is an average of all 32 symptoms, with a range of 0–4 and a minimal important difference of 0.20–0.45.[12] The physical symptom (PHYS) subscale is the average score of 6 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. The psychological symptom (PSYCH) subscale is the average of 4 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. 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.

Overall, 79 patients were evaluable for symptoms by the MSAS.[12] At the time of the analysis (data cut-off: 9th July 2013), the most commonly reported baseline symptoms on the MSAS were lack of energy (n=68 patients, 86%), a feeling of drowsiness (n=57 patients, 72%), and difficulty sleeping (n= 47 patients, 60%). Overall, 30 of 32 symptoms had decreased in frequency at the time of the best reported total score on the MSAS (TMSAS) compared to baseline and the median TMSAS score was significantly lower for patients on treatment (Figure 12 and Figure 13). The symptoms

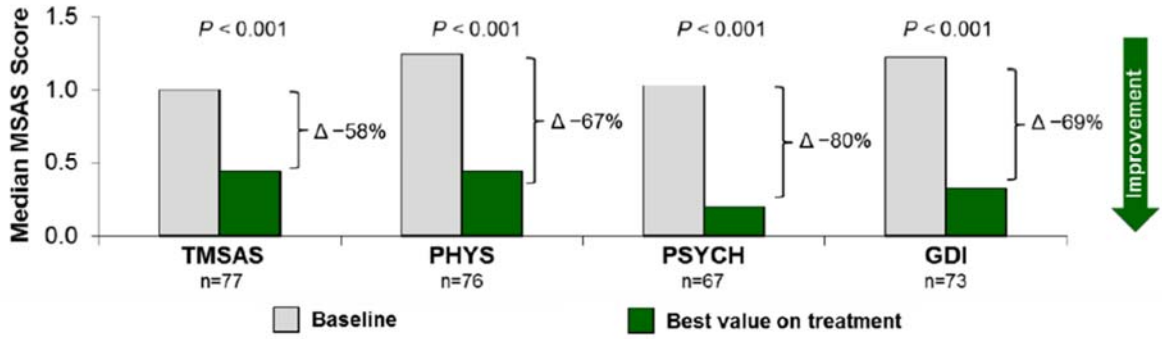
that did not decrease were nausea and vomiting, which are AEs that are known to be associated with midostaurin. Importantly, there was a significant decrease in median MSAS score across all subscales, including PHYS, PSYCH and GDI with a median best percentage change in MSAS score of 67%, 80% and 69%, respectively (Figure 13).

Figure 12: Total MSAS scores per symptom in D2201



Analysis data cut-off: 9th July 2013; n=79 evaluable patients.
Symptoms at baseline for evaluable patients shown in decreasing prevalence in a clockwise direction in grey shading. The same symptoms assessed for each patient at the time of the best total MSAS score value on treatment shown in green shading.
Abbreviations: TMSAS: total score on the Memorial Symptom Assessment Scale.
Source: Gotlib *et al.* (2016).[12]

Figure 13: Median MSAS scores per subscale in D2201



Analysis data cut-off: 9th July 2013; evaluable patients.
Delta values correspond to the median best percentage change from baseline and p-values were calculated using 2-sided Wilcoxon 2-sample test (t approximation).
Abbreviations: GDI: global distress index; PHYS: physical subscore; PSYCH: psychological subscore; TMSAS: total score on the Memorial Symptom Assessment Scale.
Source: Gotlib *et al.* (2016).[12]

Patient-reported symptoms (data cut-off: 1st December 2014)

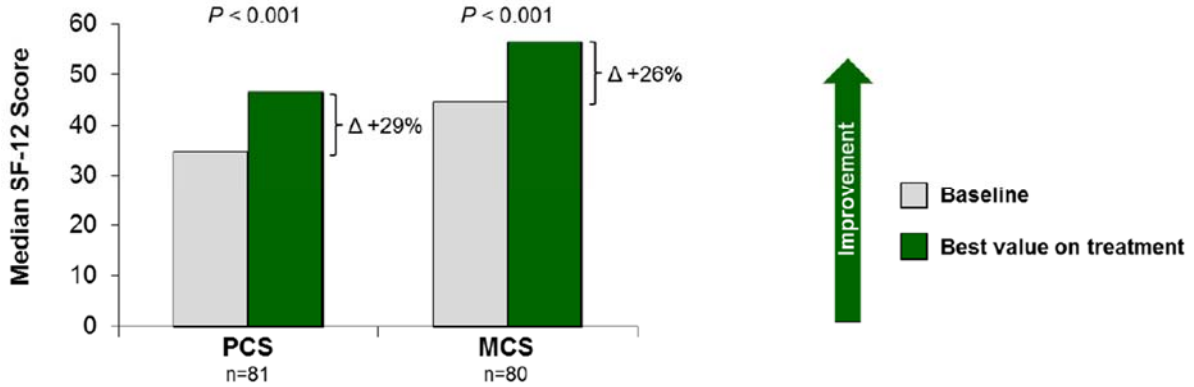
At the time of the analysis (data cut-off: 1st December 2014), the proportion of patients in the PEP with ≥50% decrease in MSAS scores relative to baseline for at least 168 days was 22.5% (n=20) for TMSAS score, 28.1% (n=25) for the MSAS-GDI score, and 23.6% (n=21) for the MSAS-PSYCH score.

Health-related quality of life (HRQoL) (data cut-off: 9th July 2013)

In D2201, HRQoL was assessed using the Medical Outcomes Study 12-Item Short-Form Health Survey (SF-12), which evaluates 12 measures, providing 2 scales of the patient's HRQoL: the physical composite score and the mental composite score.[84] The physical composite score 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 mental composite score includes questions regarding vitality (e.g. energy level), emotional role functioning (e.g. being emotionally able to perform work and other activities), mental health, and social functioning. The mental component score and the physical component score of the SF-12 both have a range of 0–100 and a minimal important difference of 4 points.

Median SF-12 scores for both the physical (PCS) and the mental components (MCS) were significantly higher than baseline, showing significant improvement with midostaurin (Figure 14).[12] The median percentage change from baseline was 29% for the best reported physical composite scores and 26% for the best reported mental composite scores on treatment. HRQoL data from this data cut-off were mapped to the EQ-5D-3L per NICE reference case[85] and used to inform the economic analysis in Section B.3.4.1.

Figure 14: Median physical and mental SF-12 composite scores in D2201



Analysis data cut-off: 9th July 2013; evaluable patients.
Delta values correspond to the median best percentage change from baseline and p-values were calculated using 2-sided Wilcoxon 2-sample test (t approximation).
Abbreviations: MCS: mental composite score; PCS: physical composite score; SF-12: Medical Outcomes Study 12-Item Short-Form Health Survey.
Source: Gotlib *et al.* (2016).[12]

B.2.6.2 A2213 (NCT00233454)

A2213 was an investigator-initiated, multicentre, single-group, open-label, phase II trial, which enrolled 26 patients from July 2005 to April 2010. Clinical data for the different outcomes were identified for 2 data cut-off points as follows:

- **Data cut-off: 3rd December 2012**
    - This analysis includes the analysis of overall response, OS, PFS, DoR, TTR, safety and tolerability.
    - Only safety data from this analysis have been presented in this submission where safety data from DeAngelo *et al.* (2018) (data cut-off: 1st March 2017) were unavailable[61]
    - Data are reported from the European Public Assessment Report (EPAR) and the Australian Public Assessment Report (APAR)[9, 80]
- **Data cut-off: 1st March 2017**
    - This analysis includes the analysis of overall response, OS, PFS, DoR, TTR, safety and tolerability.
    - Unless otherwise stated, all data presented for A2213 within this submission are from this data cut-off and are reported in the published manuscript by DeAngelo *et al.* (2018).[61]

No other prior or subsequent analyses of A2213 have been identified outside of conference abstracts.[76, 86, 87]

No data from A2213 was used in the economic analysis, since, although the results from A2213 were consistent with those reported in D2201, treatment with midostaurin was discontinued in patients who did not respond, which is not consistent with the SmPC and current UK experience of midostaurin. Moreover, as A2213 was investigator-initiated, Novartis did not have access to the latest individual patient-level data.

Primary endpoint

Best overall response (data cut-off: 1st March 2017)

In A2213, a confirmed response was defined as any MR or PR within the first 2 treatment cycles and maintained for ≥8 weeks based on published Valent and Cheson criteria.

At the end of stage 1 (11 patients), the response rate was 67% (n=6/9 evaluable patients), which was significantly greater than the prespecified 10% threshold for rejection of the null hypothesis.[76]

At the time of the analysis (data cut-off: 1st March 2017), the best overall response rate for the FAS within the first 12 cycles was 69% (n=18/26 patients; 95% CI: 50–88), with 50% having a MR (n=13/26 patients) and 19% having a PR (n=5/26 patients).[61] Details of the types of response observed in the FAS in the first 12 weeks of treatment (main trial protocol) are presented in Table 15. With follow-up beyond 12 cycles, the ORR did not change, but the quality of response in 2 patients improved from a MR-incomplete remission to complete remission. The median follow-up time in this analysis was 124 months (range 82–140 months) and the median duration of treatment was 19 months (range 2–132 months).

Table 15: Types of response in A2213

Type of response	Number of responders (n)	Proportion (%)
Overall response	**18**	**69**
Major response	13	50
Complete remission	0	0
Incomplete remission	10	38
Pure clinical response	3	12
Partial response	5	19
Good partial response	4	15
Minor partial response	1	4
Stable disease	**5**	**19**
Progressive disease	**3**	**12**

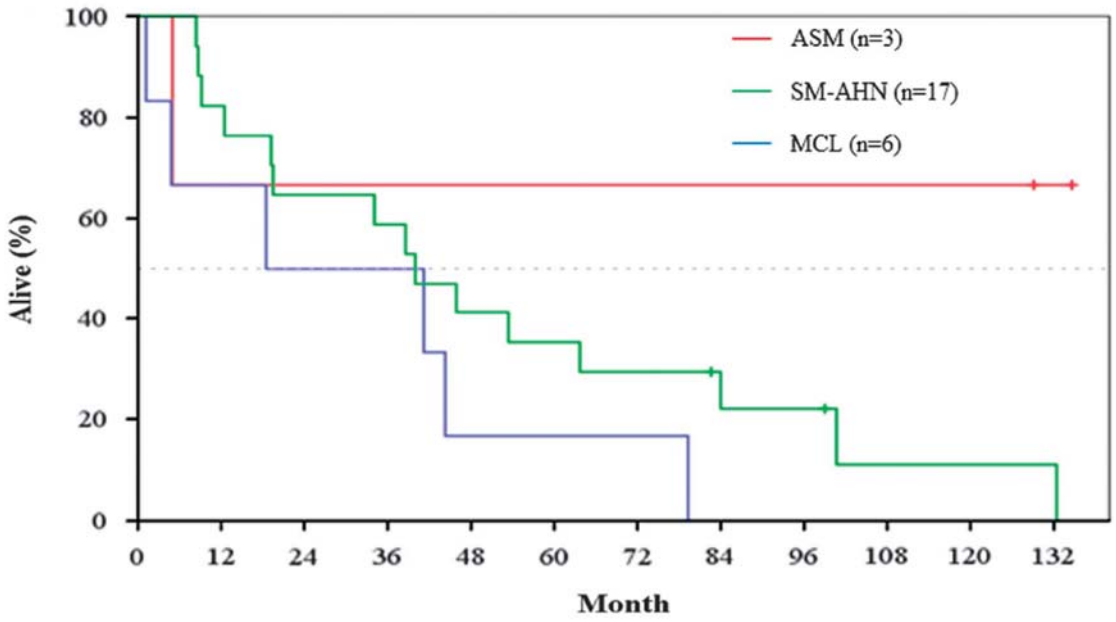
Analysis data cut-off: 1st March 2017; FAS.
Source: DeAngelo et al. (2018).[61]

Secondary endpoints

Overall survival (OS) (data cut-off: 1st March 2017)

In A2213, OS was defined as the time from the first treatment dose of midostaurin until the date of death or data cut-off. Median OS was 40.0 months (95% CI: 27.3–52.7; range 1.2–134.6 months) for the FAS and four patients (15%) were still alive (Figure 15).[61]

Figure 15: Kaplan-Meier plot of OS in A2213



Analysis data cut-off: 1st March 2017; FAS.
Abbreviations: ASM: aggressive systemic mastocytosis; MCL: mast cell leukaemia; SM-AHN: systemic mastocytosis with associated haematological neoplasm.
Source: DeAngelo *et al.* (2018).[61]

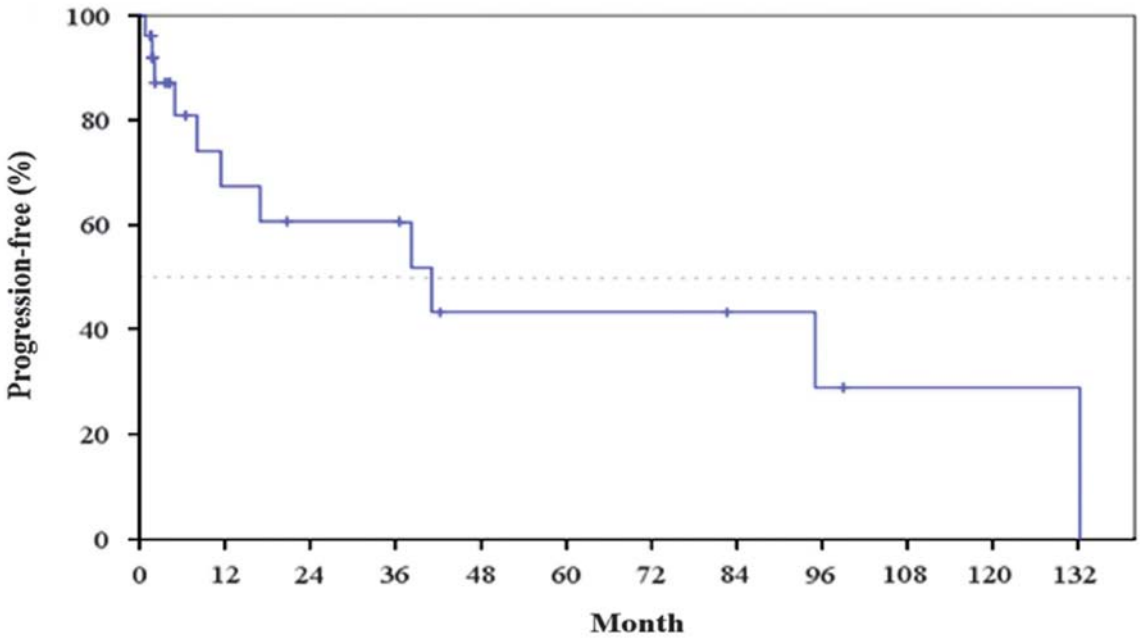
Progression-free survival (PFS) (data cut-off: 1st March 2017)

In A2213, PFS was defined as time from the first day of midostaurin treatment to the date of disease progression (SM or AHN component) or death, with data censored in cases of adverse

events, unsatisfactory treatment effect or study withdrawal and for those patients continuing treatment.

Median PFS was 41.0 months (95% CI: 4.4–77.6; Figure 16).[61] Progression on midostaurin was defined as disease progression (n=7) or death (n=3), with 16 patients censored as follows: adverse event (n=3), unsatisfactory treatment effect (n=8), withdrawal of consent (n=3) and continuing on treatment (n= 2).

Figure 16: Kaplan-Meier plot of PFS in A2213



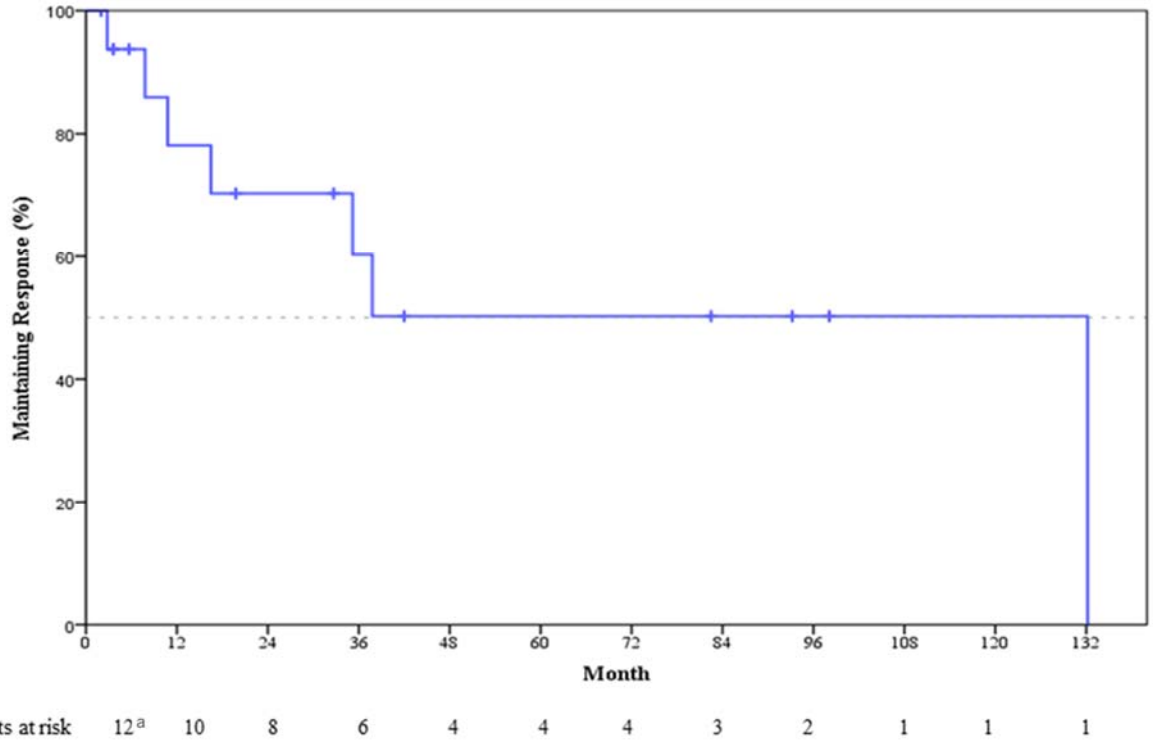
Analysis data cut-off: 1st March 2017; FAS.
Source: DeAngelo *et al.* (2018).[61]

Duration of response (DoR) (data cut-off: 1st March 2017)

In A2213, DoR was defined as the time from the first date of a (later confirmed) C-finding response until the date of loss of response (disease progression of SM or AHN component or death among patients showing a clinical response per Valent criteria), with data censored in cases of adverse events, unsatisfactory treatment effect or study withdrawal and for those patients continuing treatment.

Median DoR among the 18 main protocol responder patients was 132 months (95% CI: not estimated), with loss of response observed in 7 patients (39%; Figure 17).[61] This median DoR was reached when a patient with SM-AHN who had been on therapy for 11 years progressed to AML. Previously, the median DoR was not reached at 37.8 months and the DoR probability was 50.2%.

Figure 17: Kaplan-Meier plot of DoR in A2213



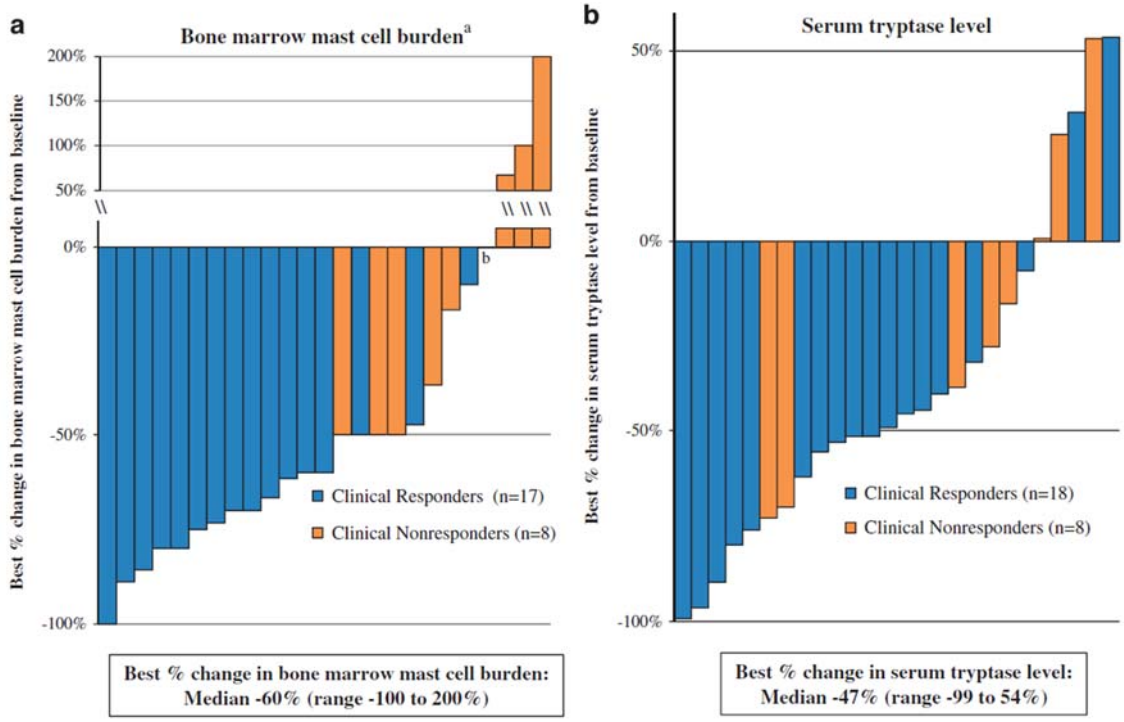
Analysis data cut-off: 1st March 2017; FAS.
Source: DeAngelo *et al.* (2018).[61]

Histopathologic response (data cut-off: 1st March 2017)

In A2213, histopathologic response was not defined, but mast cell infiltration in the bone marrow and changes in serum tryptase levels were assessed as part of ORR evaluation.[78]

At the time of the analysis (data cut-off: 1st March 2017), median best percentage change in bone marrow mast-cell burden among the 25 evaluable patients was -60% (range -100% to 200%)(Figure 18.A).[61] A decrease in bone marrow mast cell burden of ≥50% was observed in 68% of patients (n=17/25), with 40% of patients (n=10/25) maintaining a response for at least two consecutive biopsies. Median best percentage change in serum tryptase level among all 26 patients was -47% (range -99% to 54%)(Figure 18.B). A decrease in serum tryptase level of ≥50% was observed in 46% of patients (n=12/26), with 31% of patients (n=8/26) maintaining a response for at least 2 cycles. A ≥50% decrease in both marrow mast cell burden and serum tryptase level were observed in 31% of evaluable patients.

Figure 18: Histopathologic response in A2213



[a]Total number of evaluable patients was 25 out of 26, as one responder did not have quantification of bone marrow mast cells at baseline; described as 'focally involved'.
[b]Responder with best value of 0% change in bone marrow mast cells versus baseline.
Panel A shows best percentage change in bone marrow mast cell burden with midostaurin therapy in 25 patients who had a baseline evaluation and at least one postbaseline evaluation. Panel B shows best percentage change in serum tryptase level in all 26 patients in the FAS.
Analysis data cut-off: 1st March 2017; FAS.
Source: DeAngelo *et al.* (2018).[61]

B.2.7 *Subgroup analysis*

B.2.7.1 D2201 (NCT00782067)

Primary endpoint: best overall response (data cut-off: 9th July 2013)

In the analysis of D2201 (data cut-off: 9th July 2013), PEP subgroup analyses were conducted for ORR based on disease subtype (ASM, SM-AHN or MCL), KIT D816V mutation status (positive, negative or unknown) and number of prior therapies (0 or ≥1).[12]

Across disease subtypes, patients with ASM had the highest response rate of 75% (n=12/16 patients; 95% CI: 48–93), compared to 58% (n=33/57 patients; 95% CI: 44–71) and 50% (n=8/16 patients; 95% CI: 25–75) for patients with SM-AHN and patients with MCL, respectively (

Table 16; Figure 19). Responses were observed in all subgroups according to KIT D816V mutation status, including patients who were positive for KIT D816V (ORR 63%; 95% CI: 51–74) and those with a negative or unknown KIT D816V status (ORR 44%; 95% CI: 20–70)(Table 17). The proportion of patients with ≥1 previous therapies who showed treatment response (ORR 62%; 95% CI: 45–78) was similar to the proportion of responders with no prior therapies (ORR 58%; 95% CI: 43–71).

Table 16: Response rate by subtype of SM in D2201

Type of response	SM Subtype		
	ASM (n=16)	SM-AHN (n=57)	MCL (n=16)
Overall response, n (%)	**12 (75)**	**33 (58)**	**8 (50)**
Major response, n (%)	10 (62)	23 (40)	7 (44)
Complete remission, n (%)	0	0	0
Incomplete remission, n (%)	6 (38)	9 (16)	4 (25)
Pure clinical response, n (%)	4 (25)	9 (16)	2 (12)
Unspecified, n (%)	0	5 (9)	1 (6)
Partial response, n (%)	2 (12)	10 (18)	1 (6)
Good partial response, n (%)	1 (6)	10 (18)	0
Minor partial response, n (%)	1 (6)	0	1 (6)
Stable disease, n (%)	**1 (6)**	**7 (12)**	**3 (19)**
Progressive disease, n (%)	**1 (6)**	**6 (11)**	**3 (19)**
Patient could not be evaluated for response, n (%)[a]	**2 (12)**	**11 (19)**	**2 (12)**

[a]Reasons that patients could not be evaluated for response were concurrent use of high-dose glucocorticoids (n=9 patients), not enough time receiving treatment (n=3 patients), death (n=1 patient), red-cell transfusion (n=1 patient), and neutropenia (n=1 patient). Patients who could be evaluated for response had an assessment at baseline and at least one post-baseline assessment during the first 6 cycles of treatment.
Analysis data cut-off: 9th July 2013; PEP.
Abbreviations: ASM: aggressive systemic mastocytosis; MCL: mast cell leukaemia; SM-AHN: systemic mastocytosis with associated haematologic neoplasm; SM: systemic mastocytosis.
Source: Gotlib *et al.* (2016).[12]

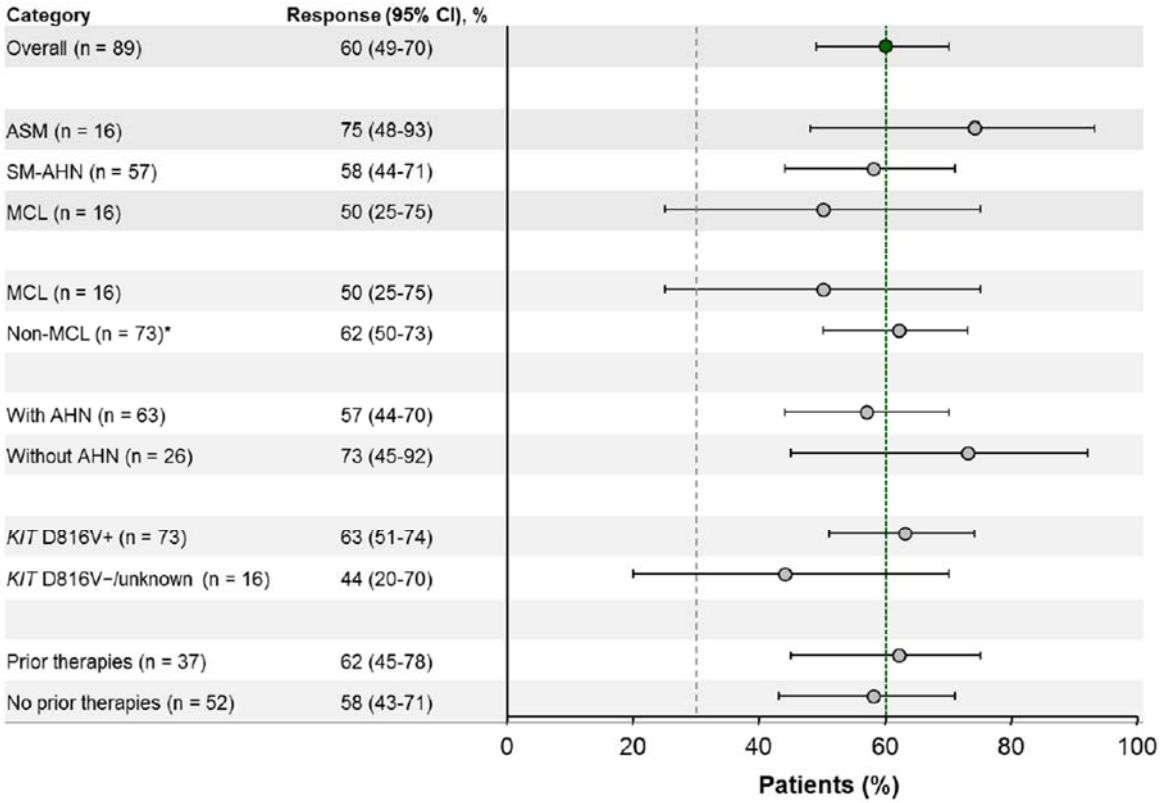
Table 17: Summary response rate by subgroup in D2201

Subgroup	Total number of patients (n)	Number of responders (n)[a]	ORR (%)	95% CI
Subtype of advanced SM				
ASM	16	12	75	48–93
SM-AHN	57	33	58	44–71
MCL	16	8	50	25–75
Presence of MCL				
MCL	16	8	50	25–75
Non-MCL	73[b]	45	62	50–73
Presence of AHN				
With AHN	63[c]	36	57	44–70
Without AHN	26	19	73	45–92
***KIT* D816V mutation status**				
Positive	73	46	63	51–74
Negative/Unknown	16	7	44	20–70
Number of previous therapies				
0	52	30	58	43–71

≥1	37	22	62	45–78

[a]Number of responders derived from the total number of patients in each subgroup multiplied by the respective ORR.
[b]Non-MCL represents patients with ASM or SM-AHN.
[c]With AHN represented patients with SM-AHN and patients with MCL-AHN.
Analysis data cut-off: 9th July 2013; PEP.
Abbreviations: AHN: associated haematological neoplasm; ASM: aggressive systemic mastocytosis; CI: confidence intervals; D816V: substitution of aspartic acid in position 816 to valine; MCL: mast cell leukaemia; ORR: overall response rate; SM-AHN: systemic mastocytosis with an associated haematological neoplasm.
Source: Gotlib *et al.* (2016).[12]

Figure 19: Response rate by subgroup in D2201



Green dashed line indicates overall proportion of responders in D2201.
Analysis data cut-off: 9th July 2013; PEP.
Abbreviations: ASM: aggressive systemic mastocytosis; CI: confidence intervals; D816V: substitution of aspartic acid in position 816 to valine; MCL: mast cell leukaemia; SM-AHN: systemic mastocytosis with associated haematologic neoplasm; SM: systemic mastocytosis.
Source: Gotlib *et al.* (2016).[12]

Primary endpoint: best overall response (data cut-off: 1st December 2014)

Data from this analysis (data cut-off: 1st December 2014) have not been presented separately as they are in agreement with data presented above (data cut-off: 9th July 2013).[9, 80]

Secondary endpoints: OS, PFS, DoR (data cut-off: 9th July 2013)

PEP subgroup analyses were conducted for OS, PFS and DoR in the analysis (data cut-off: 9th July 2013) based on disease subtype (ASM, SM-AHN or MCL).[12] Median OS was not reached for ASM patients (95% CI: 28.7–not estimated), but was reached at 20.7 months for patients with SM-AHN (95% CI: 16.0–44.4) and at 9.4 months for patients with MCL (95% CI: 7.5–not estimated; Table 18). The Kaplan-Meier plot indicated that OS was highest for patients with ASM (Figure 20).[12, 73] Median PFS was also highest for patients with ASM at 28.7 months (95% CI: 24.8–not

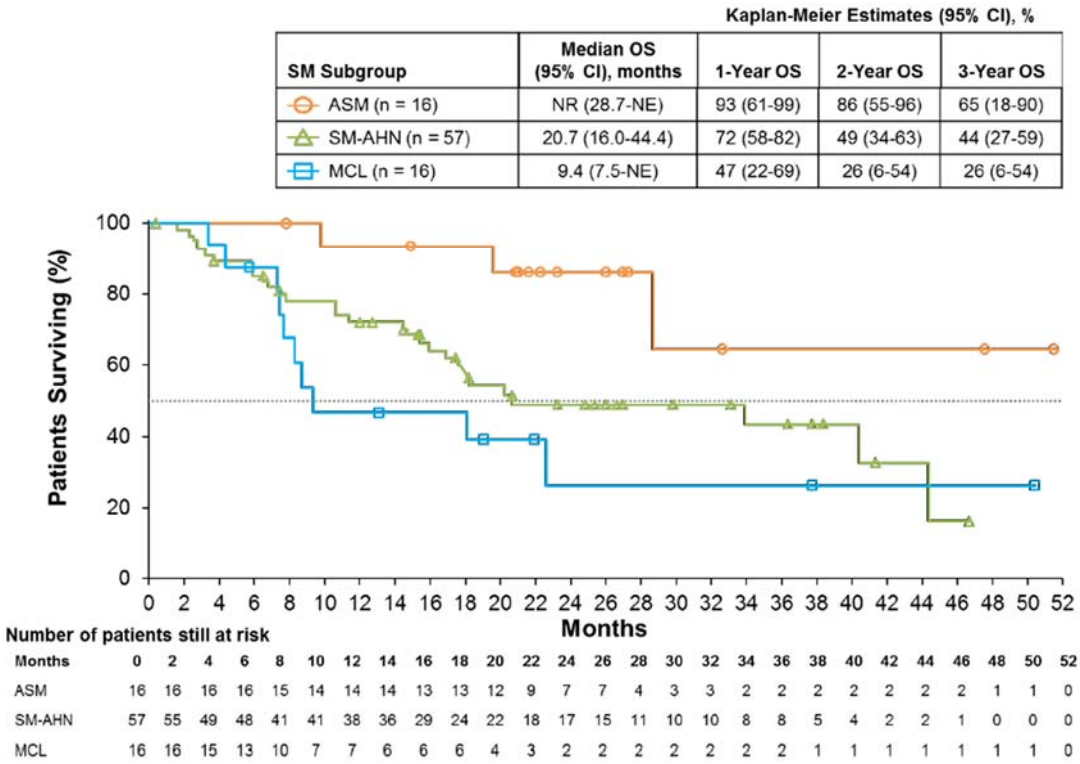
estimated) compared to 11.0 months for patients with SM-AHN (95% CI: 7.4–17.0) and 11.3 months for patients with MCL (95% CI: 2.8–not estimated; Figure 21).[12] Median DoR was not reached in patients with ASM (95% CI: 24.1–not estimated) and patients with MCL (95% CI: 3.6–not estimated), but was reached at 12.7 months in patients with SM-AHN (95% CI: 7.4–31.4; Figure 22).[12]

Table 18: Secondary endpoints by subgroup in D2201

Endpoint	ASM (n=16)	SM-AHN (n=57)	MCL (n=16)
OS – months			
Median	NR	20.7	9.4
95% CI	28.7–NE	16.0–44.4	7.5–NE
PFS – months			
Median	28.7	11.0	11.3
95% CI	24.8–NE	7.4–17.0	2.8–NE
DoR – months			
Median	NR	12.7	NR
95% CI	24.1–NE	7.4–31.4	3.6–NE

Analysis data cut-off: 9th July 2013; PEP.
Abbreviations: ASM: aggressive systemic mastocytosis; CI: confidence intervals; DoR: duration of response; MCL: mast cell leukaemia; NE: not estimated; NR: not reached; OS: overall survival; PFS: progression-free survival; SM-AHN: systemic mastocytosis with associated haematologic neoplasm.
Source: Gotlib *et al.* (2016).[12]

Figure 20: Kaplan-Meier plot of OS by subgroup in D2201

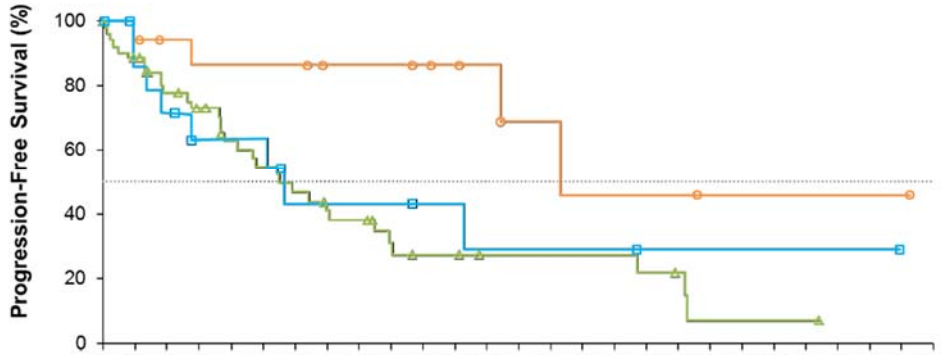


Analysis data cut-off: 9th July 2013; PEP.
Abbreviations: ASM: aggressive systemic mastocytosis; CI: confidence intervals; MCL: mast cell leukaemia; NE: not estimated; NR: not reached; OS: overall survival; SM-AHN: systemic mastocytosis with associated haematologic neoplasm.
Source: Gotlib *et al.* (2016).[12]

Figure 21: Kaplan-Meier plot of PFS by subgroup in D2201

Kaplan-Meier Estimates (95% CI), %

SM Subgroup	Median PFS (95% CI), months	1-Year PFS	2-Year PFS	3-Year PFS
ASM (n = 16)	28.7 (24.8-NE)	87 (56-96)	87 (56-96)	46 (8-79)
SM-AHN (n = 57)	11.0 (7.4-17.0)	47 (31-61)	28 (14-43)	22 (9-39)
MCL (n = 16)	11.3 (2.8-NE)	44 (16-69)	29 (6-59)	29 (6-59)



Number of patients still at risk

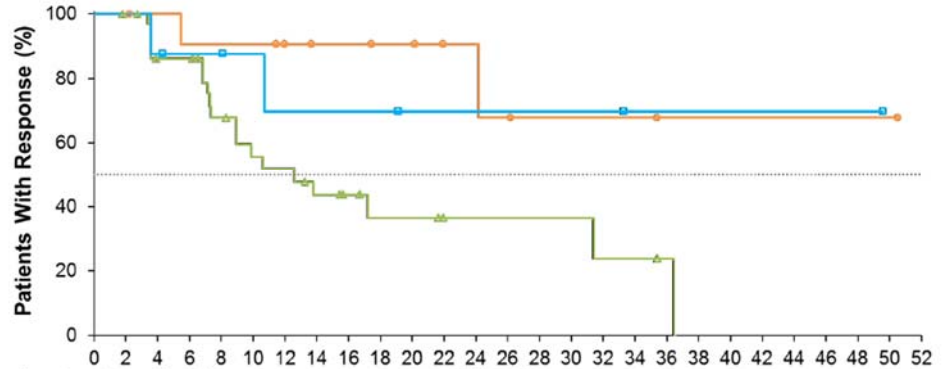
Months	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52
ASM	16	15	13	12	12	12	11	9	9	9	7	6	5	3	3	2	2	2	2	1	1	1	1	1	1	1	0
SM-AHN	57	43	35	30	24	21	17	14	13	9	7	7	5	5	5	5	5	4	3	1	1	1	1	0	0	0	0
MCL	16	12	10	7	7	7	4	4	4	4	3	3	2	2	2	2	2	1	1	1	1	1	1	1	1	0	0

Analysis data cut-off: 9th July 2013; PEP.
Abbreviations: ASM: aggressive systemic mastocytosis; CI: confidence intervals; MCL: mast cell leukaemia; NE: not estimated; PFS: progression-free survival; SM-AHN: systemic mastocytosis with associated haematologic neoplasm.
Source: Gotlib *et al.* (2016).[12]

Figure 22: Kaplan-Meier plot of DoR by subgroup in D2201

Kaplan-Meier Estimates (95% CI), %

SM Subgroup	Median DOR (95% CI), months	1-Year DOR	2-Year DOR	3-Year DOR
ASM (n = 12)	NR (24.1-NE)	91 (51-99)	91 (51-99)	68 (16-92)
SM-AHN (n = 33)	12.7 (7.4-31.4)	52 (32-69)	38 (17-56)	24 (6-49)
MCL (n = 8)	NR (3.6-NE)	70 (22-92)	71 (6-49)	70 (22-92)



Number of patients still at risk

Months	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52
ASM	12	12	11	10	10	9	7	7	6	6	5	4	3	2	2	2	2	1	1	1	1	1	1	1	1	1	0
SM-AHN	33	32	26	25	18	14	13	10	8	5	5	4	3	3	3	3	2	2	1	0	0	0	0	0	0	0	0
MCL	8	8	7	6	6	5	4	4	4	4	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1	0	0

Analysis data cut-off: 9th July 2013; n=53 patients with documented response.
Abbreviations: ASM: aggressive systemic mastocytosis; CI: confidence intervals; DoR: duration of response; MCL: mast cell leukaemia; NE: not estimated; PFS: progression-free survival; SM-AHN: systemic mastocytosis with associated haematologic neoplasm.
Source: Gotlib *et al.* (2016).[12]

Secondary endpoints: OS, PFS, DoR (data cut-off: 1st December 2014)

PEP subgroup analyses (Table 19) were conducted for OS, PFS and DoR in the analysis (data cut-off: 1st December 2014) based on disease subtype (ASM, SM-AHN or MCL).[9, 80] Results remained similar to those of the earlier data cut-off (9th July 2013) for PFS and DoR, however median OS was reached for patients with ASM and was highest at 51.1 months (95% CI: 28.7–not estimated), compared to 20.7 months for patients with SM-AHN (95% CI: 16.3–33.9) and 9.4 months for patients with MCL (95% CI: 7.5–not estimated).

Table 19: Secondary endpoints by subgroup in D2201

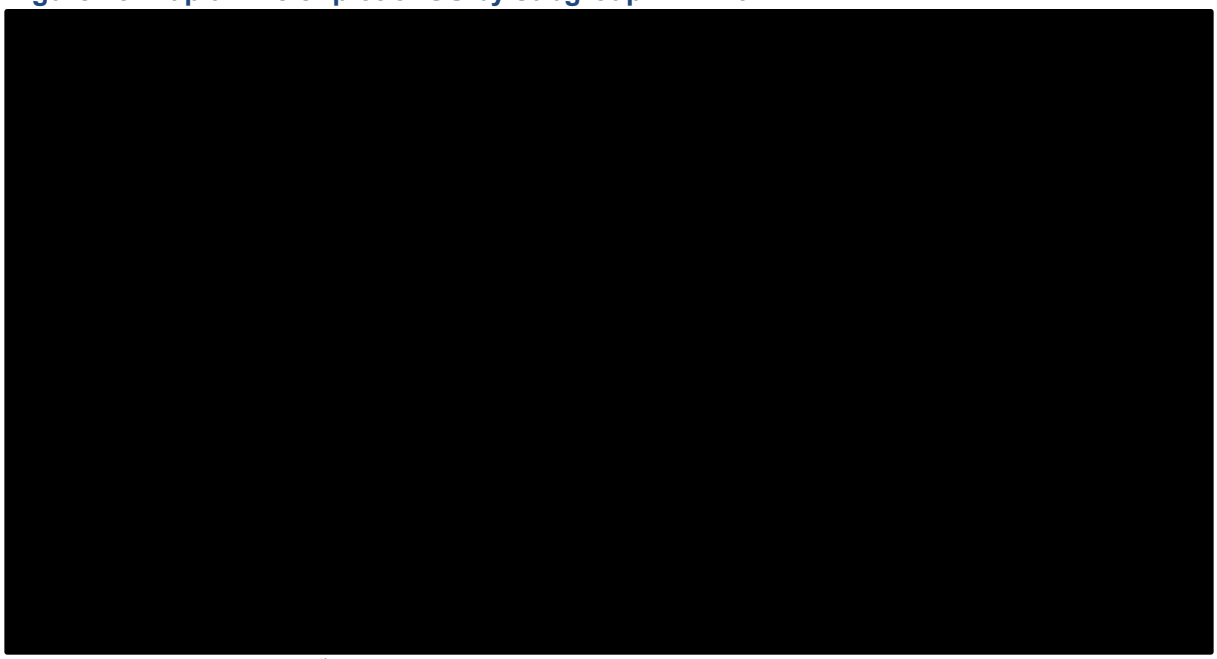
Endpoint	ASM (n=16)	SM-AHN (n=57)	MCL (n=16)
OS – months			
Median	51.1	20.7	9.4
95% CI	28.7–NE	16.3–33.9	7.5–NE
PFS – months			
Median	NR	11.0	11.3
95% CI	–	7.4–17.9	2.8–NE
DoR – months			
Median	NR	12.7	–
95% CI	–	7.4–31.4	–

Analysis data cut-off: 1st December 2014; PEP.
Abbreviations: ASM: aggressive systemic mastocytosis; CI: confidence intervals; DoR: duration of response; MCL: mast cell leukaemia; NE: not estimated; NR: not reached; OS: overall survival; PFS: progression-free survival; SM-AHN: systemic mastocytosis with associated haematologic neoplasm.
Source: Australian Public Assessment Report of Midostaurin (2019).[80]

Secondary endpoints: OS, PFS, DoR (data cut-off: 24th August 2017)

Subgroup analyses were conducted for OS in the final analysis (data cut-off: 24th August 2017; PEP) based on disease subtype (ASM, SM-AHN or MCL).[73] Median OS was [redacted] for ASM patients (95% CI: [redacted]), but was reached at [redacted] months for patients with SM-AHN (95% CI: [redacted]) and at [redacted] months for patients with MCL (95% CI: [redacted]Table 18). The Kaplan-Meier plot indicated that OS [redacted] for patients with ASM (Figure 23).[73]

Figure 23: Kaplan-Meier plot of OS by subgroup in D2201



Final analysis data cut-off: 24th August 2017; PEP.
Abbreviations: ASM: aggressive systemic mastocytosis; MCL: mast cell leukaemia; SM-AHNMD: systemic mastocytosis with an associated non-mast cell lineage clonal haematological disease, synonymous to SM-AHN.
Source: D2201 CSR Report (data cut-off: 24th August 2017).[73]

Full results of subgroup analyses of D2201 are presented by Gotlib *et al.* (2016) and summarised in Appendix E.[12]

Since D2201 is a single-arm, open-label phase II study in an extremely heterogeneous population with very limited patient numbers for each subgroup (n=16, n=16, and n=57 for the ASM, MCL and SM-AHN subgroups, respectively), subgroup analyses of the individual disease subtypes in the economic modelling would be associated with considerable uncertainty. However, following discussions with UK clinical experts and preliminary discussions with NICE and the ERG in the lead up to this appraisal, it was recognised that there remains a large unmet medical need for further therapies for patients with advanced SM and, in particular, for patients with SM-AHN and MCL. Together, these two populations represent 82% of the population included in the pivotal D2201 trial, and have a recognised poorer prognosis than ASM, with a shorter life expectancy compared to the overall population of advanced SM.

Consequently, a subgroup analysis for the pooled population of patients with SM-AHN + MCL is considered in this submission alongside the results for the overall licensed advanced SM population (comprising ASM, SM-AHN and MCL). This approach was considered reasonable by clinical experts, with the acknowledgement that a subgroup analysis constituting the SM-AHN + MCL subtypes represents a poor prognosis population of SM patients with a shorter life expectancy (compared with ≥41 months for the ASM subtype), and a high degree of unmet medical need for effective therapies to improve survival.

B.2.7.2 A2213 (NCT00233454)

Primary endpoint: best overall response (data cut-off: 1st March 2017)

In the analysis of A2213 (data cut-off: 1st March 2017), FAS subgroup analyses were conducted for ORR based on disease subtype (ASM, SM-AHN or MCL), *KIT* D816V mutation status (positive,

negative or other), number of prior therapies (0 or ≥1), C-findings present at baseline (anaemia, thrombocytopaenia, neutropenia or non-haematologic C-findings) and additional SM-related findings (pleural effusions and increased alkaline phosphatase)(Table 20).[61] In contrast to results from D2201, patients with ASM in A2213 had the lowest response rate across disease subgroups with an ORR of 33%, compared to 76% and 67% for patients with SM-AHN and patients with MCL, respectively (Table 20). Response rates for patients who were positive for KIT D816 (ORR 80%) were higher than those seen in patients with a negative *KIT* D816 status or who were positive for other mutations (ORR 33%). The proportion of patients with ≥1 previous therapies who showed treatment response (ORR 67%) was similar to the proportion of responders with no prior therapies (ORR 80%). Importantly, the differences in ORR observed in A2213 were not statistically significant across subgroups analysed by disease type, KIT D816V mutation status and number of prior therapies.

Responses were observed in all subgroups according to C-findings present at baseline, except for transfusion-dependent thrombocytopaenia (n=0/2, ORR 0%), neutropenia (n=0/1, ORR 0%) and lytic lesions (n=0/9, ORR 0%). Response rates were similar across haematologic and non-haematologic C-findings, with ORRs between 50–100% (Table 20).[61]

Table 20: Response rate by subgroup in A2213

Subgroup	Number of patients (n)	Number of responders (n)	ORR (%)	p-value[a]
Subtype of advanced SM				NS
ASM	3	1	33	
SM-AHN	17	13	76	
MCL	6	4	67	
***KIT* D816 mutation status**				0.051
Positive	20	16	80	
Negative/Other	6	2	33	
Number of previous therapies				NS
0	5	4	80	
≥1	21	14	67	
C-findings present at baseline				NR
Anaemia				
All	15	8	53	
Not transfusion-dependent	12	7	58	
Transfusion-dependent	3	1	33	
Thrombocytopaenia				
All	10	5	50	
Not transfusion-dependent	8	5	63	
Transfusion-dependent	2	0	0	
Neutropenia	1	0	0	
Non-haematologic				
Hypoalbuminemia	12	9	75	
Ascites	12	8	67	
Weight loss[b]	12	6	50	

Lytic lesions	9	0	0	
Increased total bilirubin	3	2	67	
Increased ALT or AST	2	2	100	
Additional SM-related findings				NR
Pleural effusions	4	3	75	
Increased alkaline phosphatase	23	11	48	

Analysis data cut-off: 1st March 2017; FAS.
[a]Fisher's Exact Test used for comparison of category subgroups.
[b]Medically documented loss of at least 10% of body weight within 12 months before study.
Abbreviations: ASM: aggressive systemic mastocytosis; ALT: alanine aminotransferase; AST: aspartate aminotransferase; D816: mutation in codon for aspartic acid in position 816; MCL: mast cell leukaemia; NR: not reported; NS: not significant; SM: systemic mastocytosis; SM-AHN: systemic mastocytosis with associated haematologic neoplasm.
Source: DeAngelo *et al.* (2018).[61]

Secondary endpoints (data cut-off: 1st March 2017)

In addition, subgroup analyses were conducted for OS based on disease subtype (ASM, SM-AHN or MCL). Median OS was not reached for ASM patients (95% not estimated), but was reached at 40.0 months for patients with SM-AHN (95% CI: 24.2–55.9) and at 18.5 months for patients with MCL (95% CI: 0–62.2; Table 21). The Kaplan-Meier plot is presented in Section B.2.6.2 (Figure 15) and indicated that OS was highest for patients with ASM.

Table 21: OS by subgroup in A2213

Endpoint	ASM (n=3)	SM-AHN (n=17)	MCL (n=6)
OS – months			
Median	NR	40.0	18.5
95% CI	NE	24.2–55.9	0–62.2

Analysis data cut-off: 1st March 2017; FAS.
Abbreviations: ASM: aggressive systemic mastocytosis; CI: confidence intervals; MCL: mast cell leukaemia; NE: not estimated; NR: not reached; OS: overall survival; SM-AHN: systemic mastocytosis with associated haematologic neoplasm.
Source: DeAngelo *et al.* (2018).[61]

Full results of subgroup analyses carried out in A2213 are presented by DeAngelo *et al.* (2018) and summarised in Appendix E.[61] As described in Section B.2.2, data from A2213 are not considered in the economic analysis (other than as part of the pooled analysis for OS by Reiter *et al.* [2017]).[23]

B.2.8 *Meta-analysis*

Not applicable.

B.2.9 *Indirect and mixed treatment comparisons*

As previously discussed in Section B.2.2, the relevant clinical evidence for midostaurin is from D2201 and A2213, which were both single-arm trials. Given the issues associated with conducting robust RCTs in orphan diseases, data for the comparators of interest as defined in the decision problem are also limited to single arm studies. Therefore, given the lack of comparative efficacy data of midostaurin versus the relevant comparators, an indirect treatment comparison was not possible.

The SLR identified three publications that reported on a comparison of the efficacy of midostaurin in terms of overall survival with historical control data, one from a German registry (Reiter *et al.* [2017])[23] and two from a French registry (CEREMAST) [64, 65] (Section B.2.2). These historical control studies are described in detail in Section B.2.9.1 since they provide the only available evidence of the overall survival benefit of midostaurin over the current SoC.

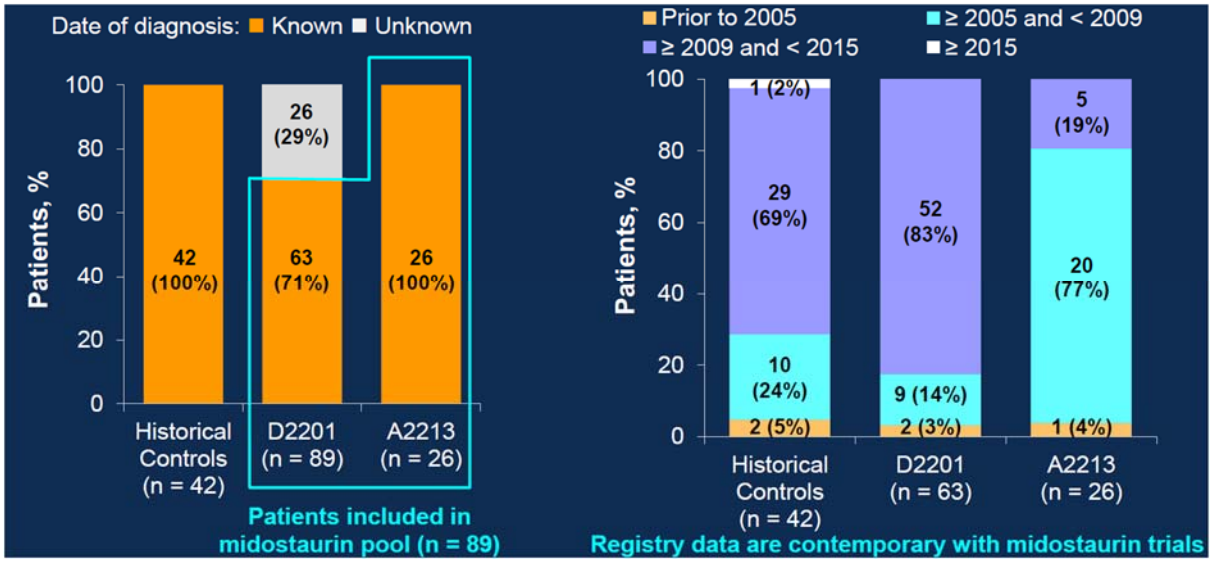
Evidence identified for the comparators defined in the final NICE scope is described in Section B.2.2.2 and the study characteristics and findings of these studies are summarised in Section B.2.9.2.

B.2.9.1 Summary of historical control data from the SLR

The pooled analysis of midostaurin D2201 and A2213 versus German registry

In order to make the most use of the available data for midostaurin (D2201 and A2213), and maximise the overall sample size, the analysis published by Reiter *et al.* (2017) pooled survival data from both trials in order to investigate a comparison to historical controls.[23] Patients for whom a date of diagnosis was known were considered in the analysis, including 63 patients of the PEP in D2201, all 26 patients of the FAS in A2213 and 42 patients from a German patient registry contemporary with both trials (Figure 24).

Figure 24: Patients included in the pooled survival analysis



Source: Reiter *et al.* 2017.[23]

The historical OS comparison was conducted to determine if baseline characteristics and subgroup analyses affected median OS and risk of death, presented as hazard ratio (HR). Survival data used in this analysis corresponds to the data cut-off of 1st July 2016 for the midostaurin pool and 9th May 2017 for the registry data.

An overview of the baseline characteristics of patients included in the historical OS comparison is presented in Table 22.[23] Overall, patient baseline characteristics were comparable between the two groups except for age. Over half of patients were male, with 65% in the midostaurin group and 69% in the registry control group, and a median of 2 patients had received previous therapies in both groups. Disease subtypes were proportionally similar, with 18% and 21% of patients diagnosed with ASM, 66% and 67% of patients diagnosed with SM-AHN and 16% and 12% of patients diagnosed with MCL in the midostaurin group and the registry control group, respectively.

The majority of patients were positive for a KIT D816 mutation, with rates of 82% in the midostaurin group and 93% in the registry control. Additionally, time from diagnosis to start of last therapy was under a year, with a median of 2.2 months for midostaurin-treated patients and 7.3 months for registry controls.

The key difference between the patient populations in the midostaurin group and the registry control group was primarily related to patient age at diagnosis, as 42% of patients in the midostaurin group were diagnosed with advanced SM after the age of 65, compared to 71% of registry control patients.

Table 22: Baseline characteristics of patients in the historical OS comparison study

	Midostaurin group (N=89)	Registry controls[a] (N=42)
Age at diagnosis – n patients (%)		
>65 years	37 (42)	30 (71)
Sex – n (%)		
Male	58 (65)	29 (69)
Number of previous therapies – n		
Median (range)	2 (1–5)	2 (0–5)
Subtype of advanced SM – n (%)		
ASM	16 (18)	9 (21)
SM-AHN	59 (66)	28 (67)
MCL	14 (16)	5 (12)
***KIT* D816 mutation status – n (%)**		
Positive	73 (82)	39 (93)
Unknown	1 (1)	0 (0)
Serum tryptase level – µg/L (range)		
At diagnosis	–	195 (14.0–1675.0)
Prior to last treatment	267 (22.2–12069.0)	–
Time from diagnosis to start of last therapy – months		
Median (IQR)	2.2 (0.5–7.8)	7.3 (1.0–26.1)

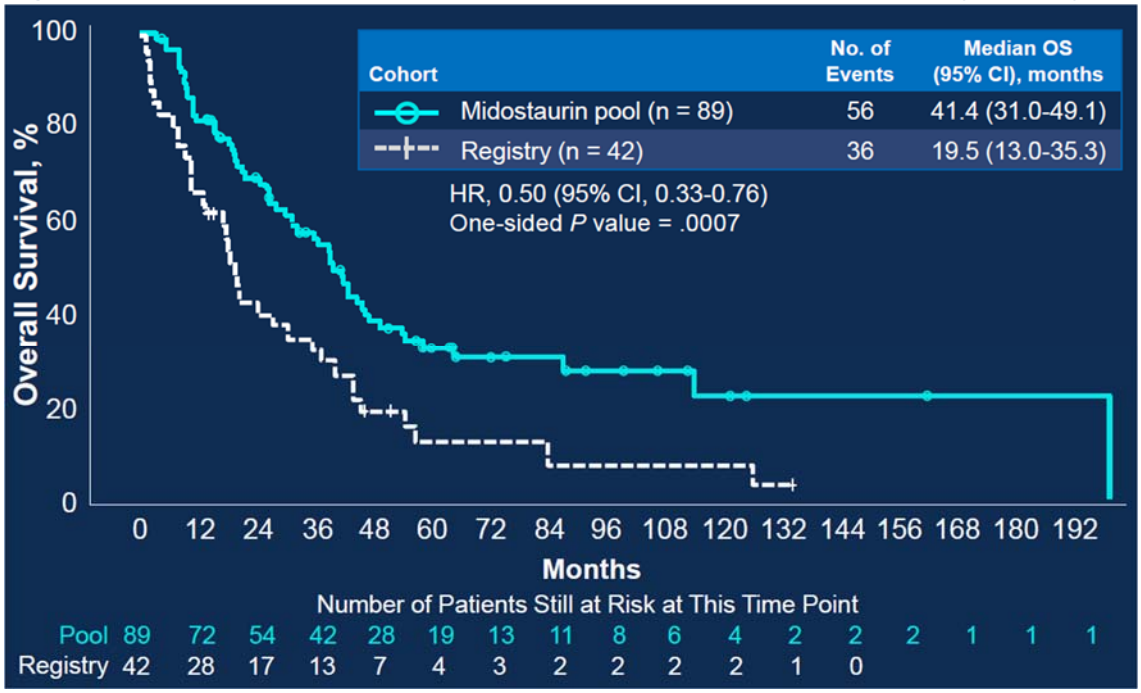
[a]Registry included 51 patients with advanced SM. Patients were excluded based on prior midostaurin exposure (n=8) and misdiagnosis (n=1). The remaining 42 patients were included in analysis; no matching was performed for selection of patients.
Abbreviations: ASM: aggressive systemic mastocytosis; D816: mutation in codon for aspartic acid in position 816; IQR: interquartile range; MCL: mast cell leukaemia; SM: systemic mastocytosis; SM-AHN: systemic mastocytosis with associated haematologic neoplasm.
Source: Reiter *et al.* 2017.[23]

For the primary analysis of this study, OS was evaluated from time of diagnosis to death and only patients with known dates of diagnosis were included. Median OS was 41.4 months (95% CI: 31.0–49.1) in the midostaurin group and 19.5 months (95% CI: 13.0–35.3) in the registry group (Figure 25). Median exposure to midostaurin was 12.9 months. Median duration of follow-up from time of diagnosis to data cut-off was 79.5 months (range 51.4–234.0) in the midostaurin group and 84.2 months (range 22.3–176.3 months) in the registry group.

The primary analysis revealed that the risk of death was 50% lower in midostaurin-treated patients compared to registry controls (HR: 0.50; 95% CI: 0.33–0.76; p=0.0007; unadjusted comparisons)

(Table 23). The survival benefit of midostaurin treatment was also maintained after multivariate adjustment (HR: 0.517; 95% CI: 0.319–0.839; one-sided p=0.0075).

Figure 25: Kaplan-Meier plot of OS in the historical OS comparison study primary analysis



Abbreviations: CI: confidence interval; HR: hazard ratio; OS: overall survival.
Source: Reiter *et al.* (2017).[23]

The primary analysis also included propensity score matching based on age group at diagnosis, disease subtype (ASM, MCL or SM-AHN), prior lines of treatment and sex (n=42 patients in the midostaurin group and n=42 patients in the registry control group). A stratified Cox model by matched pairs demonstrated that midostaurin reduced risk of death by 36% compared to registry controls (HR: 0.636; 95% CI: 0.326–1.244) (Table 23). To compensate for potential bias in patient selection, a sensitivity analysis was carried out using time from start date of last treatment to death. It was established that midostaurin reduced the risk of death by 56% compared to registry controls (HR: 0.44; 95% CI: 0.29–0.67; p<0.0001) (Table 23).

Table 23: Summary of results from the historical OS comparison study

Analysis	Midostaurin group			Registry controls			Results	
	Patients(n)	Events (n)	Median OS (95% CI)	Patients (n)	Events (n)	Median OS (95% CI)	HR (95% CI)	p-value
Primary, unadjusted comparisons	89	56	41.4 (31.0–49.1)	42	36	19.5 (13.0–35.3)	0.50 (0.33–0.76)	p=0.0007
Primary, multivariate adjustment	89	56	41.4 (31.0–49.1)	42	36	19.5 (13.0–35.3)	0.517 (0.319–0.839)	p=0.0075[a]
Primary, propensity score	42	31	27.8 (19.3–44.6)	42	36	19.5 (13.0–35.3)	0.636 (0.326–1.244)	–
Sensitivity analysis	115	75	28.7 (19.2–34.7)	39[b]	33	5.7 (2.2–11.7)	0.44 (0.29–0.67)	p<0.0001

[a]One-sided p-value.

[b]Three patients in the registry were not treated.
Abbreviations: CI: confidence interval; HR: hazard ratio; OS: overall survival; pts: patients.
Source: Reiter *et al.* 2017.[23]

Subgroup analysis of OS from the date of diagnosis showed a significant difference in the midostaurin group favouring female patients (HR: 0.30; 95% CI: 0.15–0.62; one-sided p=0.0006) with SM with AHN (HR: 0.45; 95% CI: 0.27–0.72; one-sided p=0.0006) and *KIT* D816V positive disease (HR: 0.45; 95% CI: 0.28–0.70; one-sided p=0.0003) (Table 24).

Table 24: Subgroup analyses of OS from diagnosis date from the historical OS comparison study

Subgroup	Midostaurin group, n	Registry controls, n	HR (95% CI)	One-sided p-value
Age at diagnosis ≤65 years	52	12	0.58 (0.28–1.20)	p=0.0720
Age at diagnosis >65 years	37	30	0.60 (0.35–1.02)	p=0.0307
Male	58	29	0.70 (0.42–1.18)	p=0.0905
Female	31	13	0.30 (0.15–0.62)	**p=0.0006**
SM without AHN	16	9	0.48 (0.16–1.49)	p=0.1031
SM with AHN	59	28	0.45 (0.27–0.72)	**p=0.0006**
MCL	14	5	0.69 (0.18–2.60)	p=0.2897
KIT D816V positive	67	39	0.45 (0.28–0.70)	**p=0.0003**

Significant p-values in bold.
Abbreviations: AHN: associated haematologic neoplasm; CI: confidence interval; D816: mutation in codon for aspartic acid in position 816; HR: hazard ratio; MCL: mast cell leukaemia; SM: systemic mastocytosis.
Source: Reiter *et al.* 2017.[23]

Consequently, the HR for OS from the primary multivariate analysis (0.517 (0.319–0.839) was used in the base case economic analysis (Section B.3.3.2, B.3.3.6) since the results of the multivariate analysis were consistent with those from the primary analysis and can be considered more methodologically appropriate compared to the other analyses conducted (e.g. matched analysis) since:

- the multivariate analyses considered the simultaneous impact of multiple baseline characteristics (on the HR for OS whilst maintaining the large sample size (n=89 for midostaurin vs n=42 for registry controls)
- the matched analysis using propensity scoring excluded a large proportion of patients and was based on a reduced sample size (n = 42 for midostaurin and n= 42 of registry controls)

The analysis of midostaurin in a French Compassionate use programme versus French registry

The study was conducted by The French National Reference Center for Mastocytosis (CEREMAST) as a prospective survey of patients with mastocytosis who were treated with midostaurin under a transitory-use authorisation program.[64, 65] Overall, 28 patients were included, as follows: 4 with ASM, 18 with SM-AHN, 3 with MCL, 1 with mast-cell sarcoma (MCS) and 2 with progressive smouldering SM (SSM). Patients were treated with midostaurin at a dose of 100 mg twice daily, which aligns with the licensed dose of midostaurin in this indication.

In CEREMAST, OSS, OS, DoR and safety were defined as study endpoints. Treatment response was assessed using modified Valent and Cheson criteria as applied in D2201 (Section B.2.3.1). In addition, OS data were compared between patients receiving midostaurin and a control group of 44 patients matched for age at diagnosis and subtype of mastocytosis, as defined by the WHO,

who did not receive midostaurin. Data were analysed using propensity-score matching with a logistic-regression method.

Baseline characteristics

At baseline, there were no significant differences between the two groups according to demographic or disease characteristics (Table 25). The control group had received more treatment lines, notably cladribine (49% in the control group versus 21% in the midostaurin group). Mean follow-up time from diagnosis was similar across both groups.

Table 25: Baseline characteristics of patients in CEREMAST

	Midostaurin-treated group (N=28)	French historical OS control group (N=44)
Age (years)		
Median (range)	67 (29–85)	NR
Median age at diagnosis (range)	65 (12–84)	66 (14–87)
Sex – n (%)		
Male	24 (85)	27 (61)
Number of previous therapies – n		
Median (range)	1.5 (1–3)	2 (1–4)
Subtype of advanced SM – n (%)		
ASM	4 (14)	5 (11)
SM-AHN	18 (64)	33 (75)
MCL	3 (11)	2 (5)
MCS	1 (4)	2 (5)
Progressive SSM	2 (7)	2 (5)
***KIT* D816 mutation status – n (%)**		
Positive	27 (96.5)[a]	37 (84)[a]
Negative	1 (3.5)	7 (16)

[a]All patients were positive for the *KIT* D816V mutation. The number of patients was calculated on the basis of the reported percentage and the size of the midostaurin-treated group (N=28).
Abbreviations: ASM: aggressive systemic mastocytosis; D816: mutation in codon for aspartic acid in position 816; MCL: mast cell leukaemia; MCS: mast-cell sarcoma; NR: not reported; OS: overall survival; SM: systemic mastocytosis; SM-AHN: systemic mastocytosis with associated haematologic neoplasm; SSM: smouldering systemic mastocytosis.
Source: Chandesris *et al.* (2017).[65]

Clinical effectiveness results

Best overall response

The ORR in the midostaurin group was 71% (n=20), with a MR in 57% (n=16) of patients, a PR in 14% (n=4), SD in 11% (n=3), and PD in 18% (n=5). Median treatment duration was 10.5 months (range 2–32) and median follow-up was 18.5 months (range 3–36). Responses were detectable within the first 3 months after the initiation of midostaurin.

The ORR according to advanced SM disease subtype was as follows: 75% (n=3) for patients with ASM, 72% (n=13) for patients with SM-AHN and 66% (n=2) in patients with MCL.[65] No response

was observed in the patient with MCS (ORR 0%). Conversely, an ORR of 100% (n=2) was observed in patients with progressive SSM.

Duration of response (DoR)

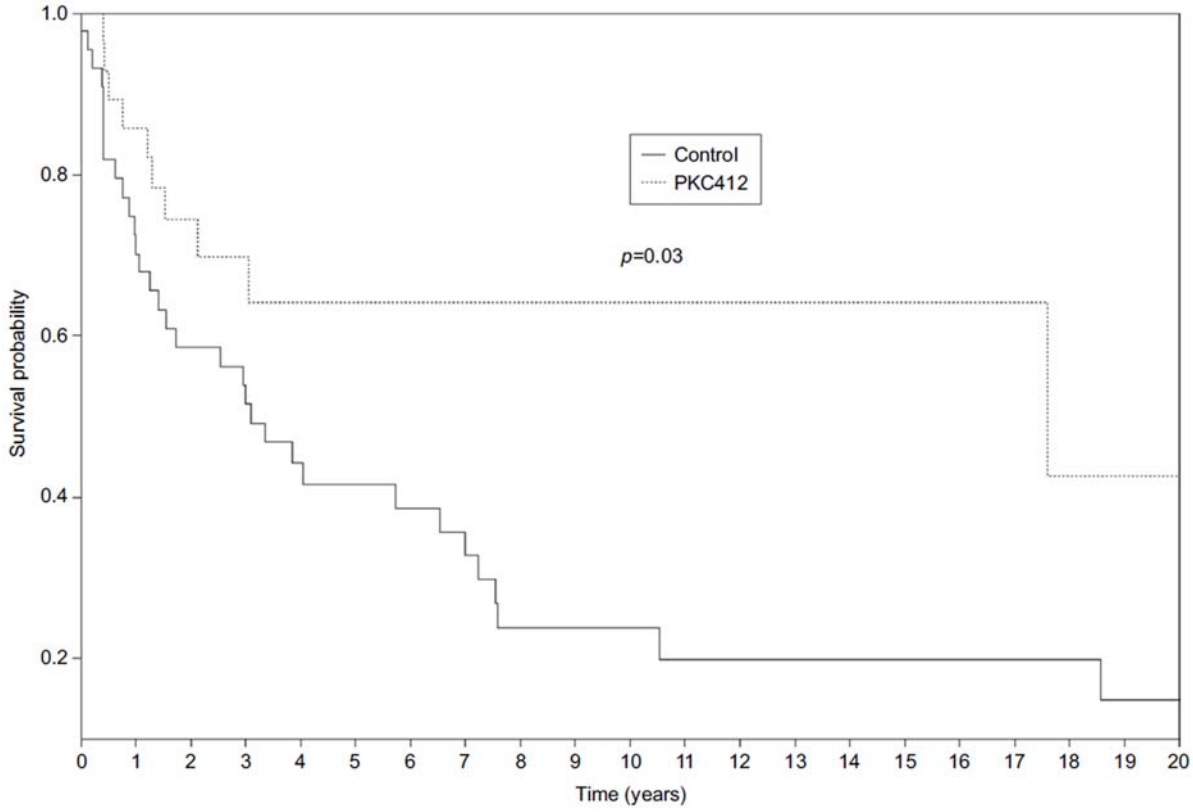
Median duration of response was 17 months (range 5–32).

Overall survival (OS)

The OS rate was 42.7% (95% CI: 18.0–1.0) in the midostaurin group and 14.9% (95% CI: 6.0–36.0) in the control group (p=0.03). The risk of death in the control group was more than two times higher than that in the midostaurin group (HR: 2.20; 95% CI: 1.08–4.47; p=0.02).

In a multivariate analysis, OS was significantly affected by the age at diagnosis, signs of organ dysfunction, and midostaurin treatment. The risk of death in the control group that was three times higher than that in the midostaurin group. In the midostaurin group, 80% of deaths were related to progression of the AHN, but not to mastocytosis.

Figure 26: Kaplan-Meier plot of OS in CEREMAST



Survival curves in midostaurin-treated patients (PKC412) (n=28) and historical control (n=44) groups at the last follow-up in April 2015.
Abbreviations: PKC412: midostaurin.
Source: Chandesris *et al.* (2017).[65]

B.2.9.2 Summary of clinical evidence for comparators from the systematic literature review

As described previously in Section B.2.2.2, data from 8 studies (9 publications) from the 22 unique studies (23 records) included in the SLR were considered and extracted for the comparator therapies: Barete *et al.* (2015),[30] Hauswirth *et al.* (2004),[60] Hochaus *et al.* (2015),[35] Jawhar *et al.* (2017a),[66] Lim *et al.* (2009),[18, 70] Pagano *et al.* (2008),[71] Pardanani *et al.* (2009)[72] and Verstovsek *et al.* (2008)[36]).

All of these studies were single-arm trials or observational studies and since there were no RCTs, an indirect treatment comparison versus the midostaurin single-arm trials was not feasible. A summary of the available evidence identified in the SLR is provided below.

Study design, baseline characteristics and comparability to D2201

The majority of studies for the comparator treatments were observational studies and of poor quality as assessed by the Downs and Black checklist (Table D.11.1; Appendix D.11).

It is important to note that some of the studies of the comparator treatments included patients with non-advanced SM, such as patients with ISM, and in addition, the proportion of patients with the different subtypes of advanced SM (ASM, SM-AHN and MCL) was different across studies and D2201. For the majority of studies, it was also unclear how advanced SM disease groups were defined and, in particular, whether patients with non-advanced types of mastocytosis with AHN, such as ISM-AHN and SSM-AHN, were considered within the SM-AHN disease subtype. In this context, cross-study comparisons of the clinical outcomes (Table 27 and Table 28), should be interpreted with caution given the differential prognoses of patients with advanced SM (including the different subtypes of the disease) versus non-advanced SM with or without an AHN. Consequently, D2201 and A2213 are the only trials conducted in the patient population for which midostaurin is licensed.

A number of patient characteristics were only reported for the entire study cohort, including non-advanced SM patients and/or patients receiving treatment with different comparator and non-comparator therapies. Compared to D2201, a similar proportion of *KIT* D816V positive patients was included in Barete *et al.* (2015)[30] and Verstovsek *et al.* (2008)[36] and patients with a similar median age and gender distribution were included in Jawhar *et al.* (2017a),[66] Lim *et al.* (2009),[70] Pagano *et al.* (2008),[71] and Pardanani *et al.* (2009).[72] Full details on the characteristics of each study are presented in Table D.4.1.2 (Appendix D.4.1).

Table 26: Overview of study design and comparability of comparator studies to D2201

Study	Study design, Quality[a]	Overall cohort, N	Intervention/ Comparator	Disease classification		*KIT* D816V mutational status, n (%)	Age, median (range) years	Gender n (%)
				Adv./Non-adv.	N			
				Subtype	n/N, (%)			
D2201	Single-arm trial, Good quality	89	Midostaurin	Advanced SM	89	**Positive:** 73/89 (82.0) **Negative:** 14/89 (15.7) **Unknown:** 2/89 (2.2)	64 (25–82)	**Male:** 57 (64.0) **Female:** 32 (36.0)
				ASM	16/89 (18.0)			
				SM-AHN	57/89 (64.0)			
				MCL	16/89 (18.0)			
Barete *et al.* (2015)[30]	Retrospective study, Reasonable quality	68	Cladribine	Advanced SM	32	***Positive:*** *58/72 (80.6)* ***Negative:*** *NR* ***Unknown:*** *NR*	*54 (17–83)*	***Male:*** *NR* ***Female:*** *35 (51.5)*
				ASM	14/32 (43.8)			
				SM-AHN	17/32 (53.1)[b]			
				MCL	1/32 (3.1)			
				Non-advanced SM	*36*			
Hauswirth *et al.* (2004)[60]	Case series, Poor quality	5	Interferon alpha ± prednisolone	Advanced SM	5	NR	52 (22–59)	**Male:** 3 (60.0) **Female:** 2 (40.0)
				ASM	3/5 (60.0)			
				SM-AHN	2/5 (40.0)			
				MCL	0/5 (0.0)			
Hochhaus *et al.* (2015)[35]	Single-arm trial, Reasonable quality	61	Nilotinib	Advanced SM	41	NR	NR	NR
				ASM	37/41 (90.2)	**Positive:** 22/37 (59.5) **Negative:** 2/37 (5.4) **Unknown:** 13/37 (35.1)	49 (29–79)	**Male:** 21 (56.8) **Female:** NR
				SM-AHN	1/41 (2.4)[c]	**Positive:** 1/1 (100) **Negative:** NA **Unknown:** NA	NR	NR
				MCL	3/41 (7.3)	**Positive:** 2/3 (66.7) **Negative:** NR **Unknown:** NR	NR	NR
				Non-advanced SM	*20*	*NA*		
	Series,	28[d]	Cladribine	Advanced SM	6	***Positive:*** *19 (67.9)*	*67 (45–82)*	***Male:*** *16*

Study	Study design, Quality[a]	Overall cohort, N	Intervention/ Comparator	Disease classification		*KIT* D816V mutational status, n (%)	Age, median (range) years	Gender n (%)
				Adv./Non-adv.	N			
				Subtype	n/N, (%)			
Jawhar *et al.* (2017a)[66]	Poor quality		(treatment-naïve)	ASM	0/6 (0.0)	***Negative:*** *9 (32.1)*		*(57.1)* ***Female:*** *NR*
				SM-AHN	0/6 (0.0)			
				MCL	6/6 (100.0)			
			Non-comparator (midostaurin cladribine mix)	*Advanced SM*	*22*			
Lim *et al.* (2009)[70]	Retrospective study, Poor quality	108[e]	Cladribine	Advanced SM	16	***Positive:*** *31/48 (64.6)* ***Negative:*** *NR* ***Unknown:*** *NR*	*62 (21–85)*	***Male:*** *64 (59.3)* ***Female:*** *NR*
				ASM	3/16 (15.4)			
				SM-AHN	13/16 (84.6)[c]			
				MCL	0/16 (0.0)			
				Non-advanced SM	*10*			
			Interferon alpha ± prednisolone	Advanced SM	36			
				ASM	14/36 (38.9)			
				SM-AHN	22/36 (61.1)[c]			
				MCL	0/36 (0.0)			
				Non-advanced SM	*11*			
			Non-comparator (HU)	*Advanced SM*	*29*			
				Non-advanced SM	*1*			
			Imatinib	Advanced SM	19	***Positive:*** *18/21 (85.7)* ***Negative:*** *3/21 (14.2)* ***Unknown:*** *NR*		
				ASM	4/19 (21.0)			
				SM-AHN	14/19 (73.7)[c]			
				MCL	1/19 (5.3)			
				Non-advanced SM	*8*			
Pagano *et al.* (2008)[71]	Retrospective study,	24[e]	Cladribine	Advanced SM	3	***Positive:*** *13/18 (72.2)* ***Negative:*** *4/18 (22.2)*	*59 (36–75)*	***Male:*** *13 (54.2)*
				ASM	*12/24 (50.0)*			

Study	Study design, Quality[a]	Overall cohort, N	Intervention/ Comparator	Disease classification		*KIT* D816V mutational status, n (%)	Age, median (range) years	Gender n (%)
				Adv./Non-adv.	N			
				Subtype	n/N, (%)			
	Poor quality			*SM-AHN*	*4/24 (16.7)[c]*	***Unknown:*** *NR*		***Female:*** *11 (45.8)*
				MCL	*8/24 (33.3)*			
			Interferon alpha	Advanced SM	8			
				ASM	*12/24 (50.0)*			
				SM-AHN	*4/24 (16.7)[c]*			
				MCL	*8/24 (33.3)*			
			Imatinib	Advanced SM	17			
				ASM	*12/24 (50.0)*			
				SM-AHN	*4/24 (16.7)[c]*			
				MCL	*8/24 (33.3)*			
			Non-comparator (allo- HSCT)	*Advanced SM*	*2*			
			Non-comparator (chemotherapy)	*Advanced SM*	*8*			
			Non-comparator (steroids)	*Advanced SM*	*2*			
			Non-comparator (radiotherapy)	*Advanced SM*	*1*			
Pardanani *et al.* (2009)[72]	Retrospective study, Poor quality	123[e]	Cladribine	Advanced SM	11	***Positive:*** *50/80 (62.5)* ***Negative:*** *NR* ***Unknown:*** *NR*	*67 (20–87)*	***Male:*** *86 (69.9)* ***Female:*** *NR*
				ASM	0/11 (0.0)			
				SM-AHN	11/11 (100.0)[c]			
				MCL	0/11 (0.0)			
			Interferon	Advanced SM	23			

Study	Study design, Quality[a]	Overall cohort, N	Intervention/ Comparator	Disease classification		*KIT* D816V mutational status, n (%)	Age, median (range) years	Gender n (%)
				Adv./Non-adv.	N			
				Subtype	n/N, (%)			
			alpha ± prednisolone	ASM	0/23 (0.0)			
				SM-AHN	23/23 (100.0)[c]			
				MCL	0/23 (0.0)			
			Imatinib	Advanced SM	21			
				ASM	0/21 (0.0)			
				SM-AHN	21/21 (100.0)[c]			
				MCL	0/21 (0.0)			
			Non-comparator (HU)	*Advanced SM*	*27*			
Verstovsek *et al.* (2008)[36]	Single-arm trial, Reasonable quality	67	Dasatinib	Advanced SM	15	***Positive:*** *28/33 (84.8)* ***Negative:*** *4/33 (12.1)* ***Unknown:*** *1/33 (3.0)*	*57 (29–74)*	***Male:*** *14 (42.4)* ***Female:*** *19 (57.6)*
				ASM	9/15 (60.0)			
				SM-AHN	6/15 (40.0)[c]			
				MCL	0/15 (0.0)			
				Non-advanced SM	*18*			

Where data were not reported separately for the advanced SM patient population treated with a specific comparator (but were, for example, reported for the entire study cohort that included non-advanced SM patients or patients receiving treatment with different comparator and non-comparator medicines) they have been presented in grey.
[a]Quality was assessed using the Downs and Black checklist.
[b]Disease subgroup also included patients with ISM-AHN or SSM-AHN; unclear whether patients with MCL-AHN were included.
[c]Unclear whether patients with ISM-AHN, SSM-AHN or MCL-AHN were included.
[d]Patients receiving midostaurin, or cladribine after switching from midostaurin
[e]Some patients received multiple treatments.
Abbreviations: allo-HSCT: allogenic haematopoietic stem cell transplant; ASM: aggressive systemic mastocytosis; HU: hydroxyurea; KIT D816V: substitution of aspartic acid in position 816 to valine in the KIT gene; MCL: mast cell leukaemia; NR: not reported; SM: systemic mastocytosis; SM-AHN: systemic mastocytosis with associated haematologic neoplasm; SM-AL: systemic mastocytosis with acute leukaemia; SM-CMML: systemic mastocytosis with chronic myelomonocytic leukaemia; SM-MDS: systemic mastocytosis with myelodysplastic syndrome; SM-MPN: systemic mastocytosis with myeloproliferative neoplasm.

Overall response rates (ORR) and duration of response (DoR)

ORR for the overall advanced SM population was reported for all comparators except for nilotinib. In patients with ASM, an ORR was reported for each of the comparators by at least one study. In patients with SM-AHN, ORR was reported for all comparators except for nilotinib. In patients with MCL, ORR was only reported for cladribine (Barete *et al.* [2015][30] and Jawhar *et al.* [2017a][66]) and imatinib (Lim *et al.* [2009][70]).

As described previously, several of the studies for the different comparator treatments included patients with different proportions of ASM, SM-AHN or MCL and it was unclear whether patients with non-advanced types of mastocytosis with AHN (ISM-AHN and SSM-AHN) were considered within the SM-AHN disease subtype. Additionally, differences in assessment of response in the different studies means that cross-study comparisons of response rates should be interpreted with caution.

DoR data were only reported by Lim *et al.* (2009)[70] for cladribine, interferon alpha ± prednisolone and imatinib. However, as described previously, these data were only available for a mixed population of patients including non-advanced SM (ISM); hence, they should be interpreted with caution.

Table 27: Overview of response rates reported by comparator studies

Study	Intervention/ Comparator	Patient population	Overall response rate, n/N (%)	Duration of response, median (95% CIs) months	Criteria for response	Timepoint for response
D2201	Midostaurin	Advanced SM	53/89 (59.6)	21.4 (10.8–NE)	Modified Valent response criteria and Cheson criteria	Best ORR in the first six 4-week treatment cycles and maintained for at least 8 weeks
		ASM	12/16 (75.0)	not reached (NR–NR)		
		SM-AHN	33/57 (57.8)	12.7 (7.4–31.4)		
		MCL	8/16 (50.0)	NR (NR–NR)		
Barete *et al.* (2015)[30]	Cladribine	Advanced SM	16/32 (50.0%)	NR	NR	Overall
		ASM	6/14 (42.9)			
		SM-AHN	10/17 (58.8)			
		MCL	0/1 (0.0)			
Hauswirth *et al.* (2004)[60]	Interferon alpha ± prednisolone	Advanced SM	3/5 (60.0)	NR	Modified Valent criteria	Overall
		ASM	1/3 (33.3)			
		SM-AHN	2/2 (100.0)			
		MCL	No pts included			
Hochhaus *et al.* (2015)[35]	Nilotinib	Advanced SM	NR/41[a]	NR	Valent criteria	Minor response or better lasting a minimum of 4 weeks
		ASM	8/37 (21.6)			
		SM-AHN	NR/1[a]			

Study	Intervention/ Comparator	Patient population	Overall response rate, n/N (%)	Duration of response, median (95% CIs) months	Criteria for response	Timepoint for response
		MCL	NR/3[a]			
Jawhar *et al.* (2017a)[66]	Cladribine (treatment-naïve)	Advanced SM	1/6 (16.7)	NR	IWG-MRT and ECNM criteria	Response by month 6 or at the end of treatment due to progression/death prior to month 6
		ASM	No pts included			
		SM-AHN	No pts included			
		MCL	1/6 (16.7)			
Lim *et al.* (2009)[70]	Cladribine	Advanced SM	NR/16[a]	*11 (NR)*	Modified Valent criteria	Overall
		ASM	1/2 (50.0)			
		SM-AHN	6/11 (54.5)			
		MCL	No pts included			
	Interferon alpha ± prednisolone	Advanced SM	NR/36[a]	*12 (NR)*		
		ASM	6/10 (60.0)			
		SM-AHN	9/20 (45.0)			
		MCL	No pts included			
	Imatinib	Advanced SM	NR/19[a]	*19.6 (NR)*		
		ASM	2/4 (50.0)			
		SM-AHN	1/11 (9.1)			
		MCL	NR/1[a]			
Pagano *et al.* (2008)[71]	Cladribine	Advanced SM	3/3 (100.0)	NR	Valent criteria	Overall
		ASM	NR			
		SM-AHN	NR			
		MCL	NR			
	Interferon alpha	Advanced SM	3/8 (37.5)			
		ASM	NR			
		SM-AHN	NR			
		MCL	NR			
	Imatinib	Advanced SM	5/17 (29.4)			
		ASM	NR			

Study	Intervention/ Comparator	Patient population	Overall response rate, n/N (%)	Duration of response, median (95% CIs) months	Criteria for response	Timepoint for response
		SM-AHN	NR			
		MCL	NR			
Pardanani *et al.* (2009)[72]	Cladribine	Advanced SM	6/11 (54.5)	NR	Valent criteria	Overall
		ASM	No pts included			
		SM-AHN	6/11 (54.5)			
		MCL	No pts included			
	Interferon alpha ± prednisolone	Advanced SM	11/23 (47.8)			
		ASM	No pts included			
		SM-AHN	11/23 (47.8)			
		MCL	No pts included			
	Imatinib	Advanced SM	11/21 (52.4)			
		ASM	No pts included			
		SM-AHN	11/21 (52.4)			
		MCL	No pts included			
Verstovsek *et al.* (2008)[36]	Dasatinib	Advanced SM	5/15 (33.3)	NR (IPD)	Valent criteria for ASM, descriptive criteria for SM-AHN	Response after a minimum of three treatment cycles
		ASM	3/9 (33.3)			
		SM-AHN	2/6 (33.3)			
		MCL	No pts included			

Where data were not reported separately for the advanced SM patient population treated with a specific comparator (but were, for example, reported for the entire study cohort that included non-advanced SM patients) they have been presented in grey.

[a]No ORR was reported for this patient population, so data are presented as NR out of the total number of treated patients in the study.

Abbreviations: ASM: aggressive systemic mastocytosis; CI: confidence intervals; ECNM: European Competence Network on Mastocytosis criteria; IPD: individual patient data; IWG-MRT: International Working Group-Myeloproliferative Neoplasms Research and Treatment criteria; MCL: mast cell leukaemia; NE: not estimated; NR: not reported; ORR: overall response rate; pts: patients; SM: systemic mastocytosis; SM-AHN: systemic mastocytosis with associated haematologic neoplasm.

Overall survival (OS), progression-free survival (PFS) and adverse events (AEs)

No data for OS or PFS were reported in the overall advanced SM population for any of the comparators; however, relapse-free survival (RFS; defined as the time between the date of the last consecutive course of cladribine considered for endpoint response and relapse) was reported for cladribine in Barete *et al.* (2015).[30]

In the advanced SM disease subgroups (ASM, SM-AHN and MCL), limited OS data were reported by Barete *et al.* (2015),[30] Hochhaus *et al.* (2015)[35] and Verstovsek *et al.* (2008)[36]; however, it should be noted that these data include mixed populations (including non-advanced SM), so cross-study comparisons of the clinical outcomes should be interpreted with caution.

Additionally, safety data for the overall advanced SM population or any of the advanced SM disease subtypes were limited and only available in Hauswirth *et al.* (2004).[60] Data from mixed patient populations, including non-advanced SM patients, were available from Barete *et al.* (2015),[30] Hochhaus *et al.* (2015),[35] Lim *et al.* (2009)[70] and Verstovsek *et al.* (2008)[36].

Table 28: Overview of survival and safety outcomes reported by comparator studies

Study	Intervention/ Comparator	Patient population	OS, median (95% CIs) months	PFS, median (95% CIs) months	AEs (Grade 3 or 4 in ≥5% of patients), n (%)
D2201	Midostaurin	Advanced SM	[redacted]	17.0 (10.2–24.8)	• **Nausea:** [redacted] • **Vomiting:** [redacted] • **Diarrhoea:** [redacted] • **Anaemia:** [redacted] • **Fatigue:** [redacted] • **Pyrexia:** [redacted] • **Thrombocytopaenia:** [redacted] • **Neutropenia:** [redacted] • **Pneumonia:** [redacted]
		ASM	[redacted]	not reached (NR–NR)	
		SM-AHN	[redacted]	11.0 (7.4–17.9)	
		MCL	[redacted]	11.3 (2.8–NE)	
Barete *et al.* (2015)[30]	Cladribine	Advanced SM	NR	NR	• ***Acute neutropenia:*** *32 (47.1)* • ***Prolonged lymphopenia:*** *56 (82.4)* • ***Infectious complications:*** *15 (22.1)* • ***Fever:*** *4 (5.9)*
		ASM	28.6 months (estimated OS)	38.5 months (estimated RFS)	
		SM-AHN	77.6 months (estimated OS)[a]	71.4 months (estimated RFS)[a]	
		MCL	NR	NR	
	Interferon alpha ± prednisolone	Advanced SM	NR	NR	• **Fever:** 2.5 (40.0)[b] • **Flu-like symptoms:** 2/5 (40.0)[b]
		ASM			

Study	Intervention/ Comparator	Patient population	OS, median (95% CIs) months	PFS, median (95% CIs) months	AEs (Grade 3 or 4 in ≥5% of patients), n (%)
Hauswirth *et al.* (2004)[60]		SM-AHN			
		MCL			
Hochhaus *et al.* (2015)[35]	Nilotinib	Advanced SM	NR	NR	• ***Diarrhoea:*** *4/61(6.6)* • ***Thrombocytopaenia:*** *6/58 (10.3)* • ***Anaemia:*** *6/60 (10.0)* • ***Neutropenia:*** *4/58 (6.9)* • ***Decreased serum phosphate:*** *10/58 (17.2)* • ***Increased serum lipase:*** *9/53 (17.0)* • ***Increased serum bilirubin (total):*** *8/60 (13.3)* • ***Increased serum ALT:*** *6/59 (10.2)* • ***Decreased sodium:*** *4/60 (6.7)*
		ASM	NR (9/37 deaths occurred during the study)		
		SM-AHN	NR		
		MCL	NR (2/3 deaths occurred during the study)		
Jawhar *et al.* (2017a)[66]	Cladribine (treatment-naïve)	Advanced SM	NR	NR	NR
		ASM			
		SM-AHN			
		MCL			
Lim *et al.* (2009)[70]	Cladribine	Advanced SM	NR	NR	• ***Myelosuppression:*** *NR (NR)[bc]* • ***Infection:*** *NR (NR)[bc]*
		ASM			
		SM-AHN			
		MCL			
	Interferon alpha ± prednisolone	Advanced SM	NR	NR	• ***Fatigue:*** *NR (NR)[bc]* • ***Depression:*** *NR (NR)[bc]* • ***Thrombocytopaenia:*** *NR (NR)[bc]*
		ASM			
		SM-AHN			
		MCL			
	Imatinib	Advanced SM	NR	NR	• ***Diarrhoea:*** *NR (NR)[bc]* • ***Peripheral oedema:*** *NR (NR)[bc]* • ***Interstitial pneumonitis:*** *2 (NR)[bc]*
		ASM			
		SM-AHN			
		MCL			

Study	Intervention/ Comparator	Patient population	OS, median (95% CIs) months	PFS, median (95% CIs) months	AEs (Grade 3 or 4 in ≥5% of patients), n (%)
Pagano *et al.* (2008)[71]	Cladribine	*Advanced SM*	*24 (NR)*	NR	NR
	Interferon alpha	*ASM*	*NR*		
		SM-AHN	*NR*		
	Imatinib	*MCL*	*NR*		
Pardanani *et al.* (2009)[72]	Cladribine	*Advanced SM*	*NR*	NR	NR
	Interferon alpha ± prednisolone	*ASM*	*NR*		
		SM-AHN	*NR*		
	Imatinib	*SM-MPN*	*~31 (NR)*		
		SM-CMML	*~15 (NR)*		
		SM-MDS	*~13 (NR)*		
		SM-AL	*~11 (NR)*		
		MCL	*NR*		
Verstovsek *et al.* (2008)[36]	Dasatinib	Advanced SM	NR	NR	• ***Headache:*** *5/67 (7.5)* • ***Platelets/haemoglobin:*** *6/67 (9.0)* • ***Pleural effusion:*** *7/67 (10.4)*
		ASM	NR		
		SM-AHN	2 deaths occurred during the study		
		MCL	NR		

Where data were not reported separately for the advanced SM patient population treated with a specific comparator (but were, for example, reported for the entire study cohort that included non-advanced SM patients) they have been presented in grey.
[a]Disease subgroup also included patients with ISM-AHN or SSM-AHN, which have a better prognosis than ASM-AHN patients; unclear whether patients with MCL-AHN were included.
[b]Reported as 'substantial side effects'; grade unknown.
[c]Reported as 'major toxicities'; grade and frequency unknown.
Abbreviations: AEs: adverse events; ALT: alanine aminotransferase; ASM: aggressive systemic mastocytosis; CI: confidence intervals; MCL: mast cell leukaemia; NE: not estimated; NR: not reported; OS: overall survival; PFS: progression-free survival; RFS: relapse-free survival; SM: systemic mastocytosis; SM-AHN: systemic mastocytosis with associated haematologic neoplasm.

Clinical evidence for comparators used in the economic model

There was a paucity of evidence for comparator treatments identified in the SLR. In addition, identified studies reported results for highly heterogeneous populations, with considerable variation in the proportion of patients with different subtypes of advanced SM (ASM, SM-AHN and MCL) compared with D2201, and with some studies including patients with non-advanced SM subtypes. For the majority of studies, it was also unclear how advanced SM disease groups were defined and, in particular, whether patients with ISM-AHN and SSM-AHN (who are not considered to have advanced SM) were considered within the SM-AHN disease subtype. These studies may therefore not reflect the patient population in D2201, and thus the outcomes reported across these studies may not accurately reflect the efficacy and safety of the comparator treatments in this population.

ORR data was available for all or nearly all comparators for both the overall advanced SM population and two of the advanced SM disease subtypes (ASM and SM-AHN). However, ORR data for patients with MCL was very limited. For the economic analysis, evidence for response rates for individual subgroups was used (ASM, SM-AHN, MCL), with response rates weighted to better reflect the population included in the D2201 trial, to provide a fairer comparison against midostaurin and account for possible differences in response rate between subgroups. When no specific evidence for advanced SM was available, evidence from a mixed population was used, and, similarly, when no data were available for MCL, the response rate estimated in the ASM/SM-AHN population was used as a proxy for MCL. Consequently, these assumptions in the absence of further evidence are likely to be optimistic and favourable for the comparator therapies since these therapies have been shown to be associated with limited and short-lived responses due to the development of resistance.[14, 28-36]

No data for OS or PFS were reported in the overall advanced SM population for any of the comparators and OS and PFS data for each of the advanced SM disease subtypes (ASM, SM-AHN and MCL) were extremely limited. As such, OS and PFS for the comparator treatments were estimated by applying a HR to the OS curve for midostaurin (based on the results of Reiter *et al.* [2017]).[23]

Finally, data on the prevalence of Grade 3/4 AE for the overall advanced SM population or any of the advanced SM disease subtypes was limited. In this context, a simplifying assumption was made in the model where the prevalence of adverse events for all treatments comprising clinical management in the UK are based on those reported for cladribine.

In conclusion, it is considered that the efficacy data for midostaurin are compelling relative to what is historically known for the non-licensed comparator therapies such as interferon-α and cladribine, for which the evidence base is much weaker, and mostly from retrospective investigations (and some small single-arm studies).[9]

B.2.10 *Adverse reactions*

Assessment of safety

- The safety and tolerability of midostaurin for the treatment of advanced SM was evaluated as a secondary endpoint in D2201 and A2213.[12, 61] In both trials, patients were monitored for AEs from the first day of midostaurin administration until 28 days after discontinuing the study drug

Treatment exposure

- The median duration of exposure in D2201 was [redacted] (longest duration of exposure was [redacted]), and [redacted] and [redacted] had at least 12 months and 24 months of exposure, respectively.[73] In D2201 dose reduction was undertaken in [redacted] and re-escalation to the initial dose of midostaurin was feasible in [redacted] of those patients ([redacted])[73]
- The median duration of exposure in A2213 was 9.8 months (longest duration of exposure was 81 months), and 12 patients (46%) and 9 patients (35%) had at least 12 months and 24 months of exposure, respectively.[80] In A2213, a dose reduction was undertaken in 6 patients (23%) and re-escalation to the initial dose of midostaurin was feasible in 2 patients (33%)[61]
- The median relative dose intensity was >99% of the intended daily dose in both trials

Adverse events

- The most frequent adverse events (AEs) in D2201 were low-grade nausea ([redacted]), vomiting ([redacted]), and diarrhoea ([redacted]).[73] The most frequent AEs in A2213 were low-grade nausea (88%), vomiting (69%), and constipation (46%)[61]
- These AEs were manageable with prophylactic antiemetics and drug administration with meals in both D2201 and A2213[12, 61]
- Overall, [redacted] patients in D2201 and 5 patients in A2213 died on treatment or within ≤28 days after discontinuing midostaurin.[61, 73] All causes of death were considered unrelated to midostaurin in both trials
- The most frequent serious adverse events (SAEs) in D2201 were pneumonia [redacted] and sepsis [redacted]; no Grade 5 SAEs were reported in D2201[73]
- The most common SAEs regardless of study drug relationship reported in A2213 were sepsis, febrile neutropenia, facial bone fracture due to mechanical fall, elevated total bilirubin and hypercalcaemia (4% each) and only 1 SAE was reported at Grade 5[61]
- Treatment discontinuations due to AEs occurred in [redacted] of patients in D2201 and 23.1% of patients in A2213[61, 73]
- No unexpected toxicities occurred in D2201 and A2213[61, 73]
- Overall, treatment of advanced SM with midostaurin was well-tolerated

The safety and tolerability of midostaurin for the treatment of advanced SM was evaluated as a secondary endpoint in D2201 and A2213. Safety data for D2201 and A2213 are presented in this section together. Safety data for D2201 are presented for the SES from the final OS and safety analysis (data cut-off: 24th August 2017). Safety data for A2213 are presented for the SES from

the follow-up analysis of efficacy and safety (data cut-off: 1st March 2017) or from a prior analysis (data cut-off: 3rd December 2012), where more recent data were not available.

In D2201, monitoring and recording potential adverse events (AEs) was carried out according to according to Common Terminology Criteria for Adverse Events (CTCAE, version 3.0) and MedDRA (version 20.0). In A2213, monitoring and recording potential AEs was carried out according to according to CTCAE (version 3.0).

In both trials, patients were monitored for AEs from the first day of midostaurin administration until 28 days after discontinuing the study drug. In both studies, safety assessments consisted of all AEs (including severity and relationship to study drug), serious adverse events (SAEs; those that resulted in death, were life threatening, or met a number of other criteria), laboratory parameters (including haematology and blood chemistry), assessment of vital signs, ECG monitoring, physical examination and documentation of all concomitant therapies. As described in Table 11 in Section B.2.4, the SES included all patients who received study medication as part D2201 or A2213, respectively.

B.2.10.1 Treatment exposure

Patients received treatment with midostaurin until disease progression, death, development of unacceptable toxic effects or withdrawal of consent through the main trial protocol of D2201 and an extension trial protocol of A2213. Dose interruptions and dose adjustments were permitted for pre-defined haematological and non-haematological toxicities. Following dose interruption, treatment could be restarted at a reduced dose of 50 mg twice daily on recovery of toxicities within a set timeframe of 14–21 days. Escalation to a full dose of 100 mg twice daily was recommended for patients tolerating the reduced dose. Alternatively, treatment discontinuation was advised in the event of persisting or recurring toxicities at the reduced dose of midostaurin. Full details of the toxicity-related treatment modification schedules of D2201 and A2213 are presented in Appendix F and further details on AEs requiring dose adjustments, treatment interruption or study discontinuation are presented in Section B.2.10.2.

At the time of the final analysis of D2201 (data cut-off: 24th August 2017), the median duration of exposure in D2201 was [redacted] (longest duration of exposure was [redacted]), and [redacted] and [redacted] had at least 12 months and 24 months of exposure, respectively.[73] At the time of the analysis of A2213 (data cut-off: 3rd December 2012), the median duration of exposure in A2213 was 9.8 months (longest duration of exposure was 81 months), and 12 patients (46%) and 9 patients (35%) had at least 12 months and 24 months of exposure, respectively.[80] The median relative dose intensity was >99% of the intended daily dose in both trials. Full details of treatment exposure in D2201 and A2213 are presented in Table 29 below.

At the time of the final analysis of D2201 (data cut-off: 24th August 2017), a dose reduction was undertaken in [redacted].[73] Re-escalation to the initial dose of midostaurin was feasible in [redacted] of those patients ([redacted]). At the time of the follow-up analysis of A2213 (data cut-off: 1st March 2017), a dose reduction was undertaken in 6 patients (23%).[61] Re-escalation to the initial dose of midostaurin was feasible in 2 patients (33%).

Table 29: Treatment exposure to midostaurin in D2201 and A2213

	D2201 (N=116)	A2213 (N=26)
Duration of exposure (months)		
Mean (SD)	[redacted]	21.8 (24.95)
Median (range)	[redacted]	9.8 (1–81)
Exposure categories – n (%)		
At least 6 months	[redacted]	15 (57.7)
At least 12 months	[redacted]	12 (46.2)
At least 24 months	[redacted]	9 (34.6)
Patient-years	[redacted]	565.9
Average daily dose (mg)		
Mean (SD)	-	197.9 (5.33)
Median (range)	[redacted]	200.0 (176–200)
Relative dose intensity (%)		
Mean (SD)	-	98.0 (4.33)
Median (range)	[redacted]	99.9 (84–100)

Final analysis of D2201 data cut-off: 24th August 2017; SES. Analysis of A2213 data cut-off: 3rd December 2012; SES.
Abbreviations: SD: standard deviation.
Source: Australian Public Assessment Report of Midostaurin (2019),[80] D2201 CSR (data cut-off: 24th August 2017).[73]

Concomitant medication

All patients in D2201 (data cut-off: 1st December 2014; SES) and A2213 (data cut-off: 3rd December 2012; SES) received at least 1 concomitant medication.[9] In D2201, prophylaxis for the prevention of nausea and vomiting was recommended to be administered to all patients. In Study A2213, prophylaxis for the prevention of nausea and vomiting was also recommended to be taken prior to each dose of midostaurin.

B.2.10.2 Adverse events

Across both trials, all patients experienced at least 1 AE.[61, 73, 80] At the time of the final analysis of D2201 (data cut-off: 24th August 2017; SES) and the analysis of A2213 (data cut-off: 3rd December 2012; SES), a similar proportion of patients across both trials experienced AEs which were suspected to be related to midostaurin administration, with [redacted] in D2201 and 25 patients (96.2%) in A2213. A higher proportion of patients in D2201 experienced Grade 3/4 AEs, with [redacted] compared to 16 patients (61.5%) in A2213. The rate of SAEs was similarly higher in D2201, with [redacted] compared to 12 patients (46.2%) in A2213. Finally, AEs leading to discontinuation were observed in [redacted] in D2201, which was similar to the most recent data available for A2213, where 6 patients (23.1%) were affected by AEs leading to discontinuation at the time of the follow-up analysis (data cut-off: 1st March 2017). A summary of the AEs from D2201 and A2213 is presented in Table 30.

Data on adverse events from D2201 (data cut-off: 24th August 2017; SES) were used to inform the economic analysis in Section B.3.3.6.

Table 30: Summary of AEs from D2201 and A2213

Adverse event, n (%)	D2201 (N=116)	A2213 (N=26)	
All causality AEs	[redacted]	26 (100)	
Grade 3/4	[redacted]	16 (61.5)	
Suspected to be drug-related	[redacted]	25 (96.2)	
SAEs	[redacted]	12 (46.2)	
Grade 3/4	[redacted]	-	
Suspected to be drug-related	[redacted]	4 (15.4)	
AEs leading to discontinuation	[redacted]	4 (15.4)	6 (23.1)[a]
Suspected to be drug-related	[redacted]	1 (3.8)	
AEs leading to dose adjustment/interruption	-	13 (50.0)	
AEs leading to dose reduction	[redacted]	-	
AEs leading to dose interruption	[redacted]	-	

[a]More recent data; analysis of A2213 data cut-off: 1st March 2017; SES.
Final analysis of D2201 data cut-off: 24th August 2017; SES. Analysis of A2213 data cut-off: 3rd December 2012; SES.
Abbreviations: AE: adverse event; SAE: serious adverse event.
Source: Australian Public Assessment Report of Midostaurin (2019),[80] D2201 CSR (data cut-off: 24th August 2017),[73] DeAngelo *et al.* (2018).[61]

AEs regardless of study drug relationship

Nausea was the most common AE regardless of study drug relationship, with [redacted] in D2201 and 23 patients (88%) in A2213 experiencing an event of any grade.[61, 73] Vomiting was the second most common AE across D2201 and A2213, with [redacted] and 18 patients (69%), respectively. Diarrhoea was the third most common AE in D2201, with [redacted] experiencing an event of any grade.[73] Conversely, the third most common AE in A2213 was constipation, which affected 12 patients (46%).[61] Importantly, low-grade AEs such as nausea, vomiting and diarrhoea were manageable with prophylactic antiemetics and drug administration with meals in both D2201 and A2213.[12, 61]

In D2201, the most common Grade 3/4 AE regardless of study drug relationship was anaemia, with [redacted] affected.[73] In A2213, the most common Grade 3/4 AE regardless of study drug relationship was increased lipase, with 4 patients (15%) affected.[61] A summary of all AEs occurring in ≥10% patients regardless of study drug relationship from D2201 and A2213 is presented in Table 31. Treatment-related AEs in ≥10% patients from D2201 and A2213 are presented in Appendix F.

Table 31: AEs in ≥10% patients regardless of study drug relationship from D2201 and A2213

Adverse event, n (%)	D2201 (N=116)		A2213 (N=26)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Total	[redacted]	[redacted]	-	-
Nausea	[redacted]	[redacted]	23 (88)	0 (0)
Vomiting	[redacted]	[redacted]	18 (69)	0 (0)
Diarrhoea	[redacted]	[redacted]	7 (27)	0 (0)
Anaemia	[redacted]	[redacted]	7 (27)	3 (12)
Oedema peripheral	[redacted]	[redacted]	9 (35)	0 (0)

Abdominal pain	[redacted]	[redacted]	4 (15)	0 (0)
Fatigue	[redacted]	[redacted]	9 (35)	2 (8)
Pyrexia	[redacted]	[redacted]	-	-
Constipation	[redacted]	[redacted]	12 (46)	0 (0)
Headache	[redacted]	[redacted]	8 (31)	0 (0)
Back pain	[redacted]	[redacted]	-	-
Arthralgia	[redacted]	[redacted]	-	-
Pruritus	[redacted]	[redacted]	-	-
Thrombocytopaenia	[redacted]	[redacted]	6 (23)	2 (8)
Cough	[redacted]	[redacted]	-	-
Dyspnoea	[redacted]	[redacted]	5 (19)	2 (8)
Viral upper respiratory tract infection	[redacted]	[redacted]	-	-
Musculoskeletal pain	[redacted]	[redacted]	-	-
Neutropenia	[redacted]	[redacted]	3 (12)	2 (8)
Urinary tract infection	[redacted]	[redacted]	-	-
Dizziness	[redacted]	[redacted]	-	-
Pneumonia	[redacted]	[redacted]	-	-
Epistaxis	[redacted]	[redacted]	-	-
Pleural effusion	[redacted]	[redacted]	-	-
Ascites	[redacted]	[redacted]	-	-
Depression	[redacted]	[redacted]	-	-
Electrocardiogram QT prolonged	[redacted]	[redacted]	-	-
Hypotension	[redacted]	[redacted]	-	-
Muscle spasms	[redacted]	[redacted]	-	-
Upper respiratory tract infection	[redacted]	[redacted]	-	-
Insomnia	[redacted]	[redacted]	-	-
Lipase increased[a]	-	-	5 (19)	4 (15)
Elevated alkaline phosphatase	-	-	5 (19)	2 (8)
Hyperglycaemia	-	-	5 (19)	1 (4)
Light-headedness	-	-	4 (15)	0 (0)
Hypokalaemia	-	-	4 (15)	1 (4)
Decreased concentration	-	-	3 (12)	-
Gas/bloating	-	-	3 (12)	-
Tremors	-	-	3 (12)	-

Final analysis of D2201 data cut-off: 24th August 2017; SES. Analysis of A2213 data cut-off: 1st March 2017; SES during the first 12 cycles of treatment (main protocol).
[a]Asymptomatic without evidence of clinical pancreatitis.
Source: D2201 CSR (data cut-off: 24th August 2017),[73] DeAngelo *et al.* (2018).[61]

Deaths

In D2201, [redacted] patients died on treatment or within ≤28 days after discontinuing midostaurin.[73] Among these, [redacted] deaths were due to disease progression and [redacted] were due to other causes: cardiac

disorders (n=5), multiple organ dysfunction syndrome (n=3), sepsis (n=3), pneumonia (n=1) and acute myeloid leukaemia (n=1). All causes of death were considered unrelated to midostaurin.

In A2213, 5 patients died on treatment or within ≤28 days after discontinuing midostaurin.[61] Among these, 2 deaths were due to disease progression and 3 were due to other causes: non-neutropenic sepsis (n = 2) and bacterial urinary tract infection (n = 1). All causes of death were considered unrelated to midostaurin.

SAEs regardless of study drug relationship

The most common SAEs regardless of study drug relationship reported in D2201 were pneumonia, with [redacted] experiencing an event of any grade, and sepsis, with [redacted] all experiencing a Grade 3/4 event. No Grade 5 SAEs were reported in D2201.[73] A summary of SAEs in ≥1% patients regardless of study drug relationship from D2201 is presented in Table 32.

Table 32: SAEs in ≥1% patients regardless of study drug relationship from D2201

Serious adverse event, n (%)	D2201 (N=116)	
	Any grade	Grade 3/4
Total	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Gastrointestinal haemorrhage	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]
Acute myeloid leukaemia	[redacted]	[redacted]
Ascites	[redacted]	[redacted]
Pleural effusion	[redacted]	[redacted]
Renal failure	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Acute kidney injury	[redacted]	[redacted]
Coronary artery disease	[redacted]	[redacted]
Epistaxis	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Leucocytosis	[redacted]	[redacted]
Multiple organ dysfunction syndrome	[redacted]	[redacted]
Seizure	[redacted]	[redacted]
Toxic skin eruption	[redacted]	[redacted]
Upper gastrointestinal haemorrhage	[redacted]	[redacted]
Acute leukaemia	[redacted]	[redacted]
Aorticvalvestenosis	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]

Cardiac arrest	[redacted]	[redacted]
Cardiac failure	[redacted]	[redacted]
Colitis	[redacted]	[redacted]
Disease progression	[redacted]	[redacted]
Erysipelas	[redacted]	[redacted]
Gastric ulcer	[redacted]	[redacted]
Gastrointestinal disorder	[redacted]	[redacted]
General physical health deterioration	[redacted]	[redacted]
Hepatic failure	[redacted]	[redacted]
Hyperglycaemia	[redacted]	[redacted]
Hypotension	[redacted]	[redacted]
Malaise	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]
Oedema peripheral	[redacted]	[redacted]
Oesophageal varices haemorrhage	[redacted]	[redacted]
Respiratory failure	[redacted]	[redacted]
Skin ulcer	[redacted]	[redacted]
Splenic infarction	[redacted]	[redacted]
Ventricular tachycardia	[redacted]	[redacted]

Final analysis data cut-off: 24th August 2017; SES.
A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
Source: D2201 CSR (data cut-off: 24th August 2017).[73]

The most common SAEs regardless of study drug relationship reported in A2213 during the first 12 cycles of treatment (main protocol) were sepsis, febrile neutropenia, facial bone fracture due to mechanical fall, elevated total bilirubin and hypercalcaemia, with 1 patient each (4%) experiencing an event of any grade.[61] Only 1 SAE was reported at Grade 5 in A2213, which was sepsis (1 patient [4%]). A summary of SAEs in ≥1% patients regardless of study drug relationship from A2213 during the first 12 cycles (main protocol) is presented in Table 33. A summary of SAEs in ≥1% patients regardless of study drug relationship from A2213 during the extension protocol are presented in Appendix F.

Table 33: SAEs in ≥1% patients regardless of study drug relationship from A2213

Serious adverse event, n (%)	A2213 (N=26)		
	Any grade	Grade 3/4	Grade 5
Sepsis	1 (4)	–	1 (4)
Febrile neutropenia	1 (4)	1 (4)	–
Facial bone fracture due to mechanical fall	1 (4)	1 (4)	–
Elevated total bilirubin	1 (4)	–	–
Hypercalcaemia	1 (4)	–	–

Analysis data cut-off: 1st March 2017; SES during the first 12 cycles of treatment (main protocol).
Source: DeAngelo *et al.* (2018).[61]

AEs leading to study drug discontinuation

In D2201, a total of [redacted] patients ([redacted]) discontinued treatment with midostaurin due to AEs.[73] The most common AEs leading to study drug discontinuation were nausea and electrocardiogram QT prolongation, which affected [redacted] patients ([redacted]) each. A summary of AEs in >2 patients leading to study drug discontinuation by preferred term and maximum Grade from D2201 is presented in Table 34.

Table 34: AEs in >2 patients leading to study drug discontinuation by preferred term and maximum Grade from D2201

Adverse event, n (%)	D2201 (N=116)				
	Any grade	Grade 1	Grade 2	Grade 3	Grade 4
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Electrocardiogram QT prolonged	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Final analysis data cut-off: 24th August 2017; SES.
Source: D2201 CSR (data cut-off: 24th August 2017).[73]

In A2213, a total of 6 patients (23.1%) discontinued treatment with midostaurin due to AEs.[61] The most common AE leading to study drug discontinuation was sepsis, with 1 patient (3.8%) having a Grade 3/4 event and 2 patients (7.7%) experiencing a Grade 5 event. A summary of AEs in 2 patients leading to study drug discontinuation by preferred term and maximum Grade A2213 is presented in Table 35.

Table 35: AEs in >2 patients leading to study drug discontinuation by preferred term and maximum Grade from A2213

Adverse event, n (%)	A2213 (N=26)				
	Any grade	Grade 1	Grade 2	Grade 3/4	Grade 5
Total[a]	6 (23.1)	0	0	4 (15.3)	2 (7.7)
Sepsis	3 (11.5)	0	0	1 (3.8)	2 (7.7)

Analysis data cut-off: 1st March 2017; SES including the first 12 cycles of treatment (main protocol) and the extension protocol.
[a]These numbers have been calculated as the sum of the respective grades of all AEs and SAEs reported as reasons for discontinuation.
Abbreviations: AE: adverse event; SAE: serious adverse event.
Source: DeAngelo et al. (2018).[61]

AEs of special interest (AESI)

In D2201, severe infections, leukopenia, pulmonary toxicity, cardiac dysfunction and reproductive and developmental toxicity were predefined as AESIs.

Severe infection AESIs occurred in 77 patients (66.4%), with 37 patients (31.9%) having a Grade 3/4 event. Among these, the most frequently reported AE of any grade were viral upper respiratory tract infection (20 patients [17.2%]), urinary tract infection (17 patients [14.7%]), pneumonia (16 patients [13.8%]), and upper respiratory tract infection (13 patients [11.2%]). The most frequently reported Grade 3/4 AEs were sepsis (11 patients [9.5%]) and pneumonia (10 patients [8.6%]). Deaths occurred in three patients (2.6%) due to sepsis and one patient (0.9%) due to pneumonia.

Leukopenia AESIs occurred in 26 patients (22.4%), with 21 patients (18.1%) having a Grade 3/4 event. Among these, neutropenia was the most common AE reported, with 17 patients (14.7%) experiencing an event of any grade and 13 patients (11.2%) experiencing a Grade 3/4 event.

Pulmonary toxicity AESIs occurred in 16 patients (13.8%), with 5 patients (4.3%) having a Grade 3/4 event. Among these, the most frequently reported AE of any grade was pleural effusion, which occurred in 14 patients (12.1%).

Cardiac dysfunction AESIs occurred in 11 patients (9.5%), with 6 patients (5.2%) having a Grade 3/4 event. Among these, cardiac failure was the most common AE, 6 patients (5.2%) having an event of any grade and 3 patients (2.6%) experiencing a Grade 3/4 event. Five patients (4.3%) died due to cardiac disorders, and one of these deaths (0.9%) was due to cardiac failure.

Reproductive and developmental toxicity (including phimosis, aplasia and hydrocele) AESIs occurred in 4 patients (3.4%), with 2 patients (1.7%) having a Grade 3/4 event.

A summary of AESIs in >2 patients regardless of study drug relationship by preferred term and maximum Grade from D2201 is presented in Table 36.

Table 36: AESIs in >2 patients regardless of study drug relationship by preferred term and maximum Grade from D2201

Adverse event of special interest, n (%)	D2201 (N=116)	
	Any grade	Grade 3/4
Severe infections	[redacted]	[redacted]
Viral upper respiratory tract infection	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]
Bronchitis	[redacted]	[redacted]
Cystitis	[redacted]	[redacted]
Herpes zoster	[redacted]	[redacted]
Oral herpes	[redacted]	[redacted]
Sinusitis	[redacted]	[redacted]
Erysipelas	[redacted]	[redacted]
Gastroenteritis	[redacted]	[redacted]
Influenza	[redacted]	[redacted]
Tooth infection	[redacted]	[redacted]
Wound infection	[redacted]	[redacted]
Candida infection	[redacted]	[redacted]
Folliculitis	[redacted]	[redacted]
Gastroenteritis viral	[redacted]	[redacted]
Peritonitis	[redacted]	[redacted]
Pyelonephritis	[redacted]	[redacted]
Pyoderma	[redacted]	[redacted]
Rhinitis	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]

Leukopenia	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]
Pulmonary toxicity (including pleural effusion and interstitial lung disease)	[redacted]	[redacted]
Pleural effusion	[redacted]	[redacted]
Interstitial lung disease	[redacted]	[redacted]
Cardiac dysfunction	[redacted]	[redacted]
Cardiac failure	[redacted]	[redacted]
Pulmonary oedema	[redacted]	[redacted]
Reproductive and developmental toxicity	[redacted]	[redacted]
Phimosis	[redacted]	[redacted]

Final analysis data cut-off: 24th August 2017; SES.
Source: D2201 CSR (data cut-off: 24th August 2017).[73]

B.2.10.3 Conclusions on the safety of midostaurin

Overall, midostaurin has demonstrated a manageable safety profile with gastrointestinal and haematological toxicities being the most common AEs.[9]

The most frequent AEs of low-grade nausea, diarrhoea, vomiting and constipation were manageable with prophylactic antiemetics and drug administration with meals

The most frequent Grade 3/4 AEs across both trials were anaemia, thrombocytopaenia and neutropenia, however, it was difficult to determine whether these cytopaenias were related to treatment with midostaurin or disease progression. 30 patients died across both studies; however, no deaths were deemed to be related to study treatment and no new or unexpected safety concerns were identified compared with the use of midostaurin in other indications.

B.2.11 *Ongoing studies*

No further analyses or trial data from D2201 or A2213 are expected in the next 12 months.

B.2.12 *Innovation*

Advanced SM has a significant impact on life expectancy and is associated with a wide range of debilitating symptoms caused by mast cell infiltration and activity which can result in organ dysfunction such as organomegaly, organopathy or even organ failure.[18] The wide spectrum of varied and severe symptoms confers a substantial negative impact on the health related quality of life of patients as well as a considerable burden on carers.[21, 22] Over half of advanced SM patients reported extended impact of the disease resulting in depression (54%), anxiety (62%), difficulty sleeping (69%) and difficulty concentrating (85%).[21] Over 90% of patients also reported the disease to interfere substantially with family life and social interactions, as well as work, daily activities and leisure time.[21] (Section B.1.3.1) There are no disease specific HRQoL instruments for advanced SM, however the MSAS administered in D2201 measures the most important disease related symptoms associated with ASM, SM-AHN or MCL and the SF-12 questionnaire evaluates the patient's symptoms, function and quality of life.[77] As such, the results of the MSAS showed that, compared to baseline, the frequency of 30 out of 32 symptoms decreased at the time of the best reported total score and there was a significant decrease in median MSAS score across all subscales of the questionnaire. Moreover, median scores for both the physical and the mental

components of the SF-12 questionnaire were significantly higher than baseline, showing significant improvement with midostaurin (Section B.2.6.1).

Given the rare nature of the disease and the non-specific symptoms, patients with advanced SM are often underdiagnosed or misdiagnosed for many years. Significant clinical experience is limited to a small number of specialist centres and there is no established treatment pathway or UK-specific clinical guidelines for advanced SM in the UK. There are no licensed treatment options in Europe other than midostaurin, which has demonstrated significant disease-modifying activity with a high and durable overall response rate corroborated by a substantial decrease in the bone marrow mast cell burden, serum tryptase level and *KIT* D816V allele burden.[4, 8] Consequently, midostaurin has the potential to fulfil the unmet need for clinically effective therapies to limit mast cell burden and its associated debilitating symptoms as well as improving survival. In recognition of this and the rare nature of advanced SM, midostaurin was granted orphan designation by the EMA for this indication[10] representing a step change in the management of this disease as the first targeted therapy available for the treatment of patients with advanced SM.

B.2.13 *Interpretation of clinical effectiveness and safety evidence*

Principal findings from the clinical evidence base

Midostaurin is the only licensed cytoreductive therapy to demonstrate significant disease modifying activity with a high and durable rate of response, supported by clear improvements in mast cell burden and reductions in serum tryptase in patients with ASM, SM-AHN and MCL in 2 single arm trials. The ORR as assessed by Valent criteria in D2201 and A2213 was found to be consistent at 60% (95% CI: 49–70) and 69% (95% CI: 50–88), respectively.[12, 61]

Midostaurin demonstrated a median PFS of 17.0 months (95% CI: 10.2–24.8) and 41.0 months (95% CI: 4.4–77.6) in D2201 and A2213, respectively. Median OS was found to be 26.8 months (95% CI: 17.6–34.4) in D2201 and 40.0 months (95% CI: 27.3–52.7) in A2213.[61, 73] A comparison of a pooled analysis of patients treated with midostaurin in D2201 and A2213 with patients who had not received midostaurin in a German registry showed a significant improvement in OS with midostaurin with a median OS of 41.4 months for patients receiving midostaurin compared with 19.5 months for comparator therapies in the registry controls.[23]

The median best reported quality of life improvements as per the SF-12 questionnaire statistically significantly improved versus baseline and there was a significant decrease in median MSAS score across all subscales. The most commonly reported AEs observed with midostaurin were mainly GI, haematological, abdominal pain and bone pain related events, all of which are characteristic symptoms of advanced SM. With the exception of GI events, which were reported at a higher incidence than that observed at baseline, the incidence of the commonly reported events following treatment with midostaurin was found to be similar to the prevalence at baseline and consequently, midostaurin was found to be a well tolerated drug with a manageable safety profile.[80]

The clinical evidence for the non-licensed comparator therapies constituting current clinical management (e.g. interferon-α, cladribine and imatinib) is primarily derived from retrospective studies or single-arm studies conducted in mixed populations of advanced and non-advanced SM subtypes that have shown variable response rates associated with considerable toxicity. Data on the impact of these therapies on survival and HRQoL are lacking and consequently given these challenges, the efficacy of midostaurin in relation to current management is difficult to interpret.

Strengths and limitations of the clinical evidence base

The evidence base informing this appraisal has been derived from a comprehensive clinical SLR, conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and the methodological principles of conduct for systematic reviews from the University of York Centre for Reviews and Dissemination's "Guidance for Undertaking Reviews in Health Care".[74, 75]

The strengths of the evidence base include:

- **The evidence for the safety and efficacy of midostaurin in advanced SM is underpinned by two prospective, single arm, phase II clinical trials**

Whilst there are no phase III, randomised, controlled trials conducted for midostaurin in this indication, the safety and efficacy of midostaurin in advanced SM has been demonstrated in two non-randomised, open label, single arm trials (D2201, A2213), with the D2201 study representing the largest prospectively conducted clinical trial, with a long median duration of follow up (76 months) in this rare population.

Furthermore, given the rare nature of the disease and lack of effective treatment options, the study design was considered acceptable, in the context of advanced SM as a rare disease, the efficacy and safety of midostaurin, with the study accepted by various regulatory bodies to inform the marketing authorisation application for midostaurin.[9, 80]

- **The patient cohort in D2201 is reflective of patient profiles in UK clinical practice**

Although the D2201 study was an international and multicentre study, the trial included 4 patients from 3 UK sites and is considered representative of the population seen in UK clinical practice[1]

- **Overall response rate was considered a reasonable primary efficacy endpoint and is a good measure of clinical benefit**

The response criteria developed for SM were dependent on the presence or absence of clinical findings which are representations of end organ damage and improvement in markers of end organ damage translated into clinical benefit for the patient, therefore the criteria were specifically designed to capture clinical significant manifestations of the disease[80]

- **Long-term efficacy data are provided by the A2213 study**

The 2213 study provides long-term (10-year data on midostaurin)

- **Historical control data provides evidence of the overall survival benefit of midostaurin over the SoC**

In the absence of head to head trials, the historical German and French registries provide supportive evidence of the clinical benefit of midostaurin on overall survival in relation to the current SoC

The limitations of the evidence base include:

- **No randomised, Phase III trials for midostaurin or comparators of interest**

As described previously, the evidence for midostaurin is supported by single arm open label trials, in which the absence of a control arm limits the interpretation of outcomes in relation to comparative efficacy and safety. Additionally, the limited evidence for the comparators makes indirect treatment

comparisons (other than historical control comparisons) infeasible, with data for the comparative efficacy of midostaurin with the standard of care derived from historical control data

- **Primary analyses were not based on PFS/OS, which were secondary endpoints**

Although ORR was considered a reasonable primary efficacy endpoint, improvements in OS usually provide unequivocal evidence of clinical benefit in oncology trials, OS was a secondary end point in both D2201 and A2213 and the single arm nature of the study designs makes OS difficult to interpret

B.2.13.1 End of life criteria

Midostaurin should be considered as an end of life treatment for patients with advanced SM given (a) patients with advanced SM have a short life expectancy, normally less than 2 years and (b) there is sufficient evidence to indicate that the treatment offers an extension to life of at least an additional 3 months, compared with current NHS treatment.

Further details to support midostaurin as an end of life treatment are provided below.

The treatment is indicated for patients with a short life expectancy, normally less than 24 months

The life expectancy of patients with advanced SM varies significantly across disease subtypes. In patients with ASM without AHN, a median survival from diagnosis ranging between 41 months[18] to 11 years[24] has been reported in the literature and in patients with MCL, a median survival from diagnosis ranging between 2 months[18] to 9.2 months[25] has been described.

As highlighted in Section B.2.3.1, the pivotal trial (D2201) and the key supportive trial (A2213) included only advanced SM patients (patients with ASM or MCL ± AHN) with measurable C-findings and, therefore, the evidence base is limited to this population. In patients with SM-AHN, a median survival from diagnosis ranging between 24 months[18] to 4.4 years[16] has been reported in the literature; however, these survival estimates include both patients classified with advanced SM as per the pivotal trial (measurable C-findings, i.e ASM-AHN) as well as patients with indolent disease (i.e ISM-AHN). It is unclear from these studies how many patients with SM-AHN have "truly" advanced disease (ASM-AHN) or indolent disease (ISM-AHN) and therefore the "true" survival for patients defined as SM-AHN (ASM-AHN) as per D2201 and A2213 is unknown. Consequently, the estimates from the literature provide a very optimistic upper bound estimate of survival, given the better prognosis of patients with indolent disease.

Reiter *et al.* (2017) reported the median survival from diagnosis in a contemporary German registry of patients with advanced SM similar to those enrolled in D2201 and A2213 (patients with ASM or MCL ± AHN), who had not been treated with midostaurin (n=42) to be 19.5 months (95% CI 13.0 - 35.3).[23] These data represent the only source of survival data for patients with advanced SM as defined in the pivotal D2201 and the supportive A2213, and they demonstrate that the median survival for the overall advanced SM population (patients with ASM or MCL ± AHN) is less than 24 months. Considering the poorer prognosis of patients with ASM-AHN and MCL disease subtypes, median survival is likely to be lower than that reported by Reiter *et al.* (2017) and, therefore, midostaurin meets the criteria for an end of life medicine.

It should be noted that the median survival reported in studies described above and Reiter *et al.* (2017) is from diagnosis and data reported from diagnosis are likely to provide an overestimate of the survival of the patient population that would be eligible for midostaurin. Furthermore, D2201

and A2213 included a mix of patients with no prior line of therapies and patients who had received prior treatments. Based on the available evidence, it is clear that patients with advanced SM have a short life expectancy, normally less than 24 months. This was confirmed by five clinical experts with considerable expertise in the management of patients with advanced SM, who considered the life expectancy for the overall population of patients with advanced SM to be normally less than 24 months, with life expectancy further reduced in the subgroup of patients with SM-AHN + MCL.

These data are consistent with results from the economic model which predicted a mean undiscounted life years of 1.90 for the overall advanced SM population and 1.46 for the subgroup of patients with SM-AHN + MCL, confirming that the majority of patients in both populations have a short life expectancy, (normally less than 2 years) and that midostaurin meets the NICE end of life criteria for the licensed indication under review.

There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment

There are no direct comparisons between midostaurin and current clinical management; however, Reiter *et al.* (2017)[23] demonstrated a survival benefit of 21.9 months for patients treated with midostaurin (median OS 41.4 months) in the pooled analysis of D2201 and A2213 compared with current clinical management (median OS 19.5 months) observed in a German cohort which included similar patients.

Consequently, there is sufficient evidence to indicate that midostaurin offers an extension of life of at least an additional 3 months compared with current NHS treatment. This is further supported by the economic model, where the incremental life years gained (LYG) predicted by the model for midostaurin compared with current management was estimated to be [redacted] and [redacted] for the overall population and SM-AHN + MCL subgroup respectively, an increment that is considerably greater than 3 months.

Table 37: End of life criteria

Criterion	Data available					Reference in submission
	ASM	SM-AHN	MCL	Overall advanced SM population	Source	
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	NR	NR	NR	Median OS from diagnosis: 19.5 months	Reiter *et al.* 2017[23]	Section B.2.9.1; page 70
	NR	Mean undiscounted life years: [redacted] ([redacted] months)		Mean undiscounted life years: [redacted] ([redacted] months)	Economic model prediction	Section B.3.7; page 156 Section B.3.9; page 165
There is sufficient evidence to	NR	NR	NR	21.9 months (difference in median OS)	Reiter *et al.* 2017[23]	Section B.2.9.1; page 70

indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	NR	Incremental life years gained: [redacted] ([redacted] months)	Incremental life years gained: [redacted] ([redacted] months)	Economic model prediction	Section B.3.7; page 156 Section B.3.9; page 165

Abbreviations: ASM: aggressive systemic mastocytosis; MCL: mast cell leukaemia; OS: overall survival; SM-AHN: systemic mastocytosis with associated haematologic neoplasm.

B.3 Cost effectiveness

Summary of the cost-effectiveness analysis

- A *de novo* cost-utility model was developed for the economic evaluation of midostaurin compared with current clinical management in the UK, in accordance with the NICE reference case. The analysis was conducted from an NHS/PSS perspective, with a lifetime time horizon and with costs and outcomes discounted at 3.5% per annum.
- Efficacy data for midostaurin were derived from D2201[12] and efficacy data for the comparators (defined as treatments that comprise current UK management [cladribine, (peg)-interferon alpha, imatinib and "AML-like" treatments]) were derived from an indirect comparison of midostaurin from a pooled analysis of D2201 and A2213 data versus a German historical cohort.[23]
- Health-state utility values were estimated from SF-12 data collected in D2201 mapped to the EQ-5D-3L, and resource utilisation estimates were derived from a clinician survey among five advanced SM UK clinical experts.[1]

Base case cost-effectiveness results

- Base case deterministic results show that midostaurin (when provided with the existing confidential PAS) is associated with higher costs but also higher QALYs than current clinical management, with an incremental cost per QALY gained of [redacted] in the overall advanced SM population and [redacted] in the SM-AHN + MCL subgroup. [redacted]

Sensitivity analyses

- Probabilistic sensitivity analyses (PSA) and deterministic sensitivity analyses (DSA) were conducted to assess uncertainty in the economic analysis and demonstrate that the base case cost-effectiveness results were robust to an extensive number of scenario analyses.
- The DSA shows that results were mostly sensitive to the HR applied for OS for the comparator, and the discount rate for benefits and utility values.
- An extensive range of scenario analyses were also conducted, with the results generally robust to most parameters and structural assumptions of the economic analysis. The ICERs across the majority of the scenario analyses performed with the existing confidential PAS remained within 10% of the base case ICER.

Summary

- Advanced SM is a rare disease, with no other licensed treatments to fulfil the large unmet medical need. This economic analysis presents a robust evaluation of midostaurin against current clinical management in the UK. [redacted]; however, it is important to note that had midostaurin been considered via the HST process (a process specifically designed for rare diseases such as advanced SM), as opposed to the current STA process, it is possible that a different conclusion may have been reached given the broader decision-making framework, different attitudes to uncertainty, and higher willingness-to-pay (WTP) thresholds considered in the HST process.
- [redacted]

B.3.1 *Published cost-effectiveness studies*

An economic SLR was conducted to identify any relevant economic evaluations previously published in patients with advanced SM. The searches were conducted in October 2019 and full details of the SLR search strategy, study selection process and results are reported in Appendix G.

In total, two economic evaluations in advanced SM were identified in the SLR (Table 38). One study (Cariou *et al.* [2018]),[88] presented valid outcomes in the form of quality-adjusted life years (QALYs) and life-years (LYs) in the patient population relevant to this appraisal, but did not model costs. The second study represented an economic evaluation conducted from an Australian health care system perspective but included limited details of the model used.[89]

Given the limited applicability of the identified published economic evaluations to decision-making in England, a *de novo* cost-effectiveness model was constructed for the purposes of this appraisal.

Table 38: Summary list of published cost-effectiveness studies

Study	Year	Summary of model	Patient population	QALYs	Costs (currency)	ICER (cost per QALY gained)
Cariou *et al.* (2018)	2018	Partitioned survival model	Patients with advanced SM	Midostaurin: 3.25 SoC: 1.35 QALYs gained: 1.90	NR	NR
PBAC (2008)	2008	A non-randomised case series with no further modelling	Patients with advanced SM	NR	Midostaurin: NR Imatinib: 45,000–75,000[a] (AUD)	NR

[a]Incremental costs per extra responder for advanced SM.
Abbreviations: AUD: Australian dollar; ICER: incremental cost-effectiveness ratio; NR: not reported; PBAC: Pharmaceutical Benefits Advisory Committee; QALYs: quality-adjusted life years; SM: systemic mastocytosis; SoC: standard of care.
Source: Cariou *et al.* (2018),[88] PBAC (2008).[89]

B.3.2 *Economic analysis*

The objective of this economic analysis was to assess the cost-effectiveness of midostaurin compared with current clinical management in the UK for patients with advanced SM. In line with the NICE reference case, the analysis was conducted from the perspective of the NHS and Personal Social Services (PSS) and included direct medical costs only over a lifetime time horizon.[85]

B.3.2.1 Patient population

The patient population considered within the economic analysis reflects the patient population in the two pivotal trials for midostaurin, D2201 and A2213: patients with advanced SM, specifically patients with ASM, SM-AHN and MCL.[12, 61] This is consistent with the population defined in the NICE final scope, the decision problem for this appraisal, and the European marketing authorisation for midostaurin in this indication.[3, 4]

The baseline characteristics of the patients in the pivotal D2201 and A2213 trials have been described previously in Section B.2.3.2 and the final NICE scope stipulates that economic subgroup analyses should be explored if evidence allows.

Analysis of the pivotal D2201 and A2213 trial data revealed that the benefit of midostaurin in terms of ORR (evaluated using the Valent response criteria) was observed across all pre-specified patient subgroups investigated, regardless of the subtype of advanced SM, KIT mutation status, or exposure to previous therapy (Section B.2.7).[12, 61]

Although economic subgroup analyses were initially considered by Novartis for the three advanced SM disease subgroups (ASM, SM-AHN and MCL) individually, it proved to be extremely challenging to conduct a robust economic analysis for the MCL and ASM populations separately given the small sample size of these disease subtypes in the D2201 trial (n=16 for MCL and n=16 for ASM). The limited data for these subgroups made it challenging to fit the different parametric functions to the trial outcomes for extrapolation, and any ensuing results would have been associated with substantial uncertainty.

Following discussions with UK clinical experts and preliminary discussions with NICE and the ERG in the lead up to this appraisal, it was recognised that there remains a large unmet medical need for further therapies for patients with advanced SM and in particular for patients with SM-AHN and MCL. Together, these two populations represent 82% of the population included in the pivotal D2201 trial, and have a very poor prognosis. Whilst the overall advanced SM population considered in this appraisal already have a short life expectancy, normally less than 2 years on average as shown by Reiter *et al.* (2017),[23] the life expectancy for the subgroup of patients with SM-AHN + MCL is further reduced (Section B.1.3.1, B.2.13). Consequently, a subgroup analysis for the pooled population of patients with SM-AHN + MCL is considered in this submission alongside the results for the overall licensed advanced SM population (comprising ASM, SM-AHN and MCL).

B.3.2.2 Model structure

A *de novo* cohort partitioned survival model (PSM) was developed in Microsoft Excel® to reflect the natural history and clinical pathway of advanced SM in the UK.

Justification of model structure

A key challenge when conducting an economic evaluation for a rare disease such as advanced SM is the limited amount of available evidence and small patient numbers from the studies available. These challenges need to be recognised in the context of the modelling approach.

Economic models for anti-cancer therapies typically follow two key approaches:

1. a partitioned survival model (PSM) approach whereby curves are fitted directly to the trial outcomes and deal with health state occupancy (rather than transition between states) or

2. a general state-transition model approach whereby OS is considered a function of the time spent in an intermediate health state, with PFS typically used as a surrogate outcome for OS.

The choice of approach needs to be based on (a) the evidence available but also (b) the ability to ensure that the model captures the key features of the condition/intervention.

The PSM approach was selected for this economic evaluation, instead of a state-transition approach, to reflect both the quality and quantity of the evidence available for both midostaurin and current clinical management in the UK (as described in Section B.2.2 and B.2.9.2).

The pivotal D2201 and A2213 trials are single-arm studies and therefore no direct head-to-head evidence exists for midostaurin versus current clinical management for advanced SM in the UK. In the absence of head-to-head evidence, the key evidence for OS for the comparators is derived from an indirect treatment comparison in the form of HRs (Section B.2.9).

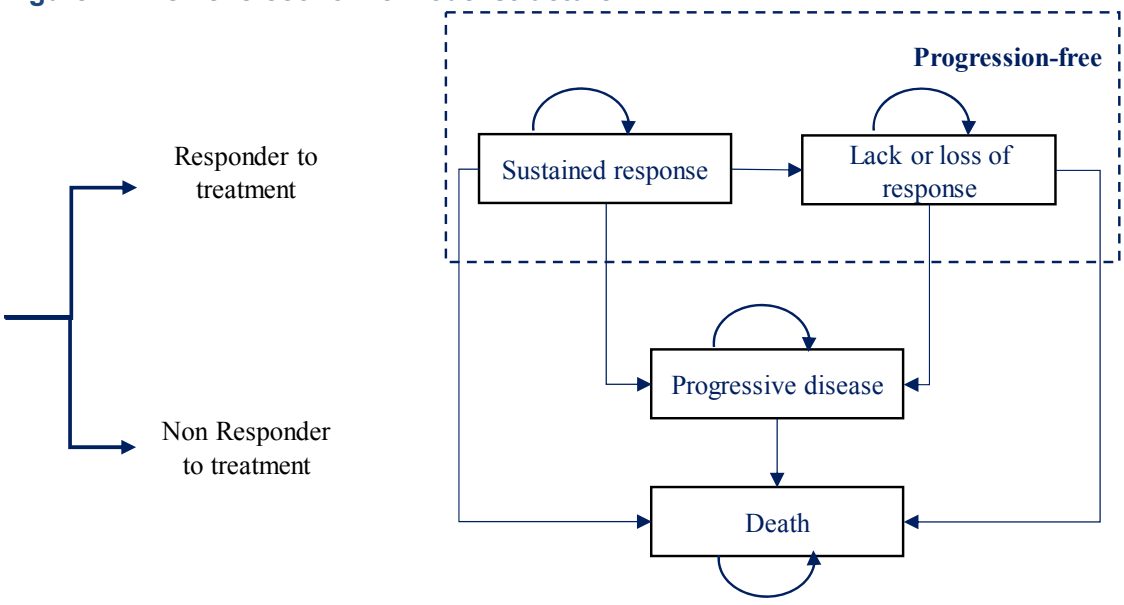
Since the OS and PFS data for patients receiving midostaurin are relatively mature in the D2201 and A2213 trials, it was considered appropriate to fit parametric functions directly to the observed data. No direct or indirect evidence was available for PFS for the comparators of interest, restricting the use of an alternative approach such as a state-transition model, whereby OS would need to be modelled as a function of the time in PFS and time post-progression.

Using response as a surrogate outcome for either PFS or OS would rely on a large number of arbitrary assumptions. In addition to the paucity and quality of the data, the effect of response on PFS and OS is likely to be different between treatments due to the different mechanisms of action.

The model structure (Figure 27) and PSM approach were validated by UK clinical experts who considered that this approach appropriately captures the key feature of advanced SM (disease progression).[1] The model consists of four mutually exclusive health states; (1) progression-free – sustained response, (2) progression-free – lack or loss of response, (3) progressive disease (PD) and (4) death, and therefore includes a decision tree prior to entry into the PSM, to reflect that patients may start the model in the progression-free health state (with or without response).

The model structure does not allow for improvements in health state, reflecting the progressive nature of advanced SM and therefore the health states typically considered when modelling anti-cancer therapies. Despite movements of patients between health states, transitions are not explicitly modelled but the proportion of patients in each health state at each cycle is determined by the area under the curves for OS, PFS and duration of response (DoR) for midostaurin, with a treatment effect applied to the comparator arm.

Figure 27: *De novo* economic model structure



Progression-free health state (PFS)

Patients enter the model in the PFS health state in either the "sustained response" or "lack or loss of response" category, based on the response rate achieved by the treatment received (midostaurin or the comparator). The separation of the "progression-free" health state into "sustained response" and "lack or loss of response" allows consideration for the potential differences in HRQoL between these health states.

- Patients who are responders after treatment initiation can:
    - Remain in the "sustained response" health state in the event of continued response
    - Move to the "lack or loss of response" health state in the event of losing their response
    - Move to the progressive disease health state on disease progression *or*
    - Die from advanced SM or other causes
- Patients who are non-responders after treatment initiation can:
    - Remain in the "lack or loss of response" health state
    - Move to the progressive disease health state on disease progression *or*
    - Die from advanced SM or other causes

Progressive disease health state (PD)

Patients enter the progressive disease health state on disease progression and can:

- Remain in this health state or
- Die

Death state

The death state is an absorbing state.

Despite not being a "true" health state, time on treatment is also considered within the model to account for both costs and the impact of the mode of administration on HRQoL (Section B.3.4.5).

Features of the economic analysis

The economic analysis was conducted in accordance with the NICE reference case,[85] employing a lifetime time horizon (patients are followed in the economic model for a maximum of 500, 28-day cycles, until 99.99% of the population have died). This was considered appropriate given a mean starting age of 63 years and given the economic perspective was that of a direct NHS and PSS perspective (2018/2019 price year).

A 4-week cycle length (28 days) was used to reflect the cycle duration for treatment with midostaurin and was considered short enough to capture any differences in outcomes between treatment arms. A half cycle correction was not deemed necessary given the short duration of the cycle length.

The lifetime time horizon was selected to reflect the chronic nature of the disease and to fully capture the costs and benefits associated with the use of midostaurin in this indication. Both costs and benefits were discounted at 3.5% per annum as per the NICE reference case and the impact

of the discount rate was examined in sensitivity analyses (Section B.3.8). The results of the cost-effectiveness analysis are reported in terms of discounted costs per QALY gained.

The key features of the economic analysis are described in Table 39. There have been no previous appraisals conducted by NICE for this indication, reflecting the lack of effective treatments for this population and the resulting high unmet need.

Table 39: Features of the economic analysis

Factor	Previous appraisals	Current appraisal	
		Chosen values	Justification
Time horizon	N/A (There have been no previous NICE appraisals in this indication)	Lifetime (until 99.99% of patients have died)	• In line with the NICE reference case[85] • Sufficient to capture all meaningful differences in technologies compared
Discount rate		3.5% discounting per annum applied for both costs and benefits	In line with the NICE reference case[85]
Cycle length		4-week cycle	Based on the treatment cycle duration for midostaurin and short enough to capture any differences in clinical outcomes between treatments
Perspective		NHS/PSS	In line with the NICE reference case[85]
Treatment waning effect?		• OS, PFS and DoR for midostaurin were estimated from parametric functions fitted to the Kaplan-Meier curves for these outcomes from the D2201 trial • OS for the comparators was estimated using the HR from a pooled analysis of D2201 and A2213 versus historical control data (Reiter *et al.* [2017])[23] and applied over the lifetime time horizon	• The data for midostaurin is incorporated directly into the model from the D2201 trial • Patients with advanced SM treated with current clinical management are expected to have a short life expectancy and the HR for OS is estimated using long-term data. Therefore, assuming the HR to be constant was deemed to be appropriate
Source of utilities		• Utility values were estimated from SF-12 data from the D2201 trial, mapped onto the EQ-5D-3L (Section B.3.4.1 and B.3.4.2) • Decrements in utility associated with subcutaneous and injection administrations versus oral treatments were also included in the economic model (Section B.3.4.5) • Utility values were adjusted for the decreased in HRQoL associated with older age	• Utility values based on the EQ-5D-3L were included in line with the NICE reference case[85] • As a simplifying assumption, the same utilities were used for midostaurin and the comparators due to the absence of evidence for the comparator. • The HRQoL benefits associated with the oral mode of administration

			has been included in previous NICE appraisals[90, 91]
Source of costs		• NHS reference costs 2017/2018 were used for resource use unit costs • Drug costs were derived from the BNF, eMIT and published costs where appropriate[11, 92, 93] • An existing confidential PAS is included for midostaurin. [redacted]	In line with the NICE reference case[85]

Abbreviations: Advanced SM: advanced systemic mastocytosis; BNF: British National Formulary; eMIT: electronic market information tool; EQ-5D-3L: EuroQol 5 Dimensions 3 Levels; HR: hazard ratio; HRQoL: health-related quality of life; N/A: not applicable; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; PAS: patient access scheme; PSS: Personal and Social Services; OS: overall survival; VPAS: Voluntary Scheme for Branded Medicines Pricing and Access.

B.3.2.3 Intervention technology and comparators

Intervention

- The intervention of interest is midostaurin 100 mg administered orally, twice daily (i.e. 200 mg daily) as a continuous cycle of 28 days. This is line with the regimen used in the key pivotal trials D2201 and A2213 supporting this submission, and the SmPC for midostaurin.[4, 12, 61]
- According to the SmPC for midostaurin, "treatment should be continued as long as clinical benefit is observed or until unacceptable toxicity occurs". Patients enrolled in the investigator-initiated A2213 study discontinued treatment if they did not respond after 2 cycles of treatment, as per the study protocol.[61] In contrast, in the D2201 trial, patients remained on treatment as long as clinical benefit was observed. [51] As this is a very rare disease there is a small number of clinicians that specialise in the treatment of advanced SM and can be considered as experts in the UK. Discussion with these local experts indicated that the measurement of response is not routinely applied in UK clinical practice; it is more relevant in a trial setting and difficult to implement in practice. Clinical experts with experience of prescribing midostaurin in the UK also stated that treatment with midostaurin should continue for as long as a clinical benefit is observed. This is consistent with the SmPC for midostaurin, and supporting evidence from a company-sponsored UK-based compassionate use programme.[94]
- Consequently, the economic analysis does not consider a stopping rule for midostaurin, and treatment is considered in the model as per the study D2201 protocol, and modelled as per the expected use of midostaurin in clinical practice in the UK.

Comparators (defined as current clinical management in the UK)

As described in Section B.1.3.2, other than midostaurin, there are no other therapies licensed for the treatment of advanced SM in the UK, therefore current treatment/management strategies for advanced SM comprise of a mix of treatments. The treatment mix assumed for the comparator within this economic analysis is consistent with the treatments defined in the NICE final scope,[3] supplemented by discussions with five UK clinical experts,[1, 51] who described peg-interferon alpha and "AML-like" treatments as additional treatment options used in UK clinical practice for patients with advanced SM (Table 40).

Table 40: Comparators included in the economic analysis

Comparator	Regimen assumed	Proportion used in the UK (overall advanced SM population)	Proportion used in the UK (SM-AHN + MCL)
NICE final scope			
Cladribine	0.14 mg/kg given day 1-5, maximum number of 9 cycle	53.65%	52.12%
Interferon alpha (Roferon-A)	3-5 MU thrice weekly	2.05%	1.53%
Imatinib	400 mg daily	4.50%	3.64%
UK clinical experts			
Peg-interferon alpha (Pegasys)	Start at 45 MU per week, with gradual increase	24.23%	23.74%
"AML-like" treatments, defined as treatment typically used to treat AML	Based on TA552[95]	15.56%	18.97%

Abbreviations: Advanced SM: advanced systemic mastocytosis; AML: acute myeloid leukaemia; MCL: mast cell lymphoma; MU: million units; NICE: National Institute for Health and Care Excellence; SM-AHN: systemic mastocytosis with associated haematological neoplasm; TA: technology appraisal; UK: United Kingdom.

"AML-like" treatments, as described by UK clinical experts, are those typically used to treat AML, including intensive chemotherapies for patients fit for high-dose chemotherapy (e.g. DA [cytarabine plus daunorubicin] induction followed by high-dose cytarabine consolidation [HiDAC], or FLAG-IDA [fludarabine, high-dose cytarabine with granulocyte-colony stimulating factor] for adverse risk, and for patients deemed unfit for high-dose chemotherapy (e.g. low-dose cytarabine, or hypomethylating agents [azacitidine]).

It is important to note that whilst nilotinib and dasatinib were included in the NICE final scope, UK clinical experts noted that these TKIs are rarely used in UK clinical practice due to the limited clinical evidence base available for these therapies.[1] Consequently, these therapies were excluded from the treatment mix adopted for the comparator of current clinical management in the base economic analysis for this submission; however, the economic model maintains the flexibility to include these treatments within the mix of treatments comprising current clinical management within scenario analyses.

UK clinical experts also noted that a majority of patients with advanced SM are too frail or cytopenic to receive cytoreductive therapies and instead receive what is defined as supportive/palliative care (including watch and wait or hydroxyurea for symptom control). Clinical experts noted that the resource use associated with this management strategy is typically intensive and that these patients would not be eligible for midostaurin as they are considered too frail or cytopenic to receive active treatments. Supportive care was therefore not considered a comparator in the economic analysis for this submission.

UK clinical experts further noted that a proportion of patients with advanced SM may enter clinical trials. Additionally, as described in Section B.1.3.2, clinical experts also noted that allo-HSCT is rarely used for patients with advanced SM in the UK and, should midostaurin be available to the NHS, midostaurin would not displace allo-HSCT, but be used alongside it as a debulking agent and/or bridge to transplant in a small proportion of patients.

Since the comparator in the base case economic analysis is defined as current clinical management and therefore includes a mix of treatments used in UK, the costs and QALYs for the comparator are weighted by the proportion of treatments administered in UK clinical practice as estimated by 5 UK clinical experts (Table 40), after excluding the supportive care category and patients entering clinical trials.[1]

For transparency and completeness, the results for each individual treatment/management strategy (cladribine, (peg)interferon-based regimens [Roferon-A and Pegasys], imatinib, nilotinib, dasatinib and "AML-like" treatments [azacitidine and intensive chemotherapies]) are presented separately in scenario analyses in Section B.3.8.3.

B.3.3 *Clinical parameters and variables*

The sources for the clinical parameters used in the economic model are summarised below in Table 41 and discussed in turn below.

Given a key challenge in the modelling of advanced SM is the lack of evidence in terms of the quantity and quality for the comparators, a large number of assumptions were necessary to address these data gaps and for transparency and completeness, these assumptions are further described below.

Key efficacy data for midostaurin come from the pivotal D2201 trial where individual patient-level clinical data (IPD) from the latest data cut-off: 1st December 2014 for PFS/DoR and 24th August 2017 for OS (Section B.2.6) were used to inform the base case economic analysis.

Efficacy data for the comparator (current clinical management) comes from indirect evidence from a pooled analysis of the D2201 and A2213 trials against an historical cohort (Section B.2.9). Additional data identified in the clinical SLR (Section B.2.9.1) were also used for the comparator.

Table 41: Summary of sources of data used in the economic model

Parameter	Midostaurin	Current clinical management	Reference in Submission
Baseline characteristics	D2201	Assumed same as D2201	Section B.3.3.1
OS	D2201	Reiter *et al.* (2017)[23]	Section B.3.3.2 Section B.2.9.1
PFS	D2201	Reiter *et al.* (2017)[23] [HR assumed to be the same as for OS]	Section B.3.3.3
Response rates	D2201	Barete *et al.* (2015);[30] Jawhar *et al.* (2017a);[66] Lim *et al.* (2009);[70] Pardanani *et al.* (2009);[72] Hauswirth *et al.* (2004)[60]	Section B.3.3.4
DoR	D2201	Lim *et al.* (2009)[70]	Section B.3.3.4
Duration of treatment	D2201	Based on PFS, Barete *et al.* (2015),[30] TA552[95]	Section B.3.3.5
AEs	D2201	Barete *et al.* (2015)[30] SmPC cladribine[96]	Section B.3.3.6

Abbreviations: AEs: adverse events; DoR: duration of response; HR: hazard ratio; OS: overall survival; PFS: progression-free survival; SmPC: Summary of product characteristics.

Efficacy data from A2213 was not used in the economic model for the following reasons:

- Since the A2213 study was an investigator-initiated study, IPD from the latest data cut-off of this study (Section B.2.6.2) were not available to Novartis and therefore it was not possible to pool the latest data from D2201 and A2213 studies for use in the economic model.
- As described in Section B.2.3.1, in A2213, treatment with midostaurin was discontinued after 2 cycles in the absence of response, and this does not reflect how midostaurin will be used in the UK.

Finally, whilst A2213 is not used directly in the economic model, long-term evidence from the A2213 trial (DeAngelo et al. [2018])[61] was used to inform the choice of extrapolation.

B.3.3.1 Baseline characteristics

The baseline characteristics for the modelled cohort in terms of age, gender distribution and weight were derived from D2201 since the patients in the trial were deemed representative of patients in UK clinical practice (Table 42). The mean age and gender distribution was used in the model alongside UK life tables[97] to incorporate general population mortality when extrapolating survival curves (to avoid the extrapolated hazard to be less than the expected hazard of death in the general population). Weight was primarily used in the economic evaluation to calculate drug acquisition costs for cladribine.

Table 42: Baseline characteristics

Baseline characteristic	Population	
	Overall advanced SM population (n=89)	SM-AHN + MCL (n=73)
Age	63.00 (SD: 11.59)	[redacted]
Gender distribution (% male)	64.04%	[redacted]
Weight	71.59 (SD: 13.93)	[redacted]

Abbreviations: Advanced SM: advanced systemic mastocytosis; MCL: mast cell lymphoma; SD: standard deviation; SM-AHN: systemic mastocytosis with associated hematologic neoplasm.
Source: Gotlib *et al.* (2016).[12]

B.3.3.2 Overall survival (OS)

OS in patients initiating midostaurin

The Kaplan-Meier curve for the final OS analysis from D2201 (data cut-off: 24th August 2017) is presented in Figure 28 for both the overall advanced SM population and the SM-AHN + MCL subgroup.

Figure 28: Kaplan-Meier curve for OS from D2201

Abbreviations: KM: Kaplan-Meier; MCL: mast cell leukaemia; OS: overall survival; SM-AHN: systemic mastocytosis with associated haematological neoplasm.
Source: Analysis of D2201 individual patient-level data.[12]

In accordance with the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14,[98] a range of standard parametric distributions (exponential, Weibull, Gompertz, loglogistic, lognormal and generalised gamma) and more flexible models (i.e spline models) were explored in the extrapolation of the clinical trial data beyond the observed period. Spline models (hazard) with one and two knots were estimated in R using the FlexSurv package, and although additional knots were examined, they did not significantly improve the fit to the data.

Different parametric models incorporate different hazard functions. For instance, exponential models are only suitable if the observed hazard is approximately constant and positive. Weibull and Gompertz models incorporate monotonic hazards, while the logged model (lognormal) can incorporate non-monotonic hazards but typically has a long tail due to a reducing hazard as time increases beyond a certain point.

TSD 14 also recommends that the most appropriate distribution is selected based on consideration of: (a) the visual fit of the predicted models to the observed Kaplan-Meier, (b) the statistical goodness-of-fit of the model relative to all other fitted models (measured using the Akaike Information Criterion [AIC] or Bayesian Information Criterion [BIC]), (c) an assessment of the observed hazards and (d) the plausibility of the long-term extrapolation.

The fit of each parametric function relative to the Kaplan-Meier curve is presented in Figure 29 and it can be seen that with the exception of the exponential and the Weibull distributions, all other distributions provided a good visual fit to the observed Kaplan-Meier for both populations of interest. It should be noted that a constraint was added in the economic model so that the predicted extrapolated hazard is not lower compared with the hazard of death observed in the general population.[97]

Figure 29: Comparison of parametric distribution fits to midostaurin in D2201 for OS during the observed period (a) overall advanced SM population (b) SM-AHN + MCL subgroup

a) overall advanced SM population

b) SM-AHN + MCL subgroup

Abbreviations: exp: exponential; gengam: generalised gamma; gomp: Gompertz; KM: Kaplan-Meier; lnorm: lognormal; llog: loglogistic; MCL: mast cell leukaemia; OS: overall survival; SM: systemic mastocytosis; SM-AHN: systemic mastocytosis with an associated haematological neoplasm; weib: Weibull.

The statistical goodness of fit in terms of AIC and BIC, was also relatively similar between the different distributions (Table 43), with the lognormal distribution having the lowest AIC and BIC.

Table 43: Summary of AIC and long-term plausibility for the different distributions

Parametric Function	Overall advanced SM population			SM-AHN + MCL subgroup		
	AIC	BIC	[redacted]	AIC	BIC	[redacted]
Exponential	623.15	625.63	[redacted]	537.74	540.03	[redacted]
Weibull	624.93	629.91	[redacted]	539.71	544.29	[redacted]
Gompertz	621.61	626.59	[redacted]	537.47	542.05	[redacted]
Lognormal	615.87	620.85	[redacted]	531.38	535.96	[redacted]
Loglogistic	617.93	622.91	[redacted]	533.07	537.65	[redacted]
Generalised gamma	616.65	624.12	[redacted]	532.64	539.52	[redacted]
Spline model with one knot	**618.42**	**625.88**	[redacted]	**534.29**	**541.16**	[redacted]
Spline model with two knots	619.86	629.82	[redacted]	535.50	544.66	[redacted]

Abbreviations: Advanced SM: advanced systemic mastocytosis; AIC: Akaike information criteria; BIC: Bayesian information criteria; MCL: mast cell leukaemia; SM-AHN: systemic mastocytosis with associated haematological neoplasm.

Whilst the statistical goodness of fit only provides an indication of the fit to the observed data, assessment of the plausibility of the long-term extrapolation beyond the observed period is important. Assessment of the long-term extrapolation for OS was informed by both (i) clinical expert opinion and (ii) external validation using long-term evidence from the A2213 trial. The A2213 study provides long-term data on the outcomes of patients treated with midostaurin and although IPD from the latest data cut-off of A2213 were not available to Novartis as this is an Investigator-based trial, external validation of OS was based on data available in the public domain published by DeAngelo *et al.* (2018).[61]

With the exception of the exponential and Weibull distribution (which did not provide a good visual fit to the observed period), predictions for OS at 15 years were relatively similar between the remaining distributions, ranging between [redacted] for the overall advanced SM population and [redacted] for the SM-AHN + MCL subgroup (Figure 30). Although OS Kaplan-Meier curves for the overall advanced SM population in study A2213 is not reported by DeAngelo *et al.* (2018),[61] time-to-event data for OS for each of the subgroups in advanced SM (ASM, SM-AHN and MCL) is reported separately in the publication (Section B.2.6.2, Figure 15). Visual inspection of the published Kaplan-Meier curves shows that:

- For patients with SM-AHN (n=17), OS at 10 years (120 months) is approximately 15%, with survival falling to zero at 11 years (132 months). It should be noted that this decline in survival is a statistical anomaly, attributable to the very limited number of patients at risk after 9 years and therefore does not represent a real decline in survival. It should also be noted that a patient was censored at month 84 with another one at month 96.
- For patients with ASM (n=3), 2 patients were censored between months 120-132.
- All patients with MCL (n=6) died before 8 years, with the median survival around 3.5 years.

Clinical opinion was sought to identify the most appropriate parametric function to use in the base case, with the clinical experts agreeing that, with the exception of the exponential and Weibull distributions, all distributions provided a similar and a plausible estimation of OS in line with the long-term data for midostaurin in study A2213 and their own clinical experience with midostaurin. Since the extrapolations all provided similar estimates of OS, the clinical experts could not confidently choose between functions as they considered them all to be clinically plausible.[1]

Since OS for the comparator was estimated by applying a HR to the OS curve for midostaurin (Section B.2.6.1), proportional-hazard (PH) compatible models (exponential, Weibull, Gompertz and spline hazard models) were considered most appropriate for the extrapolation of the midostaurin arm.

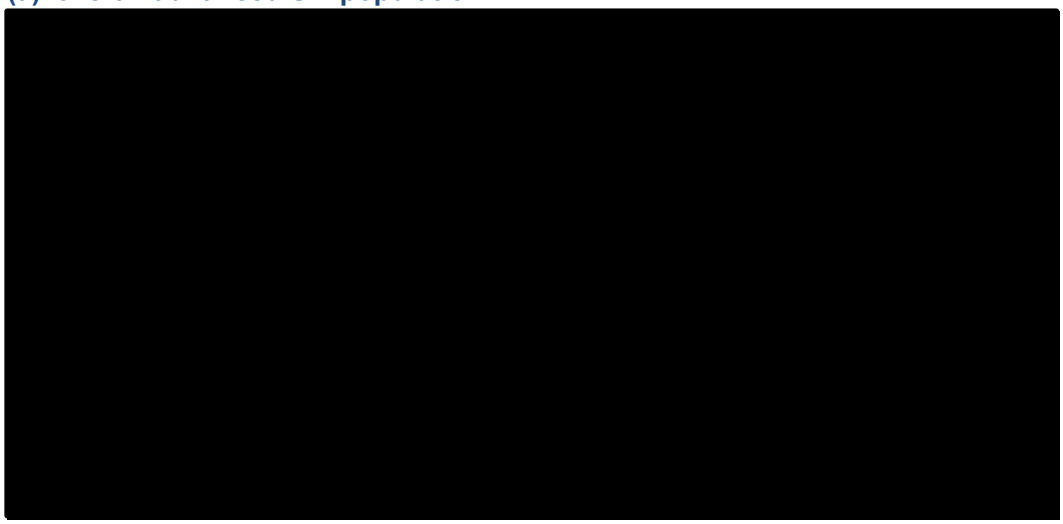
Consequently, the base case economic analysis adopts the Spline (hazard) model with one knot since this was a PH-compatible model, and provided both a reasonable fit to the observed period and a plausible long-term extrapolation. It should however be noted that in previous NICE TAs, when PH models were considered inappropriate or when alternative distributions provided a superior fit to the data and more plausible extrapolation, HRs have been applied to non PH-compatible models.

Extensive scenario analyses were conducted using spline knot models with different knots, Gompertz and plausible non-PH compatible models (lognormal, loglogistic, generalised gamma), with a limited impact on the results (Section B.3.8).

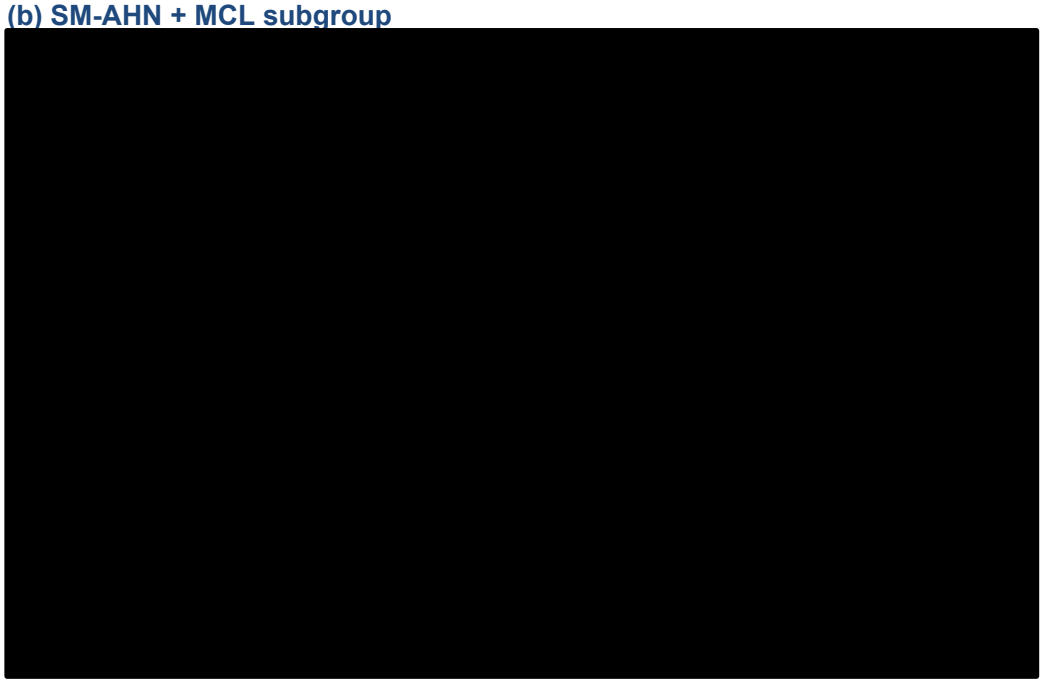
In addition to fitting parametric functions directly to the Kaplan-Meier for OS, an additional scenario analysis was conducted whereby the Kaplan-Meier curve (for all survival functions) was used up to the last event, with the parametric function extrapolation used thereafter. Again, this had limited impact on results (Section B.3.8).

Figure 30: Long-term predictions for OS for midostaurin (a) overall advanced SM population (b) SM-AHN + MCL subgroup

(a) overall advanced SM population



(b) SM-AHN + MCL subgroup



Abbreviations: Advanced SM: advanced systemic mastocytosis; exp: exponential; gengam: generalised gamma; gomp: Gompertz; KM: Kaplan-Meier; lnorm: lognormal; llog: loglogistic; MCL: mast cell leukaemia; OS: overall survival; SM: systemic mastocytosis; SM-AHN: systemic mastocytosis with an associated haematological neoplasm; weib: Weibull.

OS in patients initiating current clinical management in the UK

OS for the comparators was estimated by applying a treatment effect to the baseline OS curve for midostaurin. As described in Section B.2.9, two key sources of evidence that could inform the relative treatment effect of midostaurin on OS compared with current clinical management were identified (Reiter *et al.* [2017] and Chandesris *et al.* [2016])[23, 64] (Figure 25 and Figure 26).

Reiter *et al.* (2017) reported the HR for OS estimated by comparing OS in the pooled D2201/A2213 trials (n=89 included; 26 excluded) against the survival observed in an historical German cohort (n=42) and in addition to the unmatched HR of 0.50 (95% CI: 0.33–0.76), the authors estimated a:

- HR of 0.636, (95% CI: 0.326–1.244) using a matched-pair approach (n=42 for midostaurin and n=42 for registry controls)
- HR of 0.517 (95% CI: 0.319–0.839) using a multivariate analysis to adjust for differences in baseline characteristics (n=89 and n=42 for midostaurin and registry controls respectively)
- HR of 0.44 (95% CI: 0.29–0.67) using time from start of last treatment to death (n=115 and n=39 for midostaurin and registry controls respectively)

HRs were also reported in a study by Chandesris *et al.* (2017) comparing a historical cohort of patients treated with treatments other than midostaurin (n=44) with those who received midostaurin as part of a French compassionate use programme (n=28). The risk of death in the control group was more than two times higher than that in the midostaurin group (HR: 2.20; 95% CI: 1.08–4.47). In multivariate analysis the risk of death was three time higher.

In the absence of a direct comparison (head-to-head trial) between midostaurin and current clinical management, the HR for OS is uncertain and reflected by the different estimates according to the different analysis undertaken. Whilst matching approaches are often preferred, the limitations of include the fact that less than two third of patients initiating midostaurin in the pooled analysis of the D2201 and A2213 studies were subsequently excluded from this analysis (reducing the sample size from 115 to 42), making the results highly uncertain and potentially less generalizable. Additionally, since matched analyses can only account for *observed* differences in the baseline characteristics, it is not clear if there were any *unobserved* differences in patient characteristics or other systematic differences between the midostaurin and registry data that may have affected the comparison.

Equally, the multivariate analysis, whilst adjusting for baseline characteristics may also suffer from inherent limitations and also may not account for all (unobserved) differences. The HRs from the different sources and analyses are summarised below in Table 44.

Table 44: HRs for OS identified through the SLR and explored in the economic analysis

Source	Analysis	HR		
		Mean	LCI	UCI
Reiter *et al.* (2017)[23]	Multivariate (midostaurin n=89; registry n=42)	0.517	0.319	0.839
	Matched (midostaurin n=42; registry n=42)	0.636	0.326	1.244
	Unmatched (midostaurin n=89; registry n=42)	0.500	0.330	0.760

	From last treatment (midostaurin n=115; registry n=39)	0.440	0.290	0.670
Chandesris *et al.* (2017)[65]	Univariate (matched) (midostaurin n=28; registry n=44)	0.447	NR	NR
	Multivariate (matched) (midostaurin n=28; registry n=44)	0.333	NR	NR
Barete *et al.* (2015)[30]	Unmatched (derived) (n=16 in D2201) (n=14 in Barete *et al*. [2015])	0.22	NE	NE

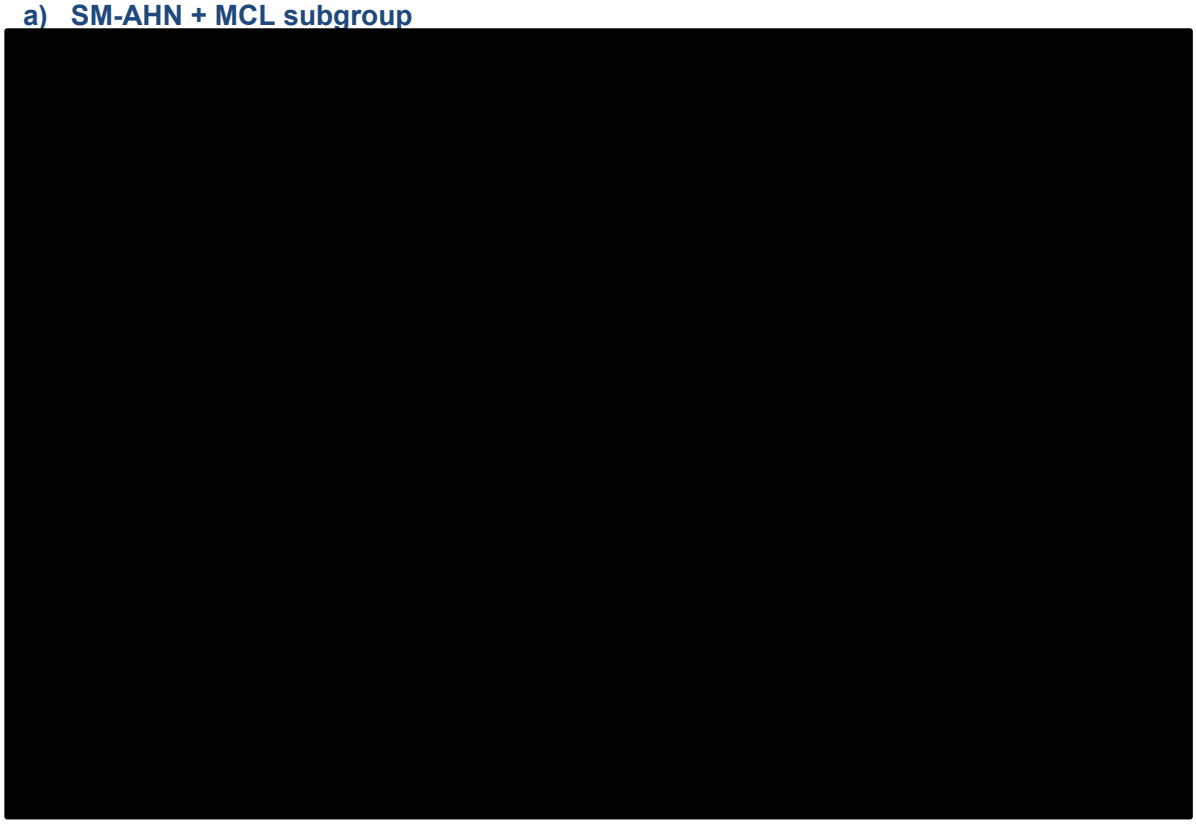
Abbreviations: HR: hazard ratio; LCI: lower confidence interval; NE: not estimated; NR: not reported; OS: overall survival; UCI: upper confidence interval.

In order to generate the predicted OS curves for the comparator treatments (current clinical management), the HRs from the different analyses were applied to the baseline OS curve for midostaurin (Spline hazard model with one knot function). Individual clinical experts were then asked to rank the predicted OS curves for the comparator treatments according to their plausibility and perception biases amongst the experts was reduced by not revealing the study methodology behind each HR. The same process was repeated for both the overall study population and the SM-AHN and MCL subgroup, with OS predictions for current clinical management displayed below in Figure 31.

Figure 31: Long-term predictions for overall survival for current clinical management (a) overall advanced SM population, (b) SM-AHN + MCL subgroup compared with OS prediction in patients initiating midostaurin

a) overall advanced SM population

a) SM-AHN + MCL subgroup



Abbreviations: Advanced SM: advanced systemic mastocytosis; MCL: mast cell leukaemia; OS: overall survival; SM: systemic mastocytosis; SM-AHN: systemic mastocytosis with an associated haematological neoplasm; trt: treatment.

In summary, for both the overall advanced SM population and the SM-AHN + MCL subgroup, clinical experts considered the predictions for OS using the matched HR (grey curve) reported by Reiter *et al.* (2017) to be above (optimistic) what they expect to see in clinical practice. Clinical experts also noted that predictions in the middle (between the matched analysis from Reiter (grey curve, Figure 31) and the matched multivariate analysis from Chandesris *et al.* (2017) (brown curve, Figure 31) to be reasonable with the predictions using the multivariate HR from the Reiter analysis (orange curve, Figure 31) to be more plausible. The clinical experts also considered this estimate as conservative since patients treated with clinical management typically have a short life expectancy in the absence of effective treatments for advanced SM and considered the multivariate analysis methodologically more appropriate than the matched analysis since the latter excluded a large proportion of patients.[1]

Consequently, the multivariate HR of 0.517 reported by Reiter *et al.* (2017) was used in the base case analysis, with extensive scenario analyses (Section B.3.8.3) conducted with the alternative HRs from the various previously reported different analyses (Table 44). It should also be noted that clinical expert opinion deemed it reasonable to use the same HR for all comparators and the overall and SM-AHN + MCL population in the absence of alternative evidence.

In addition to the Reiter *et al.* (2017) and Chandesris *et al.* (2017) papers, an additional scenario analysis is conducted using the HR derived from Barete *et al.* (2015). As described in Section B.2.9.2, the median survival in patients with ASM was 2.2 years. The survival in patients with ASM in D2201 was around 86% at 2.2 years, leading to a HR around 0.22. It should be noted that although the authors report the survival for a population defined as SM-AHN, following further inspection, this population consisted of a mix of patients with indolent (n=6) and ASM (n=11), making any comparison with the population included in D2201 challenging.

B.3.3.3 Progression-free survival (PFS)

PFS in patients initiating midostaurin

The Kaplan-Meier curve for the analysis of PFS in D2201 (data cut-off: 1st December 2014) is presented in Figure 32 for both the overall advanced SM population and the SM-AHN and MCL subgroup. The data cuts for PFS and OS (data cut-off: 24th August 2017) used in the economic model are different because per study protocol, PFS required adjudication and PFS was not re-assessed at the time of the final OS analysis.

Figure 32: Kaplan-Meier curve for PFS from D2201

Abbreviations: KM: Kaplan-Meier; MCL: mast cell lymphoma; SM-AHN: systematic mastocytosis with associated haematological neoplasm.
Source: Analysis of D2201 individual patient-level data.[12]

The selection process for extrapolation of PFS for midostaurin was similar to that described previously for OS, and a constraint was added to ensure that the extrapolation of PFS was consistent with that of OS and therefore the minimum between PFS and OS is taken.

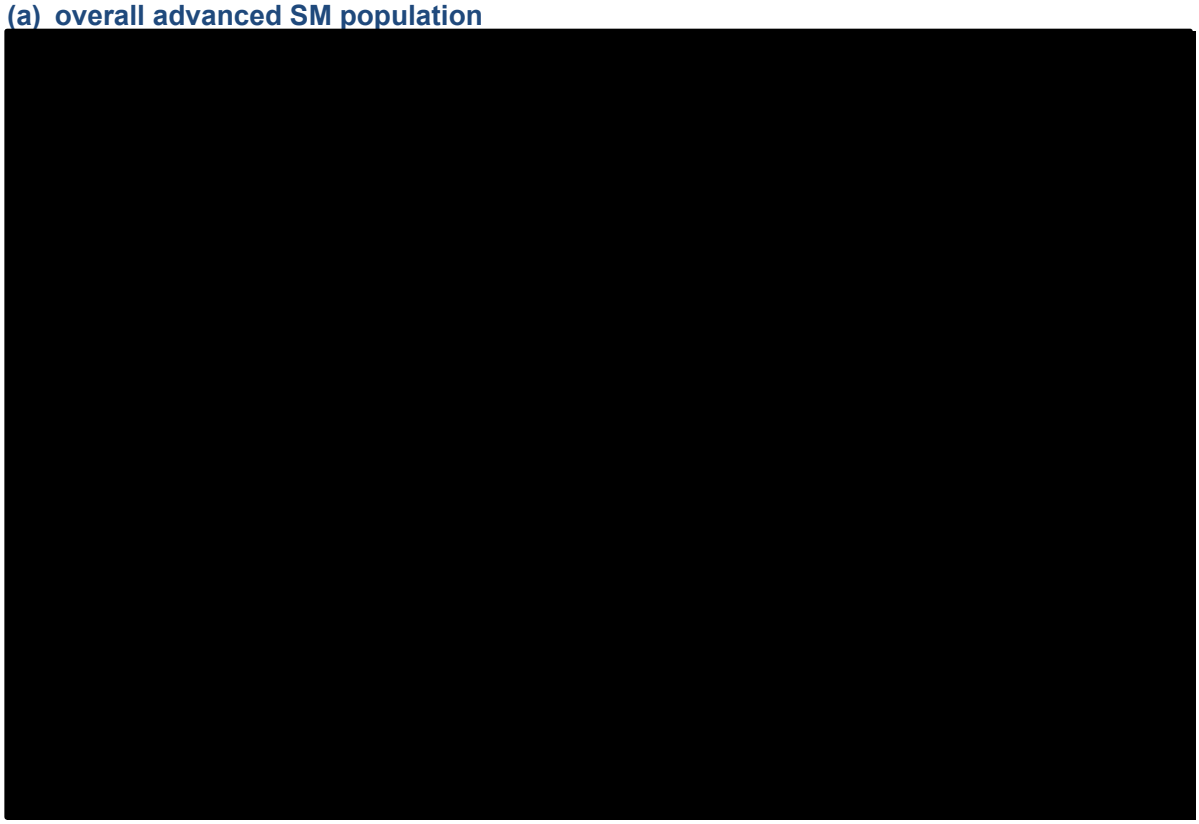
The exponential and Weibull distributions did not provide a good visual fit to the data for both the overall advanced SM population and SM-AHN + MCL subgroup and therefore were not considered further (Figure 33). Although the Gompertz distribution had the best statistical fit in terms of AIC/BIC (Table 45), the PFS curve crossed the OS extrapolation at around 4 years, leading to a moderate change in hazard (as the minimum of OS and PFS was used) and therefore the Gompertz distribution was not considered further since it was deemed inconsistent with the selected OS curve (one-knot spine). Of the remaining distributions, the spline (hazard) model with two knots provided a better visual fit compared with the spline (hazard) model with one knot, with the statistical goodness of fit measures very similar. Consequently, the spline (hazard) model with two knots was selected in the base-case as it provided (a) a good visual fit, (b) a plausible long term extrapolation (consistent with the hazard for OS with only minimal crossing) and (c) is PH compatible (facilitate the use of a HR for the comparator). Alternative distributions are explored in scenario analysis (B.3.8.3). The impact on the ICER was limited.

Long-term data for patients receiving midostaurin from the A2213 study (DeAngelo *et al.* [2018])[61] estimates PFS at 10 years (120 months) to be approximately 25% (Section B.2.6.2, Figure 16), with the survival curve declining to 0% at 11 years (132 months). As described previously with the long-term OS data from A2213, the decline in PFS is a statistical artefact of the small number of patients at risk after 8 years, and therefore doesn't represent a real decline in survival.

The predicted PFS using the spline model with two knot at 10 years was [redacted], and therefore lower compared with DeAngelo *et al.* This is in part because of the selected curve for OS.

Figure 33: Comparison of parametric distribution fits to midostaurin in D2201 for PFS during the observed period (a) overall advanced SM population, (b) SM-AHN + MCL subgroup

(a) overall advanced SM population



(b) SM-AHN + MCL subgroup

Abbreviations: exp: exponential; gengam: generalised gamma; gomp: Gompertz; KM: Kaplan-Meier; lnorm: lognormal; llog: loglogistic; MCL: mast cell leukaemia; PFS: progression-free survival; SM: systemic mastocytosis; SM-AHN: systemic mastocytosis with an associated haematological neoplasm; weib: Weibull.

Table 45: Summary of AIC/BIC and plausibility for the different distributions (whether the PFS curve crosses the OS curve)

Parametric function	Overall advanced SM population			SM-AHN + MCL		
	AIC	BIC	Plausibility assessment	AIC	BIC	Plausibility assessment
Exponential	404.43	406.92	[redacted]	345.88	348.17	[redacted]
Weibull	400.26	405.24	[redacted]	343.79	348.37	[redacted]
Gompertz	394.95	399.93	[redacted]	339.12	343.70	[redacted]
Lognormal	397.55	402.53	[redacted]	342.34	346.92	[redacted]
Loglogistic	396.74	401.71	[redacted]	340.40	344.98	[redacted]
Generalised gamma	399.36	406.83	[redacted]	343.63	350.50	[redacted]
Spline model with one	399.74	407.21	[redacted]	344.15	351.02	[redacted]
Spline model with two	**399.92**	**409.88**	[redacted]	**343.62**	**352.78**	[redacted]

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; MCL: mast cell leukaemia; SM-AHN: systemic mastocytosis with associated haematological neoplasm.

Progression-free survival in patients initiating current UK clinical management

No data for PFS for current clinical management were identified in the clinical SLR (Section B.2.9.2, Table 28) and in the absence of evidence, clinical experts opinion deemed it reasonable to assume the HR for PFS to be the same as that for OS.[1] This assumption is consistent with the HR for OS and PFS observed in other conditions, whereby the HR for PFS is typically larger than that for OS. Given the uncertainty around the HR for PFS, the impact of varying the HR is explored in the scenario analyses (Section B.3.8.3).

B.3.3.4 Response rates

Response rate data for midostaurin and treatments considered current clinical management in the UK that were included in the economic model are summarised in Table 46 alongside the source used for each subgroup (ASM, SM-AHN, MCL).

Response rates in patients initiating midostaurin

Response rates in patients initiating midostaurin for both the overall advanced SM population and the SM-AHN + MCL subgroup were taken directly from the D2201 trial.

Response rates in patients initiating current UK clinical management

The evidence for the response rates for the comparator treatments that form current UK clinical management has been previously is summarised in Section B.2.9.2 (Table 27) and were derived from various sources often conducted in a mixed population and not reflective of the population included in the pivotal D2201 and A2213 trials.

For the economic analysis, evidence for response rates relative to each subgroup was used when available (ASM, SM-AHN, MCL) with the response rates weighted according to the population included in the D2201 trial, to provide a fair comparison against midostaurin and reflect possible differences in response rate between subgroups (Table 46).

It should be noted that in a number of studies, it is unclear whether patients classified as SM-AHN includes patients with advanced disease (ASM-AHN) or those with indolent disease (ISM-AHN), and when no specific evidence for advanced SM was available, evidence from a mixed population was used. Similarly, when no data was available for MCL, the response rate estimated in the ASM/SM-AHN population was used as a proxy for MCL.

For any given treatment, if data were available for patients with ASM-AHN and a mixed SM-AHN population (ASM-AHN and ISM-AHN), only data for patients with ASM-AHN were used to inform the response rate for SM-AHN patients, since these patients more closely align with the patients included in the D2201 trial.

Table 46: ORRs used in the economic model

Treatment	Response rate used in the economic model		Source		
	Overall advanced SM population	SM-AHN + MCL	ASM	SM-AHN	MCL
Midostaurin	59.5%	56.2%	D2201 trial[12]	D2201 trial[12]	D2201 trial[12]
Cladribine	[redacted]	[redacted]	Barete *et al.* (2015),[30] Lim *et al.* (2009)[70]	Barete *et al.* (2015)[30]	Jawhar *et al.* (2017a)[66]
Interferon-based regimens	[redacted]	[redacted]	Lim *et al.* (2009),[70] Hauswirth *et al.* (2004)[60]	Hauswirth *et al.* (2004),[60] Pardanani *et al.* (2009)[72]	Derived from ASM and SM-AHN
Imatinib	[redacted]	[redacted]	Lim *et al.* (2009),[70] Pardanani *et al.* (2009)[72]	Lim et al. (2009),[70] Pardanani *et al.* (2009)[72]	Pardanani *et al.* (2009)[72]
"AML-like" treatments	[redacted]	[redacted]	Assumption (same as cladribine)		

Abbreviations: MCL: mast cell leukaemia; SM-AHN; systemic mastocytosis with associated haematological neoplasm.

Duration of response in patients initiating midostaurin

Data from the 1st December 2014 data cut-off in the D2201 study was used to calculate the duration of response (DoR) in patients who experienced a response using the Valent criteria (Section B.2.6.1).

DoR is calculated from randomisation (rather from the time to response). The DoR Kaplan-Meier (Figure 34) shows that the curve is flat for the first 3 cycles given the time to response assessment in the D2201 study. In order to account for the flattening of the curve during the initial trial period, parametric functions were fitted from cycle 3 onwards. The same process used for OS and PFS was employed to identify and select the most appropriate parametric function(s) for extrapolation. Only the Gompertz, generalised gamma and spline (hazard) models provided a reasonable visual fit to the data (Appendix J). In the economic model, a constraint was added to ensure than the extrapolation of DoR was consistent with that of PFS.

Figure 34: Kaplan-Meier plot for DoR in D2201

Abbreviations: KM: Kaplan-Meier; MCL: mast cell leukaemia; SM-AHN: systemic mastocytosis with associated haematological neoplasm.
Source: Analysis of D2201 individual patient-level data.[12]

Table 47: Summary of statistical goodness of fit for DoR and plausibility (whether the curve crossed PFS or OS)

Parametric Function	Overall advanced SM population			SM-AHN + MCL		
	AIC	BIC	Plausibility assessment	AIC	BIC	Plausibility assessment
Exponential	215.23	217.20	[redacted]	184.00	185.71	[redacted]
Weibull	215.40	219.34	[redacted]	184.89	188.32	[redacted]
Gompertz	209.43	213.37	[redacted]	179.77	183.20	[redacted]
Lognormal	210.09	214.03	[redacted]	179.56	182.99	[redacted]

Loglogistic	212.31	216.25	[redacted]	181.15	184.58	[redacted]
Generalised gamma	206.03	211.94	[redacted]	176.84	181.98	[redacted]
Spline model with one knots	**207.04**	**212.95**	[redacted]	**177.08**	**182.22**	[redacted]
Spline model with two knots	209.01	216.89	[redacted]	178.71	185.56	[redacted]

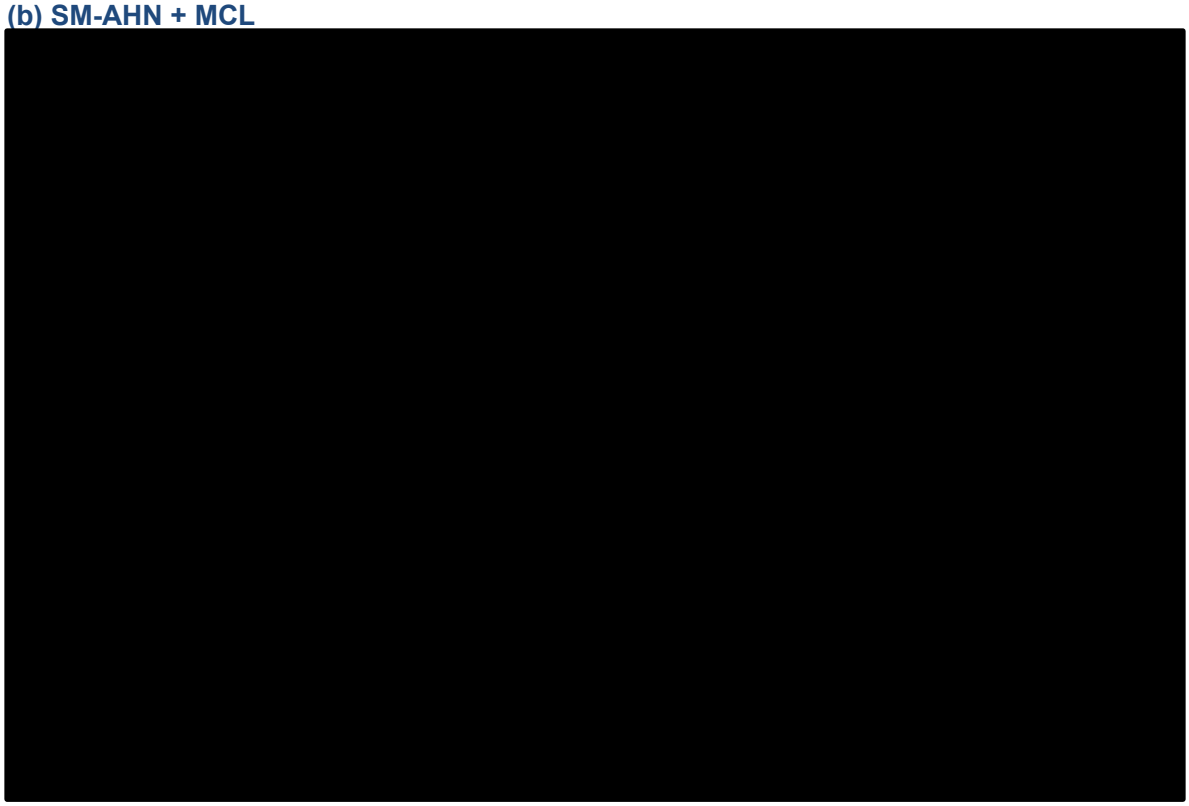
Abbreviations: AIC: Akaike information criteria; BIC: Bayesian information criteria; MCL: mast cell leukaemia; SM-AHN: systemic mastocytosis with associated haematological neoplasm.

Long-term plausibility was assessed by comparing predictions for DoR in the overall advanced SM population (including patients who responded or not) against the predicted PFS (red curve in Figure 35) in order to identify whether curves were more appropriate than other (consistency with PFS). All of the distributions that provided a good visual fit were associated with mild to moderate crossing of PFS (Table 47). Spline models provided a better visual fit compared with the generalised gamma. The spline model with one knot distribution was therefore selected in the base case as this had a better AIC/BIC compared with the spline model with two knots. Alternative parametric functions were examined in scenario analysis (Section B.3.8.3).

Figure 35: Comparison of parametric distribution fits to midostaurin in D2201 for DoR versus predicted PFS during the observed period (a) overall advanced SM population, (b) SM-AHN + MCL subgroup

(a) overall advanced SM population

(b) SM-AHN + MCL



Abbreviations: exp: exponential; gengam: generalised gamma; gomp: Gompertz; KM: Kaplan-Meier; lnorm: lognormal; llog: loglogistic; MCL: mast cell leukaemia; PFS: progression-free survival; SM: systemic mastocytosis; SM-AHN: systemic mastocytosis with an associated haematological neoplasm; weib: Weibull.

Duration of response in patients initiating current UK management

As described in Section B.2.9.2, there is limited evidence for DoR for the comparators, and as such, evidence from a mixed population of indolent and advanced SM patients (Lim *et al.* 2009) was used in the economic model. In this study, a median DoR of 11 months, 19.6 months and 12 months was reported for cladribine, imatinib and IFN-a respectively. It should be noted that since this study included patients with indolent disease (who have a better prognosis than those with advanced disease), the median DoR reported in this study could be considered optimistic.

The DoR in patients initiating current clinical management was estimated by applying a HR to the baseline midostaurin curve. The HR was derived by comparing the median survival against the DoR probability from D2201 when the median DoR was reached for the respective treatments. The derived HR are displayed below in Table 48.

Table 48: HR for DoR used in the economic model

Comparator treatment	Median DoR for comparator	DoR probability for midostaurin when median reached	Derived HR	Source
Cladribine	11.0	[redacted]	[redacted]	Derived from Lim *et al.* (2009) and D2201
Interferon alpha/peg-interferon alpha	12.0	[redacted]	[redacted]	
TKIs (imatinib, nilotinib, dasatinib)	19.6	[redacted]	[redacted]	
"AML-like" treatments	11.0	[redacted]	[redacted]	Assumed to be the same as cladribine

Abbreviations: AML: acute myeloid leukaemia; DoR: duration of response; HR: hazard ratio; TKI: tyrosine kinase inhibitor.

In the absence of further evidence, the same HRs for DoR were assumed for both the overall advanced SM population and the SM-AHN + MCL subgroup.

B.3.3.5 Duration of treatment

Duration of treatment in patients initiating midostaurin

The Kaplan–Meier curve for the time to treatment discontinuation in D2201 (data cut-off: 1st December 2014) present in Figure 36 was used directly in the economic model given that it was complete and all patients had discontinued treatment in the trial. This data was used in the calculation of midostaurin treatment costs.

Figure 36: Kaplan-Meier for time to treatment discontinuation

Abbreviations: KM: Kaplan-Meier; MCL: mast cell leukaemia; SM-AHN: systemic mastocytosis with an associated haematological neoplasm.

Duration of treatment for patients initiating existing current UK clinical management

Patients treated with interferon-based regimens (Roferon-A and Pegasys) and TKIs (imatinib) were assumed to be treated until progression, with PFS used as a proxy for the time to discontinuation. This assumption was supported by clinical experts in the absence of alternative evidence. A conservative scenario analysis was conducted whereby only people remaining on treatment after 6 cycles remain on treatment (e.g. DoR is used as proxy for the time to treatment discontinuation after 6 cycles).

Patients initiating cladribine are assumed to receive a fixed number of courses of treatment based on the treatment regimen reported in Barete *et al.* (2015).[30] Clinical experts noted that in practice, patients receive a maximum of 9 cycles. In the economic model, patients were assumed to receive 3.68 courses of treatments on average in the first year based on Barete *et al.* (2015).[30] The economic analysis further considered that a proportion (around 14.7%) of patients initiating cladribine receive an additional 2 courses of treatment, as reported in Barete *et al.* (2015).[30] This assumption was considered appropriate by UK clinical experts and in line with the use of the treatment regimen in the UK.

The cost associated with “AML-like” treatments was applied as a one-off cost at the start of the model based on the costs reported in TA552 for second-line treatments in AML.[93] The duration of treatment was based on data from the MEDPACT database and was assumed to be a reasonable proxy for the duration of treatment in patients with advanced SM receiving treatments typically given for AML.

B.3.3.6 Adverse events (AEs)

The potential impact of AEs on costs and HRQoL were included in the model; the base case economic analysis considered Grade 3/4 AEs that occurred in more than 5% of patients treated with midostaurin (Table 31) that are likely to affect either HRQoL or resource use.

The absence of head-to-head trial data and the breadth of the evidence available for the comparators with regards to AE reporting, in addition to the large number of treatments included in this economic evaluation makes the evaluation of the differential impact of AEs between midostaurin and current clinical management challenging. Whilst toxicities associated with the use of midostaurin are transparently reported in the literature (Section B.2.10), data on toxicities associated with the comparators (in a similar population) is lacking. Furthermore, where AE data is available for the comparators as identified in the SLR (Section B.2.9.2) these data only provide a brief narrative of the most common AEs of interest, or limit AEs to those that are only treatment-related (rather than any AEs). AE data identified for the comparators are as follows:

- In patients initiating cladribine, the prevalence of patients experiencing Grade 3/4 acute neutropenia, Grade 3/4 prolonged lymphopenia and Grade 3/4 infection was taken from Barete *et al.* (2015) in SM patients. Barete *et al.* (2015) also reported a prevalence of 5.9% for fever. No data were available on the prevalence associated with other AEs included in the economic model (nausea, fatigue, etc.). The prevalence for these AEs was therefore taken from the summary of AE reported in the EMA submission in hairy cell leukaemia (HCL). The prevalence of dyspnoea was assumed the same as that for midostaurin in the absence of evidence.
- In patients initiating interferon, Hauswirth *et al.* (2004) reported a prevalence of 40% (n=2/5) for both fever and flu-like symptoms, whilst Lim *et al.* (2009) only mentioned that the most common major toxicities included thrombocytopaenia and fatigue. A rapid review of trials conducted using interferon-based regimens showed a very large heterogeneity in the reported prevalence of AE between studies. In particular, the prevalence of AEs varied widely between condition and the dosage received. Studies typically focused on treatment-related AEs rather than any AEs.
- Data on the prevalence/incidence of AEs in patients initiating imatinib was also limited, with a focus on treatment-related AEs and only few AEs described.

Given the challenges with the evidence base for AEs associated with the comparators, a simplifying assumption was made in the base case economic analysis whereby the prevalence of AEs for all treatments comprising clinical management in the UK was based on those reported for cladribine (Table 49). A scenario analysis was conducted assuming no differential impact (e.g. removing AEs) and, as expected, the impact on the cost-effectiveness results was minimal (Section B.3.8.3).

Table 49: AE rates used in the economic model

Adverse events	Midostaurin		Clinical management in the UK	
	Prevalence	Source	Prevalence	Source
Nausea	[redacted]	Pooled D2201/A2213	16.50%	Cladribine SmPC[96]
Vomiting	[redacted]		7.00%	Cladribine SmPC[96]
Diarrhoea	[redacted]		7.50%	Cladribine SmPC[96]
Anaemia	[redacted]		14.00%	Cladribine SmPC[96]
Fatigue	[redacted]		25.00%	Cladribine SmPC[96]
Thrombocytopaenia	[redacted]		20.79%	Cladribine SmPC[96]

Dyspnoea	[redacted]		6.34%	Assumed to be the same as midostaurin[12]
Neutropenia	[redacted]		47.06%	*Barete et al. (2015)*[30]
Infection	[redacted]	D2201	22.06%	*Barete et al. (2015)*[30]
Lymphopenia	[redacted]		82.35%	*Barete et al. (2015)*[30]

Abbreviations: AE: adverse event; SmPC: summary of product characteristics; UK: United Kingdom.

B.3.4 *Measurement and valuation of health effects*

B.3.4.1 Health-related quality-of-life data from clinical trials

As described in Section B.2.6.1, HRQoL was assessed in D2201 using the MSAS and SF-12 questionnaires. Per study protocol, assessments for both questionnaires were scheduled to occur at baseline (on Day 1, Cycle 1) and subsequently, at the end of every treatment cycle until Cycle 12 and at study completion/discontinuation if occurring prior to cycle 12.[77]

Analysis of the trial-based SF-12 showed that median SF-12 scores for the physical and the mental components of the questionnaire were significantly higher than baseline, showing significant improvement with midostaurin (Figure 14).[12] The median percentage change from baseline was 29% for the best reported physical composite scores and 26% for the best reported mental composite scores on treatment.

Since the SF-12 is not a preference-based measure of HRQoL and does not conform to the NICE reference case,[85] data from the SF-12 was mapped to the EQ-5D-3L using published algorithms in the literature (Section B.3.4.2).

B.3.4.2 Mapping

The NICE methods guide stipulates that data obtained using the EQ-5D preference-based measure is the preferred choice for use in economic evaluations when available, although other preference-based instruments (such as the Short-Form Health Survey-6D [SF-6D], the Health Utilities Index [HUI] or other condition-specific measure) may be considered if generic utility data are not available or appropriate. In addition, when utility data from generic validated instruments are not available, then methods can be used to estimate EQ-5D utility data by mapping (also known as 'cross-walking').

EQ-5D data were not available from either D2201 or A2213 therefore in order to satisfy the recommendations of the NICE Methods Guide and generate EQ-5D data, SF-12 data from the D2201 study were mapped onto the EQ-5D-3L using published algorithms based on UK tariffs. Four algorithms, using UK tariffs were considered based on those examined in Yang *et al.* (2019):[99]

- Franks *et al.* (2003):[100] linear model
- Franks *et al.* (2004):[101] linear model
- Lawrence *et al.* (2004):[102] linear model
- Gray *et al.* (2006)[103] – using the MCS and PCS dimension: response mapping.

The mapping algorithms are directly available in the respective papers.

It should be noted that two response mapping algorithms were reported by Gray *et al.* (2006); using the individual questions of the SF-12 or using the MCS and PCS dimension. The algorithm

developed by Gray *et al.* (2006) using individual questions of the SF-12 was not considered relevant for this submission as it uses individual questions from the SF-12 version 1 (version 2 was used in D2201). This was less of a challenge with the other algorithms considered as they use the physical and mental dimensions, rather than the responses to the individual questions.

For the linear models (Frank *et al.*, 2003, Frank *et al.*, 2204 and Lawrence *et al.*, 2004), data were checked to ensure that the predicted values did not exceed one.

Predictions were relatively similar between mapping algorithms. Consequently, in the base case, response mapping (using dimensions) using the Gray *et al.* (2006) algorithm was selected as this was the most recent algorithm. Scenario analysis were conducted using the alternative algorithms described previously as well as an analysis using the direct SF-6D (Section B.3.8.3).

B.3.4.3 Health-related quality-of-life studies

An SLR was conducted to identify relevant HRQoL data in patients with advanced SM. Searches were conducted in October 2019 and full details of the SLR search strategy, study selection process and results are reported in Appendix H.

In total, only one study reporting HRQoL data in advanced SM was identified (Table 50). This study used data from D2201 with the SF-12 mapped onto the EQ-5D using a US algorithm (Sullivan *et al.* [2006]) and therefore is not considered further as US tariff are higher than UK tariff. The full results of this study are presented in Appendix H.

Table 50: Publications reporting health-related quality-of-life data included in the SLR

	Author, year	Citation
1	Cariou *et al.* (2018)[88]	Cariou C, Tremblay G, Dolph M, *et al.* PSY217 – Incremental quality-adjusted survival analysis when no head to head data are available: a case study of midostaurin (MIDO) versus standard of care (SOC) in patients with advanced systemic mastocytosis (Adv SM). Value in Health 2018;21:S473

Abbreviations: SLR: systematic literature review.

B.3.4.4 Adverse reactions

The results of the D2201 trial demonstrated that midostaurin is generally well-tolerated, with the most common AEs during treatment relating to low-grade nausea, vomiting, and diarrhoea (Section B.2.10.2).

Since the health-state utility values in the model are estimated from the D2201 trial, the impact of AEs in HRQoL associated with midostaurin is already accounted for.

In the absence of utility data for the comparator, the same utility values were used for patients initiating current clinical management as those used for midostaurin, therefore it was assumed that the effect of AEs on HRQoL is the same between treatments. To reflect the differences in prevalence of AEs between current clinical management and midostaurin, a one-off QALY decrement/increment was included at the start of the model for the comparator arm by calculating the expected incremental decrement in HRQoL between midostaurin and the comparator, based on the prevalence of AEs and disutilities.

Based on the prevalence of AEs reported in Table 49 and disutility associated with AEs reported in Table 51, treatment with midostaurin was estimated to generate a QALY decrement of -0.0080,

compared with a QALY decrement of -0.0121 for current clinical management. This equated to an incremental decrement in QALYs for current clinical management in the UK (compared with midostaurin) of 0.0041. The disutility and respective duration of the AEs in the economic model were derived from previous TAs (TA400, TA460).[104, 105] and is shown in Table 51.

Table 51: Disutilities used in the economic model

AE	Disutility	Duration	Source
Nausea	-0.048	7	TA400[104]
Vomiting	-0.048	3	Assumption (assumed to be the same as nausea)
Diarrhoea	-0.0468	7	TA400[104]
Anaemia	-0.119	28	TA460[105]
Fatigue	-0.115	28	TA460[105]
Thrombocytopaenia	-0.09	28	TA460[105]
Dyspnoea	-0.05	28	TA460[105]
Neutropenia	-0.09	28	TA460[105]
Infection	-0.1215	28	TA460[105]
Lymphopenia	-0.09	7	Assumption (assumed to be the same as neutropenia)

Abbreviations: AE: adverse event; TA: technology appraisal.

B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

The utility values used in the economic model are summarised in Table 52.

Table 52: Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (standard error)	95% confidence interval	Justification
Baseline HRQoL	[redacted]	[redacted]	Gray *et al.* (2006) algorithm estimated from D2201
Increment in utility values			
PFS – sustained response	[redacted]	[redacted]	Gray *et al.* (2006) algorithm estimated from D2201
PFS – lack or loss of response	[redacted]	[redacted]	Gray *et al.* (2006) algorithm estimated from D2201
Progressive disease	0	0	Assumed to be the same as baseline in the base case
Decrement in utility/QALY associated with administration versus oral			
Interferon alpha (3 weekly subcutaneous injection)	-0.04 (disutility)	SE assumed to be 20%	Estimate from Matza *et al.* (2015) doubled to reflect higher frequency
Peg-interferon (weekly	-0.02 (disutility)	SE assumed to be 20%	Taken from Matza *et al.* (2015)

subcutaneous injection)			
Cladribine/"AML-like" treatments	-0.0407 (QALY decrement)	SE assumed to be 20%	Based on Matza *et al.* (2013) and length of treatment for cladribine (206 days)
One-off decrement in QALY associated with AE (applied to the comparator arm)			
One-off QALY decrement	-0.0039	NA	Difference in prevalence of AEs

Abbreviations: AML: acute myeloid leukaemia; AE: adverse event; HRQoL: health-related quality of life; PFS: progression-free survival; QALY: quality-adjusted life year.
Source: D2201,[12] Matza *et al.* (2013),[106] Matza *et al.* (2015)[107] and Barete *et al.* (2015).[30]

To calculate the health state utilities for the key health states, a regression model for utility was fitted to the D2201 trial using generalised estimating equation (GEE) regression model, with a Gaussian error term and the identity link, to account for multiple observations per patient. The regression was estimated using Stata 13 and the regression model is presented in Table 53.

Table 53: Regression model for utility value

Abbreviations: avg: average; GEE: generalised estimating equation; max: maximum; min: minimum; obs: observations; PFS: progression-free survival; QoL: quality of life; SE: standard error.

The utilities for each health state were then calculated by estimating the average predicted utility values for each health state based on the estimated coefficients, with the resulting utility values for each health state presented in Table 52. In the absence of data for the comparator, the same utility values were used for patients initiating midostaurin or current clinical management.

The mean utility values for the PD health state ([redacted]) were estimated to be higher than those at baseline ([redacted]). This inconsistency is potentially attributable to the fact that patients initiating

midostaurin experienced a large improvement in HRQoL, therefore, despite experiencing a subsequent decline in HRQoL following progression, the reduction in HRQoL may not outweigh the initial gain. The PD health state estimate may also not represent the more advanced stage of progression. Consequently, in the base case, patients with progressed disease are assigned the utility value estimated at baseline. A scenario analysis was conducted using the value estimated for progressed disease (Section B.3.8.3).

The same utility estimates were used for the overall advanced SM population and the subgroup analysis. This was justified by the absence of difference when the subgroup was included as a covariate in the GEE model.

Decrement in utility associated with the mode of administration

The economic model includes the benefits in terms of HRQoL associated with the availability of an oral treatments over existing treatments as highlighted by clinical and patient experts, and recognised in previous NICE appraisals.[90, 91]

A rapid review (further details is provided in Appendix L) identified two relevant UK studies (using time trade-off [TTO] and short time horizon):

- Matza *et al.* (2013)[106] estimated the decrement in utilities associated with different mode of administration, using a TTO approach using a 2-year time horizon among 121 members of the public for treatments for bone cancer. The authors reported a decrement in utility of -0.004 (SD: 0.036) associated with one injection once a month and a decrement in utility of -0.037 (SD: 0.106) in patients receiving a 2hr intravenous infusion once every four weeks.
- Matza *et al.* (2015)[107] estimated a decrement in utility of -0.02 associated with a weekly injection plus oral treatment versus oral treatment only, using TTO (one year time horizon) in 182 members of the public for treatments in hepatitis C in the UK.

A decrement in utility of -0.02 was assumed for peg-interferon (given once weekly). This decrement in utility was doubled in patients receiving interferon alpha given the more frequent administration schedule (three times weekly rather than weekly).

In patients initiating cladribine (and “AML-like” treatments) the decrement in utility was transformed into a decrement in QALY applied at the start of the model. This was derived from a decrement in utility of -0.072 (estimated from Matza *et al*. [2013][106] and doubled to reflect the greater frequency of administration [day1-5 versus once every 4 weeks]) and the expected duration of treatment (calculated to be 206 days from Barete *et al.* [2015][25]).

Given the uncertainty in the assumptions adopted to estimate the decrement in utility for mode of administration, the decrement in utility/QALY was varied in sensitivity analyses (halved or 1.5 time higher) (Section B.3.8.3)

Reduction in HRQoL associated with older ages

Health state utility values were adjusted for the natural reduction in HRQoL associated with older age based on a published algorithm using UK tariff by Ara *et al.* (2010).[108] Utility values used in the model estimated from D2201 already account for some of the reduction in HRQoL associated with older age. To avoid double counting, health state utility values were adjusted after [redacted] cycles to reflect the mean duration of last HRQoL collection point ([redacted]) in patients who participated to the HRQoL analysis. Scenario analyses were conducted assuming no age-adjustment or adjustment from the start of the economic evaluation (Section B.3.8.3).

B.3.5 *Cost and healthcare resource use identification, measurement and valuation*

An SLR was conducted to identify relevant cost or resource use studies for incorporation in the model. The searches were run in October 2019 and full details of the SLR search strategy, study selection process and results are presented in Appendix I.

In total, eight studies reporting on cost or healthcare resource use data in advanced SM were identified (Table 54). Seven of the eight studies reported resource use data exclusively in the form of prior treatment modalities for advanced SM patients. One study reported Australian cost data associated with testing for genetic abnormalities in ASM patients. None of the identified studies were conducted in the UK or presented data specifically for a UK patient population, limiting their applicability to clinical practice in England. Consequently, no data from these studies were used in the economic model.

Table 54: Publications reporting healthcare resource use data included in the SLR

#	Author, year	Citation
1	Criscuolo *et al.* (2018)	Criscuolo M, Fianchi L, Maraglino A, *et al.* Management of systemic mastocytosis in a single center experience. European Hematology Association. Conference: 23rd Congress of the European Hematology Association. 2018;PB2305
2	Elena *et al.* (2017)	Elena C, Merante S, Ferretti VV, *et al.* Selection and efficacy of cytoreductive agents in patients with mastocytosis included in the registry of the european competence network on mastocytosis (ECNM). Blood. Conference: 59th Annual Meeting of the American Society of Hematology, ASH 2017;130.
3	Jawhar *et al.* (2017a)	Jawhar M, Schwaab J, Meggendorfer M, *et al.* The clinical and molecular diversity of mast cell leukemia with or without associated hematologic neoplasm. Haematologica 2017;102:1035-1043.
4	Jawhar *et al.* (2018)	Jawhar M, Schwaab J, Naumann N, *et al.* A New Prognostic Score for Advanced Systemic Mastocytosis Based on Clinical and Genetic Characteristics of 210 Consecutive Patients. Blood. Conference: 60th American Society of Hematology Annual Meeting and Exposition 2018:132;349.
5	PBAC *et al.* (2008)	Pharmaceutical Benefits Advisory Committee. Imatinib mesylate, tablets, 100 mg and 400 mg (base), Glivec®. 2008.
6	Radia *et al.* (2019)	Radia D, Deininger MW, Gotlib J, *et al.* Avapritinib, a potent and selective inhibitor of kit d816v, induces complete and durable responses in patients (PTS) with advanced systemic mastocytosis (ADVSM): European Hematology Association: Conference: 24th Congress of the European Hematology Association. 2019;S830
7	Reiter *et al.* (2017)	Reiter A., Kluin-Nelemans H, George T, *et al.* Pooled Survival Analysis Of Midostaurin Clinical Study Data (D2201+ A2213) In Patients With Advanced Systemic Mastocytosis Compared With Historical Controls. European Hematology Association. Conference: 22nd Congress of the European Hematology Association. 2017;S788
8	Tsonis *et al.* (2018)	Tsonis I, Kanellias N, Lazaris V, *et al.* Systemic Mastocytosis: Management and Outcome. Data Analysis from the Greek Registry. Blood. Conference: 60th American Society of Hematology Annual Meeting and Exposition. 2018:132;5463

Abbreviations: PBAC: Pharmaceutical Benefits Advisory Committee; SLR: systematic literature review.

B.3.5.1 Intervention and comparator costs and resource use

Costs included in the economic model included treatment costs, costs associated with the management of advanced SM/monitoring associated with treatments, costs associated with subsequent therapies, costs associated with the management at the end of life, and the costs associated with the management of AEs. Treatment costs include both drug acquisition and administration costs. Monitoring was not included separately, but was considered to be the same between treatments and considered within the management costs.

Treatment costs

Drug acquisition and administration costs for treatments included in this economic evaluation are summarised in Table 55.

Dosing schedule assumed in the economic model

The dosing schedules assumed for treatments included in the economic model is presented in Table 55. This was based on discussion with clinical experts, the dosing schedule from which efficacy data was taken from and/or published sources.

Drug acquisition costs

The list price for the intervention (midostaurin) and the following comparators; cladribine (subcutaneous form), interferon-based regimens (interferon alpha [Roferon-A], peg-interferon alpha [Pegasys]) were taken from the BNF (Table 55). Since imatinib is available to the NHS as a generic medicine, the cost of imatinib was calculated from the eMIT based on the number of prescriptions. Prednisolone is often given in patients receiving interferon-based therapies. The cost was not considered within the economic analysis as it is considered to be minimal.

The costs associated with “AML-like” treatments (including azacitidine, cytarabine + daunorubicin, cytarabine + idarubicin, cytarabine + mitoxantrone, mitoxantrone + etoposide + cytarabine and FLAG-IDA) are taken directly from the costs estimated in TA552 in patients with AML receiving second-line therapies, which were subsequently derived from the BNF and eMIT. Costs were taken directly from those calculated in TA552, as these were considered appropriate by the ERG and to avoid introducing further uncertainties in the economic model.

Midostaurin is currently provided to the NHS at a [redacted] discount off the current NHS list price. [redacted]. A confidential PAS is available for azacitidine in the NHS, and assumed to be 85% in our base case as this was unknown.

Table 55: Summary of treatment costs used in the economic model

	Vial/pack concentration and volume	Number of tablets	Cost per vial/pack (NHS list price)	Cost per vial/pack (PAS)	Number of packs/vials required per 28 days cycle	Cost per 28 days cycle	Administration costs	Source
Midostaurin	25 mg	56	£5,609.94	[redacted]	4	[redacted]	£0	D2201
Interferon alpha (Roferon-A) (solution for injection pre-filled syringes)	6 MU/0.5ml	1	£28.37	N/A	12	£340.44	£69.22	Lim *et al.* (2009) (single use syringe)
Peg-interferon alpha	90micrograms/0.5ml	1	£76.51	N/A	4	£306.04	£23.07	Expert opinion (single use syringe)
Imatinib	400 mg	30	Generic £172.29 (SD: £207.47) Glivec £1933.21 (SD: £49.22)	N/A	<1	£506.67	£0	eMIT (calculated based on number of prescription)
One-off cost								
Cladribine (Litak Injection Vial)	10mg/5ml	1	£159.50	N/A	N/A	£3,173.33	£8,634.10	Barete *et al.* (2015)
"AML-like" treatments (azacitidine)	-	-	-	-	-	£3,842.40*	£14,135	TA552[95]
"AML-like" treatments (Others)	-	-	-	-	-	£6,882	£18,327	TA552[95]

* PAS of 85% assumed.
Abbreviations: AML: acute myeloid leukaemia; eMIT: electronic market information tool; N/A: not applicable; PAS: patient access scheme; SD: standard deviation; TA: technology appraisal.

A one-off cost was applied at the start of the model in patients initiating cladribine, based on the number of courses of treatment reported in Barete *et al.* (2015). A one-off cost was also applied at the start of the economic model in patients initiating "AML-like" treatments, based on the costs calculated in TA552 for second-line treatments in AML. The mean number of cycles per treatment was obtained from the CancerMPact 2015 report. This is a simplifying assumption in the absence of evidence in advanced SM. Whilst the treatment costs for "AML-like" treatments in advanced SM are challenging to calculate and uncertain, it should be noted that costs reported in first-line were significantly higher (notably for administration), and therefore using the costs calculated in second-line only could be deemed a conservative assumption. It was further assumed that of the people receiving "AML-like" treatment, [redacted] would incur the cost associated with azacitidine based on the treatment mix estimated by clinical experts.

Dose intensity/dose reduction was included in the economic model when possible:

- The relative dose intensity (RDI) and relative dose interruption for midostaurin was calculated from the pivotal D2201 trial. The RDI was estimated to be [redacted] and the relative dose interruption to be [redacted] for the overall advanced SM population and [redacted] and the relative dose interruption to be [redacted] for the SM-AHN + MCL subgroup. Wastage was considered in the calculation in the base case economic analysis and a scenario analysis was conducted assuming no wastage (see Section B.3.8.3). This was considered by calculating the number of opened pack as patient go through the model.
- The dose intensity/interruption for cladribine was calculated based on the median cumulative dosage (2.25mg/kg) and the median number of cycle (3.68) reported in Barete *et al.* (2015). Five vials were required per course of treatment, including wastage
- Roferon-A 6 million units (MU) was used to calculate drug acquisition costs associated with interferon alpha. Patients were assumed to receive 15MU weekly, split in 3 injections as described in Lim *et al.* (2009). The syringes are supplied in a single-patient-use syringe, and therefore three syringes are required weekly using Roferon-A 6MU. Alternative syringe dosage (4.5MU and 3MU) was used in a scenario analysis (see Section B.3.8.3)
- Pegasys 90 MU was used for costing peg-interferon. The syringes are supplied in a single-patient-use form
- No dose reduction/interruption was assumed for imatinib in the absence of evidence.

Drug administration costs

Administration costs (Table 55) were included for cladribine (administered subcutaneously), interferon-based regimens (Roferon-A and Pegasys) and "AML-like" treatments following discussion with clinical experts:

- Cladribine: patients initiating cladribine were assumed to receive 3.68 cycles on average, with 14.7% retreated with an additional 2 courses of treatments based on Barete *et al.* (2015). The majority of administration is done as an outpatient basis (5 days). However, clinical experts noted that 35% of patients initiating cladribine receive their first course on an inpatient basis, requiring 9 hospital days based on assumptions made in HCL.[109] As such, 5% of the remaining cycles were assumed to be given on an inpatient basis. The unit costs associated with cladribine administration in the outpatient setting were taken from NHS reference costs based on the cost for delivery of chemotherapy at first attendance and subsequent treatments (Table 56). The unit cost per hospital day was calculated from NHS reference costs based on the weighted average cost per day for patients admitted for elective inpatient and non-elective long stay for Other Haematological or Splenic Disorders (SA08G:J)[110]

- Interferon-based regimens: The majority of patients treated with interferon-based regimens (85%) were assumed to self-inject (or with the help of a family member) and therefore did not incur any administration costs. Clinical experts noted that between 10% to 20% of patients with advanced SM required nurse administration. Unit costs associated with injection administration was taken from the NHS reference cost [district nurse – face to face][110]
- "AML-like" treatments: Administration costs associated with these regimens were taken directly from those calculated in TA552 (liposomal cytarabine–daunorubicin for untreated acute myeloid leukaemia)[95]

Table 56: Unit costs used for calculation of administration costs

NHS reference cost code	Description	Unit cost	Source
SB14Z	Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance	£374.52	NHS reference costs
SB15Z	Deliver Subsequent Elements of a Chemotherapy Cycle	£312.34	NHS reference costs
SA08G:J	Other Haematological or Splenic Disorders	£666.28	Derived from NHS reference cost (weighted across elective and non-elective inpatient)
NA02AF	District Nurse, Adult, face to face	£38.45	NHS Reference cost

Abbreviations: NHS: National Health System.

Monitoring

Monitoring was not included within the model separately, but was considered to be the same between treatments and considered within the management costs.

Subsequent therapies (costs applied at the point of progression)

Subsequent therapy costs were included at the point of progression. For simplicity, patients were assumed to incur the costs (drug and administration costs = £11,807) associated with cladribine therapy at the point of progression. In the base case economic analysis, 50% of patients were assumed to receive subsequent therapy. This is a simplification in the absence of evidence. Scenario analyses were conducted varying the proportion between 0% to 100%. Scenario analyses were also conducted assuming the cost associated with "AML-like" treatments or peg-interferon. (see Section B.3.8.3)

B.3.5.2 Health-state unit costs and resource use

The economic SLR (Section B.3.1) identified no previous economic evaluations, UK cost studies or NICE appraisals for advanced SM and thus resource utilisation data for the management of this condition is not available.

To address this data gap, five UK clinical experts with expertise in the management of patients with advanced SM were asked to estimate the frequency (and nature) of resource use in patients with advanced SM that are free of progression and with progressive disease. Resource use categories were defined per health states (rather than treatment); thus, the same resources were assumed irrespective of the treatment initiated.

The PFS health state was separated into 6 monthly cycles (month 0-6, 6-12 and 12+) to reflect the more frequent resource use associated with the monitoring of the treatment considered at the beginning. No distinction was made between the progression-free response and non-response health states given the limitations with the PSM ability to track time.

Four out of the five questionnaires were returned complete and, as expected, there was some variation between responses given the rare nature of the disease and lack of UK clinical guidelines. The base case economic analysis therefore assumes an average of the frequency of estimates provided by the experts (Table 57) and the individual responses are explored in scenario analyses (Section B.3.8.3). It should be noted that the same resource use was assumed for the overall advanced SM population or subgroup of patients with SM-AHN or MCL.

Unit costs were derived from the NHS reference costs, and PSSRU published costs. The expected calculated per-28-day-cycle cost was estimated to be [redacted] in progression-free between 0-6 months, 6-12 month and after 12 months+, respectively. The calculated per-28-days cycle cost for patients with progressive disease was estimated to be [redacted]

Cost associated with terminal care

A one-off cost of £7,797.92 for terminal/palliative care is applied within the model at the point of death taken from the cost used in ID1140, calculated from the Kings Fund Report (2004) and inflated up to 2018.[111]

Table 57: Estimated per cycle resource use and unit costs

Resource	PFS (0-6 m)	PFS (6-12 m)	PFS (12+ m)	PD	Unit cost	Reference
Primary/Community care visits						
GP visit - Surgery	[redacted]	[redacted]	[redacted]	[redacted]	£39.00	PSSRU (2019):[112] Per surgery consultation lasting 9.22 minutes, including direct care staff costs (including qualifications). p120
GP visit - home visit	[redacted]	[redacted]	[redacted]	[redacted]	£100.62	PSSRU (2019).[112] Assume 11.4 minutes for consultations and 12 minutes for travel (based on assumption in TA400).[104] p120
District/community nurse	[redacted]	[redacted]	[redacted]	[redacted]	£38.45	NHS reference cost 2017/2018; district nurse (N02AF) face to face[110]
Cancer nurse visit	[redacted]	[redacted]	[redacted]	[redacted]	£42.69	Assumed to be 66.7% of community nurse cost as per TA400[104]
Pain and symptom management	[redacted]	[redacted]	[redacted]	[redacted]	£104.17	Based on TA181.[113] NHS Reference Costs 2017-2018: Community Health Services, (N21AF): specialist nursing, palliative/respite care, adult, face-to-face[110]
Depression assessment and management	[redacted]	[redacted]	[redacted]	[redacted]	£81.31	Based on TA181.[113] NHS Reference Costs 2017-2018: Community Health Services, Allied Health Professionals (A06A1): occupational health, adult, one-to one[110]
Hospitalisation ED/ICU Outpatient visits						
Outpatient visit	[redacted]	[redacted]	[redacted]	[redacted]	£194.39	NHS Reference Costs 2017-2018, Outpatient attendance data, Consultant Led (face to face - Follow up), Clinical Oncology[110]
ED use	[redacted]	[redacted]	[redacted]	[redacted]	£253.67	Based on TA460.[105] NHS Reference Costs 2017-2018: Emergency medicine. VB01Z, VB04Z, VB05Z, VB07Z, VB08Z[110]
Hospitalisation days	[redacted]	[redacted]	[redacted]	[redacted]	£666.28	NHS Reference Costs 2017-2018: SA08G, SA08H, SA08J[110]
ICU	[redacted]	[redacted]	[redacted]	[redacted]	£1,602.04	Based on TA460.[105] NHS Reference Costs 2017-2018: Critical Care XC01Z - XC07Z[110]

Diagnostic tests						
Bone marrow biopsy	[redacted]	[redacted]	[redacted]	[redacted]	£272.94	Based on TA460.[105] NHS Reference Costs 2017-2018: Diagnostic Bone Marrow Extraction (SA33Z)[110]
ECG	[redacted]	[redacted]	[redacted]	[redacted]	£264.80	NHS Reference Costs 2017–2018, Complex ECG, HRG code EY50Z[110]
CT scan	[redacted]	[redacted]	[redacted]	[redacted]	£106.88	NHS Reference Costs 2017-2018, Diagnostic Imaging, Outpatient, HRG code RD24Z (two areas with contrast)[110]
Chest X Ray	[redacted]	[redacted]	[redacted]	[redacted]	£106.88	Assume same as CT scan (assumption in TA400)[104]
US scan	[redacted]	[redacted]	[redacted]	[redacted]	£89.08	NHS Reference Costs 2017-2018, Diagnostic Imaging, Outpatient, HRG code RD24Z (two areas with contrast)[110]
MRI scan	[redacted]	[redacted]	[redacted]	[redacted]	£202.64	NHS Reference Costs 2017–2018, Diagnostic Imaging, Magnetic Resonance Imaging Scan of Two or Three Areas, with Contrast, Outpatient, RD05Z[110]
Blood test	[redacted]	[redacted]	[redacted]	[redacted]	£2.51	NHS Reference Costs 2017–2018, Directly Accessed Pathology Services, Haematology, DAPS05 (98)[110]
Bone Densitometry	[redacted]	[redacted]	[redacted]	[redacted]	£71.72	NHS Reference Costs 2017-2018: DIAGNOSTIC IMAGING (RD50Z)[110]

Abbreviations: CT: computerised tomography; ECG: electrocardiogram; ED: emergency department; GP: general practitioner; HRG: Healthcare Resource Group; ICU: intensive care unit; MRI: magnetic resonance imaging; NHS: national health service; PD: progressive disease; PFS: progression-free survival; PSSRU: Personal Social Services Research Unit; US: ultrasound.

B.3.5.3 Adverse reaction unit costs and resource use

The unit costs and/or assumptions associated with the management of AEs considered in the economic model are taken from those used in recent NICE appraisals (TA400 and TA460) and displayed in Table 58. The appraisals were selected as they were recent and reported unit costs for the AEs of interest.

Table 58: Adverse reaction unit costs and resource use

Adverse reactions	Value	Reference in submission
Nausea	£182	TA400
Vomiting	£182	Assumption (assumed to be the same as nausea)
Diarrhoea	£182	TA400
Anaemia	£211.73	TA460
Fatigue	£91.68	TA460
Thrombocytopaenia	£280.28	TA460
Dyspnoea	£422.41	TA460
Neutropenia	£808.28	TA460
Infection	£517.68	TA460
Lymphopenia	£808.28	Assumption (assumed to be the same as neutropenia)

Abbreviations: TA: technology appraisal.
Source: NICE TA400,[104] NICE TA460.[105]

Based on the prevalence of AEs reported in Table 49 and unit costs associated with AEs reported in Table 58, the management costs associated with AEs was estimated to be £411 in patients initiating midostaurin and £1,354 in those initiating current clinical management. This equated to an incremental cost for clinical management in the UK (compared with midostaurin) of £942.

B.3.5.4 Miscellaneous unit costs and resource use

No miscellaneous unit costs or resource use were included.

B.3.6 *Summary of base case analysis inputs and assumptions*

B.3.6.1 Summary of base case analysis inputs

A summary of the base case model inputs is provided in Table 59.

Table 59: Summary of variables applied in the economic model

Variable	Value		Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
	Overall advanced SM population	SM-AHN + MCL Subgroup		
NICE reference case				
Time horizon	500 cycles		Not varied	Section B.3.2.2
Discount rate for costs	3.5%		Not varied	
Discount rate for benefits	3.5%		Not varied	

Baseline characteristics				
Age	63.00	[redacted]	Normal	Section B.3.3.1
Gender distribution (male %)	64.04%	[redacted]	Beta	
Weight	71.59	[redacted]	Normal	
Response rate				
Midostaurin	59.6%	56.16%	Beta	Section B.3.3.4
Cladribine	[redacted]	[redacted]	Beta	
Interferon-based Regimens	[redacted]	[redacted]	Beta	
Imatinib	[redacted]	[redacted]	Beta	
“AML-like”-treatments	[redacted]	[redacted]	Beta	
Relative effectiveness (comparators)				
HR for OS	[redacted]		Lognormal (95% CI: 0.319 – 0.839)	Section B.3.3.2
HR for PFS	[redacted]		Lognormal	Section B.3.3.3
HR for DoR – Cladribine	[redacted]		Lognormal (SE assumed to be 20%)	Section B.3.3.4
HR for DoR – Interferon-based regimens	[redacted]		Lognormal (SE assumed to be 20%)	
HR for DoR – TKIs (imatinib, dasatinib, nilotinib)	[redacted]		Lognormal (SE assumed to be 20%)	
HR for DoR – “AML-like” treatments	[redacted]		Lognormal (SE assumed to be 20%)	
HRQoL				
PFS – response	[redacted]		Multivariate normal	Section B.3.4.5
PFS – no response	[redacted]		Multivariate normal	
Progressive disease	[redacted]		Multivariate normal	
Decrement in utility/QALYs associated with mode of administration				
Decrement in utility associated with injection	Weekly injection: -0.02 (yearly utility decrement) Thrice weekly injection:-0.04 (yearly utility decrement)		Beta (SE assumed to be 20%)	Section B.3.4.5
Cladribine/”AML-like” treatments	QALY decrement -0.04 (one-off)		Beta (SE assumed to be 20%)	
Drug costs assumptions				
Number of initial cladribine cycle	3.68		Normal (SE assumed to be 20%)	Section B.3.5.1
Proportion of patients retreated	14.7%		Beta	
Proportion treated as inpatients in first cycle	35%		Beta (SE assumed to be 20%)	

Proportion treated as inpatients in remaining cycles	5%		Beta (SE assumed to be 20%)	
Drug administration costs				
Proportion requiring nurse for injection	15%		Beta (SE assumed to be 20%)	Section B.3.5.1
Administration cost for midostaurin	£0			
Administration cost for cladribine	£8,634.10		Normal distribution for number of cycles and Gamma for costs	
Administration cost for interferon alpha	£69.22		Beta for proportion and Gamma for unit costs	
Administration cost for Peg-interferon	£23.07		Beta for proportion and Gamma for unit costs	
Administration cost for Imatinib	£0			
Administration cost for “AML-like” treatments	£16,297		Gamma (SE assumed to be 20%)	
Patient access scheme (reduction in NHS list price)				
Midostaurin	[redacted]			Section B.3.5.1
Cladribine	0%			
Interferon alpha	0%			
Peg-interferon	0%			
Imatinib	0%			
“AML-like” treatments (azacitidine)	85%			
“AML-like” treatments (Others)	0%			
Treatment distribution in the UK				
Cladribine	53.65%	52.12%	Dirichlet (assuming N to number of patients in D2201)	Section B.3.2.3
Interferon alpha	2.05%	1.53%		
Peg-interferon	24.23%	23.74%		
Imatinib	4.50%	3.64%		
“AML-like” treatments	15.56%	18.97%		
Drug acquisition costs per cycle unless stated				
Proportion azacitidine in “AML-like” treatment category	48%		Beta	Section B.3.5.1
Midostaurin	[redacted]			
Cladribine	£3,173.33 (one off)			
Interferon alpha	£340.44			
Peg-interferon	£306.04			
Imatinib	£506.67			
“AML-like” treatments	£5,410.1			
Other costs				

Secondary costs	£11,807.4	Gamma (SE assumed to be 20%)	Section B.3.5.1
End of life	£7,797.92	Gamma (SE assumed to be 20%)	Section B.3.5.2

Abbreviations: AML: acute myeloid leukaemia; CI: confidence interval; DoR: duration of response; HR: hazard ratio; HRQoL: health-related HRQoL; MCL: mast cell leukaemia; OS: overall survival; PFS: progression free survival; QALY: quality-adjusted life year; SE: standard error; SM-AHN: systemic mastocytosis with associated haematological neoplasm.

B.3.6.2 Assumptions

The assumptions used in the base case analysis are described in Table 60, with a description of the scenarios conducted to explore the potential impact of these assumptions, where appropriate.

Table 60: List of assumptions for the base case analysis model

Assumption	Description of assumption for the base case	Justification	Addressed in scenario analysis
Population			
D2201 is generalisable to UK clinical practice	Baseline characteristics (age, gender, weight) of patients who would receive midostaurin in clinical practice are reflective of those included in D2201 trial	Clinical experts specialising in the treatment of patients with advanced SM deemed the trial to be representative of UK practice.	N/A
Licensed population includes the 3 subtypes of advanced SM; ASM, SM-AHN and MCL	Full licensed population alongside a subgroup analysis for patients with SM-AHN + MCL	Patients with SM-AHN and MCL have a short life expectancy of less than 2 years. It would be highly challenging to conduct separate subgroup analyses in patients with MCL or ASM only due to the very small numbers of patients (n=16) for each indication	N/A
Comparators			
The comparator in the economic case is current clinical UK management (including a mix of treatments)	Costs and QALYs for current clinical management are weighted according to the distribution of treatments used in UK clinical practice (estimated by UK clinical experts specialising in the treatment of advanced SM)	There are no currently licensed or recommended treatments for advanced SM in the UK, with treatment consisting of a mix of treatments including cladribine, interferon-based regimens, imatinib and “AML-like” treatments	Results are presented for each individual treatment in scenario analysis.
Efficacy for midostaurin			
Parametric distribution to extrapolate OS	Spline hazard model with one knot distribution used in the base-case	Selected following (1) visual fit, (2) statistical goodness of fit, (3) long-term plausibility (external + clinical validation) and (4) PH compatible	Alternative distributions are used in scenario analysis
Parametric distribution to extrapolate PFS	Spline hazard model with two knots distribution used in the base-case	Selected following (1) visual fit, (2) statistical goodness of fit, (3) long-term plausibility (consistency with OS – no crossing) and (4) PH compatible	Alternative distributions used in scenario analysis
Parametric distribution to extrapolate DoR	Spline hazard model with one knot used in the base-case	Selected following (1) visual fit, (2) statistical goodness of fit, (3) long-term plausibility (consistency with PFS)	Alternative distributions used in scenario analysis

Extrapolation is bounded for general population mortality	The maximum hazard of death between general population mortality (life table) and extrapolation is used	Avoids the hazard of death in the model being lower than death from general causes.	N/A
Efficacy for current clinical management			
OS in patients initiating current clinical management	Estimated by applying a HR to the baseline OS curve for midostaurin	The D2201 and A2213 are single-arm studies. Indirect evidence is available on the relative efficacy of midostaurin versus the comparators	N/A
HR for OS derived from a study of midostaurin compared with historical German control data (Reiter *et al.* 2017)	The HR from the multivariate analysis is used in the base-case	Clinical experts indicated the HR from the multivariate analysis provides a more plausible estimate for OS for current existing treatments compared with the matched analysis. Clinical experts further noted that the matched analysis excluded a large number of patients.	HRs from the matched analysis (Reiter *et al.*, 2017) and alternative sources (Chandesris and Barete) are used in Scenario analysis
The same HR for OS was used for all treatments and populations	All treatments part of current clinical UK management are assumed to have the same OS and PFS. The relative treatment effect is also assumed to be same in the overall advanced SM population and subgroup	This assumption was necessary in the absence of evidence specific to each comparator. Moreover, this assumption was supported and considered reasonable by UK clinical experts, given that current treatments are not expected to affect survival. The SM-AHN + MCL subgroup represents a large proportion of the overall advanced SM population (82% of the D2201 trial population), and therefore was deemed appropriate	N/A
HR for PFS	The HR for PFS is assumed to be the same as for OS	No evidence on PFS was identified in the systematic literature review. This assumption was considered reasonable by clinical experts	Scenario analysis are conducted varying the HR
HR for DoR	Estimated based on evidence in a mixed population (Lim *et al.*, 2009)	No evidence on DoR was identified in the systematic literature review specific to advanced SM	Scenario analysis are conducted varying the HR
Time on treatment			
A stopping rule is not considered for midostaurin	The Kaplan-Meier for time to treatment discontinuation from D2201 is used directly	UK clinical experts consider that patients would continue treatment for as long as a clinical benefit is observed. This is consistent with the SmPC for midostaurin, and supporting	N/A

		evidence from a company-sponsored UK-based compassionate use programme All patients have now discontinued the trial, and therefore the Kaplan-Meier is complete. This also reflect the efficacy data	
Time on treatment for patients receiving interferon-based regimens and TKIs	PFS is used as proxy for time on treatment	Assumption was made in the absence of evidence. This assumption was supported by clinical experts.	A scenario analysis is conducted whereby only patients with a response remain on treatment after cycle 6 (assumption).
Treatment costs for "AML-like" treatments are based on second-line treatment of AML	"AML-like" treatments consists of a basket of multiple therapies from TA552 since the regimens and duration of treatments is unknown.	This is a simplification to limit the number of assumptions around the multiple AML therapies available and the costs in TA552 for the treatment of AML were validated and found appropriate by the ERG. Using the cost in second-line (rather first-line) is likely to be under-estimated and therefore conservative.	The cost for "AML-like" treatment is varied in scenario analysis.
Response rates			
Comparability of response rate between studies	Response rates was assumed to be assessed at the same time and according to the same criteria despite some differences between the comparator studies. Responses rate from a mixed population was used when not available for advanced SM	These simplifying assumptions were made given the paucity of the evidence base	N/A
Response rate for Peg-interferon	Assumed to be the same as interferon-a	In the absence of evidence for Peg-interferon, clinical experts considered it reasonable to assume the same response rate given the same mechanism of action	N/A
Response rate for "AML-like" treatment	Assumed to be the same as cladribine	No evidence was identified for "AML-like" treatment in SM.	N/A
HRQoL			

Trial based SF-12 mapped onto EQ-5D	Mapping algorithm by Gray *et al.* (2006) used in the base-case	EQ-5D (using UK tariff) preferred by NICE. The Gray *et al.* (2006) was used in the base case as this was the most recent algorithm available. Predictions were also similar between mapping algorithms	Utility values estimated using alternative mapping algorithms are used in scenario analysis
Decrements in utility associated with the mode of administration	Injection and subcutaneous treatments are assumed to be associated with a decrement in HRQoL (compared with oral treatment)	The benefits associated with the availability of an oral treatment was compared with current existing treatments was highlighted by clinical experts. The negative impact associated with the mode of administration has also been recognised and accepted in previous appraisals. A targeted review of the literature confirmed the negative impact associated with the mode of administration. The estimate for the decrement in utility identified in the literature was doubled to reflect the higher frequency of administration for current treatments in adv SM, an assumption considered reasonable by clinical experts.	Varied in sensitivity analysis
Subsequent therapy costs			
Costs of subsequent therapy upon progression	The costs of subsequent therapy is based on the cost for cladribine and applied at the point of progression	In the absence of evidence, this simplifying assumption was considered reasonable	Scenario analysis were conducted varying the cost and proportion of patients incurring these costs.
Adverse events			
Adverse events	The effect of AEs on costs and HRQoL is included in the base-case analysis	The impact of AE is included in the base-case to reflect the NICE reference case (rely on a large number of assumptions).	Given the challenges described in Section B.3.3.6, a scenario analysis

			is conducted excluding the effect of AEs.
Resource use			
Resource estimates	The type and frequency of resource use was estimated from the average resource use estimated by 5 clinical experts	In the absence of evidence for NHS resource use for patients with advanced SM. a resource utilisation questionnaire was sent to 5 UK clinical experts. The average frequency derived from answers to the questionnaires from 4/5 clinical experts was used in the base case	Individual clinician responses were used in scenario analyses.

Abbreviations: AE: adverse event; AML: acute myeloid leukaemia; ASM: aggressive systemic mastocytosis; DoR: duration of response; ERG: evidence review group; EQ-5D: EuroQol 5 Dimensions; HR: hazard ratio; N/A: not applicable; NHS: national health service; NICE: National Institute for Health and Care Excellence; MCL: mast cell leukaemia; OS: overall survival; PFS: progression-free survival; QALY: quality-adjusted life year; SF-12: Short form 12; SM: systemic mastocytosis; SM-AHN: systemic mastocytosis with associated haematological neoplasm; SmPC: summary of product characteristics; TKI: tyrosine kinase inhibitor; UK: United Kingdom.

B.3.7 *Base case results*

Results of the economic analysis for the overall advanced SM population (patients with ASM, SM-AHN and MCL) are presented below in Section B.3.7.1 and the results for the subgroup of patients with SM-AHN or MCL are presented in Section B.3.9.

B.3.7.1 Base case incremental cost-effectiveness analysis results

Table 61 presents the base case results of the economic evaluation for the overall advanced SM population. A confidential PAS already exists for midostaurin in patients with newly diagnosed FLT3 mutation-positive AML and as such, the same PAS has been included for this current indication.

This population of patients meets the NICE end of life criteria based on the short life expectancy of less than 2 years and the improvement in survival conferred by midostaurin, and therefore the higher WTP threshold of £50,000 per QALY gained would apply.

[redacted] all cost-effectiveness analyses presented within this submission incorporate the current PAS, representing the current net drug acquisition cost of midostaurin to the NHS.

The base case incremental cost-effectiveness results in the overall advanced SM population show that over a lifetime time horizon, the total costs associated with midostaurin are estimated to be [redacted] compared with £39,189 for patients treated with current clinical management in the UK (an incremental cost of [redacted]).

The total QALYs for patients receiving midostaurin are estimated to be [redacted] compared with [redacted] for patients treated with current clinical management in the UK (an incremental QALY gain of [redacted]) in the overall advanced SM population, resulting in an ICER of [redacted] per QALY gained.

Table 61: Base case incremental cost-effectiveness results – overall advanced SM population (midostaurin at current PAS price)

Technologies	Total costs (£)	Total LYG (undiscounted)	Total QALYs	Incr. costs (£)	Incr. LYG (undiscounted)	Incr. QALYs	ICER (£/QALY)
Current clinical management	£39,189	1.90	1.10	-	-	-	-
Midostaurin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: all results presented are discounted unless otherwise stated.
Abbreviations: ICER: incremental cost-effectiveness ratio; Incr.: incremental; LYGs: life years gained; QALYs: quality-adjusted life years; PAS: patient access scheme; SM: systemic mastocytosis.

Clinical outcomes from the cost-effectiveness model, the proportion of the cohort in each health state over time (Markov trace), and the disaggregated results of the base case incremental cost-effectiveness analysis are reported in Appendix J.

B.3.8 *Sensitivity analyses*

B.3.8.1 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was conducted in order assess the simultaneous effect of uncertainty in the different model parameters. A Monte-Carlo simulation with 1,000 iterations was performed and, in each iteration, model inputs were randomly sampled from the specified probability distributions in Table 62. An arbitrary SE of 20% around the mean was assumed when the SE or 95% CI was not available. The majority of input parameters were varied. For the parameter using the Drichlet distribution (treatment mix for instance), assumption was made about the N. Finally, all survival curves were varied with the exception of the TTD curve, as the KM curve was complete (and no parametric distribution was fitted).

Table 62: PSA parameters and distributions

Parameter	Distribution	Mean	Alpha	Beta	SE
Patient characteristics					
Age	Normal	63	-	-	1.23
Weight	Normal	71.59	-	-	1.48
% Male	Beta	0.64	57	89	-
Survival distributions for midostaurin					
OS	Bootstrap	Spline model with one knot	-	-	-
PFS	Bootstrap	Spline model with two knots	-	-	-
DoR	Multivariate normal	Spline model with one knot	-	-	-
HR for OS					
HR for OS	Lognormal	1.93	-	-	95% CI: 1.19, 3.13
HR for DoR					
HR for DoR	Lognormal	Table 48	-	-	Assumed to be ±20% of the mean
Response rates					
Response rates	Beta	Table 59	-	-	-
Utility values					
Health states	Multivariate normal	Table 52	-	-	-
Utility decrement associated with mode of administration	Beta	Table 52	-	-	Assumed to be ±20% of the mean
Cost and resource use					
Unit costs	Gamma	Table 56	-	-	Assumed to be ±20% of the mean

Treatment mix distribution	Dirichlet	Table 40	-	-	N based on D2201
RDI for midostaurin	Normal	[redacted]	-	-	[redacted]
Treatment-free interval for midostaurin	Beta	[redacted]	-	-	[redacted]

Abbreviations: DoR: duration of response; HR: hazard ratio; OS: overall survival; PFS: progression-free survival; PSA: probabilistic sensitivity analysis; RDI: relative dose intensity; SE: standard error.

The results of the PSA are presented in Table 63 and show that in the overall advanced SM population, over a lifetime time horizon, midostaurin is associated with greater QALYs ([redacted]), at a greater cost ([redacted]) compared to current clinical management in the UK (1.15 QALYs and £40,365 respectively). As such, the average PSA ICER was estimated to be [redacted] per QALY gained, with a [redacted] probability of midostaurin being a cost-effective treatment option at a £50,000/QALY gained willingness-to-pay (WTP) threshold as the overall advanced SM population meet end of life criteria (Section B.2.13). [redacted].

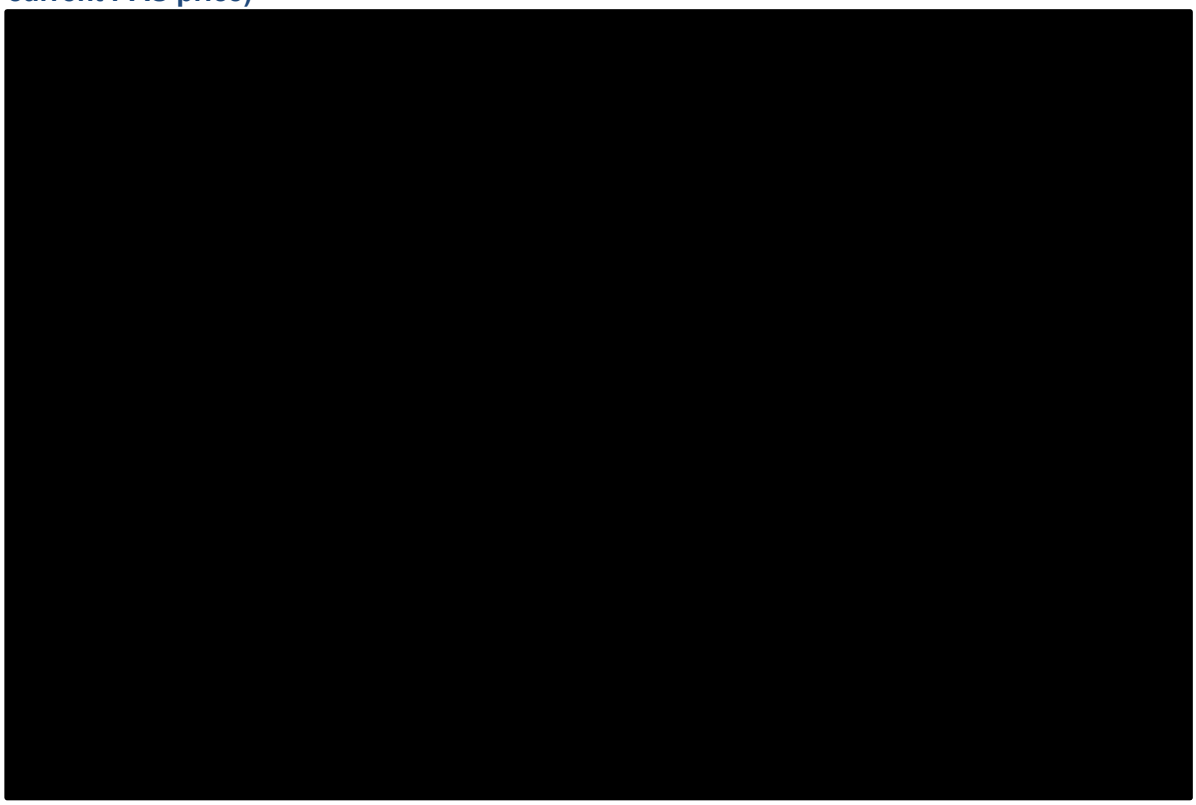
The cost-effectiveness plane and cost-effectiveness acceptability curves resulting from the PSA for the overall advanced SM population are presented in Figure 37 and Figure 38.

Table 63: PSA results – overall advanced SM population (midostaurin at current PAS price)

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	Probability of cost-effectiveness[a]
Current clinical management	£40,365	1.15	-	-	-	-
Midostaurin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a]The probability of midostaurin being cost-effective versus current clinical management in the UK at a WTP threshold of £50,000/QALY gained.
Note: all results presented are discounted unless otherwise stated.
Abbreviations: ICER: incremental cost-effectiveness ratio; Incr.: incremental; QALYs: quality-adjusted life years; PAS: patient access scheme; PSA: probabilistic sensitivity analysis; WTP: willingness-to-pay.

Figure 37: PSA cost-effectiveness plane – overall advanced SM population (midostaurin at current PAS price)



Abbreviations: Advanced SM: advanced systemic mastocytosis; QALYs: quality-adjusted life years; PAS: patient access scheme; PSA: probabilistic sensitivity analysis; WTP: willingness-to-pay threshold.

Figure 38: PSA cost-effectiveness acceptability curve – overall advanced SM population (midostaurin at current PAS price)

Abbreviations: Advanced SM: advanced systemic mastocytosis; QALYs: quality-adjusted life years; PAS: patient access scheme; PSA: probabilistic sensitivity analysis; WTP: willingness-to-pay threshold.

B.3.8.2 Deterministic sensitivity analysis

In order to assess the robustness of the base case cost-effectiveness results, deterministic sensitivity analyses (DSA) were conducted by varying one model input at a time to assess which parameters had the most impact on the ICER. Parameters were varied within their 95% CI where available (or possible to calculate) or within a reasonable range.

Table 64 summarises the 10 most influential parameters assessed in the DSA and the ICERs calculated at the upper and lower bounds, sorted from the widest to narrowest range of ICER values to highlight the parameters with the strongest influence on the cost-effectiveness results. The results for the 10 most influential parameters are also shown graphically in the tornado plot in Figure 39. The results of the DSA show that results were most sensitive to the HR for OS, the discount rate used for benefits, and utility values.

Table 64: Top 10 most influential variables assessed in DSA and resulting ICERs – overall advanced SM population (midostaurin at current PAS price)

Variable	ICER (lower bound) (£/QALY)	ICER (upper bound) (£/QALY)
HR for OS (95% CI)	[redacted]	[redacted]
Discount rate for benefits (1.5% - 5.0%)	[redacted]	[redacted]
Baseline utility value (95% CI)	[redacted]	[redacted]
Utility value PFS response (95% CI)	[redacted]	[redacted]
HR PFS OS (95% CI)	[redacted]	[redacted]

Discount rate for costs (1.5% - 5.0%)	[redacted]	[redacted]
Relative dose intensity (95% CI)	[redacted]	[redacted]
Start utility adjustment for gen pop (none - from start)	[redacted]	[redacted]
Response rate midostaurin (95% CI)	[redacted]	[redacted]
Management cost PFS (12 month+)	[redacted]	[redacted]

Note: all results presented are discounted unless otherwise stated.
Abbreviations: Advanced SM: advanced systemic mastocytosis; CI: confidence interval; DSA: deterministic sensitivity analysis; HR: hazard ratio; ICER: incremental cost-effectiveness ratio; OS: overall survival; PFS: progression-free survival; RDI: relative dose intensity.

Figure 39: Tornado diagram based on DSA results – overall advanced SM population (midostaurin at current PAS price)

[redacted]

Abbreviations: Advanced SM: advanced systemic mastocytosis; CI: confidence interval; DSA: deterministic sensitivity analysis; HR: hazard ratio; ICER: incremental cost-effectiveness ratio; OS: overall survival; PAS: patient access scheme; PFS: progression-free survival; QALY: quality-adjusted life year.

B.3.8.3 Scenario analyses

Extensive scenario analyses were conducted altering important variables in the cost-effectiveness model. Results of the scenario analyses are reported below in Table 65.

From the results of the scenario analyses, it can be seen that most inputs/assumptions had a minimal (less than 5% change) or limited (less than 10% change) impact on the ICER. The base case ICER was affected the most:

- When the exponential or Weibull distribution were used to extrapolate OS. However, as described in Section B.3.3.2, these two distributions are not considered plausible as they

provided a poor fit to the data. These are therefore only presented here for transparency and completeness.

- HR for OS for the comparator. In the base case economic analysis, OS in patients initiating current clinical management in the UK was estimated by applying an HR to the baseline OS in patients initiating midostaurin. Three sources were identified (Reiter *et al.* [2017];[23] Chandesris *et al.* [2017][65] and Barete *et al.* [2015][30]). Discussion with clinical experts indicated that the predicted survival using the HR from Reiter *et al.* (2017)[23] estimated using multivariate analysis more closely resembled the survival expected for this population. Clinical experts considered that the HR estimated using the matched analysis predicted longer survival compared to what they have seen in clinical practice. Therefore, the HR from Reiter *et al.* (2017)[23] using the multivariate analysis was used in the base case economic analysis.
- HR for PFS for the comparator. The ICER improved if the HR for PFS for the comparator was larger than the HR for OS.

Table 65: Scenario analysis results: overall advanced SM population (midostaurin at current PAS price)

	Incr. costs (£)	Incr. LYs (undiscounted)	Incr. QALYs	ICER (£/QALY)
Base case	[redacted]	[redacted]	[redacted]	[redacted]
Individual comparators				
Comparator = Cladribine	[redacted]	[redacted]	[redacted]	[redacted]
Comparator = Interferon alpha	[redacted]	[redacted]	[redacted]	[redacted]
Comparator = Peg-interferon	[redacted]	[redacted]	[redacted]	[redacted]
Comparator = Imatinib	[redacted]	[redacted]	[redacted]	[redacted]
Comparator = Nilotinib	[redacted]	[redacted]	[redacted]	[redacted]
Comparator = Dasatinib	[redacted]	[redacted]	[redacted]	[redacted]
Comparator = “AML-like” treatments	[redacted]	[redacted]	[redacted]	[redacted]
KM + extrapolation				
KM + extrapolation	[redacted]	[redacted]	[redacted]	[redacted]
Parametric extrapolation for OS				
Exponential[a]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull[a]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]
Loglogistic	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Spline2	[redacted]	[redacted]	[redacted]	[redacted]
Parametric extrapolation for PFS				
Exponential[a]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull[a]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]
Loglogistic	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Spline1	[redacted]	[redacted]	[redacted]	[redacted]

Parametric extrapolation for DoR				
Exponential[a]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull[a]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]
Loglogistic	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Spline2	[redacted]	[redacted]	[redacted]	[redacted]
HR for OS for comparator				
Reiter *et al.* (2017) - Matched [b]	[redacted]	[redacted]	[redacted]	[redacted]
Reiter *et al.* (2017) - Unmatched	[redacted]	[redacted]	[redacted]	[redacted]
Reiter *et al.* (2017) - From Last	[redacted]	[redacted]	[redacted]	[redacted]
Chandesris *et al.* (2017) - Univariate	[redacted]	[redacted]	[redacted]	[redacted]
Chandesris *et al.* (2017) - Multivariate	[redacted]	[redacted]	[redacted]	[redacted]
Barete *et al.* (2015) – derived	[redacted]	[redacted]	[redacted]	[redacted]
HR for PFS				
HR for PFS = 5	[redacted]	[redacted]	[redacted]	[redacted]
HR for PFS = 2.5	[redacted]	[redacted]	[redacted]	[redacted]
HR for PFS = 1.66	[redacted]	[redacted]	[redacted]	[redacted]
HR for PFS = 1.25	[redacted]	[redacted]	[redacted]	[redacted]
Mapping algorithm SF-12 onto EQ-5D				
Frank *et al.* (2003)	[redacted]	[redacted]	[redacted]	[redacted]
Frank *et al.* (2004)	[redacted]	[redacted]	[redacted]	[redacted]
Lawrence *et al.* (2004)	[redacted]	[redacted]	[redacted]	[redacted]
SF-6D	[redacted]	[redacted]	[redacted]	[redacted]
Utility value progressive disease				
Utility for PD = estimated	[redacted]	[redacted]	[redacted]	[redacted]
Secondary costs				
“AML-like” treatment costs	[redacted]	[redacted]	[redacted]	[redacted]
Peg-interferon costs	[redacted]	[redacted]	[redacted]	[redacted]
No costs	[redacted]	[redacted]	[redacted]	[redacted]
Estimate of resource use				
Resource use based on Expert1	[redacted]	[redacted]	[redacted]	[redacted]
Resource use based on Expert2	[redacted]	[redacted]	[redacted]	[redacted]
Resource use based on Expert3	[redacted]	[redacted]	[redacted]	[redacted]
Resource use based on Expert4	[redacted]	[redacted]	[redacted]	[redacted]
Duration of treatment for interferon-based regimens and TKIs				
PFS + DoR used as a proxy for TTD	[redacted]	[redacted]	[redacted]	[redacted]
Exclusion of wastage				
Wastage excluded	[redacted]	[redacted]	[redacted]	[redacted]
Exclusion of AEs				
AEs excluded	[redacted]	[redacted]	[redacted]	[redacted]
Roferon-A vial size				
4.5MU vial for Roferon-A	[redacted]	[redacted]	[redacted]	[redacted]
3MU vial for Roferon-A	[redacted]	[redacted]	[redacted]	[redacted]

[a]Not considered plausible extrapolations given the poor fit to the data (refer to section B.3.3.2).

[b]It should be noted that this matched analysis resulted in the loss of ~50% of the dataset thus the results of this scenario analysis are associated with considerable uncertainty and should be interpreted with caution.
Note: all results presented are discounted unless otherwise stated.
Abbreviations: Advanced SM: advanced systemic mastocytosis; AE: adverse event; AML: acute myeloid leukemia; DoR: duration of response; EQ-5D-3L: EuroQol 5 Dimensions 3 Levels; HR: hazard ratio; ICER: incremental cost-effectiveness ratio; LYs: life years; MIU: million IU; NHS: national health system; OS: overall survival; PFS: progression-free survival; QALYs: quality-adjusted life year; PAS: patient access scheme; SF-12: Short form 12; TTD: time to treatment discontinuation.

B.3.8.4 Summary of sensitivity analyses results

An extensive range of sensitivity and scenario analyses were conducted to test the robustness of the model inputs and structural assumptions of the economic analysis. The key driver was the HR for OS for the comparator (current clinical management), and the discount rate for benefits and utility values.

In the absence of a head-to-head trial between midostaurin and current clinical management in the UK, OS in patients initiating current clinical management was estimated by applying an HR to the baseline OS in patients initiating midostaurin. Three sources were identified for this (Reiter *et al.* [2017],[23] Chandesris *et al.* [2017][65] and Barete *et al.* [2015][30]), and discussion with clinical experts indicated that the predicted survival using the HR from Reiter *et al.* (2017)[23] using the multivariate analysis more closely resembled the survival expected for this population and therefore represented the most plausible HR to inform the base case. Clinical experts considered that the HR estimated using the matched analysis predicted longer survival compared to what they have seen in practice and was therefore unlikely to represent a realistic scenario. This analysis was also associated with a loss of about 2/3 of patients and therefore any ensuing results are associated with considerable uncertainty and should be interpreted with caution.

Overall, the sensitivity analyses show that the base case ICER increases when using the HR for OS estimated from the matched analysis, however the survival predicted by the matched HR was considered implausible by our clinical experts. In contrast, the ICER improved when other plausible values identified by the systematic literature review were used.

In summary, the base case ICER was relatively stable when tested in both sensitivity and scenario analyses, with most input/assumptions having a minimal (less than 5% change) or limited (less than 10% change) impact on the overall cost-effectiveness results especially when the scenarios deemed implausible by clinicians are disregarded.

B.3.9 *Subgroup analysis*

A subgroup analysis was conducted in patients with SM-AHN + MCL as these populations have an even shorter life expectancy and high unmet need, representing 82% of the population included in the D2201 trial. As for the overall advanced SM population (see Section B.2.13), this population of patients meets the NICE end of life criteria based on the short life expectancy of less than 2 years and the improvement in survival conferred by midostaurin, and therefore the higher WTP threshold of £50,000 per QALY gained would apply.

Over a lifetime time horizon, the total costs associated with midostaurin for the SM-AHN + MCL subgroup are estimated to be [redacted] compared to £37,836 for patients treated with current clinical management in the UK (an incremental cost of [redacted]).

The total QALYs for patients receiving midostaurin in the SM-AHN + MCL subgroup are estimated to be [redacted] compared to 0.85 for patients treated with current clinical management in the UK (an

incremental QALY gain of [redacted]), resulting in an ICER of [redacted] per QALY gained. [redacted].

Table 66: Cost-effectiveness results – SM-AHN + MCL subgroup (midostaurin at current PAS price)

Technologies	Total costs (£)	Total LYG (undiscounted)	Total QALYs	Incr. costs (£)	Incr. LYG (undiscounted)	Incr. QALYs	ICER (£/QALY)
Current clinical management	£37,836	1.46	0.85	-	-	-	-
Midostaurin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: all results presented are discounted unless otherwise stated.
Abbreviations: ICER: incremental cost-effectiveness ratio; LYGs: life years gained; QALYs: quality-adjusted life years; MCL: mast cell lymphoma; PAS: patient access scheme; SM-AHN: systemic mastocytosis with associated haematological neoplasm.

The results of the PSA for this subgroup analysis are presented in Table 67 and show that over a lifetime time horizon, midostaurin is associated with greater QALYs [redacted], at a greater cost of [redacted] compared to current clinical management in the UK (0.89 QALYs and £38,640 respectively) in the SM-AHN + MCL subgroup. As such, the average PSA ICER was estimated to be [redacted] per QALY gained, with a [redacted] probability of midostaurin being a cost-effective treatment option at a £50,000 per QALY gained WTP threshold. [redacted].

The cost-effectiveness plane and cost-effectiveness acceptability curves resulting from the PSA for the SM-AHN + MCL subgroup are presented in Figure 40 and Figure 41 respectively.

Table 67: PSA results – SM-AHN + MCL subgroup (midostaurin at current PAS price)

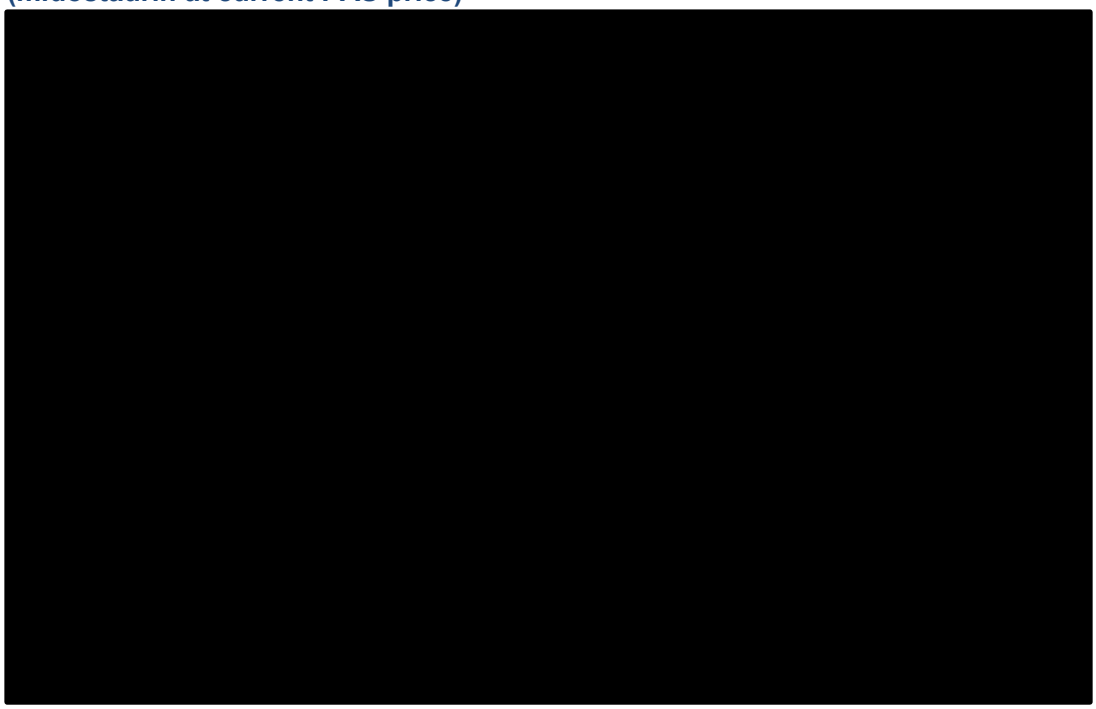
Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	Probability of cost-effectiveness[a]
Current clinical management	£38,640	0.89	-	-	-	-
Midostaurin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a]The probability of midostaurin being cost-effective versus current clinical management in the UK at a WTP threshold of £50,000/QALY gained.
Abbreviations: ICER: incremental cost-effectiveness ratio; Incr.: incremental; QALYs: quality-adjusted life years; PAS: patient access scheme; PSA: probabilistic sensitivity analysis; WTP: willingness-to-pay.

Figure 40: PSA cost-effectiveness plane – SM-AHN + MCL subgroup (midostaurin at current PAS price)

Abbreviations: MCL: mast cell lymphoma; PAS: patient access scheme; PSA: probabilistic sensitivity analysis; QALYs: quality-adjusted life years; SM-AHN: systemic mastocytosis with associated haematological neoplasm; WTP: willingness-to-pay threshold.

Figure 41: PSA cost-effectiveness acceptability curve – SM-AHN + MCL subgroup (midostaurin at current PAS price)



Abbreviations: MCL: mast cell lymphoma; PAS: patient access scheme; PSA: probabilistic sensitivity analysis; QALYs: quality-adjusted life years; SM-AHN: systemic mastocytosis with associated haematological neoplasm; WTP: willingness-to-pay threshold.

Results from the DSA and scenario analysis for the SM-AHN + MCL subgroup analysis are presented in Figure 42 and Table 68 respectively. In line with the sensitivity analysis results for the overall advanced SM population (Section B.3.8), the sensitivity analysis results for this subgroup were most sensitive to the HR used for OS, and the discount rate for benefits and utility values.

Figure 42: Tornado diagram based on DSA results – SM-AHN + MCL subgroup (midostaurin at current PAS price)

Abbreviations: Advanced SM: advanced systemic mastocytosis; CI: confidence interval; DSA: deterministic sensitivity analysis; HR: hazard ratio; ICER: incremental cost-effectiveness ratio; OS: overall survival; PAS: patient access scheme; PFS: progression-free survival; QALY: quality-adjusted life year.

Table 68: Scenario analysis results: individual comparator-based analyses – SM-AHN + MCL subgroup (midostaurin at current PAS price)

	Incr. costs (£)	Incr. LYs	Incr. QALYs	ICER (£/QALY)
Base case	[redacted]	[redacted]	[redacted]	[redacted]
Individual comparators				
Comparator = Cladribine	[redacted]	[redacted]	[redacted]	[redacted]
Comparator = Interferon alpha	[redacted]	[redacted]	[redacted]	[redacted]
Comparator = Peg-interferon	[redacted]	[redacted]	[redacted]	[redacted]
Comparator = Imatinib	[redacted]	[redacted]	[redacted]	[redacted]
Comparator = Nilotinb	[redacted]	[redacted]	[redacted]	[redacted]
Comparator = Dasatinib	[redacted]	[redacted]	[redacted]	[redacted]
Comparator = “AML-like” treatments	[redacted]	[redacted]	[redacted]	[redacted]
KM + extrapolation				
KM + extrapolation	[redacted]	[redacted]	[redacted]	[redacted]
Parametric extrapolation for OS				
Exponential[a]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull[a]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]

Loglogistic	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Spline2	[redacted]	[redacted]	[redacted]	[redacted]
Parametric extrapolation for PFS				
Exponential[a]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull[a]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]
Loglogistic	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Spline1	[redacted]	[redacted]	[redacted]	[redacted]
Parametric extrapolation for DoR				
Exponential[a]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull[a]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]
Loglogistic	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Spline2	[redacted]	[redacted]	[redacted]	[redacted]
HR for OS for comparator				
Reiter *et al.* (2017) - Matched[b]	[redacted]	[redacted]	[redacted]	[redacted]
Reiter *et al.* (2017) - Unmatched	[redacted]	[redacted]	[redacted]	[redacted]
Reiter *et al.* (2017) - From Last Treatment	[redacted]	[redacted]	[redacted]	[redacted]
Chanderis *et al.* (2017) - Univariate (Matched)	[redacted]	[redacted]	[redacted]	[redacted]
Chanderis *et al.* (2017) - Multivariate (matched)	[redacted]	[redacted]	[redacted]	[redacted]
Barete *et al.* (2015) - derived	[redacted]	[redacted]	[redacted]	[redacted]
HR for PFS				
HR for PFS = 5	[redacted]	[redacted]	[redacted]	[redacted]
HR for PFS = 2.5	[redacted]	[redacted]	[redacted]	[redacted]
HR for PFS = 1.66	[redacted]	[redacted]	[redacted]	[redacted]
HR for PFS = 1.25	[redacted]	[redacted]	[redacted]	[redacted]
Mapping algorithm SF-12 onto EQ-5D				
Frank *et al.* (2003)	[redacted]	[redacted]	[redacted]	[redacted]
Frank *et al.* (2004)	[redacted]	[redacted]	[redacted]	[redacted]
Lawrence *et al.* (2004)	[redacted]	[redacted]	[redacted]	[redacted]
SF-6D	[redacted]	[redacted]	[redacted]	[redacted]
Utility value progressive disease				
Utility for PD = estimated	[redacted]	[redacted]	[redacted]	[redacted]
Secondary costs				
“AML-like” treatment costs	[redacted]	[redacted]	[redacted]	[redacted]
Peg-interferon costs	[redacted]	[redacted]	[redacted]	[redacted]
No costs	[redacted]	[redacted]	[redacted]	[redacted]
Estimate of resource use				
Resource use based on Expert1	[redacted]	[redacted]	[redacted]	[redacted]
Resource use based on Expert2	[redacted]	[redacted]	[redacted]	[redacted]
Resource use based on Expert3	[redacted]	[redacted]	[redacted]	[redacted]

Resource use based on Expert4	[redacted]	[redacted]	[redacted]	[redacted]
Duration of treatment for interferon-based regimen and TKIs				
PFS + DoR used as a proxy for TTD	[redacted]	[redacted]	[redacted]	[redacted]
Exclusion of wastage				
Wastage excluded	[redacted]	[redacted]	[redacted]	[redacted]
Exclusion of AEs				
AE excluded	[redacted]	[redacted]	[redacted]	[redacted]
Roferon-A vial size				
4.5MU vial for Roferon-A	[redacted]	[redacted]	[redacted]	[redacted]
3MU vial for Roferon-A	[redacted]	[redacted]	[redacted]	[redacted]

[a]Not considered plausible extrapolations given the poor fit to the data (refer to section B.3.3.2).
[b]It should be noted that this matched analysis resulted in the loss of ~50% of the dataset thus the results of this scenario analysis are associated with considerable uncertainty and should be interpreted with caution.
Abbreviations: Advanced SM: advanced systemic mastocytosis; AE: adverse event; AML: acute myeloid leukemia; D0R: duration of response; EQ-5D-3L: EuroQol 5 Dimensions 3 Levels; HR: hazard ratio; ICER: incremental cost-effectiveness ratio; KM: Kaplan-Meier; LYs: life years; MIU: million IU; NHS: national health system; OS: overall survival; PFS: progression-free survival; QALYs: quality-adjusted life year; PAS: patient access scheme; SF-12: Short form 12; TTD: time to treatment discontinuation.

B.3.10 *Validation*

B.3.10.1 Validation of cost-effectiveness analysis

During the development of the *de novo* cost-effectiveness model, five UK clinical experts specialising in the treatment of advanced SM patients were consulted to develop and evaluate the model structure, key assumptions, parameters and efficacy estimates.[1] In the absence of evidence for this rare disease, the experiences of clinical experts in treating patients in the UK are likely to provide relevant data on the aspects of advance SM disease management in clinical practice including survival rates, current treatments and resource utilisation.

Quality-control (QC) procedures for verification of input data and coding were performed and two checklists (for technical and stress test checks) were used to ensure that the model generated accurate results which were consistent with input data and robust to extreme values. An independent reviewer who was not involved in model development performed the technical and stress test QC checks, and the complete checklists are documented in Table M.1 and Table M.2 respectively, in Appendix M. As part of the technical QC, all model calculations were reviewed, including standalone formulae, equations and Excel macros programmed in VBA. The correct functioning of the sensitivity and scenario analyses was also reviewed. The stress test ensured that the expected effect is observed when key inputs are varied in the model (e.g. when utilities for all health states and for AEs are set to 0, all QALYs should result equal to 0).

To ensure external validity, model predictions were compared to observed data where possible and, as described in Section B.3.3, the short-term outcomes predicted by the model are in-line with those observed in the D2201 trial. Moreover, in the absence of long-term data, the long-term predictions were considered clinically plausible by clinical experts.

B.3.11 *Interpretation and conclusions of economic evidence*

No full economic evaluations were identified by the economic SLR described in Section B.3.1, hence it was not possible to compare the results of this analysis with prior cost-effectiveness analyses conducted in this indication.

The deterministic results of the base case economic analysis show that midostaurin is associated with higher costs but also higher QALYs than current clinical management in the UK, with an incremental cost per QALY gained of [redacted] (with midostaurin at the current PAS price).

The ICER in the subgroup of patients with SM-AHN + MCL who have a poor prognosis and shortest life expectancy was [redacted].

The model estimated life years gained for patients receiving current clinical management was 1.90 years in the overall population and 1.46 years in the SM-AHN + MCL subgroup, confirming that patients with advanced SM have a short life expectancy (normally less than 2 years), with a shorter life expectancy in those patients with SM-AHN or MCL. Furthermore, the model predicted incremental LYG for midostaurin compared with current management was estimated to be [redacted] for the overall population and [redacted] for the SM-AHN + MCL, demonstrating an additional extension to life of greater than 3 months. These results provide supportive evidence that midostaurin fulfils the NICE criteria for an end of life treatment and subsequently qualifies for the higher WTP threshold of £50,000/QALY.

Sensitivity analyses indicated the ICER to be robust to plausible changes in most of the comparators considered, with most inputs/assumptions having a minimal (less than 5% change) or limited (less than 10% change) impact on the ICER .

Strengths of the economic analysis include:

- The economic analysis is underpinned by a well-designed single-arm trial (D2201) that is broadly representative of the population expected to be treated with midostaurin in England and Wales. It is also important to note that this trial is the largest trial conducted in patients with advanced SM to date and included UK patients
- The model structure and assumptions were developed with input from five key UK clinical experts specialising in the treatment of advanced SM. These experts also considered that the long-term survival predictions for midostaurin and the comparators were clinically plausible[1]
- Uncertainty in the model inputs and assumptions has been explored in a large number of scenario and sensitivity analyses that demonstrate the robustness of the model results
- Long-term evidence (10-year follow-up data) for midostaurin is available in advanced SM in the A2213 study and these data were used to validate the long-term OS extrapolations

Limitations of the analysis include:

- The absence of a head to head trial between midostaurin and current clinical management meant that indirect evidence in the form of historical control comparisons was used to estimate OS in patients receiving current clinical management in the UK, thus there is uncertainty surrounding the estimates
- There is a paucity of evidence available for the efficacy (PFS, OS and DoR) and safety (incidence of AEs) of the comparators as described in Section B.2.9.2 and in the absence of

such evidence a number of assumptions have been made, leading to uncertainty in the estimates.

- Although the D2201 study is the largest study to date conducted in advanced SM, the number of patients included in the study can be considered small (as would be expected with a rare disease), particularly when considering the numbers that make up the different disease subtypes for subgroup analyses (ASM, SM-AHN, MCL)
- There are a number of evidence gaps and uncertainties often associated with rare diseases. However, by enlisting input from the five top clinical experts who specialise in treating advanced SM in the UK, and by conducting numerous sensitivity analyses we have put together the most robust case based on the available evidence.

Concluding remarks

Patients with advanced SM have a poor prognosis with a short life expectancy. There is no licensed or accepted standard therapy for advanced SM patients in Europe and the response rates associated with current treatment options may be variable and short-lived with many patients developing resistance.[14, 28-36] Consequently, there remains a high unmet medical need for a well-tolerated and effective therapy to reduce disease burden, improve survival rates and HRQoL.

Midostaurin is the only licensed targeted therapy to show a clinically meaningful efficacy in reducing the high underlying mast cell burden, ameliorating disease-related organ dysfunction and improving the survival of advanced SM patients. In addition, midostaurin has demonstrated to be associated with a manageable safety profile with good tolerability. It is the only targeted therapy licensed for the treatment of advanced SM, having demonstrated significant disease-modifying activity, as well as the ability to inhibit *KIT* signalling, cell proliferation and histamine release, and induce apoptosis in mast cells.[8]

The cost-effectiveness analysis shows that at the £50,000/QALY WTP, threshold, midostaurin [redacted] However, it should be noted that had midostaurin in advanced SM been considered via the HST process (as opposed to the current STA), it is possible that a different conclusion may have been reached, given the broader decision making framework, different attitudes to uncertainty and higher WTP thresholds in the HST process.

[redacted]

B.4 References

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B.5 Appendices

Appendix C: Summary of Product Characteristics (SmPC) and European public assessment report (EPAR)

Appendix D: Identification, selection and synthesis of clinical evidence

Appendix E: Subgroup analysis

Appendix F: Adverse reactions

Appendix G: Published cost-effectiveness studies

Appendix H: Health-related quality-of-life studies

Appendix I: Cost and healthcare resource identification, measurement and valuation

Appendix J: Clinical outcomes and disaggregated results from the model

Appendix K: Checklist of confidential information

Appendix L: Rapid review for studies reporting on decrement in utilities associated with the route of administration

Appendix M: Cost-effectiveness model validation checklists

Appendix N: Parametric distribution fits to midostaurin in D2201 for DoR

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Technical engagement response form

Midostaurin for treating advanced systemic mastocytosis [ID1573]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments **5pm** on **Wednesday 29 July 2020**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential

information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Leukaemia Care, The UK Mastocytosis Support Group**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**Leukaemia Care – n/a** **The UK Mastocytosis Support Group – n/a**

Questions for engagement

Issue 1: Generalisibility of trial results	
Is clinical practice in the trials generalisable to the NHS setting?	Advanced systemic mastocytosis patients represent a very heterogeneous population and, due to lack of treatment options, treatment varies by the individual in all countries. Midostaurin is standard of care in other countries and so it is hard to get a picture of standard of care without midostaurin in any location.
Issue 2: Comparator treatment	
Are AML-like treatments used in the NHS in England to treat mastocytosis?	AML-like treatments may be used in rare circumstances; clinical advice suggests that it is likely to be used to treat any associated haematological neoplasms or prior to transplant.
What are the most appropriate comparators in the UK? Please provide details of which are most used, e.g. treatment 1: 60% of people, treatment 2: 10% of people, and so on.	As midostaurin is already standard of care elsewhere, it is difficult to be precise about the proportions on other treatments. As outlined in our submission, comparators that may be considered include: interferon alpha, imatinib, nilotinib, dasatinib, and cladribine [redacted]
Is it appropriate to have a composite comparator?	

Issue 3: Subgroups	
Are the 3 subgroups, aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated haematological neoplasm (SM-AHN) and mast cell leukaemia (MCL), distinguishable in clinical practice?	It would be unfair to examine subgroups, due to the rarity of the condition. Therefore, we do not believe that subgrouping is an appropriate analysis to undertake. Appraising this treatment via the HST route would have allowed analyses to be performed and a degree of flexibility for this small patient population that would have addressed this question more effectively than an STA allows.
Are people in the 3 subgroups offered different treatment options in the NHS in England? For each subgroup please provide details of which are most used, e.g. treatment 1: 60% of people, treatment 2: 10% of people, and so on.	Our clinical advisors report that treatments are specific to the individual patient, given the heterogeneity of this population. All of these patients have extremely limited options and require access to midostaurin.
Is it appropriate to combine people with SM-AHN and people with MCL in 1 subgroup?	As per our previous comments, the group should remain as one population in this appraisal. The rarity of the condition has meant that it is not possible to collect enough data to allow analysis of subgroups without significant uncertainty.
Issue 4: Comparative effectiveness data sources	
Is clinical practice for managing mastocytosis in France and Germany comparable to clinical practice in the NHS in England?	The leading clinicians in all three countries participated in the international trials of midostaurin and have experience implementing similar protocols.
Is it appropriate to assume that outcomes from the studies in Germany and France are comparable to the NHS in England?	We are not aware of historical data from the UK (before midostaurin became available on trial or through the compassionate use program) that would allow comparison of the outcomes preceding the midostaurin trials. During the trials the same protocols were followed, and we would expect a similar standard of care, and similar outcomes.
Is it appropriate to combine results from D2201 and A2213, as done in Reiter et al.?	Advanced SM is a rare illness. Given this rarity, we believe the all available data on midostaurin trials should be utilised in attempting to meet the STA requirements. This includes the paper by Reiter et al. (2017).
Issue 5: Overall survival	

How many people would you expect to be still alive at 5, 10 and 15 years on midostaurin? At 15 years, is 5% to 10% an appropriate estimate?	
How many people would you expect to be still alive at 5, 10, and 15 years on standard of care?	It is difficult to answer this due to the lack of data on comparators, arising from the rarity of the condition. The Reiter data on overall survival and the hazard ratios suggests the number of patients alive on standard of care is likely to be much less than that for midostaurin.
What is to most appropriate hazard ratio to estimate overall survival of the comparators? Is any of the hazard ratios in Reiter et al. appropriate? What is the clinically plausible range for this hazard ratio?	We believe the best available estimate comes from Reiter et al (2017). There are few other sources of data due to the rarity of the condition.
Is it appropriate to use the same hazard ratio for all comparators assuming similar effectiveness of comparators?	
Is it appropriate to use the same hazard ratio for the subgroups?	
Issue 6: Progression-free survival	
Is it appropriate to use the same hazard ratio for progression-free survival and overall survival?	
What is to most appropriate hazard ratio to estimate progression-free survival of the comparators? Is any of the hazard ratios in Reiter et al. appropriate? What is the clinically plausible range for this hazard ratio?	
Issue 7: Partitioning survival data	
Are partitioned health states appropriate?	

A. Is the company's approach (progression-free survival partitioned based on response rates and durations) methodologically and clinically appropriate. B. What is the impact on cost-effectiveness estimates if both overall survival and progression-free survival are partitioned, using data from D2201 stratified by response status? Are such stratified data available?	
Issue 8: Utility values	
What is the impact of using alternative mapping approaches on the resulting utility values and cost-effectiveness estimates?	
Is it appropriate to manually restrict utility values, potentially underestimating the overall parameter uncertainty?	
Issue 9: Duration of treatment effect	
Is it plausible that the effect of midostaurin on survival and progression, relative to current treatments, can be maintained for a person's lifetime while on treatment?	[redacted]
If not, how long would you expect midostaurin's treatment effect to last while on treatment? e.g. 5, 10, 15 years, or other.	

If discontinued, how long would you expect midostaurin's treatment effect to last? e.g. 5, 10, 15 years, or other.	ASM is a very rare illness and we are not aware of any additional data to add to what has already been published on this.
Issue 10: End of life	
In the overall population of people with advanced systemic mastocytosis, and in the 3 subgroups (ASM, SM-AHN and MCL): A. What is the life expectancy of a person with current treatments? B. Would you expect midostaurin to increase survival by at least 3 months?	As per our previous comments, the rarity of ASM makes further breakdowns of the data inappropriate for reasonable decision making. We believe the overall population meets the criteria for end of life. The data from Reiter et al (2017), as cited in the technical engagement papers, identified as the best matched data to the trials, find a median life expectancy for a mixed population of ASM and MCL +/-AHN untreated with midostaurin to be 19.5 months (95% CI 13.0 - 35.3). Reiter et al (2017) also found a 21.9 month overall survival benefit from midostaurin based on the two portions of the midostaurin trial D2201 and A2213.
Issue 11: Cancer Drugs Fund	
Would additional data collection within the Cancer Drugs Fund reduce the uncertainty?	Further data collection is unlikely to help with decision making, due to the rarity of the condition.

NICE National Institute for Health and Care Excellence

+-- Technical engagement response form

Midostaurin for treating advanced systemic mastocytosis [ID1573]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments **5pm** on **Wednesday 29 July 2020**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential

information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Professor Stephen O'Brien
National Institute for Health and Care Excellence
Level 1A City Tower
Manchester
M1 4BT

29th July 2020

Dear Professor O'Brien,

Midostaurin for treating advanced systemic mastocytosis (advanced SM) [ID1573] – Response to Technical Report

Thank you for the opportunity to review and respond to the key issues identified by the NICE Technical Report: our response has been provided to NICE. However, there are broader issues related to this appraisal, including process issues which are not acknowledged in the technical report. Furthermore, based on discussions during the NICE technical engagement call with NICE and the ERG, we are not convinced that these broader issues have been adequately considered when interpreting the evidence base. Novartis would like to work collaboratively with NICE and NHS England to secure patient access to midostaurin, including through a potential confidential agreement [redacted], which makes midostaurin cost-effective in the licensed population. The rest of this letter details broader issues that we would like the committee to take into consideration when interpreting the evidence.

Advanced SM is an ultra-rare and heterogeneous condition with a very limited evidence base. Nevertheless, the midostaurin trial (D2201) is the largest ever trial conducted in this patient population. On the other hand, there is a very limited evidence base for the comparator, where the existing evidence is weaker than the evidence provided by the trials of midostaurin. Midostaurin is the only licensed treatment for advanced SM and was initially available to UK NHS patients via a compassionate use program.

The current highly specialised technology (HST) process was specifically designed for the evaluation of technologies for rare diseases such as advanced SM, and it is able to take into consideration broader decision-making criteria in comparison to the conventional single technology appraisal (STA) process. Advanced SM would be expected to meet the HST criteria. However, we acknowledge NICE's decision outlined in the NICE scoping consultation response: that the topic does not meet the criteria for HST because midostaurin is also used to treat FLT3-positive acute myeloid leukaemia, and because advanced SM is not currently managed in a highly specialised service, even though treatment is concentrated in only a few centres.

Notwithstanding this, and as highlighted during the scoping consultation and in other meetings with NICE, there are major challenges associated with appraising an ultra-rare condition such as advanced

SM via the STA rather than the HST route. These challenges include the availability and quality of the evidence base, and the heterogeneity of the patient population. Of note is that the key uncertainties highlighted in the ERG report arise from these challenges. Based on the stakeholder responses to the draft scope, it appears that patient groups and the clinical community were similarly concerned that sufficient flexibilities would not be afforded to this ultra-rare disease if the appraisal was routed via an STA. We welcome NICE's undertaking (see scoping consultation response) to "*take into account the scarcity of the data in its decision making through the STA process"*. On this basis, we provided our evidence submission to NICE for review through the STA process, and would like to bring this undertaking to the attention of the committee. We note some similarities between this appraisal and NICE TA588 (nusinersen [Spinraza®] for treating spinal muscular atrophy), during which the committee was "*mindful during its decision making of the need to consider whether any adjustments to its normal considerations were needed to take into account the rarity and severity of the disease*".

One area that merits further consideration by the committee is how the routing of the appraisal via STA instead of HST has brought about a major process issue – end of life. An HST appraisal for an ultra-rare condition such as advanced SM, can apply a willingness to pay threshold of £100,000 to £300,000 per QALY, without factoring in end of life criteria. This raises an inequality if a rigid consideration of the end of life criteria is applied. Nevertheless, advanced SM is expected to meet the end of life criteria as evidenced in the company submission.

Finally, we would like to re-state our commitment to working with NICE and NHS England to secure early access to midostaurin: given the resource constraints created by the COVID-19 situation, our intention is to resolve issues in as few committee meetings as possible – ideally a single meeting. To that end, we have introduced [redacted] that makes midostaurin cost-effective at the £50,000 per QALY threshold [redacted]

Thank you for your time and please do not hesitate to contact me using the details below if you would like to discuss further

Yours sincerely,

Kevin Jameson

Head of Health Economics and Outcomes Research
[redacted]

CC Helen Knight
Jasdeep Hayre

Questions for engagement

Responses to the questions for engagement are provided below, and additional economic scenario analyses supporting our responses are presented in Appendix 1 at the end of the document.

Issue 1: Generalisability of trial results	
Is clinical practice in the trials generalisable to the NHS setting?	• In the D2201 trial, there were four patients enrolled across three centres in the UK (Glasgow, London & Liverpool).[1] In addition, as part of this submission, Novartis has sought feedback from five highly experienced clinicians from UK treatment centres, which is a substantial number in the context of a rare disease such as advanced systemic mastocytosis (advanced SM). Clinical expert feedback has confirmed that patients included in the pivotal D2201 trial are reflective of those treated in UK NHS practice. Novartis are pleased to see that clinical advice to NICE is in agreement with this position. • Clinical expert feedback has further confirmed that treatment practice in the pivotal D2201 trial is reflective of UK NHS practice and how midostaurin will be used. It should be noted that midostaurin was available in the UK NHS via a compassionate use programme and treatment practice in that setting was aligned with the D2201 trial. • The supportive A2213 trial includes patients with similar baseline characteristics to patients included in the pivotal D2201 trial.[1] As such, patients included in the A2213 trial are reflective of those treated in UK NHS practice and the A2213 trial provides valuable long-term data of the efficacy and safety of midostaurin. It should be noted that in the A2213 trial, treatment with midostaurin was stopped for patients who did not achieve a response after the first two treatment cycles.[1] Therefore, clinical practice in the supportive A2213 trial is less generalisable to the UK NHS setting. The economic analysis does not consider a stopping rule for midostaurin, and treatment is considered in the model as per the study D2201 protocol, and modelled as per the

<table>
<tr><td></td><td>expected use of midostaurin in clinical practice in the UK.</td></tr>
<tr><td>ERG comment</td><td>No comment</td></tr>
<tr><td colspan="2">Issue 2: Comparator treatment</td></tr>
<tr><td>Are AML-like treatments used in the NHS in England to treat mastocytosis?</td><td>• The inclusion of acute myeloid leukaemia (AML)-like treatments in the composite comparator for the treatment of advanced SM in the UK NHS was based on feedback from UK clinical experts with experience of managing patients with advanced SM.

• As part of this submission, Novartis has sought feedback from five clinicians from UK treatment centres, four of whom indicated that AML-like treatments form part of the treatment of advanced SM and should therefore be considered as relevant comparators. Page 11 of the ERG report confirms that clinical advice to the ERG supports this clinical advice provided to Novartis.</td></tr>
<tr><td>ERG comment</td><td>No comment</td></tr>
<tr><td>What are the most appropriate comparators in the UK? Please provide details of which are most used, e.g. treatment 1: 60% of people, treatment 2: 10% of people, and so on.</td><td>• The most appropriate comparators in the UK were determined based on feedback from five clinical experts with experience in the management of patients with advanced SM. Clinical experts each completed a questionnaire on the proportion of treatments received in the UK according to disease subgroup (aggressive SM [ASM], SM-AHN and MCL). The results (Table 1) were then pooled and used in the economic model associated with this submission.

Table 1: Treatment received in the UK used in the submission for the overall advanced SM population and the SM-AHN + MCL subgroup (excluding supportive care and clinical trial)
<table>
<tr><th>Comparator</th><th>Proportion used in the UK (overall advanced SM population)</th><th>Proportion used in the UK (SM-AHN + MCL)</th></tr>
<tr><td>Cladribine</td><td>53.65%</td><td>52.12%</td></tr>
</table>
</td></tr>
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<table>
<tr><td></td><td>
<table>
<tr><td>Interferon alpha</td><td>2.05%</td><td>1.53%</td></tr>
<tr><td>Peg-interferon alpha</td><td>24.23%</td><td>23.74%</td></tr>
<tr><td>Imatinib</td><td>4.50%</td><td>3.64%</td></tr>
<tr><td>Dasatinib</td><td>-</td><td>-</td></tr>
<tr><td>Nilotinib</td><td>-</td><td>-</td></tr>
<tr><td>AML-like treatment (azacitidine)</td><td>7.53%</td><td>9.19%</td></tr>
<tr><td>AML-like treatment (other)</td><td>8.03%</td><td>9.78%</td></tr>
</table>
Abbreviations: Advanced SM: advanced systemic mastocytosis; AML: acute myeloid leukaemia; ASM: aggressive systemic mastocytosis; MCL: mast cell leukaemia; peg-interferon alpha: pegylated interferon alpha; SM-AHN: systemic mastocytosis with associated haematologic neoplasm.
</td></tr>
<tr><td>ERG comment</td><td>No comment</td></tr>
<tr><td>Is it appropriate to have a composite comparator?</td><td>

At present, there are no therapies other than midostaurin licensed for the treatment of advanced SM in the UK. There is no established treatment pathway for advanced SM in the UK and there are currently no UK-specific clinical guidelines. Therefore, patients with advanced SM are likely to receive a mix of treatments, as evidenced by clinical expert feedback (Table 1). Note that these treatments are all off-licence with very little, if any evidence of efficacy or safety.
In this context, a composite comparator was judged to be adequate for capturing the complexity of current treatment practice.
Nonetheless, whilst a composite comparator has been used in the base case economic analysis associated with this submission, the economic model has the functionality for each individual treatment to be assessed separately and scenario analyses where midostaurin was compared to each individual treatment were presented in the Company submission. It should be noted that assessment of each individual treatment separately results in incremental cost-effectiveness

</td></tr>
</table>

	ratios (ICERs) which do not differ substantially to that presented in the base case analysis of the economic model.
ERG comment	No comment
Issue 3: Subgroups	
Are the 3 subgroups, aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated haematological neoplasm (SM-AHN) and mast cell leukaemia (MCL), distinguishable in clinical practice?	• Advanced SM is a highly heterogeneous disease. As there is no clear standard therapy, treatments are considered on an individual basis for each patient from a pool of treatment options which are broadly similar across the three subgroups (ASM, SM-AHN and MCL).[2, 3]
ERG comment	No comment
Are people in the 3 subgroups offered different treatment options in the NHS in England? For each subgroup please provide details of which are most used, e.g. treatment 1: 60% of people, treatment 2: 10% of people, and so on.	• Feedback from clinical experts with experience in the management of patients with advanced SM has indicated that patients in the three subgroups of advanced SM (ASM, SM-AHN and MCL) are offered broadly similar treatment options in the UK NHS, with treatments utilised in different proportions within each subgroup (Table 1). • This has been reflected in the economic model associated with this submission and utilisation of each treatment has further been weighted according to the proportion of patients in each of the three subgroups.
ERG comment	No comment
Is it appropriate to combine people with SM-AHN and people with MCL in 1 subgroup?	• The cost-effectiveness of midostaurin was assessed in the overall population of patients with advanced SM (ASM, SM-AHN and MCL) and in a subgroup of patients with SM-AHN or MCL

	only (SM-AHN + MCL). As discussed in the main body of the submission, patients with SM-AHN or MCL have a lower life expectancy and a greater unmet need, compared to patients with ASM. • In this context, it should be noted that advanced SM is a rare disease and, within the overall disease population, MCL is the subtype with the lowest prevalence.[4] Consequently, it was not possible to conduct a separate cost-effectiveness analysis for patients with MCL due to the very small sample size of patients included in the pivotal D2201 trial of midostaurin (n=16).[5] However, pooling the two subgroups together (SM-AHN + MCL) was considered reasonable by clinical experts on the basis of the shorter life expectancy and greater unmet need of patients in these subgroups. • Although the ASM subgroup has a relatively better prognosis compared to SM-AHN and MCL, patients with ASM still face a high unmet need, with no licensed treatment. Thus, patients would benefit from access to midostaurin in the full licensed population (ASM, SM-AHN and MCL).
ERG comment	The ERG recognises that data for patients with advanced SM (overall and subgroups) are limited.
Issue 4: Comparative effectiveness data sources	
Is clinical practice for managing masotcytosis in France and Germany comparable to clinical practice in the NHS in England?	• Treatment centres from France (n=1 and 0.6% of centres included in the study) and Germany (n=64 and 36.2% of centres included in the study) were included in the pivotal D2201 trial,[1] which is considered reflective of UK NHS clinical practice, as confirmed by clinical expert feedback discussed under Issue 1 of this document. Furthermore, clinical advice to the ERG has indicated that the management of patients with advanced SM in Europe is comparable to the management of patients with advanced SM in the UK NHS. Therefore, it is probable that clinical practice for managing advanced SM in France and Germany is comparable to clinical practice in the UK NHS.

ERG comment	No comment
Is it appropriate to assume that outcomes from the studies in Germany and France are comparable to the NHS in England?	• Yes, it is appropriate to assume that outcomes from the studies in Germany and France are comparable to the NHS in England. UK clinical experts have advised that overall response rate (ORR) (the primary outcome in the D2201 trial and subsequently used in the French – CEREMAST[6, 7] and German – Reiter *et al.* 2017[8] studies) aligns with UK NHS practice.[1]
ERG comment	No comment
Is it appropriate to combine results from D2201 and A2213, as done in Reiter et al.?	• The Reiter *et al.* (2017)[8] study reports on a pooled analysis of the D2201 trial and the A2213 trial compared with historical control data from a German registry. As discussed in the main body of the submission, there are some differences between the pivotal D2201 trial and the supportive A2213 trial, namely in eligibility criteria, duration and stopping of treatment, adjudication of response, study design and endpoint definition.[1] Nonetheless, the A2213 trial had a longer follow-up and could be considered conservative, as patients had to stop treatment if they had not demonstrated a response within the first 2 treatment cycles. Data from the A2213 trial provides valuable long-term evidence of the efficacy and safety of midostaurin and allows for an increase in sample size, when pooled together with data from the D2201 trial. Consequently, it was considered appropriate to combine results across the D2201 trial and the A2213 trial, as done by Reiter *et al.* (2017).[8] • Following the ERG's request, the latest data from the D2201 trial (final analysis of OS and safety data cut-off: 24th August 2017) has now been compared separately to the German historical control and the results are comparable to the pooled (D2201 and A2213) study results (Table 2). • The updated economic model includes the option to run these scenarios and the results are presented in Appendix 1. **Table 2: Summary of updated results from the historical OS comparison study**

	Analysis / **Results** (Latest data from D2201 only versus German registry; Pooled latest data from D2201 and A2213 versus German registry)

Analysis	Latest data from D2201 only versus German registry		Pooled latest data from D2201 and A2213 versus German registry	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Primary (from date of diagnosis), unadjusted comparisons	[redacted]	[redacted]	[redacted]	[redacted]
Sensitivity analysis (from start date of last treatment), unadjusted comparisons	[redacted]	[redacted]	[redacted]	[redacted]
Primary (from date of diagnosis), multivariate adjustment	[redacted]	[redacted]	[redacted]	[redacted]
Sensitivity analysis (from start date of last treatment), multivariate adjustment	[redacted]	[redacted]	[redacted]	[redacted]

Data cut-offs: D2201: 24th August 2017; A2213: 1st July 2016; German registry: 9th May 2017.
Abbreviations: CI: confidence interval; HR: hazard ratio.

ERG comment	Thank you for providing updated results. The ERG acknowledges that the results of the separate analysis of the latest data from D2201 trial only versus German registry data are comparable to the results of the pooled latest data from D2201 and A2213 versus German registry data.
Issue 5: Overall survival	
How many people would you expect to be still alive at 5, 10 and 15 years on midostaurin? At 15 years, is 5% to 10% an appropriate estimate?	• It should be noted that the median follow-up in the D2201 trial was [redacted] months as of the 24th August 2017 data cut-off, not 26 months, as listed in the Technical report. Novartis would therefore like to raise this as a factual inaccuracy for the attention of NICE. • The D2201 and A2213 trials provide direct evidence of OS at median [redacted] months ([redacted] years) and median 124 months (10.3 years) respectively – see Table 3 below (*nb – for D2201, the number of patients known to be alive at [redacted] years was [redacted] as explained in the footnote to the table*).

- OS extrapolations as presented in the submission were:

  (a) In line with the 5- and 10-year evidence from the D2201 and A2213 trials and

  (b) Validated by five UK clinical experts with experience of managing patients with advanced SM.

- In conclusion, an OS of 5% to 10% at 15 years can be considered an appropriate estimate for the overall advanced SM population.

Table 3: Summary of OS results based on the latest data cuts of the D2201 and A2213 trials

Population	Number of patients alive, n (%)	Median OS, months (95% CI)	Survival rate (95% CI)	
			3 years	5 years
D2201 trial (data cut-off: 24th August 2017, median duration of follow-up 76 months [range 62 to 103 months])				
PEP (n=89)	[redacted]	[redacted]	[redacted]	[redacted]
FAS (n=116)	[redacted]	[redacted]	[redacted]	[redacted]
A2213 trial (data cut-off: 1st March 2017, median duration of follow-up 124 months [range 82 to 140 months])				
PEP (n=26)[c]	4 (15%)	40.0 (27.3 to 52.7)	Not reported	Not reported

[a] [redacted] patients were known to be alive (ongoing without event), an additional [redacted] patients ([redacted]) were lost to follow-up early in the trial and an additional [redacted] patients ([redacted]) were lost to follow-up but known to be alive in the 5 months before data cut-off
[b] [redacted] patients were known to be alive (ongoing without event), an additional [redacted] patients ([redacted]) were lost to follow-up early in the trial and an additional [redacted] patients ([redacted]) were lost to follow-up but known to be alive in the 5 months before data cut-off
[c] The PEP and the FAS were equivalent in the A2213 trial
Abbreviations: CI: confidence interval; FAS: full analysis set; NE: not estimated; OS: overall survival; PEP: primary efficacy population.

ERG comment	No comment
How many people would you expect to be still alive at 5, 10, and 15 years on standard of care?	• Please see response above
ERG comment	No comment
What is the most appropriate hazard ratio to estimate overall survival of the comparators? Is any of the hazard ratios in Reiter et al. appropriate? What is the clinically plausible range for this hazard ratio?	• The most appropriate hazard ratio (HR) to estimate OS for the comparators was selected on the basis of UK expert clinical feedback. Clinical experts consulted by Novartis considered the HR from the multivariate analysis from the Reiter *et al. (*2017)[8] study to be most appropriate in terms of the predictions generated for the comparator arm, as well as the nature of the analysis, which was judged to be more methodologically robust and allowed for the maximum evidence available to be used, as opposed to results from the propensity score matched analysis which excluded 2/3 of patients. It should be noted that this assessment is in agreement with feedback from the ERG.
ERG comment	No comment
Is it appropriate to use the same hazard ratio for all comparators assuming similar effectiveness of comparators?	• Advanced SM is a rare disease with a limited evidence base. The D2201 trial, which provides evidence of the effectiveness of midostaurin, is the largest and most robust trial conducted in the disease area.[5] However, evidence of the effectiveness of each comparator is very limited and of low quality. In the absence of alternative evidence, clinical experts judged it appropriate to assume similar effectiveness and use the same HR for all comparators across both the overall advanced SM population and the SM-AHN + MCL subgroup.
ERG comment	No comment

Is it appropriate to use the same hazard ratio for the subgroups?	• Advanced SM is a rare disease, and the prevalence of SM-AHN and MCL is particularly low.[4] As a result, evidence for each disease subgroup (ASM, SM-AHN and MCL) is very limited and based on a small number of patients. In this context, clinical experts indicated that sample sizes were too small to meaningfully argue a difference between subgroups and that it was appropriate to use the same HR for all disease subgroups (ASM, SM-AHN and MCL).
ERG comment	No comment
Issue 6: Progression-free survival	
Is it appropriate to use the same hazard ratio for progression-free survival and overall survival?	• In the absence of alternative data, it was not possible to model PFS in any other way, and therefore the same HR for PFS and OS was assumed. This approach was presented to clinical experts and they agreed that it would be appropriate in the absence of PFS evidence. • Novartis acknowledge the uncertainty around this approach. However, as described in the ERG report, the results of the sensitivity analyses around the PFS HR undertaken by Novartis suggested that, even if the PFS HR was five times higher than had been assumed in the base case analysis, it would only reduce the ICER per QALY gained for the comparison of midostaurin versus current clinical management by 3.6%. • As such, it is likely that even if the true PFS HR could be known, it would not make a material impact to the cost-effectiveness analysis results.
ERG comment	No comment
What is the most appropriate hazard ratio to estimate progression-free survival of the comparators? Is any of the hazard ratios in Reiter et	• As indicated above, in the absence of alternative data, it was not possible to model PFS in any other way, and therefore Novartis consider that the assumption of using the same HR for PFS and OS for current clinical management is the most appropriate approach.

al. appropriate? What is the clinically plausible range for this hazard ratio?	
ERG comment	No comment
Issue 7: Partitioning survival data	
Are partitioned health states appropriate? A. Is the company's approach (progression-free survival partitioned based on response rates and durations) methodologically and clinically appropriate. B. What is the impact on cost-effectiveness estimates if both overall survival and progression-free survival are partitioned, using data from D2201 stratified by response status? Are such stratified data available?	• In response to the ERG's concern with partitioning the PFS state based on response rates and durations, Novartis has now submitted a revised model with the flexibility to run the results based on a standard three state partitioned survival. The results are presented in Appendix 1 and demonstrate that the impact of removing partitioning is minimal, and results in a small (2%) increase from a base case ICER (with potential confidential agreement) of £44,878 • Please note that that we have used a regression model for utility (fitted to the D2201 trial) to calculate the PFS health state utility. The ERG conducted an analysis whereby the same utility value was assumed for the responder and non-responder health states, with the average utility value taken for both health states. Novartis do not consider this approach to be methodologically appropriate, but recognise that this was done as the ERG did not have access to the individual patient-level data from the midostaurin trials and could therefore not re-run the regression model to pool the PFS health state. • A summary of the rationale for our initial approach is provided below. Whilst we believe the analysis to be appropriate, we acknowledge that there is uncertainty due to the very limited evidence base for this rare disease. **Summary of the rationale for partitioning the PFS state based on response rates** Response status was a primary endpoint in both the D2201 and A2213 trials and treatments for advanced SM are likely to be associated with different response rates. As such, Novartis decided to partition the PFS health state of the economic model to account for the differences in utility values between treatment responders and non-responders.

	Typically, a simple approach can be taken by weighting the utility value based on response rates for each treatment. However, this approach does not account for differences in duration of response. Novartis acknowledge that, given a distinct paucity of data on response rates and duration of response, estimates for these values may introduce uncertainty. However, similarly, assuming the same utility value for the PFS health state for midostaurin and current clinical management is considered to be a very conservative approach, given the distinct differences in mechanisms of action of midostaurin versus the treatments comprising current clinical management. It is important to note that midostaurin is a disease modifying therapy and therefore improves symptoms relative to standard of care. There is no evidence to suggest that response rates may be used as a surrogate for OS or PFS, therefore response rates were not linked in the model to either PFS or OS, but only used to estimate quality of life. Partitioning of OS would imply building a response-based model which would not be appropriate as it would rely on (i) particularly uncertain parameters (response rates) as acknowledged by the ERG but also (ii) the strong assumption that response rates may be used as a surrogate for OS.
ERG comment	The ERG conducted an analysis whereby the same utility value was assumed for the responder and non-responder health states, with the average utility value taken for both health states; as stated by the company, this was done as the ERG did not have access to the individual patient-level data from the midostaurin trials and could therefore not re-run the regression model to pool the PFS health state.
Issue 8: Utility values	

What is the impact of using alternative mapping approaches on the resulting utility values and cost-effectiveness estimates?	• Several alternative mapping algorithms were explored by Novartis when developing the Company Submission: Franks *et al.* (2003);[9] Franks *et al.* (2004);[10] Lawrence *et al.* (2004);[11] Gray *et al.* (2006),[12] and it was found that utility predictions were relatively similar between mapping algorithms. Consequently, in the base case, response mapping (using the physical health component summary scale [PCS] and mental health component summary scale [MCS] dimensions) using the Gray *et al.* (2006)[12] algorithm was selected as this was the most recent of these four algorithms, and the alternative mapping algorithms were explored in scenario analyses. • The Company Submission presents several scenario analyses using the alternative linear model mapping algorithms and the results of these scenario analyses demonstrate that the choice of mapping algorithm had a negligible impact on the ICER.
ERG comment	No comment
Is it appropriate to manually restrict utility values, potentially underestimating the overall parameter uncertainty?	• A constraint was applied in the economic model to ensure that pre-progression utility values were higher than post-progression utility values in the partitioned survival model as would be expected based on the course of the disease. Not applying such a constraint may have resulted in utility values that lacked face validity, thus Novartis believe this restriction is appropriate. Nevertheless, the constraint has now been removed and there is no impact on the ICER
ERG comment	No comment
Issue 9: Duration of treatment effect	
Is it plausible that the effect of midostaurin on survival and progression, relative to current treatments, can be maintained for a person's lifetime while on treatment?	• Midostaurin is a disease modifying therapy and therefore the length of treatment may not necessarily explain the duration over which the treatment effect should apply, and it is plausible that the treatment effect of midostaurin would continue beyond treatment discontinuation. Please note that, as described in the company submission, the treatment effect (the multivariate HR

	derived from the historical control comparison) is applied to the midostaurin curve to estimate outcomes for current clinical management. • Novartis acknowledge the uncertainty in long-term survival estimates and have therefore conducted additional scenario analyses in response to this question with different assumptions regarding the time point for equalising progression and mortality events for midostaurin versus the composite comparator. The results of these analyses are presented in Appendix 1.
ERG comment	No comment
If not, how long would you expect midostaurin's treatment effect to last while on treatment? e.g. 5, 10, 15 years, or other.	• Please refer to the response to Issue 5. Evidence from D2201 ([redacted] months follow-up)[13] and A2213 (124 months follow-up)[14] suggest that patients treated with midostaurin have a long duration of survival. Therefore, the time point for equalising progression and mortality events for midostaurin versus the composite comparator should be at least 10 years.
ERG comment	No comment
If discontinued, how long would you expect midostaurin's treatment effect to last? e.g. 5, 10, 15 years, or other.	• Feedback from clinical experts advised that only a small minority of patients would remain alive after 5 years using current clinical management, and therefore we believe that it is not appropriate to assume the treatment effect of midostaurin wanes before at least 10 years when looking at the tail generated for the comparator arm.
ERG comment	No comment
Issue 10: End of life	

In the overall population of people with advanced systemic mastocytosis, and in the 3 subgroups (ASM, SM-AHN and MCL): A. What is the life expectancy of a person with current treatments? B. Would you expect midostaurin to increase survival by at least 3 months?	**A. What is the life expectancy of a person with current treatments?** • The life expectancy of patients with advanced SM on current clinical management is less than 2 years as evidenced by: a. The Reiter *et al.* (2017) publication, which reports the median survival from diagnosis in a contemporary German registry of patients with advanced SM similar to those enrolled in D2201 and A2213 (patients with ASM or MCL ± AHN), who had not been treated with midostaurin (n=42) to be 19.5 months (95% CI 13.0–35.3).[8] b. The Company economic model, which predicted mean undiscounted life years of 1.90 for the overall advanced SM population and 1.46 for the subgroup of patients with SM-AHN + MCL c. Clinical experts advised that in a world without midostaurin, patients with advanced SM would normally have a life expectancy of less than 2 years • It is acknowledged that there is a wide range of published median survival estimates for patients with advanced SM. This is reflective of the heterogeneity of SM disease, and how non-advanced (e.g. indolent SM-AHN [ISM-AHN]) and advanced subtypes have frequently been analysed together in the literature.[15] For example, some published estimates of survival for patients with SM-AHN report a median survival of 24 months, but these studies included patients with ISM-AHN for whom survival is significantly longer, and therefore these studies are not reflective of the population considered in this appraisal (or the marketing authorisation for midostaurin).[16, 17] Estimates of survival are further complicated by the availability of midostaurin for advanced SM since September 2017. Importantly, this creates challenges when requesting clinicians to estimate the life expectancy of patients with advanced SM. • The only published evidence for the survival of patients with SM-AHN (advanced) is from Reiter *et al.* (2017)[8] and therefore Novartis consider that the survival estimates from Reiter *et al.* (2017)[8] should be considered first and foremost by NICE in their considerations of midostaurin as an end-of-life treatment. As stated above these data are supported by the estimates from the Company

	economic model and feedback from UK clinical experts. • The above considerations should also be made in the context of a typical highly specialised technology (HST) appraisal for an ultra-rare condition such as advanced SM, which can apply a willingness-to-pay threshold of £100,000 to £300,000 per QALY gained, *without factoring end-of-life criteria*. **B: Would you expect midostaurin to increase survival by at least 3 months?** • There are no direct comparisons between midostaurin and current clinical management; however, Reiter *et al.* (2017)[8] demonstrated a survival benefit of 21.9 months for patients treated with midostaurin (median OS 41.4 months) in the pooled analysis of D2201 and A2213 compared with current clinical management (median OS 19.5 months) observed in a German cohort which included similar patients. • Consequently, there is sufficient evidence to indicate that midostaurin offers an extension of life of at least an additional 3 months compared with current NHS treatment. This is further supported by the economic model, where the incremental life years gained (LYG) predicted by the model for midostaurin compared with current management was estimated to be **** and **** for the overall population and SM-AHN + MCL subgroup respectively, an increment that is considerably greater than 3 months.
ERG comment	No comment
Issue 11: Cancer Drugs Fund	
Would additional data collection within the Cancer Drugs Fund reduce the uncertainty?	• No further data cuts are planned for the D2201 and A2213 trials. The data from both trials already presented as part of the Company Submission represent 6 years of follow-up for D2201[13] and 10 years of follow-up for A2213,[14] the longest available follow-up time for any advanced SM trials.

	• Moreover, the rarity of the advanced SM means that,[4] even if further data were able to be collected, limited data would be available in 2 years on the CDF and therefore it would not be likely to resolve any uncertainty.
ERG comment	No comment

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Appendix 1: Additional economic analyses

Additional economic analyses have been conducted to explore the following:

Alternative HRs

1. HR based on pooled data using the latest D2201 data (latest D2201 + latest A2213 vs Historical control) – multivariate
2. HR based on pooled data using the latest D2201 data alone vs Historical control – multivariate

Alternative treatment effect assumptions

3. Treatment effect of midostaurin assumed to continue for 10 years (equal progression/mortality rates between midostaurin and current clinical management at 10 years)
4. Treatment effect of midostaurin assumed to continue for 5 years (equal progression/mortality rates between midostaurin and current clinical management at 5 years)
5. Treatment effect of midostaurin assumed to continue for 3 years (equal progression/mortality rates between midostaurin and current clinical management at 3 years)

Alternative model structure assumption

6. Removal of partitioning of progression-free state based on response (ERG approach)
7. Removal of partitioning of progression-free state based on response (regression)

Results are presented below for advanced SM (both including the **current PAS** for midostaurin as well as the potential confidential agreement [redacted]), which makes midostaurin cost-effective in the full licensed population

Additional economic analyses	
ERG comment	Using the TE model, the ERG has checked that the results of the new economic analyses (deterministic and PSA) presented in Appendix 1 are accurate.

Table 4: Results of alternative economic analyses (overall advanced SM population)

SM-AHN + MCL	Current PAS			Potential Confidential Agreement		
	Incremental Cost	Incremental QALY	ICER	Incremental Cost	Incremental QALY	ICER
Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£44,878
1. HR (pooled) - updated D2201* data - multivariate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£45,884
2. HR D2201 only - updated D2201* data - multivariate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£47,781
3. Treatment effect of midostaurin: 10 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£45,476
4. Treatment effect of midostaurin: 5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£48,048
5. Treatment effect of midostaurin: 3 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£51,775
6. Removal of progression-free state partition based on response (ERG approach)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£47,463
7. Removal of progression-free state partition based on response (New regression)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£45,851

Abbreviations: ERG: Evidence review group; HR: hazard ratio. * D2201 trial (data cut-off: 24th August 2017, median duration of follow-up 76 months [range 62 to 103 months])

Table 5: PSA results - overall advanced SM population (midostaurin at potential confidential agreement)

Technologies	Costs (£)	QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Probability of cost-effectiveness at £30,000 per QALY	Probability of cost-effectiveness at £50,000 per QALY
Current clinical management	[redacted]	[redacted]	-	-	-		-
Midostaurin	[redacted]	[redacted]	[redacted]	[redacted]	£47,743	[redacted]	[redacted]

Note: all results presented are discounted unless otherwise stated.
Abbreviations: ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years; PSA: probabilistic sensitivity analysis

Figure 1: PSA cost-effectiveness plane – overall advanced SM population (midostaurin at potential confidential agreement)

Figure 2: PSA cost-effectiveness acceptability curve – overall advanced SM population (midostaurin at potential confidential agreement)

[redacted]

Table 6: Results of alternative economic analyses (SM-AHN + MCL)

SM-AHN + MCL	Current PAS			Potential Confidential Agreement		
	Incremental Cost	Incremental QALY	ICER	Incremental Cost	Incremental QALY	ICER
Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£47,312
8. HR (pooled) - updated D2201* data - multivariate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£48,320
9. HR D2201 only - updated D2201* data - multivariate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£50,225
10. Treatment effect of midostaurin: 10 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£47,565
11. Treatment effect of midostaurin: 5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£49,103
12. Treatment effect of midostaurin: 3 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£51,861
13. Removal of progression-free state partition based on response (ERG approach)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£49,706
14. Removal of progression-free state partition based on response (New regression)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£48,061

Abbreviations: ERG: Evidence review group; HR: hazard ratio. * D2201 trial (data cut-off: 24th August 2017, median duration of follow-up 76 months [range 62 to 103 months])

Table 7: PSA results - SM-AHN + MCL (midostaurin at potential confidential agreement)

Technologies	Costs (£)	QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Probability of cost-effectiveness at £30,000 per QALY	Probability of cost-effectiveness at £50,000 per QALY
Current clinical management	[redacted]	[redacted]	-	-	-		-
Midostaurin	[redacted]	[redacted]	[redacted]	[redacted]	£49,540	[redacted]	[redacted]

Note: all results presented are discounted unless otherwise stated.
Abbreviations: ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years; PSA: probabilistic sensitivity analysis;

Figure 3: PSA cost-effectiveness plane – SM-AHN + MCL (midostaurin at potential confidential agreement)

Figure 4: PSA cost-effectiveness acceptability curve – SM-AHN + MCL (midostaurin at potential confidential agreement)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Midostaurin for treating advanced systemic mastocytosis [ID1573]

Clarification questions

March 2020

File name	Version	Contains confidential information	Date
ID1573 Midostaurin Clarification Questions	FINAL	Yes	17th April 2020

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

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Please consider all highlighted information within this response documents and associated attachments as confidential with academic in confidence highlighted in yellow and commercially confidential information highlighted in turquoise.

Section A: Clarification on effectiveness data

Historical control data

A1. Priority question: Please provide, where available, additional information on the statistical methodology employed within the pooled survival analysis of Reiter *et al* 2017 and the analyses of the CEREMAST study group (Chandesris *et al* 2016; Chandesris *et al* 2017). Ideally, please provide protocols or statistical analysis plans for these analyses or alternatively please provide additional details of:

- **Method used for propensity score matching in Reiter *et al* 2017.**
- **Method(s) used to conduct survival analyses, details of censoring and justification of any assumptions (e.g. exploration of proportional hazards assumption for a Cox proportional hazard model) in the analyses described in both Reiter *et al* 2017 and Chandesris *et al* 2017.**

- **Further details and numerical results (e.g. hazard ratios and 95% confidence intervals) of multivariate analyses conducted in Chandesris *et al* 2017.**

- **Statistical hypotheses which have resulted in the reporting of one-sided p-values in Reiter *et al* 2017.**

- **Within Reiter *et al* 2017, where the pooled midostaurin data and German registry study data have different cut-off dates (1st July 2016 and 9th May 2017 respectively), do the methods employed and therefore the reported hazard ratios reflect the difference in cut-off dates?**

- **Details of other treatments received, including 'last treatments received for advanced SM' for patients in both the pooled midostaurin dataset and in the German registry study dataset.**

- **Any additional information regarding the German registry study and/or patients within this study referred to in the study by Reiter *et al* 2017.**

Please note the following responses in relation to the above requests:

- Chandesris *et al.* 2017, from the CEREMAST group, is a comparison of a prospective observational survey of 28 patients with mastocytosis treated with midostaurin in France with 44 historical controls. As such, Novartis only has access to the data in the public domain for this study and does not have access to any study protocols or statistical analysis plans.
- Reiter *et al.* 2017 is a pooled analysis of midostaurin in D2201 and A2213 compared with historical control data from a German registry. Please find enclosed the statistical analysis plan for this analysis, with further details on the methodology of this analysis (refer to attachment 'SAP_Historical_Comparison _EHA analyses'). Where possible, we have provided further clarification on the requests where details are available. We are continuing to work with our internal statistical teams to provide information on the outstanding points.
    - The different data cut-off dates for the pooled analysis of D2201 and A2213 (1st July 2016) and the registry data (9th May 2017) in the Reiter *et al*. 2017 analysis reflect the latest data available from the different sources at the time of the analysis. It should be noted that the same methodology was used for both the clinical trial and registry data in the analysis.
    - The statistical hypotheses which resulted in the reporting of one-sided p-values in Reiter *et al.* 2017 were as follows:

Ho: HR ≥ 1
Ha: HR < 1

Where HR = exp (-D) with D = loghmidostaurin – loghregistry

The midostaurin pooled overall survival (OS) will be compared to the German registry OS by providing one-sided p-value, hazard ratio (HR) and its associated 95% confidence interval coming from the un-pooled Z-test comparing the two estimated distributions of log(h) as follows:
Pvalue = 1 – FNormal(0,1)(T)
HR = exp (-D)
Lower 95%CI boundary = exp (-D - z2.5*S)
Upper 95%CI boundary = exp (-D + z2.5*S)

D2201 trial

A2. Please provide the primary clinical study report (CSR) for the D2201 trial (data cut-off 01-Dec-2014, dated 28-Jun-2016).

Please find enclosed the primary CSR for the D2201 trial dated 28-Jun-2016 (attachment "PKC412D2201_CSR_2016_01Dec14 data cut"). Please note that although some of the data from the CSR are in the public domain (e.g. the European Public Assessment Report of midostaurin), some data remain unpublished and therefore should be considered confidential. Whilst we are confident that all relevant data from the CSR have been presented within the submission with the confidentiality status marked appropriately, caution should be taken if additional information is to be considered.

A3. Protocol amendment 2 (23-Nov-2010) of the D2201 trial was issued [redacted] (D2201 CSR 2018, Section 9.8.1).

Please clarify whether the 27 patients excluded from the full analysis set (n=116) due to non-measurable C-findings had been enrolled into Stage I of the study, prior to this protocol amendment?

[redacted] patients were enrolled in Stage I of D2201 (D2201 CSR 2018, Section 9.7.9) [redacted]

[redacted] (D2201 CSR 2018, Section 9.8.1). The remaining [redacted] patients were determined to be eligible by the SSC and adjudicated for best overall response by the SSC at the end of Stage I (D2201 CSR 2018, Section 9.7.9).

Consequently, [redacted] of the patients enrolled prior to protocol amendment 2 (23rd November 2010) who were excluded from the full analysis set, [redacted] were originally enrolled at Stage I and [redacted] were enrolled in the extension phase.

A4. Please clarify why median overall survival (OS) was 'not estimated' for patients with ASM disease subtype at the latest data cut-off date of 24th August 2017 (CS, p67) yet it was reported that median OS was 51.1 months in this subgroup at the data cut-off date of 1st December 2014 (CS, Table 19).

This discrepancy can be explained by the number of censored/events and number of patients at risk at the time of the different data cut-off dates of 1st December 2014 and 24th August 2017.

At the data cut-off date of 1st December 2014, only 2 patients remained at risk after month 44, with one event occurring at month 51.1, leading to a sharp drop in the OS Kaplan-Meier curve where the median OS was reached (European Public Assessment Report of Midostaurin, Figure 21). In contrast, at the time of the final analysis, which included a longer follow-up (data cut-off date of 24th August 2017), patients who were censored in the earlier analysis due to early study termination had updated survival data available. As a result, 10 patients were at risk at month 44 (Figure 23 in CS), with only 2 patients experiencing an event and the remaining 8 patients censored after month 60.

Given that more patients were at risk after month 50 in the data cut-off of 24th August 2017, the last event observed in the early cut-off date (at month 51.1) was no longer associated with this sharp drop in survival.

A5. It is stated in Table 9 on p35 of the CS that the D2201 trial excluded patients with "Previous treatments for mastocytosis ≥3". Could you please confirm the nature of these previous treatments (i.e. other cytoreductive therapies), and how many patients were excluded from the trial based on this criterion?

Patients who had demonstrated relapse to three or more prior regimens for mastocytosis were excluded from the trial regardless of treatment regimen for supportive care. Also, as per the protocol "Patients with an associated hematologic neoplasm requiring immediate cytoreductive therapy or targeted drugs, and patients who received SM treatment within 30 days of study start were excluded.".

Unfortunately, we cannot confirm the number of patients that were excluded from the trial on the basis of more than three prior treatments or the breakdown of these prior treatments for excluded patients, as this analysis was not performed.

A6. The D2201 trial included patients with the subtype SM-AHN (CS, Table 10). This subgroup of patients can range from high to low risk depending on the nature of the

associated neoplasm. Could you please clarify if these patients were high risk, low risk or mixed risk SM-AHN patients, and in what proportion?

A study of the individual breakdown of prognostic value in SM-AHN subsets has been previously described (Pardanani *et al*. 2009). However, this is not comparable in D2201, as patients presenting with an AHN were eligible to enter the study only if the AHN portion of the disease was not life-threatening or in an acute stage. As per the study exclusions, in cases where the AHN component was life-threatening or in an acute stage, the patient was to be treated for this disorder (AHN) first, before being considered for entry into the study.

Overall, 83 patients diagnosed with SM-AHN were enrolled in D2201 (full analysis set) (Gotlib *et al.* 2016, Table S6). The types of AHN that these 83 patients had are presented in Table 1 (and Table 11.3 primary CSR 2016) and there were no further assigned risk stratifications based on the AHN subtype in analysis.

Table 1: Subtypes of AHN in patients enrolled in D2201

Disease subtype, n (%)	FAS (n=116)	PEP (n=89)
AHN	**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)

Abbreviations: AHN: associated haematological neoplasm; CEL: chronic eosinophilic leukaemia; CMML: chronic myelomonocytic leukaemia; FAS: full analysis set; MDS: myelodysplastic syndrome; MDS/MPN-U: myelodysplastic/myeloproliferative neoplasm-unclassifiable; PEP: primary efficacy population.
Source: Gotlib *et al.* 2016.

A2213 trial

A7. It is stated on p34 of the CS that the A2213 trial is 'investigator-initiated' and therefore '…since this study is not a Novartis-sponsored trial, it should be noted that the only data available to Novartis are those in the public domain.'

Please therefore clarify:

- The source of the protocol for the A2213 study, which is listed as reference 78 of the CS 'Novartis Pharmaceuticals. A2213 Clinical Trial Protocol. 2004.'

- The source of trial methodology for the A2213 study which the ERG cannot find in either the DeAngelo *et al* (2018) publication, the ClinicalTrials.gov record, the A2213 clinical trial protocol, the European Public Assessment Report of midostaurin or the Australian Public Assessment Report of midostaurin.

    - The source of the pre-planned subgroups (CS, Table 9).

- Duration of study and follow-up: study completion date of 29th December 2017 (CS, Table 9).

The source of the protocol for A2213 was a typographical error and should be revised to: "A2213 Clinical Trial Protocol. 2004" to reflect that Novartis is not the study sponsor and thus that the protocol differs from the D2201 protocol.

The subgroup analyses of A2213 as reported in Table 9 and Section B.2.7.2 of our company submission were derived from DeAngelo *et al.* 2018.

Further follow-up by Novartis with A2213 study site staff confirmed that the last patient last visit occurred on 29th December 2017 and this date was therefore used as the study completion date in our company submission. Further to this, the supporting reference should be revised to "Novartis Pharmaceuticals. Data on File. 2020."

Clinical evidence for comparators

A8. Please clarify how the judgements of 'good quality,' 'reasonable quality', 'relatively poor quality' and 'poor quality' described in Table 26 of the CS and Table D.11.2 of Appendix D to the CS for the D2201 and A2213 trials and the comparator studies were determined based on the scoring of the Downs and Black Checklist.

Reference: Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health 1998; 52:377-84.

Judgements of quality were made crudely and qualitatively, to reflect the number of items in the quality checklists that were marked as "yes", "unclear" or "no" (Table 2), with reference to the full quality checklists, since this information should be considered in full when considering the quality of the trials.

Table 2: Summary of quality assessment answers for studies included in the clinical SLR

Study	Quality points marked as 'Yes' indicative of good quality, n (%)	Quality points marked as 'No' or 'Unclear' indicative of poor quality, n (%)	Points marked as 'N/A', n (%)
Barete 2015	10 (40)	13 (52)	2 (8)
Chandesris 2016	7 (28)	18 (72)	0 (0)
D2201	13 (52)	10 (40)	2 (8)
A2213	12 (48)	11 (44)	2 (8)
Hauswirth 2004	8 (32)	13 (52)	4 (16)
Hochhaus 2015	11 (44)	12 (48)	2 (8)
Jawhar 2017a	7 (28)	18 (72)	0 (0)
Jawhar 2017b	11 (44)	14 (56)	0 (0)
Lim 2009b	9 (36)	14 (56)	2 (8)

Pagano 2008	8 (32)	16 (64)	1 (4)
Pardanani 2009	7 (28)	18 (72)	0 (0)
Verstovsek 2008	8 (32)	13 (52)	4 (16)

Abbreviations: N/A: not applicable.

Section B: Clarification on cost effectiveness data

B1. Priority request: Please provide the Kaplan-Meier analyses listed in (a) to (c) to the following specification:

- **Study data set: D2201 study, August 2017 data cut-off.**
- **Population: Patients with advanced systemic mastocytosis including those lost to follow-up or withdrawn from the study.**
- **Stratification: by all disease subgroups and the SM-AHN + MCL combined subgroup.**
- **Format: Please present analysis outputs using the format of the sample table shown below.**

a) Time to death from any cause (OS) for responders and non-responders, responders only and non-responders only

b) Time to progression (PFS) for responders and non-responders, responders only and non-responders only

c) Duration of response (DoR) (for responders)

Sample table: Example of output (SAS) required from specified Kaplan-Meier analyses - The LIFETEST Procedure

Product-Limit Survival Estimates					
DAYS	**Survival**	**Failure**	**Survival Standard Error**	**Number Failed**	**Number Left**
0.000	1.0000	0	0	0	62
1.000	.	.	.	1	61
1.000	0.9677	0.0323	0.0224	2	60
3.000	0.9516	0.0484	0.0273	3	59

7.000	0.9355	0.0645	0.0312	4	58
8.000	.	.	.	5	57
8.000	.	.	.	6	56
8.000	0.8871	0.1129	0.0402	7	55
10.000	0.8710	0.1290	0.0426	8	54
SKIP…	……	……	……	…	…
389.000	0.1010	0.8990	0.0417	52	5
411.000	0.0808	0.9192	0.0379	53	4
467.000	0.0606	0.9394	0.0334	54	3
587.000	0.0404	0.9596	0.0277	55	2
991.000	0.0202	0.9798	0.0199	56	1
999.000	0	1.0000	0	57	0

Please find enclosed the requested Kaplan-Meier analyses (refer to the attachments 'D2201 Kaplan Meier Analysis_Full population' and 'D2201 Kaplan Meier Analysis_Subgroup' for the ITT population and the MCL and SM-AHN subgroups, respectively).

B2. Priority request: The company model structure separates the progression-free health state into two health states to represent response and lack of response to first-line treatment (CS, pp106-107).

a) **Please explain the relationship between DoR, ORR and PFS, as implemented in the economic model.**

The economic model is a partitioned survival model (PSM), and therefore deals with health state occupancy, rather than transitions between health states. The progression-free health state is separated into two health states (a) sustained response and (b) lack or loss of response in order to capture the potential differences in quality of life between treatments within the progression-free health state. This reflects the feedback from clinical experts consulted in the development and validation of the economic model, who considered that patients who respond to treatment are likely to experience better quality of life compared with non-responders and was also supported by evidence from the D2201 trial (Section B.3.4.5 in CS).

In D2201, PFS was defined as the time from start of treatment to the date of first confirmed progression or death due to any cause.

Duration of response (DoR), by definition, was only calculated in patients with a confirmed major response (MR) or partial response (PR) (n=53) and was defined as the time from the start of the first confirmed response occurring before the end of Cycle 6 until the date of the first confirmed PD or death due to ASM or MCL. If a patient did not progress or die due to ASM or MCL at the time of the analysis cut-off, DoR was censored at the date of the last adequate response assessment. If a patient received any further anti-neoplastic therapy before the time of the analysis cut-off, DoR was censored at the time of last adequate response assessment prior to the start of the anti-neoplastic therapy.

Similar to the approach for OS and PFS in a PSM, it is therefore possible to separate PFS into two further health states, based on the area under the curve between PFS and DoR.

Typically, in the economic evaluation of cancer medicines, the utility value for PFS is simply weighted by the utility value for responders and non-responders based on the ORR for the treatment of interest. Since DoR is likely to be different between different treatments as shown in Lim *et al.* 2009b, we felt that using DoR (alongside ORR) provided a more accurate estimate, compared with the simple weighting of utility values based on ORR.

ORR is not linked to PFS or OS, as clinical experts considered that using ORR as a surrogate for OS and PFS was not appropriate (see below for further details).

b) Please clarify how the lack of response to first-line treatment is linked to PFS but not to OS.

As highlighted above, the economic model is a PSM and therefore deals with health state occupancy, rather than transitions between health states. In the model, ORR is neither linked to OS nor PFS, but is used to estimate the quality of life in the PFS health state by splitting this health state into sustained response and lack of/loss of response (area under the curve).

This approach was justified by discussion with clinical experts, who considered that linking ORR to PFS and OS was not appropriate, given the differences in the mechanism of action between midostaurin and treatments that are part of the current management in the UK. Whilst responders are likely to have a better survival compared with non-responders, clinical experts considered that it was not appropriate/clinically plausible to assume that the prognosis (OS, PFS) for responders and non-responders was the same irrespective of the treatment received (with the only difference being the response rate).

B3. The relative benefit (i.e. hazard ratio for OS and PFS) associated with treatment with midostaurin persists over the 38-year time horizon of the model (CS, p108). Please provide further justification for this assumption. Please note that the maximum

duration of follow-up in the D2201 study (representing 70% of patients in the midostaurin arm of the pooled analysis) is 4.5 years.

The HR for OS and PFS was applied over a lifetime horizon as it was unclear how long the HR would last. This assumption was validated and supported by clinical experts upon validation of the OS predictions for the comparator treatments. Clinical experts considered that patients receiving current clinical management have poor survival, and that only a small proportion of patients would be alive at 5 years (less than 5%). Clinical experts further noted that the tail observed with midostaurin would not be seen in patients treated with current treatment. As the HR is applied to the baseline midostaurin curve, assuming the HR to be 1 would lead to a long tail for the comparator arm, which was not considered plausible.

Furthermore, as highlighted by the ERG, D2201 represents approximately 70% of patients included in the pooled analysis, however, the HR was estimated using data from both D2201 and A2213, where the median follow-up was 79.5 months (range: 51.4–234.0). Consequently, the HR from the pooled analysis of midostaurin versus historical controls (Reiter *et al.* 2017), represents the HR estimated in patients with median follow-up of 79.5 months, rather than the duration of follow-up in D2201 only.

B4. The ORR for comparator treatments is estimated from several studies (Barate *et al* 2015; Hauswirth *et al* 2004; Jawhar *et al* 2017; Lim *et al* 2009; Pardanani *et al* 2009). The ORR for each treatment is calculated by dividing the total number of responders by the total number of patients across the relevant studies. Please explain why the weighted average approach was not used.

Response rates reported for comparator treatments were pooled for each subgroup of advanced SM (ASM, SM-AHN and MCL). This was done by dividing the total number of responders by the total number of patients pooled across the relevant studies. The resulting response rate is comparable to a weighted average of the individual response rates according to the sample sizes of each study. Given the very small numbers of patients included in the majority of the studies, this method ensured that the studies with greater numbers of patients (and thus potentially more reliable estimates of the response rate for each therapy in each subgroup) formed a greater contribution to the pooled response rate. Response rates for each advanced SM subgroup were then reweighted according to the proportions of each subgroup present in the D2201 trial population, to provide a fair comparison against midostaurin and reflect possible differences in response rate between subgroups.

It should be noted that, whilst ORR is considered in the economic model in order to capture differences in quality of life in the progression-free health state, there remains a large degree of uncertainty in the ORR for the comparators of interest given both the quantity and quality of data available for these treatments in the population of interest. Indeed, in the majority of studies identified, the proportion of patients with advanced or indolent SM-AHN was unclear and, as demonstrated by Barete *et al*. 2015, patients with ASM-AHN have a worse ORR compared with ISM-AHN patients (0.45 versus 0.83). There were also some differences in how response was assessed. More complex methods to synthesise the ORR would only lead to false accuracy, given the differences between studies.

B5. Cladribine can be administered orally, subcutaneously and intravenously. Please explain why only subcutaneous cladribine is costed in the model.

Feedback from clinical experts experienced in the treatment of advanced SM in the UK indicated that cladribine is only administered subcutaneously for advanced SM patients; therefore, only subcutaneous administration of cladribine was costed within the model.

Section C: Textual clarification and additional points

References

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Reiter A, Kluin-Nelemans HC, George T, et al. Pooled Survival Analysis Of Midostaurin Clinical Study Data (D2201+A2213) In Patients With Advanced Systemic Mastocytosis Compared With Historical Controls. Haematologica 2017:321-322.

NICE National Institute for Health and Care Excellence

Patient organisation submission

Midostaurin for treating advanced systemic mastocytosis [ID1573]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]
2. Name of organisation	The UK Mastocytosis Support Group & Leukaemia Care

3. Job title or position	JH—Chair, Board of Trustees, AD—Trustee, CM— Patient Advocacy Manager
4a. Brief description of the organisation (including who funds it). How many members does it have?	The UK Mastocytosis Support Group is a national registered charity that provides support to people with all forms of mastocytosis and with other mast cell diseases. Founded as a support group in 2004, it became a registered charity in 2013. We provide one-to-one and peer support to affected people and their families, advocate for their needs in the medical system, support research, and educate medical professionals about these conditions. The charity has approximately 250 paid members, but provides support to more than 900 people in our support forums. With the exception of a recent agreement to receive a grant from Novartis (see below), our charity is funded through small annual membership subscriptions and the donations of members and their friends and families. Leukaemia Care is a national blood cancer charity, first registered with the Charity Commission in 1969. We work to ensure that everybody affected by blood cancer has access to the right information, advice and support. Key services fall into 4 categories; • Patient services: such as a freephone helpline, nurse advisors, conferences and information booklets • Advocacy: individual advocacy, health technology appraisals, information and patient surveys • Campaigns: our biggest campaign is Spot Leukaemia, aiming to raise awareness of the signs and symptoms of leukaemia • Services for healthcare professionals, including conferences and online learning platforms. In 2016/17 and 2017/18, over 80% of our funding came from our own fundraising activities and those of our volunteers. This includes a wide range of activities – such as legacies, community events, marathons, recycling campaigns etc. Leukaemia Care also receives funding from a wide range of pharmaceutical companies, which in total represent approximately 15% of our annual income. Any funds received from the pharmaceutical industry are in accordance with the ABPI Code of Practice and the Leukaemia Care Code of Practice, our voluntary commitment that governs how we work with, and accept funding from, the pharmaceutical industry: www.leukaemiacare.org.uk/resources/code-of-practice
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator	In 2019 The UK Mastocytosis Support Group agreed to receive up to £10,000 from Novartis in support of a joint project mapping the patient experience with mastocytosis. Novartis paid an honorarium of £750 directly to the charity in 2019 and Andrew Dugdale, a trustee, received an honorarium of £750. Leukaemia Care:

products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	Bristol Myers-Squibb - £5,000 grant Janssen - £15,000 – Grant, £21,890.19 - Grant, £650 – Honorarium, £1000 - Nurses conference. Total = £38,540.19 Novartis - £25,000 – Grant, £447 – Honorarium, £7279.69 – Honorarium. Total = £32,726.69
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No.
5. How did you gather information about the experiences of patients and carers to include in your submission?	We surveyed patients and carers (in separate surveys) to ask them to describe their experiences with these conditions, and also had some one-to-one email discussions with patients to elaborate or clarify. (Respondees were given the option of giving their email addresses so we could recontact.) The respondents to our survey were mainly ASM patients, with one MCL respondent and one with SM-AHN.
Living with the condition	
6. What is it like to live with the condition? What do carers	All forms of advanced systemic mastocytosis are life shortening with current treatments. The most life threatening is mast cell leukaemia, with median overall life expectancy of 6 months, while SM-AHN has a median overall life

experience when caring for someone with the condition?	expectancy of about 24 months. Recent median overall survival data for one cohort in ASM is 41 months, so even the least at risk patients in this population have a short life expectancy. (Paradanani. Systemic Mastocytosis in Adults: 2019 update on diagnosis, risk stratification and management. Am Jour Hematol.2019:94:363-377.) Patients describe the symptoms of mastocytosis as challenging. The most common reported symptoms were itching (66%), cramping and diarrhoea (63%), weakness and fatigue (63%), upper GI symptoms (50%), bone pain (50%), low mood (50%), difficulty concentrating (50%), headaches (38%) and anaphylaxis (25%). The percentage of patient reporting each symptom shows that many are dealing with several physical issues simultaneously. Patients report these symptoms as making day to day living difficult. Physically, symptoms can prevent people from working, socialising and going on holiday. All aspects of their life are affected. • "Prior to midostaurin, I had extreme fatigue. I fell asleep while watching [sports] and movies… at lunchtime I sometimes lay on the conference room floor and took a nap. I was having bad spleen pain, as well as uncontrolled, chronic diarrhoea that sometimes did not allow me to do regular activity." • I experienced an episode of extreme GI pain, diarrhoea and vomiting lasting 1 – 1.5 hours, at least once and sometimes as much as three times in every 24 hours. These episodes occurred spontaneously… I also had intense, widespread UP with itching and hives, bone pain and fatigue" • " [I have] itching to were you want to rip your skin off. Wishing I could be able to be active like I use to be" • "I have had to close down my business and take early medical retirement, due to inability to concentrate and a memory which is similar to early Alzheimer patients." • "Due to the constant tiredness, I have become very bored, having previously been very much an outdoor sport type of person…My wife and I are fighting back by trying different types of holidays. I have found that I can go away for long weekends in Europe by leaving on a mid afternoon flight, [but] it has put the price of these breaks up quite a lot" A diagnosis of a serious illnesses in itself is upsetting but all the physical changes adds to the effect on patients emotionally and psychologically. • "ASM has made life a living nightmare. My spleen is enlarged to where I look pregnant. Going shopping I can't stand because all the different perfumes people wear and cleaning supplies aisle is horrible. • "Being covered all over my face, neck, torso and limbs in rashes is horrendous for my self-esteem. I avoid looking in mirrors and going out places. • "I always forget everything I was told last time we met someone, so I end up feeling Alzheimer'ish as I am constantly being told that 'we discussed that last time'. There is plenty of life left after advanced SM, but it is a very different life experience!"

- "[I am] isolated and housebound. Unable to go out alone due to anxiety, fatigue, brain fog and chronic bone and joint pain. Unable to eat in restaurants due to food intolerance, customers perfumes and aftershave which are high triggers. Detatchment from emotions and people and now in psychotherapy."

Living with a chronic condition also means spending a considerable amount of time at hospitals:

- "there are so many hospital appointments I have to work around it is like constantly juggling my diary. This entails long calls to the hospitals involved (I go to four different ones for constant tests and consultations with a wide range of specialists - ranging from haematology; bone metabolic specialists; respiratory; cardiology; urology; endocrinology; multiple visits to my GP; blood tests; scans etc ... all of which are appointed as and when the NHS want."

A diagnosis of any disease does not affect a patient in isolation, and AdvSM is no different. Carers are emotionally impacted themselves whilst supporting those they love.

- "This is a very onerous disease which requires mental strength, support from my wife (who is now classed as my carer - much to my and her disgust); and careful life planning."
- "It ruined our family life."
- "I looked after [him] for ten years. He could not work so I worked till the last year of his life, then he needed constant care so I took early retirement to look after him."
- "The main challenge is never knowing when my family member is going to have a 'bad' day, this makes planning events difficult at times. At times my family member attempts to perform certain tasks that may require strength, this inevitably leads to bone pain or exhaustion, the challenge here is to help him without him feeling 'useless'."
- "Well my life changed as well. We were very outgoing and then we could not go anywhere as he was very ill."
- "I think psychological support is key not just for the person but also for their immediate family members. We were able to pay for some of this support but I know that not everybody is going to be in this position. It is really hard for the sufferer and their close relatives to come to terms with the impact of the condition and this can have an adverse effect on their relationship."

As this group of illnesses often take over the lives of patients and their families, financial issues can often arise. Unfortunately, access to support is often lacking.

- "It's very hard I had to take early retirement to look after him."
- "He never work as he was ill long time before he was diagnosed"

	• "We had a family business and my family member used to work full time in the business, since he was diagnosed he has not worked. This left me on my own which slowed the business and caused the early sell of the business." • "We had to move house to a bungalow with wet room never got any financial help." AdvSM is a rare disease, and therefore patients and their families also face the additional stress of not getting expert care, sometimes knowing more than the doctors themselves. This lack of understanding extends to the support of bigger and broader charities, leaving people unable to access resources they need. • "He was taken into hospital at least 5 to 10 times a year. That was the worst as I knew more than the doctors [and] he was passed from doctor to doctor as the only doctor that knew about ASM and diagnosed [him] retired and I felt alone as the consultant he got was out of her depth. Don't get me wrong she tried everything to help but nothing did." • "I [a carer] needed a lot of support, which was met mainly by charities, although most charity workers are more familiar with 'hard cancers' rather than systemic diseases, so their ability to advise is limited."
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	UK patients are not receiving the standard of care that is given elsewhere in Europe and in the US because they do not have access to midostaurin. There is a consensus in the research literature that midostaurin is the first choice for many patients with advanced forms of systemic mastocytosis In addition, patients who might be offered allogeneic stem cell transplant, which might be truly curative, do not have access to midostaurin as a less toxic preparatory medication before the transplant. Regarding the treatments listed as comparators for this appraisal, we did not have any respondents who had tried **cladribine**, though in the research literature and in private correspondence haematologists note particular circumstances when it could be part of a treatment plan (that might also include midostaurin at a different stage of treatment) The side effects of cladribine can significant because it is not a targeted treatment, in contrast to midostaurin. One patient in our survey was given **nilotinib** and **dasatinib** but did not continue on them due to side effects or the treatment being ineffective for them. Neither is currently recommended in the research literature, due to the low ORR (Jawhar M, Gotlib, J and Reiter A. "Tyrosine Kinase Inhibitors in Systemic Mastocytosis." In Akin C ed.

	Mastocytosis: A Comprehensive Guide, Springer; 2019). One patient, who has since died of ASM and whose partner responded to the survey, was given **interferon alpha 2a**, **interferon alpha 2b, nilotinib** and **imatinib** (D816V status unknown), as well as one additional "chemotherapy" that the carer could not remember, but which resulted in anaphylaxis. It should be noted that we have been informed that the Roche Interferon alpha 2a, **Roferon**, is no longer available having been superseded by other medications for the primary indications it was used for. Regarding **imatinib** (which is not effective on mast cells with the most common D816V mutations cf Ma. Y et all, The c-KIT mutation causing human mastocytosis is resistant to STI571… Blood. 2002; 99(5):1741-4.), as techniques to detect the D816V mutations become more effective, the number of patients who are found not to have the common mutation is decreasing, and should drop further with better pathology work across all centres in the UK. (In our experience, it is patients not receiving treatment in the leading UK centres who are mistakenly diagnosed with D816V negative AdvSM.) A leading haematologist treating mastocytosis in Germany, where midostaurin is funded, wrote the following in a private correspondence (26 February 2020), "In our hands only 5-10% of patients with AdvSM are negative for KIT D816V. In some of these patients, we find D816H or D816Y etc. These patients are also treated with midostaurin. We treat the very few patients without KIT mutation primarily also with midostaurin. In some patients with very high disease burden, we sometimes primarily treat with chemotherapy, e.g. cladribine or even intensive chemotherapy in SM-AML, and use midostaurin as maintenance. The data on imatinib come from old days, I have never been convinced that it really works and we use it only very rarely, e.g. second-line in a KIT D816V-negative patient who failed on midostaurin and who is not a candidate for cladribine."
8. Is there an unmet need for patients with this condition?	We see a number of unmet needs for patients with Advanced Systemic Mastocytosis. One is the lack of knowledge around the disease; patients can react badly to treatments because of their mast cell burden and so the experimental nature of treatments is risky. Access to a treatment that has been properly tested, such as midostaurin, is a priority for these patients. Additionally, the treatments that patients usually receive are ineffective and come with significant side effects, as described in the previous section.

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Midostaurin has been shown in trials to improve the lives of people with Advanced Systemic Mastocytosis, no matter which subtype. It addresses the underlying problem—increased mast cell infiltration of the bone marrow, spleen and liver; it also decreases mast cell degranulation, improving the symptoms that are often those most disturbing to patients. Patients who are taking the drug report that it improves their quality of life. Patients speak about the improvement in their symptoms. Midostaurin prevents mast cell mediator release, the cause of anaphylaxis, skin flushing, gastrointestinal symptoms (such as diarrhoea, cramping, hyperacidity and vomiting) sensitivity to scented products and chemicals such as cleaners, perfumes etc, and ability to tolerate a varied diet. It also improves resolution of “B” and “C” findings (including osteoporosis). Tryptase levels improve, which can reflect mast cell burden in the body, and skin manifestations decrease, including urticaria pigmentosa (now called maculopapular cutaneous mastocytosis (MPCM)) and can reverse osteoporosis. The patients we spoke to described the physical symptoms as dominating their lives and being the cause of the psychological distress they and their families experiences, so any improvements in the physical symptoms is really important. • “Since taking Midostaurin all my symptoms have resolved and my UP has disappeared. Prior to taking Midostaurin my tryptase level was over 2,000. Tryptase is still regularly monitored and since taking Midostaurin it is generally about 300. I clearly still have mastocytosis but with Midostaurin I am able to live a completely normal life.” • “In my case the drug has resolved the vast majority of symptoms such as GI; maculopapular rash; it has also stopped (and indeed reversed) my bones thinning.” • “I asked my Dr. if I didn’t take this medicine how long do I have. They told me about a year. So yes, I think this medicine has been good for me, so I can see my son graduate.” • This drug made my condition so much better. My spleen has reduced in size (almost back to a normal size), my skin had cleared up, my blood levels were going towards normal levels. • (Comment from carer) “The treatment has improved their daily life. My family member now has around 8 hours a day of reasonably normal life, we are able to go on holiday and out to events which we would not have been able to do otherwise”.

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Our respondents described three disadvantages of midostaurin. One is the side effects (nausea and vomiting being the most common side effect described). Another is the need to take the medication on a daily schedule, with plans to address the "down time" when they feel sick from it. Finally, patients would prefer a curative treatment. However, as described in the previous section, patients do have fewer symptoms, and any reduction in symptoms is likely to bring relief to patients. Further, the patients who made these observations have not stopped taking the medication because for them the benefits outweigh these disadvantages. • "If taken without food Midostaurin causes nausea and vomiting however I have found these symptoms to be avoidable when taking the medication with a meal." • "The primary disadvantage is that it has to be taken 'for life'. This leaves periods of nausea following taking the drugs, and does not resolve the brain fogs…stopping Midostaurin even for a short period causes symptoms to return as soon as two days from stopping the treatment. Restarted at that time, and rapidly improved again on re-start."
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	The trial results show that midostaurin is effective in all three subtypes of mastocytosis tested, Aggressive Systemic Mastocytosis, Systemic Mastocytosis with an Associated Haematologic Disease and Mast Cell Leukaemia. In addition, in the research literature arising from clinics in countries where midostaurin is now available, midostaurin is the first line choice for most advanced SM patients no matter the form, and is part of a long term treatment strategy in nearly all AdvSM patients including in those who receive an initial treatment with another drug as induction therapy for SM or to treat an accompanying associated haematologic disease. Each group of patients with a form of Advanced SM has its own unmet needs. ASM patients live with their disease long term; as described in the "living with" section, whilst their life expectancy is slightly longer than in SM-AHN and MCL, patients have a significant burden of symptoms. This affects all aspects of their life; work, social activities, emotional and psychological state and impacts on their family, friends and carers. MCL and SM-AHN patients, in contrast, need immediate treatment due to an immediately life threatening condition; life expectancy is 6 months or less (MCL) or , so these patients need treatment that would extend their lives. Midostaurin can address the needs

	of all these groups and all patients would value access, even if the usage of the drug in each group has different goals.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	
Other issues	
13. Are there any other issues that you would like the committee to consider?	We have serious concerns about the current arrangement, in which patients who were diagnosed and offered treatment with midostaurin before it received marketing authorisation have access to this life-extending medication through a compassionate use programme, and newly diagnosed patients do not have access to it.

14. To be added by technical team at scope sign off. Note that topic-specific questions will be added only if the treatment pathway or likely use of the technology remains uncertain after scoping consultation, for example if there were differences in opinion; this is not expected to be required for every appraisal.] if there are none delete highlighted rows and renumber below	

Key messages

15. In up to 5 bullet points, please summarise the key messages of your submission:

- All forms of advanced forms of mastocytosis shorten life expectancy. In addition to experiencing the symptoms that are common to advanced haematologic diseases, such as extreme (completely overwhelming) fatigue, anaemia, lymphadenopathy and organomegaly they also have the symptoms of ongoing mast cell degranulation such as cramping, diarrhoea, vomiting, and sensitivity to environmental pollutants. Some also experience unpredictable anaphylaxis to known and unknown triggers.
- There are no licensed treatments for any form of advanced mastocytosis (with the exception of a very small subset with an unusual mutation—and that drug is no longer looked at as first line) other than midostaurin. Comparators are either unsuitable for the majority of patients, have side effects patients find intolerable and/or work best when followed by midostaurin. Additionally, unlicensed treatments come with risk of triggering anaphylaxis in these patients, due to the nature of the disease.

- Midostaurin has been shown in trials to have a clinically meaningful effect the health of Advanced SM patients, no matter which subtype. Patients who are taking the drug report that it improves their quality of life, and decreases the signs and symptoms that would be associated with advancement of their disease.

- Midostaurin has side effects. The most concerning to patients is nausea after taking the pill; however this is improved when the pill is taken with a meal. They wish it weren't a daily pill and they wish it did not have to be taken for life, but they continue taking it because the benefits for them outweigh the negatives.

- Midostaurin is effective in all forms of Advanced Systemic Mastocytosis. Doctors in countries where it is licensed and funded choose it for the vast majority of patients with aggressive systemic mastocytosis, mast cell leukaemia and systemic mastocytosis with associated haematologic disorders either alone or in concert with other treatments (in the most challenging cases). In rare diseases, trials will always have fewer participants than we would ideally like. Nonetheless, the trials have shown this to be an effective drug (unlike any of the comparators, in which there have been no trials), and the prescribing patterns of physicians with access to this drug since the trials show that it is the best medication available for advanced mastocytosis.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Midostaurin for treating advanced systemic mastocytosis [ID1573]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

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- Your response should not be longer than 13 pages.

About you	
1. Your name	Dr Steven Knapper
2. Name of organisation	Cardiff University / University Hospital of Wales (Nominated by Novartis, UK Mastocytosis Support Group and Leukaemia Care)

3. Job title or position	Clinical Reader in Haematology / Consultant Haematologist
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? **X** a specialist in the treatment of people with this condition? **X** a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it **X** other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve	Systemic mastocytosis is a chronic, highly heterogeneous condition with clinical features that vary tremendously between different patients. In advanced SM (the licensed indication for midostaurin), the main aim of the treatment is to 'debulk' the disease by reducing the burden of abnormal mast cells;

mobility, to cure the condition, or prevent progression or disability.)	depending on the distribution of the abnormal mast cells in individual patients and the 'C findings' that result from this; midostaurin treatment would therefore be aimed at improving blood counts (and reducing need for red cell or platelet transfusion), improving liver function, improving bony disease/lesions, improving malabsorption and reversing weight loss or hypoalbuminaemia. A second key aim of midostaurin treatment is to bring about sustained symptomatic improvement with associated impact on quality of life.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Given the extreme heterogeneity of SM, it is very difficult to given an objective answer to this question that is able to encompass all disease scenarios. In the phase 2 clinical investigation of midostaurin in SM (Gotlib, NEJM 2016) clinical responses were assessed objectively using the established 'Valent response criteria' which define 'overall response' as either a major response (with complete resolution of ≥1 C finding), good partial response (>50% improvement in ≥1 C finding) or minor partial response (20-50% improvement in ≥1 C finding). This formed the basis of the primary endpoint in the trials of midostaurin but would be very difficult to apply outside the formal clinical trial setting. In the trials, responses to midostaurin were also measured according to reductions in bone marrow mast cell infiltration; bone marrow biopsy is a highly invasive procedure and serial sampling would be difficult to justify outside the clinical trial situation. A meaningful clinically-significant response could be a sustained improvement in mast cell burden resulting in clinical improvements as listed in response to Q7, e.g. abolition of the need for transfusion support, regain of lost weight, improvement of bony disease or restoration of liver function. A sustained improvement in symptom burden should also be considered 'clinically significant'. Reduction in serum tryptase levels may also provide a useful surrogate for mast cell response to midostaurin treatment which can be measured non-invasively.
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. Advanced SM is a highly debilitating condition with poor prognosis and very limited therapeutic options. Prior to midostaurin, no previous agents have received marketing authorisation for this condition.
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	In the UK, SM is generally treated in secondary care through haematology clinics, and to a lesser degree in immunology clinics. Most patients will be seen in general haematology clinics; the low incidence of the condition means that most general haematologists will only have a very small number of mastocytosis patients (typically 1-2) under their follow-up. A small number of sites provide greater expertise as tertiary referral units, and some patients will be under 'shared care' between one of these centres and their local DGH.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	There is currently no UK-based clinical guideline although BCSH guidelines are in early stages of development. Clinicians may refer to the US-based National Comprehensive Cancer Network (NCCN) Guideline which is regularly updated. Additionally, the Mayo Clinic publish an annual update on best practice in the diagnosis and management of systemic mastocytosis which is used as a reference document by many haematologists – latest iteration is 'SM in adults: 2019 update on diagnosis, risk stratification and management' (Pardanani, Am J Hematol 2019); this provides a detailed summary of clinical evidence for midostaurin (and other therapeutic agents) and suggested treatment algorithms.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway of care in SM is complex, and ill-defined again mainly due to the highly heterogeneous clinical manifestations and comparative rarity of the disease. Complexities include the varied subtypes of ASM (aggressive, mast cell leukaemia, SM-AHN), the varied presentations within each subtype depending on degree and distribution of mast cell infiltration, and the varied age and co-morbidities of different patients. Most professionals involved with treating SM are only exposed to a handful of cases so will not experience all these different possible patient scenarios and will seek expert advice from regional centres and multi-disciplinary teams.

	My own experience is in Wales where I see SM patients within the myeloid haematology clinic at University Hospital of Wales (Cardiff); this includes tertiary referrals from haematologists based at other hospitals across the region.
• What impact would the technology have on the current pathway of care?	Wider availability of Midostaurin will considerably impact the current pathway of care by providing an orally-administered agent, targeted at abnormal mast cells which is relatively easy to prescribe and monitor, and well-tolerated in most patients. It would likely become the first line therapeutic agent for the majority of patients within the licensed indication of advanced SM. Access to midostaurin is currently somewhat patchy, individual funding requests are less likely to be made by haematologists who are less familiar with treating mastocytosis, leading to a non-uniform access for patients at DGHs.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Midostaurin is already in use through a combination of compassionate access programme (this was withdrawn >1 year ago when midostaurin achieved its license, but previously-established patients who continue to derive benefit have been able to remain on treatment) and patients who have been the subject of successful IFRs. It is likely to continue to be prescribed through the same haematology clinics in a broadly similar way but more equitably (see above) with access increasing to less-specialised haematology clinics at DGHs.
• How does healthcare resource use differ between the technology and current care?	It is difficult to give a generally-applicable answer to this question given that this is a rare and heterogeneous patient group with no common treatment pathway. At present, fitter patients with bulkier disease will more often receive cladribine therapy which is administered parenterally (IV or s/c) so involves haematology day units) and comes with a greater need for supportive care including transfusions, admissions for treatment of infection etc. The other main alternative, interferon, is generally self-administered by patients/relatives via s/c injections which are given at home.

• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Almost exclusively prescribed by secondary care (haematology clinics) and sometimes instigated in tertiary / specialist regional clinics.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Very little investment will be required. Midostaurin is an oral agent prescribed in secondary care. Most specialist clinicians are already familiar with its use. Some minimal education on dosing schedules prescribing information will be required for physicians who are less familiar.
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes. Based on the published phase 2 trial results. Objectivity is difficult because, for the main alternative preparations of cladribine and interferon the published evidence base is limited: mainly smaller cohort studies that were not confined to patients with advanced disease and also included cases of indolent and smouldering SM.
• Do you expect the technology to increase length of life more than current care?	This is difficult to be sure upon based on the limited numbers of patients treated in the published phase 2 studies (Gotlib 2016, de Angelo 2018) but yes, I would expect there to be some increase in length of life with the use of midostaurin. Conventional overall survival estimates for ASM patients vary according to the sub-category of disease with median expected survival quoted as 3.5yrs for patients with aggressive SM, 2 years for those with SM-AHN and under 6 months for those with mast cell leukaemia. In the Gotlib study, median overall survival was 28.7 months in the efficacy population and 33.9 months in the intention-to-treat population (it should be borne in mind that 57/89 patients had SM-AHN); median survival increased to 44 months in clinical responders (compared to 15 months in non-responders);

	increases in overall survival were particularly striking in the mast cell leukaemia population where median survival was not reached in responding cases. Longer term follow-up data (median 10yrs) presented in the de Angelo study suggests that responses are generally durable in those achieving them. Finally, a French compassionate use study (Chandesris. NEJM 2016) compared 28 midostaurin-treated patients with ASM with a 44-patient group matched for age and SM subtype. After a similar median follow-up, the risk of death in the control group was more than twice that of the midostaurin group (hazard ratio 2.2, p=0.02).
• Do you expect the technology to increase health-related quality of life more than current care?	Yes. I would expect health-related QoL to improve. Midostaurin is an easily-accessed oral medication which requires less hospital contact than cladribine or interferon, with the knock-on QoL benefits this entails. SM patients experience a number of debilitating symptoms that impact QoL on a day-to-day basis. The Gotlib phase 2 study included patient-reported outcomes using the Memorial Symptom Assessment Scale; at baseline the commonest symptoms were lack of energy, drowsiness and difficulty sleeping – across the study, 30 of 32 symptoms decreased in frequency; the 2 exceptions being nausea and vomiting, both of which are adverse events that are known to be associated with midostaurin. The total scores, physical, psychological and global-distress-index sub-scores, physical and mental composite scores all showed significant improvements with midostaurin.
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Midostaurin is active against both D816V-mutated KIT and non-mutated KIT. Approximately 90% of ASM cases have D816V mutations; the Gotlib study showed an overall response rate to midostaurin of 63% in 77 KIT-mutated cases with a slightly lower rate of 44% in 12 non-mutated cases (including 2 with unknown mutation status), although the sub-groups were too small to allow statistical significance to be reached. The alternative therapeutic agent Imatinib may remain an alternative option for those rarer SM cases known *not* to harbour a D816V mutation.

The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Midostaurin will be easier to use than most existing alternatives as it is orally-administered and can be prescribed through outpatient clinics (in contrast to cladribine which is administered parenterally generally via haematology day units and is more likely to require additional blood product support and be followed by inpatient stays for management of neutropenia-associated infections). Over the first few months of treatment, more frequent clinic visits are likely to be required to monitor tolerability and early signs of efficacy. The commonest early adverse effects are gastrointestinal (nausea, vomiting, diarrhoea) which may require prophylaxis and dose adjustment. ECG monitoring not required as standard.
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Again, the heterogeneity of the clinical manifestations of SM between patients means it is unlikely that there can be a ‘one size fits all’ way of assessing efficacy and coming to stop/go decisions. Factors used to assess effectiveness will include (for different patients): symptom control, weight gain, reduction in blood product use (and improvement of blood count parameters), and LFTs. Serum tryptase may be of use as a surrogate marker of efficacy. While bone marrow mast cell burden is possible to assess, this is highly invasive and unlikely to be routinely-justifiable outset the context of clinical trials. In the phase 2 studies, responses were assessed over the first 24 weeks of midostaurin treatment. I am not clear whether any patients showed first responses beyond that time period, but this may be a reasonable cut-off point for objective assessment of whether benefit is being derived and whether the treatment should continue.

16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	I am somewhat unfamiliar with the precise derivation of the QALY calculation. The benefits of midostaurin are likely to be complex and heterogeneous and may extend to QoL, impacts on resuming activities, returning to work etc. As stated in Q12, extension of survival remains somewhat unclear.
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes. See answers to sub-points below.
• Is the technology a 'step-change' in the management of the condition?	Yes. This is the first licensed genetically-targeted therapeutic agent targeted against the principal driver mutation underlying SM.
• Does the use of the technology address any particular unmet need of the patient population?	The SM population is particularly poorly-served by existing available medications. The population has very many unmet needs ranging across the different clinical manifestations of SM. The results of the phase 2 studies suggest superior clinical efficacy (in comparison to historical data from existing treatments such as cladribine and interferon) ranging across the different manifestations including symptom control and

	measures that reflect levels of abnormal mast cell infiltration (blood transfusion need, liver function, regaining lost weight, bone lesions etc). .
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Based on the phase 2 studies (and also the more extensive experience of using midostaurin for its other principal indication in thousands of patients with acute myeloid leukaemia) it is generally well-tolerated. The commonest side effects are relatively minor nausea/vomiting and diarrhoea which tend to be more than compensated by the improvements in disease-related symptoms. Some patients develop deepening of blood cytopenias – haematologists are experienced with dealing with this - but generally transfusion needs are reduced, and overall symptoms improved. Some patients require dose reduction from 100mg bd to 50mg bd based on GI toxicity or cytopenias (44/116 patients in Gotlib study had a sustained dose reduction) but this did not appear to compromise clinical efficacy, and could potentially have a knock-on effect in reducing drug costs in the longer term.
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes – most access to midostaurin for SM in the UK to date has been through the Novartis compassionate use programme, which had very similar eligibility to the Gotlib study.
• If not, how could the results be extrapolated to the UK setting?	Not applicable.
• What, in your view, are the most important	In ASM, measured outcomes need to encompass all the different manifestations of the disease that can affect different patients with the condition. The responses of C findings were measured in the trials in order to derive a composite endpoint of 'overall response' according to established Valent criteria. The trial

outcomes, and were they measured in the trials?	publications also reported on other important outcomes including symptomatology and quality of life which are both particularly relevant to this patient population.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Not applicable
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No – I am not aware of any.
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
21. How do data on real-world experience compare with the trial data?	The main additional 'real world evidence' was that published in the French compassionate use study (Chandesris et al) referred to in Q12. This findings in that study appears to be consistent with the published phase 2 trail data.
Equality	

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No – I am not aware of any issues that relate to 'protected characteristics' as per Equality Act 2010. Approval of this technology should improve equitability of access which is currently somewhat arbitrary through IFR applications which may be regionally-biased.
22b. Consider whether these issues are different from issues with current care and why.	
Topic-specific questions	
23. Are the following treatments considered to be established clinical practice in the NHS for treating advanced systemic mastocytosis? • nilotinib (excluded from company submission) • dasatinib (excluded from company submission) • pegylated interferon alpha (included in company base case) • AML-like treatments (included in company	Nilotinib and Dasatinib – I do not feel are really relevant as they are very seldom prescribed in the UK as they are not currently funded for this indication. The limited available trial data suggest that both are less effective than midostaurin in SM. PEG-IFN is reasonable to include. Interferon is increasingly prescribed in PEG form which requires less frequent dosing and tends to be better tolerated than non-PEG form. Direct comparisons of efficacy between midostaurin and interferon are difficult; interferon is also used in symptomatic smouldering SM cases (sometimes also very symptomatic indolent SM cases) as well which makes direct comparisons with the purer ASM population treated with midostaurin difficult. AML-like treatments such as low dose cytarabine and azacytidine I do not feel are directly relevant to this appraisal. These would most frequently be used to treat the 'non-mast cell components' of SM-AHD (i.e. the 'additional haematological disorder' such as chronic myelomonocytic leukaemia where this predominates over the SM component).

base case) please name relevant treatments	

Key messages

24. In up to 5 bullet points, please summarise the key messages of your statement.

- Advanced SM is a highly debilitating condition with poor prognosis and very limited therapeutic options.
- Prior to midostaurin, no therapeutic agents have received marketing authorisation for this disease.
- Midostaurin is active against the KIT D816V driver mutation seen in approximate 90% of SM patients
- In the largest phase 2 trial of midostaurin in SM, the overall response rate was 60%, with 45% of patients having a major response; 30 of 32 recorded symptoms decreased in frequency; responses appear to be durable
- Midostaurin is dosed orally and can be prescribed through outpatient clinics with a reduction in infrastructural needs compared to comparator treatments

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Midostaurin for treating advanced systemic mastocytosis [ID1573]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	**Dr Deepti H Radia**
2. Name of organisation	**Guy's & St Thomas NHS Foundation Trust**
3. Job title or position	**Haematology Consultant**

4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition,	Patients with advanced systemic mastocytosis (SM)have a complex rare, life limiting haematological cancer which can have a significant impact on quality of life. We have to date no reliable or reported epidemiological data for U.K.for the numbers of patients who have been treated / diagnosed with advanced SM. The spectrum clinical spectrum of patients advanced SM is heterogenous as they fall into 3 sub categories; aggressive SM, SM with an associated haematological disorder (AHN) and mast cell leukaemia (MCL). Data published from the Mayo clinic by Pardanani, 2016 American Journal of Hematology (**https://doi.org/10.1002/ajh.24553**) on reviewing 342 patients showed the median overall survival of 41 patients aggressive SM was 41 months, 138 patients with SM+AHN was 24months and 4 patients with a diagnosis of MCL was 2 months. The aim of treatment with Midostaurin is to reduce

or prevent progression or disability.)	the rate of progression of SM in these patients,increase life expectancy with improvement in symptom burden and quality of life. The efficacy of midostaurin, a targeted small molecule (tyrosine kinase inhibitor) and its activity against neoplastic mast cell has been reported in Phase 1 and 2 trials. Gotlib NEJM 2016. At Guys and St Thomas' Hospitals NHS Foundation Trust we have an ECNM registered - UKcentre of excellence in mastocytosis since 2006 for which I am the Haematology Lead and Dr Clive Grattan is the dermatology/allergy lead clinician. Over the 14 years we have discussed > 500 cases of patients with mastocytosis in our quarterly MDMs and I have seen > 150 patients in the Haematology service. As a result we have gained a significant amount of experience in managing patients with this rare condition. Patients are heterogeneous in their presentation with regard to symptoms and how this disease impacts on the quality of life so treatment does need to be individualised. Midostaurin is the only licensed *C-KIT* targeted proven in a trial to demonstrate improving overall survival rates, reducing in mast cell disease burden and improving symptom burden in patients with advanced SM.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Patients with advanced SM as per WHO 2016 Criteria need to have at least one measurable C finding. This means having a disease burden that is high enough to lead to organomegaly (enlarged spleen and/ or enlarged liver and /or enlarged lymph nodes) with the evidence of end organ damage being reflected in the blood parameters such as significant anaemia with a haemoglobin of less than 10 g/l, thrombocytopenia with a platelet count of less than 100 x109/l, in addition to abnormal liver function tests and a tryptase level > 20ug/l. The latter is reflective of total body mast cell burden in a patient. In my experience a clinically significant treatment response would mean a decrease is mast cell disease burden reflected by a decrease in an organomegaly, tryptase level, improvements in the blood profiles and improvement in QOL. Patients with advanced SM form a complex cohort with the majority of the patients will have SM+AHN where 2 haematological disorders coexist and one would not expect complete resolution of blood parameters as the midostaurin does not target both disorders. The published data (Gotlib et al, 2016) shows that upto 60% patients obtain a response; 15% achieve partial response with at least a 20% reduction of their measurable disease parameters and 45% of patients obtain a major response with the release of 50% improvement of their measurable disease parameters. These improvements have a median duration of response of 18.6 months and during this time patients can have a significantly improved performance status and quality of life as well as improved overall survival. In the 8 patients with advanced SM I have personally treated with Midostaurin since 2009 (2 as part of the Phase 2 International trial and 6 on the CUP use programme) – all 8 had a benefit with decreased mast cell burden and improved quality of life as well as increased survivals as compared to the data published. Improvements in the objective markers discussed above occurred within the first 3 – 6 months with at least a 20% - 50% improvement if in disease burden as measured by decrease in spleen size and improvement in blood parameters such as decrease in tryptase levels, improvement in FBC parameters and liver function tests. These were accompanied by improvement in symptoms – decrease in levels of fatigue and fading skin lesions if present. There were no validated QOL PROs for SM patients at the time so these are clinical assessments.

9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	**YES. I have no doubt that there is an umet need for both patients who suffer from advanced SM and healthcare professionals who treat these patients as they are denied access to the current only C-KIT targeted therapy which has shown efficacy against the neoplastic mast cells that lead to the shortened life expectancy in these patients**.This is the only treatment that has been shown to reduce mast cell burden and to increased overall survival in an international Phase 2 trial for patients with advanced SM. It is approved in USA/Europe and is available in Scotland and for patients treated in the private sector. *The Tyrosine Kinase Inhibitor Midostaurin in Systemic Mastocytosis: Report of an Open-label Compassionate Use Program in the United Kingdom was reported in 2011 and presented as a poster at the American Society of Hematology by Dr S Knapper. 11patients were on Midostaurin and 10 were evaluable for this review.* In this non-selected patient population midostaurin was well-tolerated. Clinically-relevant responses of systemic mediator symptoms were seen in a majority of patients, including durable responses sustained beyond 4 years. Patients who responded had a markedly improved quality of life with Midostaurine replacing a cocktail of drugs. Of note 2 of the 4 patients continue to benefit with midostaurin and have been treated for > 12 years without any evidence of disease progression. Over that time our diagnostic capabilities have improved with a greater understanding of the heterogeneity of the disease, more patients are being diagnosed with advanced SM in the UK. My clinical service has increased as I provide second opinions nationally/ regionally over the last 9-10 years I have seen 41 patients with advanced SM in my clinical practice. I have provided remote clinical opinions and advice for more patients who could not travel to London. As a result of increased education, improved diagnostics including genomics, availability of targeted treatment and trials we are diagnosing more patients with SM and advanced SM, so the numbers of patients are going to increase. Unfortunately we do not have any epidemiological data for the UK to refer to. I have been referred 20-22 patients with advanced SM for management advice in the last 2 years. Other targeted drugs as being used in trials but not all patients can meet the eligibility criteria and so are left to be managed either symptomatically or with non-targeted cytoreductive treatment which is sub optimal.
What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	
• Are any clinical guidelines used in the treatment of the	There are no current UK clinical guidelines on the management of SM/ Advanced SM. There are international reviews and the most comprehensive guidelines were developed by the NCCN: Systemic Mastocytosis,Version 2.2019,NCCN. Clinical Practice Guidelines in Oncology by J.Gotlib et al.(https://doi.org/10.6004/jccn.2018.0088) which provide an excellent and

condition, and if so, which?	holistic evidence framework for managing patients. There is a working group set up at part of the MPN NCRI looking at developing UK guidelines for the management of adults with systemic mastocytosis.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway of care is not well defined and there are very few options for cytoreductive / disease modifying treatments available for these patients. Treatment needs to be individualised as every patient is unique in how they will be afflicted. The only 2 available cytoreductive treatments based on small case series that might make a difference in reducing disease burden are Cladrabine and Alpha Interferon. Cladrabine (Kluin- Nelemans et al, Blood 2003 and Barete et al, Blood 2015) showed an ORR of 50% and median duration of response 2.47yrs (combination of major and partial response) with significant myelosuppression leading to increased incidences of severe sepsis. This has been reflected in the few patients I have treated with Cladrabine – their disease achieves a partial response but the severe neutropenia has led to prolonged and / or severe infections. Interferon-alpha data published Lortholary et al. *Pathol Biol*.2004 and Lim et al.*Am J Hematol* 2009) with 20 and 40 evaluable patients with indolent and advanced SM demonstrated variable efficacy, decrease in mediator symptoms and the use of prednisolone to improve tolerability but no evidence to show a decrease in mast cell disease burden. I have only treated 1 patient with interferon alpha to date and the side effect profile often mimicks the symptom profile in these patients making it a hard drug to tolerate. Imaitinib is available for the 5% of patients who are negative for the *C-KIT* D816V driver mutation and for the small number of patients with well differentiated systemic mastocytosis. This does exclude the 95% of patients who will harbor this mutation.
• What impact would the technology have on the current pathway of care?	When available within the trial or as part of compassionate use programme Midostaurin was the preferred targeted molecule for patients with advanced SM and as the UK data from 2011 demonstrated it was well tolerated and a disease modifying therapeutic option which improved survival outcomes as well as significantly improved QOL with reduction is debilitating symptoms, reduction in the numbers of medications needed to symptomatically manage the patients, disease. It would be the first line of treatment of patients with advanced SM.
11. Will the technology be used (or is it already used) in	

the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	Midostaurin has not been available in England since 2018 and patients have been denied access to the only targeted therapy available for advanced SM. As discussed above – there are 2 other cytoreductive options for SM which do not have the same efficacy or improved outcomes for patients in my experience.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	It should be used in secondary care and in specialist haematology clinics.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No significant investment is needed. Haematologists are familiar with the administration of targeted drugs and tyrosine kinase inhibitors.
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	
• Do you expect the technology to increase	Yes I do, as per discussion above.

length of life more than current care?	
• Do you expect the technology to increase health-related quality of life more than current care?	Yes I do. We carried out a survey to validate a modified MPN-symptom assessment form for patients with mast cell disorders: Radia et al was presented as a poster at EHA 2013. This survey was completed by 285 patients (80UK pts and 185 USA pts) in 4 months. The key messages we learnt were that patients with mastocytosis have a high symptom burden across all subtypes when compared to myelofibrosis ,MF,the most symptomatic of the myeloproliferative disorders with the shortest life expectancy). Patients in all subgroups of SM reported a higher QOL score compared to MF (5.0 vs 3.1) and sever anaphylactic reactions due to mediator release occurred in all subgroups with 10% of patients who had a diagnosis of advances SM experiencing anaphylactic reactions needed epipen use and hospitalisation over the prior 6 months. The median number of medications needed by the patients to manage their symptoms was 9 and some were on a combination of 15 medications. The impact of the disease can be debilitating both physically, psychologically and financially if they are unable to work. We have seen that midostaurin can lead to significant improvement in mast cell burden and symptoms leading to reduction in the total number of supportive medications needed patients.
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	This technology would be effective in this rare population of patients with advanced SM: Aggressive SM, SM+AHN and mast cell leukaemia.
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for	The use of the technology in haematology secondary care would not require any additional clinical needs that are not already in place for patients who need targeted treatment for other haematolgoicial neoplasms.

example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	We would need to ensure the same clinical eligibility criteria for use as is in the SMPC. Cardiac assessment and baseline investigations – Bone marrow/appropriate imaging/ molecular testing/baseline tryptase and blood profiles. These are not anything more than would be done for any haematological malignancy prior to staring treatment. Re- evaluation at 3-6 months would be needed to assess efficacy and clinical decision to continue.
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Please note discussion on question 12
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	Yes – as discussed this is currently the only targeted drug with proven efficacy in patients with advanced SM. The 1-2 other treatments available are non-targeted and have significant side effects.

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes. At present the alternative cytoreductive agents are not disease modifying whereas midostaurin is.
• Does the use of the technology address any particular unmet need of the patient population?	Yes – as discussed above in sections 9 & 10.
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The main adverse effects – myelosuppression can be managed by dose adjusting and blood product / growth factor support if appropriate. Nausea is related to the oral preparation and effectively managed with anti-emetics.
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	
• If not, how could the results be extrapolated to the UK setting?	No – as the technology is not yet licensed in the UK. We had 5 centres in the UK participate in the international phase 2 trial. The results of that trial apply to these UK patients. Gotlib NEJM 2016.

• What, in your view, are the most important outcomes, and were they measured in the trials?	The published data (Gotlib et al, 2016) shows that upto 60% patients obtain a response; 15% achieve partial response with at least a 20% reduction of their measurable disease parameters and 45% of patients obtain a major response with the release of 50% improvement of their measurable disease parameters. These improvements have a median duration of response of 18.6 months and during this time patients can have a significantly improved performance status and quality of life as well as improved overall survival. This was the first trial to demonstrate reduction is spleen size (MRI scans with spleen volumes calculated), reduction is mast cell burden – measuring serial tryptase levels and bone marrow mast cell burden on trephines longitudinally. A study steering committee reviewed all patient data and objectively reviewed responses against the strict Valent – Chesson criteria for overall response measurements. There needs to be an understanding of the parameters used to calculate ORR and the variable included or excluded as these were different for the same trial results between the study steering committee, FDA and EMA. Clinical improvement, which is a clinically significant and important outcome for patients was given the weighting it merits for these patients in some of the regulatory algorithms hence the large differences in ORR. Measurement of symptoms burden with a specific PRO developed for mastocytosis patients and showing improvement over time.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Surrogate markers such as response in decrease in mast cell burden and tryptase are useful markers. Recently developed prognostic scores – MARS/Mayo may be more useful to apply prospectively.
• Are there any adverse effects that were not apparent in clinical trials	None that I am aware of.

but have come to light subsequently?	
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	This is such a rare disease and there is a paucity of UK specific epidemiological data.I would look at clinicians experience and patients experiences in those who have benefited from having access the Midostaurin and the positive impact it has had on their disease and lives.
21. How do data on real-world experience compare with the trial data?	Similar outcomes in my experience.
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	Not that I am aware of in terms of ethnicity. Currently in terms of equality of access – patients are able to gain access to Midostaurin in Scotland and in the private sector.
22b. Consider whether these issues are different from issues with current care and why.	See above.
Topic-specific questions	
23. Are the following treatments considered to be established clinical practice in	Nilotinib – not established. Dasatinib – not established. PegIFN as an off label agent:

the NHS for treating advanced systemic mastocytosis? • nilotinib (excluded from company submission) • dasatinib (excluded from company submission) • pegylated interferon alpha (included in company base case) • AML-like treatments (included in company base case) please name relevant treatments	Interferon α (IFN-α) has been used frontline in patients with advSM. Published data from small retrospective series demonstrate clinical activity in a mixed group of patients.[46-52] Simon and colleagues reported 20 patients (16 ASM/4 ISM) treated with IFN-α-2b with doses escalating from 1MU/day to 5MU/m^2/day.[51] Thirteen patients with systemic and/or skin manifestations exhibited responses: seven (35%) were partial and six (30%) minor without complete responses observed, and the BM was unchanged in 12 of 13 patients. Adverse events reported were cytopenias (7/13) and depression (9/13). Four patients experienced a recurrence of symptoms post cessation of IFN-α. The Mayo Clinic reported on 47 patients treated with IFN-α at a median weekly dose of 15 MU/week (range, 3.5-30 MU/week) with or without prednisolone 20-60 mg/day with a slow taper.[52] Among 40 evaluable patients, the overall response rate (ORR) was 60% (ISM), 60% (ASM) and 45% (SM-AHN), with a median duration of response on 12 months (range 1-67 months). Absence of systemic mediator symptoms was associated with an inferior response. **While IFN-α shows activity in all categories of SM, and can improve mediator symptoms, cutaneous lesions, and skeletal findings (e.g. bone mineral density/osteoporosis), most studies indicate only a modest effect on measures of MC burden (e.g. BM MC percentage and serum tryptase level). It is more useful in slowly progressive disease, and higher doses may be required to decrease MC burden, and concurrent use of prednisolone may improve tolerance.** AML-like treatments will be used in patients with MCL and Advanced SM patients who are progressing and there is no general consensus about which: Hydroxycarbamide as a general cytoreductive agent with a view to reduce mast cell burden but will not be curative and maybe used in AdvSM where the AHN is MPN. Flag-Ida if there is an option of consolidation with a bone marrow transplant.
Key messages	

24. In up to 5 bullet points, please summarise the key messages of your statement.

- Advanced systemic mastocytosis is a rare, orphan haematological cancer with a complex sub-classifications of neoplasms under this one umbrella term
- Advanced systemic mastocytosis patients will have a life limiting cancer with a median overall survival ranging from 2month to 41 months across the spectrum
- Midostaurin is currently the only licensed targeted treatment that has been demonstrated an improved overall survival benefit and improvement in quality of life in an international Phase 2 trial context.
- Midostaurin is available in USA/Europe and Scotland currently and patients/clinicians in England denied this leading to treatment of patients with sub optimal limited cytoreductive therapies

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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ERG STA REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Midostaurin for treating advanced systemic mastocytosis [ID1573]

Confidential until published

This report was commissioned by the NIHR Evidence Synthesis Programme as project number NIHR 131327

Completed 15th May 2020

CONTAINS [redacted] AND [redacted] DATA

UNIVERSITY OF LIVERPOOL | LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Title: Midostaurin for treating advanced systemic mastocytosis [ID1573]

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Date completed: 15th May 2020.

Source of funding: This report was commissioned by the NIHR Evidence Synthesis Programme as project number 131327.

Acknowledgements: The authors would like to thank Dr Clare Oni, Clinical Fellow, Department of Haematology, Guy's and St Thomas' NHS Foundation Trust, London and Dr Rui Duarte, Deputy Director, LR*i*G, University of Liverpool who provided feedback on a draft version of the report.

Rider on responsibility for report: The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

Declared competing interests of the authors: Dr Moonim participated in an event, hosted at Guy's hospital, that was sponsored by Novartis. Dr Oni is involved in running a clinical trial of avapritinib for systemic mastocytosis. The Department of Haematology at Guy's and St Thomas' is in receipt of funding for her salary from the company who sponsors avapritinib (Blueprint Medicines).

This report should be referenced as follows: Greenhalgh J, Lambe T, Nevitt S, Mahon J, Boland A, Beale S, Dundar Y, Edwards K, Bresnahan R, McEntee, J, Moonim MT. Midostaurin for treating advanced systemic mastocytosis [ID1573]: A Single Technology Appraisal. LR*i*G, University of Liverpool, 2020

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Sarah Nevitt	Critical appraisal of the statistical evidence
James Mahon	Critical appraisal of the economic model
Angela Boland	Critical appraisal of the clinical and economic evidence, editorial input
Sophie Beale	Critical appraisal of the clinical and economic evidence, editorial input
Yenal Dundar	Critical appraisal of the adverse event data and cross checking of the company search strategies
Katherine Edwards	Critical appraisal of the clinical evidence
Rebecca Bresnahan	Critical appraisal of the clinical evidence
Joanne McEntee	Critical appraisal of the company submission
Mufaddal Moonim	Clinical advice and critical appraisal of the clinical sections of the company submission

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AE	adverse event
AESI	adverse event of special interest
allo-HSCT	allogenic haematopoietic stem cell transplant
AML	acute myeloid leukaemia
ASM	aggressive systemic mastocytosis
CCM	current clinical management
CI	confidence interval
CS	company submission
CSR	clinical study report
DoR	duration of response
ECNM	European Competence Network on Mastocytosis
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
eMIT	electronic Market Information Tool
EPAR	European Public Assessment Report
EQ-5D-3L	EuroQol-5 Dimensions-3 Levels
ERG	Evidence Review Group
FAS	final analysis set
GDI	global distress index
HR	hazard ratio
HRG	Healthcare Resource Group
HRQoL	health-related quality of life
HSCT	haematopoietic stem cell transplant
HST	highly specialised technology
ICER	incremental cost effectiveness ratio
ICU	intensive care unit
ITT	intention-to-treat
IWG-MRT	International Working Group-Myeloproliferative Neoplasms Research and Treatment
K-M	Kaplan-Meier
MCL	mast cell leukaemia
MCS	mental composite score
mL	millilitre
MR	major response
MRI	magnetic resonance imaging
MSAS	Memorial Symptom Assessment Scale
NA	not applicable
NE	not estimated
NR	not reported
NSAID	non-steroidal anti-inflammatory drugs
ONS	Office for National Statistics
ORR	overall response rate
OS	overall survival
OWSA	one-way sensitivity analysis
PAS	Patient Access Scheme
PCS	physical composite score
PD	progressed disease
PEP	primary efficacy population
PF-no-response	progression-free without response to treatment
PF-response	progression-free with response to treatment
PFS	progression-free survival
PHYS	physical symptom subscale
PPS	per protocol set
PR	partial response
PSSRU	Personal Social Services Research Unit

PSYCH	psychological symptom subscale
QALY	quality adjusted life year
RCT	randomised controlled trial
RFS	relapse-free survival
SAE	serious adverse event
SES	safety evaluation set
SF-12	short form-12
SM	systemic mastocytosis
SM-AHN	systemic mastocytosis with an associated haematological neoplasm
SmPC	Summary of Product Characteristics
SoC	standard of care
STA	Single Technology Appraisal
TA	technology appraisal
TKI	tyrosine kinase inhibitor
TMSAS	Total Memorial Symptom Assessment Scale
WHO	World Health Organization
WTP	willingness-to-pay

1 EXECUTIVE SUMMARY

1.1 Scope of the submission

The remit of the Evidence Review Group (ERG) is to comment on the clinical and cost effectiveness evidence submitted to the National Institute for Health and Care Excellence (NICE) as part of the Single Technology Appraisal (STA) process. Clinical and economic evidence has been submitted to NICE by Novartis Pharmaceuticals UK Ltd in support of the use of midostaurin for the treatment of advanced systemic mastocytosis (SM). Systemic mastocytosis is a group of rare diseases in which uncontrolled growth and accumulation of mast cells (a type of white blood cell) occur in one or more organs.

Midostaurin was granted marketing authorisation by the European Medicines Agency (EMA) as a monotherapy for the treatment of adult patients with advanced SM in September 2017. It is the only treatment licensed in Europe for the treatment of advanced SM. Further, there are no UK clinical guidelines for the treatment of advanced SM. Clinical advice is that in the NHS treatment is tailored to the symptoms and needs of individual patients.

1.2 Critique of the decision problem in the company submission

1.2.1 Population and intervention

As highlighted in Section 2.5 of this ERG report, the decision problem addressed by the company matches the final scope issued by NICE in terms of intervention (midostaurin) and population (adults with advanced SM). In the company submission (CS), the company has estimated that the number of patients in England eligible for treatment with midostaurin is 174 (Section 2.4 of this ERG report). The company has presented clinical evidence for the whole advanced SM population and separately for the three subtypes: aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated haematological neoplasm (SM-AHN) and mast cell leukaemia (MCL). However, the company highlighted that, due to small numbers, there was considerable uncertainty around the reliability of the clinical results for each subtype. Clinical advice to the company was that an exploratory analysis that combined health outcome data from patients with SM-AHN and MCL in the D2201 trial was reasonable, based on the rationale that patients with SM-AHN and MCL have a much shorter life expectancy than patients with ASM.

The evidence to support the clinical effectiveness of midostaurin (licensed dose) was generated by two single arm, open label, phase II trials (D2201 [n=116] and A2213 [n=26]). Clinical advice to the ERG was that the baseline characteristics of patients participating in these trials were similar to the characteristics of patients treated in the NHS with advanced

SM. However, the results from these trials are difficult to interpret because of the open-label design, the lack of a comparator arm and small patient numbers for each disease subtype. Further, the positioning of midostaurin in the treatment pathway is not explicitly stated by the company; patients recruited to the D2201 trial had received between zero and four prior therapies, whilst those participating in the A2213 trial had received between zero and three prior therapies.

1.2.2 Comparators

Five comparators were listed in the final scope issued by NICE. Clinical advice to the company was that only three of these comparators were relevant (cladribine, interferon alpha and imatinib) and that the other two comparators listed in the final scope issued by NICE (nilotinib and dasatinib) were rarely used in the UK. However, clinical advice to the company was that pegylated-interferon alpha and acute myeloid leukaemia (AML) -like treatments were also relevant comparators. Clinical advice to the ERG supports the clinical advice provided to the company.

1.2.3 Outcomes

The outcomes listed in the final scope issued by NICE are overall survival (OS), progression-free survival (PFS), response rate, adverse events (AEs) and health-related quality of life (HRQoL). Clinical advice to the ERG is that these are important outcomes for patients with advanced SM. Whilst results from the D2201 and the A2213 trials provide information about the effectiveness of midostaurin, there is no randomised clinical trial evidence to support the clinical effectiveness of the three relevant comparators listed in the final scope issued by NICE or the two additional comparators identified by the company. Due to the limited data available, it was not possible for the company to carry out any indirect comparisons.

Overall survival

The company identified two comparisons (by Reiter et al and by Chandesris et al) that generated OS results for patients with advanced SM treated with midostaurin versus patients treated with other (unspecified) drugs.

Reiter et al compared pooled D2201 and A2213 trial data (n=89) with data from a German registry (n=42) and reported comparative (midostaurin versus unspecified treatments) OS hazard ratios (HRs) that favour treatment with midostaurin. However, the ERG has concerns about whether the D2201 and A2213 trial data should have been pooled (Section 3.6 of this ERG report). In addition, the ERG has concerns relating to the inputs (midostaurin data and

German registry data) and notes the differences between the results presented in the published abstract and those provided in the unpublished presentation.

Chandesris et al compared data from a cohort of patients receiving midostaurin in a French compassionate use programme (n=28) versus French registry data (n=44). The ERG highlights the small numbers of patients and the differences between the French cohorts and the patients recruited to the D2201 and A2213 trials (e.g., these trials did not include any patients with mast cell sarcoma or progressive smouldering SM). The ERG also highlights uncertainty (due to a lack of published information) around the methods used by Chandesris et al. As a consequence of these issues, the ERG considers that the results reported by Chandesris et al should not be used to inform decision making

Adverse events

The ERG agrees with the company that it is difficult to establish whether the Grade 3 or 4 haematological AEs reported in the D2201 and A2213 trials were related to treatment with midostaurin or to disease progression (Section 3.5 of this ERG report). Clinical advice to the ERG is that AEs arising from treatment with midostaurin, as with current unlicensed treatments for advanced SM, require careful monitoring by a specialist clinical team with the experience to provide early recognition and management of cytoreductive therapy-related AEs, and that this can place a high burden on NHS staff and systems.

1.2.4 Other issues

The company's economic analyses were carried out in line with the final scope issued by NICE. Midostaurin is currently available to the NHS at a discounted Patient Access Scheme (PAS) price. However, the company [redacted]. Azacitidine (included in the company's basket of comparator treatments) is also available to the NHS at a discounted PAS price. However, this price is confidential and not known to the company.

1.3 Summary of the ERG's critique of the submitted cost effectiveness evidence

In Section 4.6 of this ERG report, for the comparison of treatment with midostaurin versus current clinical management (CCM), the ERG has identified four major areas of concern relating to the company model:

- OS HR
- PFS for midostaurin versus current CCM
- partitioning survival outcomes
- lifetime duration of the treatment effect of midostaurin.

The overall survival hazard ratio

The source of the OS HR used in the company model is the Reiter et al unpublished presentation. The company sought expert clinical advice to help them identify the most appropriate OS HR; however, whilst the Reiter et al mulitivariable result was considered to be the most plausible, the range over which clinical experts considered the true OS HR might lie was very wide.

The company's base case incremental cost effectiveness ratio (ICER) per quality adjusted life year (QALY) gained for the comparison of the cost effectiveness of midostaurin versus CCM was £[redacted]. Results from the company's deterministic sensitivity analyses showed that using the upper and lower 95% confidence interval OS HR estimates (0.319 and 0.839 respectively) generated ICERs per QALY gained for the comparison of the cost effectiveness of midostaurin versus CCM of £[redacted] and £[redacted] respectively, demonstrating that the OS HR is the key driver of cost effectiveness results. Thus, without a robust and accurate OS HR estimate, it is not possible to produce reliable cost effectiveness results. The ERG has not been able to identify a robust source for the OS HR and, therefore, has not been able to generate preferred cost effectiveness results.

As discussed in Section 4.7 of this ERG report, the OS HR is so important to the base case cost effectiveness results that without a level of certainty around this estimate, discussions about other model-related concerns are largely academic. The ERG has indicated whether improved modelling of these effects would be likely to increase or decrease the cost effectiveness of midostaurin versus CCM.

Progression-free survival for midostaurin versus current clinical management

The company was not able to identify any comparative PFS data. Therefore, based on clinical advice, the company set the PFS HR equal to the OS HR. There is no way of knowing whether this assumption is reasonable. However, even if the approach were valid, given the uncertainty around the magnitude of the OS HR, the PFS HR would be similarly uncertain. It is not known whether setting the PFS HR equal to the OS HR leads to an under- or over-estimate of the true PFS experience of patients receiving CCM. Thus, it is not known whether using the OS HR as a proxy for the PFS HR leads to an under- or over-estimate of the ICER per QALY gained for the comparison of midostaurin versus CCM.

Partitioning progression-free survival

The PF health state in the company model is partitioned into a PF-response health state and a PF-no-response health state to reflect the assumption that HRQoL differs between responders and non-responders. The ERG has concerns about the reliability of the overall response rates and duration of response estimates used in the company model and therefore considers that it was not appropriate to use these estimates to partition PFS (nor would it have been appropriate to use them to partition OS).

Lifetime duration of midostaurin treatment effect

In the D2201 trial, only 19% of patients were still receiving midostaurin at 3 years; however, the treatment benefit attributed to receipt of midostaurin was modelled to persist over the 38-year model time horizon. Given the proportionally short time frame over which patients received midostaurin, the ERG considers that it would be clinically implausible to assume patients benefited from this treatment for the whole model time horizon. Rather, the ERG considers that at some point before 38 years, it is likely that the progression and mortality rates of patients initially assigned treatment to midostaurin and CCM would become equal. The effect of equalising progression and mortality rates at some point during the model time horizon on the comparative cost effectiveness of midostaurin versus CCM would increase the size of the ICER per QALY gained.

1.3.1 Summary of company's case for NICE End of Life criteria being met

A technology meets NICE End of Life criteria if (i) life expectancy with standard of care treatments for the target population is under 24 months and (ii) the increase in life expectancy with the technology being appraised is at least 3 months. The company considers that midostaurin meets both criteria and should be considered as an End of Life treatment.

1.3.2 Short life expectancy (normally ≤24 months)

The life expectancy of patients with advanced SM varies significantly across disease subtypes. Published median survival times from diagnosis range from 41 months to 11 years for patients with ASM, from 24 months to 4.4 years for patients with SM-AHN and from 2 months to 9.2 months for patients with MCL. The company has suggested that published life expectancy estimates for patients with SM-AHN may be too high as they include unknown proportions of patients with indolent SM (ISM-AHN). Patients with ISM-AHN have a longer life expectancy than patients with SM-AHN and are not included in the population being considered in this appraisal.

Median OS reported by Reiter et al for a cohort of patients with ASM, SM-AHN and MCL who received treatment other than midostaurin was 19.5 months. Further, clinical advice to the company was that patients with advanced SM would normally have a life expectancy of less than 24 months and life expectancy would be even lower in the SM-AHN+MCL combined subgroup.

1.3.3 Life extension (normally ≥3 months)

Results generated by the company model and by Reiter et al suggest that treatment with midostaurin probably offers a life extension of ≥3 months when used to treat patients with advanced SM and also when used to treat the SM-AHN+MCL combined subgroup (see Table).

Estimated life extension as a consequence of receiving midostaurin

Population	Midostaurin versus CCM: life extension	
	Company model: mean	Reiter et al: median
Advanced SM	[redacted] months	21.9 months
SM-AHN+MCL subgroup	[redacted] months	NR

CCM=current clinical management; MCL=mast cell leukaemia; NR=not reported; SM=systemic mastocytosis; SM-AHN=systemic mastocytosis with an associated haematological neoplasm
Source: Company model and Reiter et al

1.4 ERG commentary on NICE End of Life criteria

Due to concerns about the reliability of available evidence, the ERG has not generated any preferred or alternative cost effectiveness results (Section 4.7 of this ERG report). This means that the ERG has been unable to present alternative survival estimates for midostaurin or CCM.

1.4.1 Short life expectancy (normally ≤24 months)

Given disease subtype is determined before treatment commences and life expectancy ranges are wide for each subtype, the ERG considers that applying End of Life criteria to the whole advanced SM population is not appropriate.

The published subtype evidence presented by the company suggests that the short life expectancy criterion is not met for patients with ASM, is possible (but unlikely) to be met for patients with SM-AHN and is met for patients with MCL. Assessing short life expectancy for the combined subgroup (SM-AHN+MCL) is therefore problematic.

1.4.2 Life extension (normally ≥3 months)

Whilst the results presented by the company demonstrate that treatment with midostaurin extends life by ≥3 months compared with treatment with CCM, concerns relating to the OS HR used to generate the overall and combined subgroup results cast considerable doubt over their validity.

1.5 Summary of exploratory and sensitivity analyses undertaken by the ERG

Due to the uncertainty around the company's OS HR estimate (the key driver of model cost effectiveness results), the ERG has not generated any preferred or alternative cost effectiveness results. Also, as the ERG considers that the company's assumption that the effect of treatment with midostaurin on OS and PFS lasts a lifetime is optimistic, this may mean that the company base case cost effectiveness results for the comparison of midostaurin versus CCM are underestimates.

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

The focus of this appraisal is on the use of midostaurin to treat adult patients with advanced systemic mastocytosis (SM).[1]

Mastocytosis encompasses a heterogenous group of rare diseases.[2,3] Advanced SM is the most severe form of mastocytosis and, following diagnosis, patients are classified as having one of three subtypes: aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated haematological neoplasm (SM-AHN) or mast cell leukaemia (MCL).[3] In Europe, advanced SM is a rare disease with a reported prevalence of 0.06 per 100,000 population across all subtypes; however, the exact prevalence in the UK is not known.[4] The disease mostly occurs in Caucasian adults (males and females) and is most frequently diagnosed in people over 60 years old.[5]

In advanced SM, mast cells infiltrate various tissues and organs, commonly the bone marrow, spleen, liver, lymph nodes and gastrointestinal tract.[3] Advanced SM is associated with a wide range of physical symptoms related to increased mast cell proliferation and activity.[3,6,7] Symptoms can include fatigue, itching, bone or muscle pain, osteoporosis, fractures or anaphylactic reactions. Patients may present with organ dysfunction (for example, organomegaly, organopathy or organ failure) which arises from mast cell accumulation within organs.[8]

For the majority of patients with advanced SM, treatment involves symptom control alongside cytoreductive therapy. Cytoreductive therapy aims to reduce the underlying mast cell burden and alleviate disease-related organ dysfunction.[9] However, UK clinical experts estimate that one third of patients with advanced SM are unable to receive cytoreductive therapy due to frailty or risk of cytopenia.[10] For these patients, disease management involves symptom control alongside supportive or palliative care. For patients with SM-AHN, the treatment pathway is influenced by the nature and severity of the associated haematological neoplasm. Clinical advice to the company was that the associated haematological neoplasm is treated separately and may be prioritised over treatment for the SM component of the disease.[11]

Life expectancy for patients with advanced SM is just under 24 months from time of diagnosis, though this varies by disease subtype.[12] Patients with MCL have the shortest life expectancy, ranging from less than 2 months to 9.2 months.[7,13] For patients with SM-AHN, life expectancy ranges from 24 months to 4.4 years,[4,7] and for patients with ASM life expectancy ranges from

41 months to 11 years.[7,14] However, the company has suggested that published life expectancy estimates for patients with SM-AHN may be too high as they include unknown proportions of patients with indolent SM. Advanced SM also has a negative impact on patient and carer health-related quality of life (HRQoL) due to symptom burden.[15,16]

2.2 Company's overview of current service provision

There is currently no established treatment pathway for patients with advanced SM; however, clinical advice to the company is that local UK-specific guidelines are expected to be published in 2021. In the company submission (CS), the company states that only three centres in England manage patients with advanced SM (CS, p15). The company has devised the treatment algorithm displayed in Figure 1 using the National Comprehensive Cancer Network[17] guidelines and feedback from their clinical advisors.

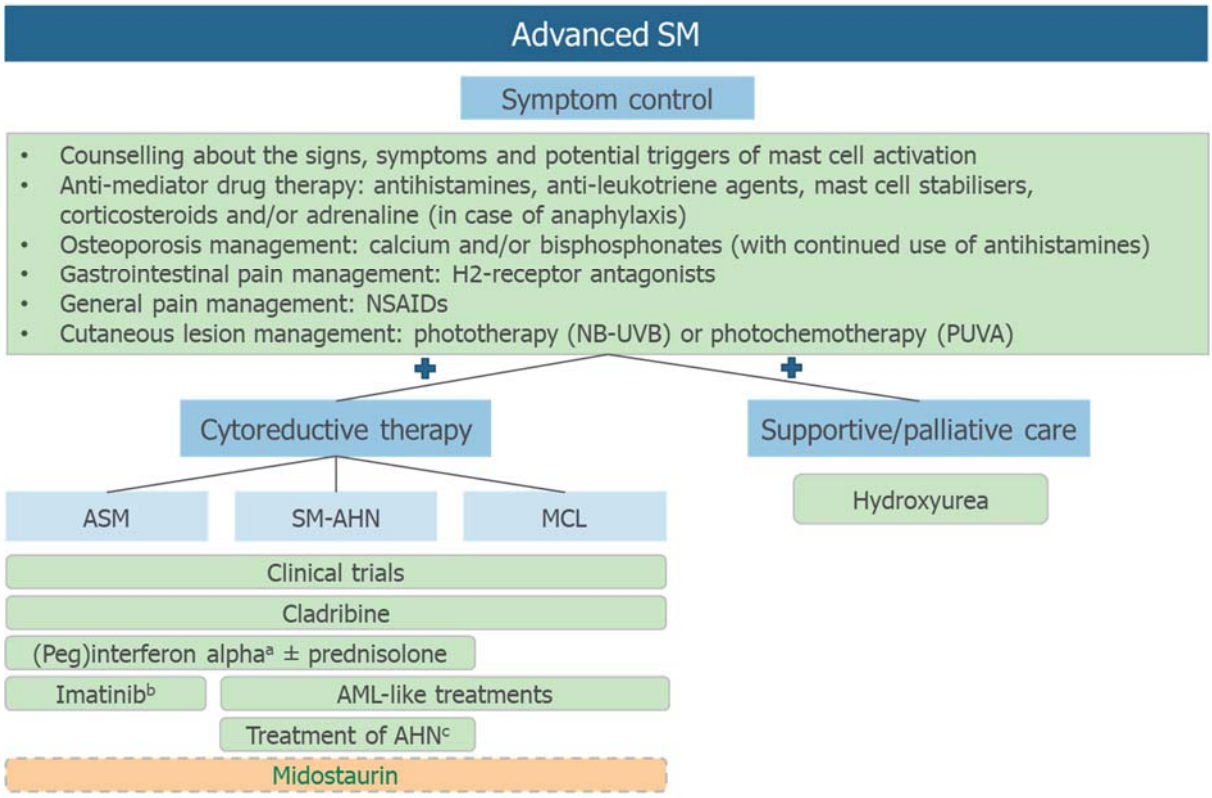

Figure 1 Anticipated pathway of care for patients with advanced SM in the UK

[a] Pegylated or un-pegylated interferon alpha with or without prednisolone
[b] Only if KIT D816V mutation negative or if eosinophilia is present with FIP1L1-PDGFRA fusion gene
[c] For patients with SM-AHN, only if SM component treatment takes precedence over AHN component treatment

AML=acute myeloid leukaemia; ASM=aggressive systemic mastocytosis; HSCT=haematopoietic stem cell transplant; MCL=mast cell leukaemia; NB-UVB=narrowband ultraviolet B; NSAIDs=non-steroidal anti-inflammatory drugs; PDGFRA=platelet dependent growth factor receptor A; PUVA=psoralen plus ultraviolet A; SM=systemic mastocytosis; SM-AHN=systemic mastocytosis with associated haematologic neoplasm
Source: CS, Figure 3

In the NHS, treatment is selected based on individual patient symptoms.[17,18] The company highlights that the diagnosis of advanced SM is challenging, given that is it is both a rare disease and has a range of non-specific symptoms. Clinical advice to the Evidence Review Group (ERG) is that time from symptom presentation to diagnosis can vary by subtype and that patients with SM-AHN are often diagnosed more quickly than patients with ASM or MCL due to the recognisable involvement of the associated haematological neoplasm.

The only curative treatment is allogenic haematopoietic stem cell transplant (allo-HSCT). Only a few patients are suitable for transplant; the vast majority are treated with cytoreductive therapy in combination with symptom management. Current cytoreductive treatment options for all patients with advanced SM are listed in the final scope[1] issued by NICE (i.e., interferon alpha, cladribine, imatinib, nilotinib and dasatinib).

Choice of cytoreductive treatment is largely patient-specific, depending on symptoms. Clinical advice to the ERG is that cladribine is usually the first treatment offered to patients. Imatinib is used only to treat patients with a sensitising mutation or a wild type mutation of advanced SM. As noted by the company, nilotinib and dasatinib are not commonly used in UK clinical practice. None of the comparator treatments listed in the final scope[1] issued by NICE has a European marketing authorisation for the treatment of advanced SM.

Following treatment with a cytoreductive therapy, symptoms are continually reassessed in line with the progressive nature of advanced SM. Treatment failure is defined as a lack of response or disease progression; on treatment failure, patients are reassessed and may receive an alternative form of cytoreductive therapy.

Other treatment options that may be considered for some patients include pegylated interferon alpha and AML-like (acute myeloid leukaemia) treatments. The company states that treatment with pegylated or un-pegylated interferon alpha has led to only minor or partial response, with best response at 1 year or more. Interferon (pegylated or un-pegylated) is also poorly tolerated, leading to toxicities in up to 75% of patients and a high dropout rate.[2,9,19] Peg-interferon alpha is more commonly used in UK clinical practice.[10]

For patients who are unable to be treated with cytoreductive therapies due to frailty or high risk of cytopenia, supportive or palliative care is provided.[10] This may include treatment with hydroxyurea to reduce mast cell burden alongside standard palliative treatments.[10]

2.3 Midostaurin

A summary of the details of the mechanism of action and the European marketing authorisation for midostaurin are shown in Box 1. The company highlights (CS, p15) that midostaurin is the only medicine to currently have a European marketing authorisation for adult patients with advanced SM.

Box 1 Midostaurin

- Midostaurin is an inhibitor to several receptor tyrosine kinases, including a mast/stem cell growth factor receptor (also known as *KIT* or CD117).[20] Up to 96% of patients with advanced SM have an active mutation in the *KIT* gene which results in mast cell proliferation and growth.[21] Midostaurin inhibits signalling in the *KIT* receptor to decrease mast cell production.[22]
- On 18th September 2017, the European Medicines Agency (EMA) granted marketing authorisation to midostaurin (Rydapt®) for use as a monotherapy for the treatment of adult patients with advanced SM (ASM, SM-AHN and MCL).[23]
- Midostaurin has also received orphan designation from the EMA for the treatment of adult patients with advanced SM.[24]
- Midostaurin is an oral therapy with a recommended dose of 100mg twice daily for patients with advanced SM.[20]

ASM=aggressive systemic mastocytosis; EMA=European Medicines Agency; MCL=mast cell leukaemia; SM=systemic mastocytosis; SM-AHN=systemic mastocytosis with associated haematologic neoplasm
Source: adapted from CS, Table 2 and CS, p15

2.4 Number of patients eligible for treatment with midostaurin

Given the rarity of the disease, the exact incidence of advanced SM is not known.[25] The company has used Danish incidence data[4] from a cohort of 547 patients diagnosed with advanced SM between 1997 and 2010, along with UK population figures from 2018,[26] to estimate the total number of patients (n=174) with advanced SM in England eligible for treatment with midostaurin. The estimated incidence and prevalence rates of advanced SM in Europe by disease subtype are presented in Table 1, whilst Table 2 shows the estimated total number of patients in England with advanced SM across the three subtypes.

Table 1 Estimated incidence and prevalence rates of advanced SM subtypes in Europe

Disease subtype	Incidence estimates per 100,000	Prevalence estimates per 100,000	Source
ASM	0.01 (0.006 to 0.03)	0.09 (0.03 to 0.21)	Cohen et al (2014)[4]
SM-AHN	0.04 (0.03 to 0.06)	0.31 (0.18 to 0.50)	Cohen et al (2014)[4]
MCL	0.01 (0.003 to 0.02)	0.00	Cohen et al (2014)[4]

ASM=aggressive systemic mastocytosis; MCL=mast cell leukaemia; SM=systemic mastocytosis; SM-AHN=systemic mastocytosis with associated haematologic neoplasm.
Source: CS, Table 5

Table 2 Assumption and calculation of the patient population with advanced SM eligible for treatment with midostaurin

Assumption		Value	Reference
Incidence			
1	Incidence of ASM	0.01/100,000	Epidemiology of SM in Denmark[4]
	Incidence of SM-AHN	0.04/100,000	
	Incidence of MCL	0.01/100,000	
	Incidence of advanced SM	**0.06/100,000**	
2	England population (2018)	55,977,000	ONS[26]
3	**England incidence of advanced SM (2018)**	**34**	**Calculation (assumption 1 x assumption 2)**
Prevalence			
4	Prevalence of ASM	0.09/100,000	Epidemiology of advanced SM in Denmark[4]
	Prevalence of SM-AHN	0.31/100,000	
	Prevalence of MCL	0.00/100,000	
	Prevalence of advanced SM	**0.40/100,000**	
5	**England prevalence of advanced SM (2018)**	**224**	**Calculation (assumption 2 x assumption 4)**
Total advanced SM population eligible for treatment			
6	**Advanced SM in England**	**258**	**Calculation (assumption 3 + assumption 5)**
7	Proportion of patients eligible for cytoreductive therapy (e.g., midostaurin)	67%	Clinical opinion (Proportion of patients *ineligible* for cytoreductive therapy=33%)[10]
8	**Patients in England eligible for treatment with midostaurin**	**174**	**Calculation (assumption 6 x assumption 7)**

ASM=aggressive systemic mastocytosis; MCL=mast cell leukaemia; ONS=Office for National Statistics; SM=systemic mastocytosis; SM-AHN=systemic mastocytosis with associated haematologic neoplasm
Source: CS, Table 6 (p21)

The company highlights (CS, p25) that NICE did not consider treatment with midostaurin to be eligible for assessment under NICE's Highly Specialised Technology (HST) process, despite the rare incidence of advanced SM. The ERG notes (from NICE's response to comments on the draft scope[27]) that treatment with midostaurin does not meet the criteria for consideration as a HST as it is already used in the NHS to treat a different disease (FLT3-positive AML) and because mastocytosis is not managed within a highly specialised service.

2.5 Critique of company's definition of the decision problem

A summary of the ERG's comparison of the decision problem outlined in the final scope[1] issued by NICE and that addressed within the CS is presented in Table 3. Each parameter is discussed in more detail in the text following the table (Section 2.6 to Section 2.11).

Table 3 Comparison between NICE scope and company's decision problem

Parameter	Final scope issued by NICE (original wording)	Decision problem addressed in the company submission with rationale
Intervention	Midostaurin	As per scope
Population	Adults with ASM, SM-AHN or MCL	As per scope, results were provided individually for each disease subtype
Comparator (s)	Current clinical management including but not limited to: • Interferon alpha • Cladribine • Imatinib • Nilotinib • Dasatinib (These treatments do not currently have a marketing authorisation in the UK for this indication)	Current clinical management including: • Interferon alpha • Cladribine • Imatinib • Pegylated interferon alpha (peg-interferon alpha) • AML-like treatments
Outcomes	The outcome measures to be considered include: • OS • PFS • Response rate • AEs • HRQoL	As per scope
Economic analysis	• The Reference Case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per QALY • The Reference Case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared • Costs will be considered from an NHS and PSS perspective • The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account	As per scope
Subgroups	If evidence allows, subgroup analysis by disease type to include: • ASM • SM-AHN • MCL	Cost effectiveness results were generated for the overall population (ASM+SM-AHN+MCL) and for the combined SM-AHN+MCL population

AE=adverse event; AML=acute myeloid leukaemia; ASM=aggressive systemic mastocytosis; HRQoL=health-related quality of life; MCL=mast cell leukaemia; OS=overall survival; PAS=patient access scheme; PFS=progression-free survival; PSS=Personal Social Services; QALY=quality adjusted life year; SM-AHN=systemic mastocytosis with associated haematological neoplasm
Source: Final scope[1] issued by NICE, CS, Table 1

2.6 Population

In accordance with the final scope[1] issued by NICE, the company has presented clinical effectiveness evidence for patients with ASM, patients with SM-AHN and patients with MCL. The company has also presented clinical effectiveness evidence for an overall population of patients with advanced SM (i.e., ASM+SM-AHN+MCL).

The evidence discussed in the CS is derived from two single arm, open label, phase II trials, the D2201[28-30] trial (n=116) and the A2213[31] trial (n=26). Clinical advice to the ERG was that the baseline characteristics of patients recruited to the D2201 and the A2213 trials were comparable to the baseline characteristics of patients with advanced SM who are treated in the NHS. However, the ERG notes that there are small numbers of patients within each disease subtype in these trials (Table 4).

Table 4 Advanced SM subtypes (D2201 and A2213 trials)

Disease subtype	D2201 (N=116)	A2213 (N=26)
ASM	22 (19%)	3 (12%)
SM-AHN	73 (63%)	17 (65%)
MCL	21 (18%)	6 (23%)

ASM=aggressive systemic mastocytosis; MCL=mast cell leukaemia; SM-AHN=systemic mastocytosis with associated haematological neoplasm
Source: Adapted from CS, Table 10

2.7 Intervention

Midostaurin is a cytoreductive therapy and is a multi-kinase inhibitor administered orally at a dose of 100mg twice daily.[23] The company has presented evidence for the licensed dose of midostaurin. Midostaurin is the only drug licensed in Europe to treat ASM, SM-AHN and MCL (CS, p24).

2.8 Comparators

As noted in Section 2.2 of this ERG report, there are no UK clinical guidelines for the treatment of advanced SM. Clinical advice to the company (CS, p21), and clinical advice to the ERG, is that in the NHS, the treatment of ASM, SM-AHN and MCL is tailored to each patient according to their symptoms.

The comparator treatments listed in the final scope[1] issued by NICE are interferon alpha, cladribine, imatinib, nilotinib and dasatinib. None of the listed comparators has a European marketing authorisation for the treatment of advanced SM. In terms of treatments for advanced SM, clinical advice (to the company [CS, p24] and to the ERG) is that in the NHS: i) nilotinib and dasatinib are rarely used; ii) imatinib is only used to treat the few patients who do not have

the *KIT* D816V mutation, and iii) pegylated interferon alpha and AML-like treatments are used (off licence).

There is no randomised controlled trial (RCT) evidence to support the clinical effectiveness of the five comparators (interferon alpha, cladribine, imatinib, nilotinib and dasatinib) listed in the final scope[1] issued by NICE, or the two comparators (pegylated interferon alpha and AML-like treatments) identified by the company for the treatment of advanced SM. However, the company identified eight[32-39] published studies (single-arm trials or observational studies) that assessed the clinical effectiveness of the individual comparators listed in the final scope[1] issued by NICE. The company also identified three publications[12,40,41] and an unpublished presentation[37] that reported the results of comparisons of health outcomes of patients with advanced SM treated with midostaurin versus patients treated with other (unspecified) drugs using data from European patient registries.

The ERG considers that the Reiter et al abstract[12] and unpublished presentation[12,42] are the most reliable sources of evidence to inform a decision about the comparative effectiveness of midostaurin versus standard of care (SoC) or midostaurin versus comparators. However, the ERG emphasises that there are several areas of uncertainty relating to the Reiter et al[12,42] methods and results (see Section 3.6 of this ERG report). The ERG highlights that only the numbers reported in the presentation[42] are used in the company cost effectiveness analyses (and that some of these unpublished values differ from those reported in the published abstract,[12] albeit the results provided in the unpublished study and subsequently used in the company base case are less favourable than the abstract).

The analysis methods used by Chandesris et al[40,41] are insufficiently described leading to uncertainty around the validity of the presented results. The ERG considers that these results should not be used to inform a decision about the comparative effectiveness of midostaurin versus SoC or midostaurin versus comparators (see Section 3.6 of this ERG report).

2.8 Line of treatment

The EMA's marketing authorisation[23] for treatment with midostaurin does not explicitly state whether midostaurin is to be used as a first-line or subsequent-line treatment; nor is line of treatment explicitly stated by the company in the CS. In the D2201 and A2213 trials, 55% and 19% of patients, respectively, had not received at least one previous treatment for advanced SM before being treated with midostaurin; data from the D2201 trial are used to populate the company's economic model.

2.9 Outcomes

Clinical advice to the ERG is that the health outcomes listed in the final scope[1] issued by NICE and addressed by the company are important outcomes for patients with ASM, SM-AHN and MCL.

No comparative progression-free survival (PFS), adverse event (AE) or HRQoL data have been published for patients with advanced SM. Furthermore, AE data for patients with advanced SM treated with midostaurin are limited to the safety outcomes of the 142 patients who were recruited to the single arm, open label, trials of midostaurin (D2201 and A2213 trials).

In the midostaurin trials and in most of the trials of the comparator treatments, objective response rate (ORR) was assessed using the modified Valent and Cheson[43] criteria. In one[44] of the comparator trials, ORR was measured using the more recently published criteria from the International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) & European Competence Network on Mastocytosis (ECNM), generally referred to as the IWG[45] criteria. Clinical advice to the ERG is that the Valent and Cheson[43] criteria and the IWG[45] criteria are measures of treatment response that are used in the NHS.

2.10 Economic analysis

As specified in the final scope[1] issued by NICE, the cost effectiveness of treatment was expressed in terms of incremental cost per quality adjusted life years (QALYs) gained. Outcomes were assessed over a 38-year time horizon. Costs were considered from an NHS and a Personal Social Services perspective.

Confidential Patient Access Scheme (PAS) discounts are in place for midostaurin and azacitidine (the latter is used in the company's basket of comparator treatments). The PAS price of azacitidine is not known to the company. The actual discounted price of midostaurin and an assumed discounted price of azacitidine were used in the company model. The company highlights (CS, p14) that [redacted]. List prices for all other comparator treatments were used in the company model.

The company has put forward a case for midostaurin to be assessed under NICE's End of Life criteria.[46]

2.11 Other considerations

In the final scope[1] issued by NICE it is stipulated that, if the evidence allows, subgroup analysis by disease subtype (ASM, SM-AHN, MCL) should be considered.

The company considers that separate economic analyses for each of the three disease subtypes (ASM, SM-AHN and MCL) would be appropriate as the clinical activity and prognosis associated with each of these disease subtypes are heterogeneous. However, the company also states (CS, pg67) that results from such analyses would be associated with 'considerable uncertainty' as the only available source of effectiveness data is the D2201 trial (a single arm, open label, trial with very limited patient numbers for each disease subtype).

Instead, the company presented the results of an exploratory cost effectiveness analysis for the combined subgroup of patients with SM-AHN and MCL. Clinical advice to the company was that an exploratory subgroup analysis using the combined health outcome data from patients with SM-AHN and MCL in the D2201 trial was reasonable, based on the rationale that patients with SM-AHN and MCL have a much shorter life expectancy than patients with ASM.

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

The full details of the company's search strategy and the methods used to identify and select the clinically relevant evidence of the effectiveness of midostaurin for the treatment of advanced SM are presented in the CS, Appendix D. The ERG did not identify any additional relevant studies to those previously identified by the company. Overall, the ERG considers that the methods used by the company to conduct a systematic review of the clinical effectiveness evidence were mostly satisfactory (Table 5).

Table 5 ERG appraisal of systematic review methods

Review process	ERG response	Note
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	Yes	See CS, Appendix D.3, Table D.3.1.
Were appropriate sources searched?	Yes	Sources searched were: MEDLINE, Embase, the Cochrane Library, peer-reviewed journals, and the ClinicalTrials.gov trial registry (including ongoing studies). Manual searches of abstracts from relevant conference proceedings were also conducted.
Was the timespan of the searches appropriate?	Yes	Searches were conducted in October 2019. Databases were searched from inception to the search date. Conference proceedings published from January 2017 to October 2019 were hand-searched in November 2019. Targeted searches were conducted in January 2020 to identify any clinical databases or patient registries for SM.
Were appropriate search terms used?	Yes	No additional ERG comments.
Were the eligibility criteria appropriate to the decision problem?	Yes	No additional ERG comments.
Was study selection applied by two or more reviewers independently?	Yes	No additional ERG comments.
Was data extracted by two or more reviewers independently?	No	Data were extracted by a single reviewer, however, extracted data were then checked and verified by a second reviewer.
Were appropriate criteria used to assess the risk of bias and/or quality of the primary studies?	Partially	The company used a modified version of the Downs and Black checklist [47] for quality assessment and used their own method of interpreting results. See Section 3.2.2 of the ERG report for details.
Was the quality assessment conducted by two or more reviewers independently?	No	Quality assessment was conducted by a single reviewer. A second reviewer confirmed the assessment and highlighted any discrepancies.
Were attempts to synthesise evidence appropriate?	N/A	The company was unable to conduct any robust indirect or mixed treatment comparisons because the evidence for midostaurin and its relevant comparators was derived from single-arm trials and observational studies.

N/A=not applicable; SM=systemic mastocytosis
Source: LRiG in-house checklist

3.2 Critique of trials: company's analysis and interpretation

3.2.1 Included trials

The company identified two trials (the D2201 trial and the A2213 trial) that provided evidence to demonstrate the clinical effectiveness of midostaurin for the treatment of advanced SM. Both trials are open label, phase II trials. In addition, both are single-arm trials and thus neither trial provides direct evidence comparing the effectiveness of midostaurin versus any of the comparators listed in the final scope[1] issued by NICE or identified by the company.

The company identified a further eight studies[32-39] that provide clinical effectiveness evidence for the five comparators listed in the final scope[1] issued by NICE, namely: interferon alpha,[32,35-37] cladribine,[34-37,39] imatinib,[35-37] nilotinib,[33] and dasatinib.[38] Two of the identified studies are single-arm trials,[33,38] two are case series studies,[33,39] and the remaining four are retrospective observational studies.[34-37] It was, therefore, not possible for the company to perform indirect treatment comparisons to estimate the relative effectiveness of midostaurin versus any of the comparators listed in the final scope[1] issued by NICE.

The company search, however, identified two historical control analyses (by Reiter et al[12,42] and Chandesris et al,[40,41]) that compared treatment with midostaurin versus treatment with SoC. The abstract[12] and presentation by Reiter et al,[42] describe results from a comparison of pooled data from the D2201 trial and the A2213 trial versus historical control data obtained from a German registry. The publications by Chandesris et al,[40,41] describe results from a comparison of prospective observational study of patients receiving midostaurin under a French compassionate use programme versus historical control data from a French registry. The Reiter et al[12,42] and Chandesris et al[40,41] publications and presentation provide the only available evidence for the comparison of treatment with midostaurin versus SoC.

Midostaurin trial characteristics

The key characteristics of the D2201 and A2213 trials are summarised in Table 6.

Both trials were non-randomised, single arm, open label, phase II trials. Although both trials were multi-centre trials, only the D2201 trial was conducted internationally; the A2213 trial was conducted across three centres, all of which were based in the USA. The D2201 trial recruited four patients from the UK; the remaining 138 patients were recruited from other European countries, Australia, and the USA. Clinical advice to the ERG is that the management of patients with advanced SM in Europe, Australia and the USA is comparable to the management of patients with advanced SM in the NHS. The ERG notes that the median

duration of follow-up for the primary outcome of ORR, was longer in the A2213 trial (124 months) than in the D2201 trial (26 months).

Table 6 Key characteristics of the D2201 and A2213 trials

Trial parameters	D2201	A2213
Design	• Phase II, multi-centre, open label, single arm, international, N=116 • Adapted Fleming[48] two-stage design	• Phase II, investigator-led, multi-centre, open label, single arm, N=26 • Simon[49] two-stage design
Patient population	• Adults (≥18 years of age) with a diagnosis of ASM, SM-AHN or MCL according to WHO criteria[50,51] • Presence of ≥1 C-findings • ECOG[52] performance status 0-3	• Adults (≥18 years of age) with histologically documented ASM, SM-AHN or MCL • Presence of ≥1 C-findings • ECOG[52] performance status 0-3
Primary outcome	Best response defined as the percentage of participants who classified as confirmed responders (MR or PR within the first 6 treatment cycles and maintained for ≥8 weeks) based on modified Valent and Cheson[43] criteria	Best response defined as the percentage of participants who classified as confirmed responders (MR or PR within the first 2 treatment cycles and maintained for ≥8 weeks) based on published Valent and Cheson[43] criteria
Median length of follow-up for ORR	26 months (range 12 to 54)*	124 months (range 82 to 140)**
ERG comment	• 4 patients recruited in the UK • No control or comparator group	• Small patient numbers • No trial centres in the UK • No control or comparator group

ASM=aggressive systemic mastocytosis; SM-AHN=systemic mastocytosis with associated haematologic neoplasm; ECOG=Eastern Cooperative Oncology Group; MCL=mast cell leukaemia; MR=major response; ORR=overall response rate; PR=partial response; SM-AHN=systemic mastocytosis with associated haematologic neoplasm; WHO=World Health Organisation
Source: Adapted from CS, Table 9 and CS, p48*, CS, p57**

Baseline characteristics of patients participating in the midostaurin trials

Full details of the baseline characteristics of patients participating in the D2201 and A2213 trials are provided in the CS (Table 10), and a summary is presented in this ERG report (Table 7). Clinical advice to the ERG is that the patients recruited to the two trials are generally representative of patients with advanced SM treated in the NHS. However, clinical advice to the ERG is also that the proportions of patients with MCL in the D2201 (18%) and A2213 (23%) trials are greater than the proportion that would be seen in NHS clinical practice with this disease subtype. Compared with patients participating in the D2201 trial, a higher proportion of the patients recruited to the A2213 trial presented with an ECOG performance status of 2 to 3, and a higher proportion presented with three or more C-findings. Data from

the trials suggest that the patients participating in the A2213 trial had greater disease burden than patients participating in the D2201 trial, and the difference is acknowledged by the company (CS, p39). Approximately half of the patients in the D2201 trial (55%) and a fifth of patients in the A2213 trial (19%) were treatment naive.

Table 7 Baseline characteristics of patients in the D2201 and A2213 trials

Baseline characteristic	D2201 (N=116)	A2213 (N=26)
Age (years)		
Median (range)	63.0 (25–82)	64.5 (24–79)
Sex – n (%)		
Male	76 (66)	15 (58)
Female	40 (34)	11 (42)
ECOG performance status – n (%)		
0	[redacted]	12 (46)
1	[redacted]	
2	[redacted]	14 (54)
3	[redacted]	
Number of previous therapies – n patients (%)		
0	64 (55)	5 (19)
1	29 (25)	8 (31)
2	15 (13)	6 (23)
≥3	8 (7)[a]	7 (27)
Subtype of advanced SM – n (%)		
ASM	22 (19)[b]	3 (12)
SM-AHN	73 (63)[b]	17 (65)
MCL	21 (18)	6 (23)[d]
***KIT* D816 mutation status – n (%)**		
Positive	98 (84)	20 (77)
Negative	13 (11)	5 (19)
Other	5 (4)[c]	1 (4)[e]
Bone marrow mast-cell burden – %		
Median (range)	40 (3–98)	50 (5–95)
Serum tryptase level – µg/L		
Median (range)	200 (2–12,069)	323 (22–1,255)
Number of C-findings per patient – n patients (%)		
1	31 (27)	3 (12)
2	20 (17)	10 (38)
≥3	38 (33)	13 (50)

[a] Therapy in some of these cases was directed toward the AHN component of SM-AHN. [b] These numbers were derived from the EPAR and calculated by subtracting the known number of patients in each category from the total number of patients in the trial. [c] KIT D816 mutation status unknown. [d] Two MCL patients had chronic myelomonocytic leukemia-1 as an AHN.
[e] The patient was positive for the KIT S451C mutation.
ASM=aggressive systemic mastocytosis; MCL=mast cell leukaemia; SM-AHN=systemic mastocytosis with associated haematologic neoplasm.
Source: Adapted from CS, Table 10

3.2.2 Quality assessment of the D2201 and A2213 trials

The company conducted a quality assessment of the D2201 and A2213 trials using a modified version of the Downs and Black[47] checklist (Table 8). To summarise and interpret the responses to the items in the modified checklist, the company used their own method (see Appendix 7.1.1 of this ERG report for ERG comment).

Table 8 Company's modifications to the Downs and Black quality assessment checklist

Company modification	Item description	ERG critique
Item 27 of the checklist	Was the study sufficiently powered to detect clinically important effects where probability value for a difference due to chance is <5%?	The company gives a simplified answer of yes, no or unclear for item 27 (0-1 points) rather than a graded answer (0-5 points). The ERG notes that this modification is widely used and accepted.
Exclusion of item 23 and 24 from the checklist	Item 23. Were study subjects randomised to intervention groups? Item 24. Was the randomised intervention assignment concealed from patients and staff until recruitment was complete?	The guidance from Downs and Black[47] is that the response to Items 23 and 24 should be 'no' for non-randomised studies.
Modification of item 5 from the checklist	Are the distributions of principal confounders in each group of subjects clearly described?	The company gives a simplified response of 'yes', 'no' or 'unclear' for item 5 (0-1 points) rather than a graded answer (0-2 points).

Source: LRiG in-house table

The company assessed the D2201 trial as being of good quality and the A2213 trial as being of reasonable quality (Table D.11.2, Appendix D.11 to the CS). The ERG considers that the company's assessments of the methodological quality of the D2201 and the A2213 trials are not reliable as the assessments are based on non-validated methodology. However, the ERG considers that the D2201 and the A2213 trials appear to be of a higher methodological quality than the studies of the comparator treatments.

The company's risk of bias assessments for the D2201 and A2213 trials, with ERG comments, are presented in Table 9. (The ERG has reinstated the two items [23 and 24]) omitted from the company's assessment). The ERG considers the strengths of the two trials are that they were well reported, patients recruited to the trials were representative of patients treated in the NHS and, that valid outcome measures were used to assess the efficacy of treatment with midostaurin. However, the ERG considers that the weaknesses of the trials are that potential confounding variables are not described or adjusted for in the analyses. The ERG also notes that the statistical methods used in both trials were appropriate, but that the A2213 trial was underpowered to detect differences in treatment responses. The ERG considers that the D2201 and the A2213 trials are of reasonable quality, but highlights that they are single-arm

trials without a control group and their results cannot be considered as reliable or robust as the results of a RCT.

Table 9 Company's quality assessment of the D2201 and A2213 trials with ERG comment

Downs and Black checklist item	D2201	A2213	ERG comment
Reporting			
Q1: Aim of the study clearly described	Yes	Yes	Agree
Q2: Outcomes to be measured clearly described	Yes	Yes	Agree
Q3: Patients characteristics clearly described	Yes	Yes	Agree
Q4: Interventions clearly described	Yes	Yes	Agree
Q5: Principal confounders clearly described	Yes	Yes	Patient characteristics are well described in both trials. However, no potential confounders or treatment effect modifiers are defined for either trial.
Q6: Main findings clearly described	Yes	Yes	Agree
Q7: Random variability for the main outcome provided	Yes	Yes	Agree
Q8: Adverse events reported	Yes	Yes	Agree
Q9: Characteristics of patients lost to follow up reported	No	No	There were minimal losses to follow-up; only two patients were lost to follow-up from the D2201 trial and no losses to follow-up in the A2213 trial
Q10: Actual p-values reported	Yes	Yes	Agree
External validity and bias			
Q11: Sample asked to participate representative of the population from which they were recruited	Unclear. The number of patients screened prior to study entry unclear	Unclear. The number of patients screened prior to study entry unclear	Clinical advice to the ERG is that the patients recruited to the trials are representative of patients treated in the NHS
Q12: Patients who agreed to participate are representative of the population from which they	Unclear. The study has not demonstrated that the distribution of the main confounding factors was the same in the study sample and the source population	Unclear. The proportion of patients screened that then gave consent not reported	Clinical advice to the ERG is that the patients recruited to the trials are representative of patients treated in the NHS
Q13: Staff participating representative of the patient's environment	Unclear. No details provided	Yes. Patients treated at cancer institutes or an academic centre	The ERG agrees that details of the treatment centres in the D2213 trial were not explicitly reported. However, author affiliations suggest that it is likely that patients were treated at cancer institutes or academic centres

Q14: Attempt to blind participants	No	No	Agree
Q15: Attempt to blind assessors	No	No	Central review of patient response to treatment was carried out in D2213
Q16: Any results based on data dredging are clearly stated	No. Subgroup analysis was performed that was not mentioned in methods	No. Extensive subgroup analyses reported in the supplementary appendix were not described in the methods	Agree. See Table 10 of this ERG report for details
Q17: Analysis adjusted for length of follow up	Unclear. No details provided	Unclear. No details provided	Adjustment of follow-up between groups is not necessary for a single-arm trial. Survival analyses of OS and PFS account for different lengths of patient follow-up
Q18: Appropriate statistical tests used?	Yes	Yes	Agree
Q19: Reliable compliance	Unclear	Unclear	Agree
Q20: Reliable and valid outcome measures	Yes	Yes	Agree
Statistical bias and power			
Q21: Were patients in the different intervention groups recruited from the same population?	NA	NA	Agree. Both trials were single-arm trials
Q22: Were patients in the different intervention groups recruited at the same time?	NA	NA	Agree. Both trials were single-arm trials
Q23. Were patients randomised to intervention groups?	This item was excluded from the company's checklist	This item was excluded from the company's checklist	No. Both trials were single-arm trials
Q24. Was the randomised intervention assignment concealed	This item was excluded from the company's checklist	This item was excluded from the company's checklist	Not applicable. Both trials were single-arm trials
Q25: Adequate adjustment in the analyses for confounding variables?	Yes	No. No adjustments reported	No confounding variables were defined (see ERG comment on Q5), therefore it is unclear if confounders have been adequately adjusted for
Q26: Losses of patients to follow up accounted for	Unclear	Unclear	Losses to follow-up were minimal (see ERG comment on Q5). Survival analyses of OS and PFS account for losses to follow-up and patients who discontinue treatment by censoring
Q27: Did the study have sufficient power to detect a clinically important event where the probability value for a difference being due to chance is less than 5%?	Yes	Unclear. No detail provided	The probability of a difference being due to chance is 9.4% in the A2213 trial (A2213 protocol, Section 7.2[53])

NA=not applicable; PFS=progression free survival; OS=overall survival
Source: Adapted from CS, Table 13 with ERG comment

3.2.3 Statistical approach adopted for the trials of midostaurin

Information relevant to the statistical approach used by the company was extracted from the clinical study reports (CSRs) of the D2201 trial (dated 28th June 2016[29] and 27th April 2018[30]) the protocols of the D2201[54] and A2213 trials, [53] and from the CS. A summary of the additional checks made by the ERG in relation to the company's pre-planned statistical approach used to analyse data from the included trials is provided in Table 10.

Table 10 ERG assessment of statistical approaches used in the midostaurin trials

Item	ERG assessment	Statistical approach with ERG comments
Were all analysis populations clearly defined and pre-specified?	Clearly defined: Yes, for both trials Pre-defined: Partly for both trials	The analysis populations (FAS, PEP, SES in both trials and additionally PPS in the D2201 study) are well defined in Table 11 of the CS. Clinical effectiveness results presented in the CS for the final analysis set (FAS) (i.e., all patients to whom study treatment had been assigned according to the ITT principle) for both trials. Clinical effectiveness results for the PEP (i.e., all patients who had measurable C-findings considered related to SM) of the D2201 trial were also reported and these results are used to inform the economic model. The ERG notes that the pre-defined PEPs outlined within the protocols of the trials (Section 10.1 of the D2201 trial protocol and Section 7.1 of the A2213 trial protocol) were different from the PEPs defined in Table 11 of the CS.
Was an appropriate sample size calculation pre-specified?	Yes, for both trials	The two-stage study designs of the D2201 and the A2213 trials are outlined in Figure 4 of the CS and pp37-38 of the CS. These designs and sample sizes were pre-specified in Section 10.4.3 of the D2201 trial protocol and Section 7.2 of the A2213 trial protocol. The ORR achieved by patients enrolled in Stage 1 were significantly greater than the pre-specified thresholds (ORR of 30% in the D2201 trial and 10% in the A2213 trial) for rejection of the null hypothesis in both trials. Therefore, both of the trials continued to enrol patients in Stage 2. The ERG is satisfied that the pre-defined Fleming[55] and Simon[49] two-stage designs are appropriate for the D2201 and A2213 trials respectively and that these designs were implemented appropriately within the trials.
Were all protocol amendments made prior to analysis?	D2201 trial: Mostly A2213: Unknown	Six protocol amendments for the D2201 trial were provided in Section 9.8.1 of the CSRs. [redacted] was issued to [redacted]. The only amendment ([redacted]) to be issued after the first data cut (9th July 2013) was [redacted]. The ERG considers that this amendment is reasonable. Trial protocol version 2.0 for the A2213 was provided. No protocol amendments were listed within this protocol or were available to the company.
Were all primary and secondary efficacy outcomes pre-defined and analysed appropriately?	Partly for both trials	The primary endpoint for both trials was best response (CS, Table 9) and was pre-defined within the trial protocols (Section 10.4.1 of the D2201 trial protocol and Section 7.1.5 of the A2213 trial protocol). For both trials, the secondary efficacy outcomes were OS, PFS, DoR, TTR and histopathologic response based on mast cell infiltration and serum tryptase levels (CS, Table 9). Response assessment based on C-findings (including non-measurable ones) was also a secondary efficacy outcome of the D2201 trial (CS, Table 9). Secondary efficacy outcomes were well defined and pre-defined in Section 10.5 and 10.6 of the D2201 trial protocol. Secondary outcome definitions were well defined within the supplementary documentation to the publication of the A2213 trial[31] but were not pre-specified within the A2213 trial protocol. Appropriate statistical analysis methods for primary and secondary efficacy outcomes of both trials were described in the CS (Table 12) and in the trial publications.[28,31] Limited details of statistical analyses were pre-specified in the

		trial protocols.
Was the analysis approach for PROs appropriate and pre-specified?	D2201 trial: Partly A2213 trial: NA	The analysis approach to PROs in the D2201 trial comprised descriptive statistics of patient responses to the SF-12 and the MSAS at each study visit (Section 10.6.2 of the D2201 trial protocol). The ERG is satisfied that the PRO definitions and analysis approaches are appropriate but notes that the analysis population of evaluable patients (CS, pp54-56) and measurement of median best percentage change from baseline in MSAS and SF-12 scores and statistical testing of PROs using two-sided Wilcoxon two-sample test (CS, Figure 13 and Figure 14) were not pre-specified in the D2201 trial protocol. PROs were not reported within the A2213 trial protocol.
Was the analysis approach for AEs appropriate and pre-specified?	Yes, for both trials	AEs were assessed and graded using the CTCAE version 3.0 classification system within the SES. AEs were estimated as numbers and percentages of patients experiencing events; no formal statistical analyses of AEs were conducted. Summaries of AEs in ≥10% of patients, AEs leading to study drug discontinuation, AEs of special interest, SAEs and death are presented in the CS for both trials (Section B.2.10, pp89-98). The ERG is satisfied that the approach employed for AEs was pre-defined (Section 7.5.1 and Section 8.1 of the D2201 trial protocol and Section 7.1.6 of the A2213 trial protocol) and is appropriate.
Was a suitable approach employed for handling missing data?	Yes, for both trials	The approach to managing missing data for both trials is described in the CS (Table 12). Patients with missing assessments were considered to be non-responders. These approaches were pre-specified in Section 10.4.4 of the D2201 trial protocol and Section 7.1.5 of the A2213 trial protocol. For secondary efficacy outcomes (OS, PFS, DoR, TTR), outcomes were censored at the last available efficacy evaluation for patients with missing data (Section 10.5.2 of the D2201 trial protocol and supplement to the A2213 trial publication).[31]
Were all subgroup and sensitivity analyses pre-specified?	Partly for both trials	Subgroup analyses for both trials were conducted for disease subtype (ASM, SM-AHN and MCL) and *KIT* D816V mutation status (positive and negative or unknown) for both trials (CS, Table 9). Subgroup analysis by number of prior therapies (0 and ≥1) was conducted for the D2201 trial and subgroup analysis for C-findings at baseline (anaemia, thrombocytopenia, neutropenia and non-haematologic C-findings) was conducted for the A2213 trial (CS, Table 9). Subgroup results for ORR of all subgroup analyses described in Table 9 of the CS are presented in Table 17 of the CS for the D2201 trial and in Table 20 of the CS for the A2213 trial. Subgroup analyses by disease subtype for OS, PFS and DoR are presented in Table 18, Table 19 and Figure 23 of the CS for the D2201 trial and in Table 21 of the CS for the A2213 trial. Additional subgroup analyses of OS by response subgroup and by *KIT* D816V mutation status and for ORR by C-findings present at baseline, age, gender, MSAS and SF-12 subscales for the D2201 trial and an analysis of time-to treatment discontinuation by response subgroup are presented in Appendix E to the CS. Only subgroup analyses of disease subtype and number of prior therapies were pre-specified in Section 10.6.5 of the D2201 protocol. Sensitivity analyses of efficacy endpoints in the FAS were pre-specified in Section 10.1 of the D2201 trial protocol. No subgroup or sensitivity analyses were pre-specified in the A2213 trial protocol.

AE=adverse event; ASM=aggressive systemic mastocytosis; CSR=clinical study report; CTCAE=common terminology criteria for adverse events; DoR=duration of response; FAS=full analysis set; ITT=intention-to-treat; MCL=mast cell leukaemia; NA=not applicable; ORR=overall response rate; OS=overall survival; PEP=primary efficacy population; PFS=progression-free survival; PPS=per protocol set; PRO=patient reported outcome; SAE=serious adverse event; SES=safety evaluation set; SF-12=12-item Short-Form health survey; SM=systemic mastocytosis; SM-AHN=systemic mastocytosis with associated haematologic neoplasm; TTR=time to response

Source: extracted from the CS, CSRs of the D2201 trial,[29,30] the protocols of the D2201[54] and A2213 trials,[53] the publications of the D2201[28] and A2213 trials,[31] the company's response to the clarification letter and ERG comment

Having carried out these checks, the ERG is satisfied with the pre-planned statistical approach employed by the company and notes that:

- the definitions of the primary efficacy population (PEP) presented in the CS for both the D2201 trial and the A2213 trial were different from those pre-specified in the protocols[53,54]
- subgroup analyses which were not pre-specified in the trial protocols[53,54] are presented in the CS
- limited details of the pre-planned statistical approach were presented in the trial protocols.[53,54]

3.3 Efficacy results from the trials of midostaurin

Efficacy results presented in the CS have been analysed using data from three different D2201 trial data-cuts and from one A2213 trial data-cut (Table 11). The median duration of follow-up is substantially longer in the A2213 trial (124 months) than the median durations of follow-up in the D2201 trial (ranges from 26 months to 76 months). The ERG considers that these differences in median duration of follow-up should be taken into account when comparing results from the D2201 and A2213 trials, particularly for outcomes such as OS, PFS and DoR which are time-dependent.

Table 11 Efficacy outcomes reported in the trials of midostaurin: PEP

Trial	Data cut-off date	Outcomes	Median duration of follow-up	Source
D2201	9th July 2013	ORR, OS, PFS, DoR, TTR	26 months (range 12 to 54 months)	Gotlib et al 2016[28]
	1st December 2014	ORR, OS, PFS, DoR, TTR, ORR and DoR by IWG criteria	43 months (range 29 to 70 months)	EPAR;[23] APAR[56]
	24th August 2017	OS (Final analysis)	[redacted]	D2201 final CSR[30]
A2213	1st March 2017	ORR, OS, PFS, DoR, TTR	124 months (range 82 to 140 months)	De Angelo et al 2018[31]

APAR=Australian public assessment report; CSR=clinical study report; DoR=duration of response; EPAR=European public assessment report; IWG=International Working Group; ORR=overall response rate; OS=overall survival; PEP=primary efficacy population; PFS=progression free survival; TTR=time to response
Source: CS, adapted from Section 2.6

Efficacy results within this section are presented for all patients and by disease subtype (ASM, SM-AHN or MCL). Further efficacy results, including OS, PFS and DoR Kaplan-Meier (K-M) data, can be found in Section 2.6 and Section 2.7 of the CS.

3.3.1 Primary outcome: best overall response

A summary of best overall response and ORR results for all patients and by disease subtype in the PEP of the trials of midostaurin are provided in Table 12. The ORR results are exactly the same in the two data cut-offs reported for the D2201 trial (9th July 2013 and 1st December 2014) and were used to inform the economic model.

Table 12 Summary of ORR results for all patients and by disease subtype in trials of midostaurin: PEP

	Disease subtype			All patients
	ASM	SM-AHN	MCL	
D2201 trial (data cut-off 1st December 2014, median duration of follow-up 43 months [range 29 to 70 months])[a]				
Number of patients	16	57	16	89
Overall response: n (%)	12 (75%)	33 (58%)	8 (50%)	53 (60%)
Major response: n (%)[b]	10 (62%)	23 (40%)	7 (44%)	40 (45%)
Partial response: n (%)[b]	2 (12%)	10 (18%)	1 (6%)	13 (15%)
Stable disease: n (%)	1 (6%)	7 (12%)	3 (19%)	11 (12%)
Progressive disease: n (%)	1 (6%)	6 (11%)	3 (19%)	10 (11%)
Not evaluable: n (%)[c]	2 (12%)	11 (19%)	2 (12%)	15 (17%)
ORR (95% CI)	75% (48 to 93%)	58% (44 to 71%)	50% (25 to 75%)	60% (49 to 70%)
A2213 trial (data cut-off 1st March 2017, median duration of follow-up 124 months [range 82 to 140 months])				
Number of patients	3	17	6	26
Overall response: n (%)	1 (33%)	13 (76%)	4 (67%)	18 (69%)
Major response: n (%)[b]	0 (0%)	11 (65%)	2 (33%)	13 (50%)
Partial response: n (%)[b]	1 (33%)	2 (12%)	2 (33%)	5 (19%)
Stable disease: n (%)	1 (33%)	3 (18%)	1 (17%)	5 (19%)
Progressive disease: n (%)	1 (33%)	1 (6%)	1 (17%)	3 (12%)
ORR (95% CI)	33% (NR to NR)	76% (NR to NR)	67% (NR to NR)	69% (50 to 88%)

[a] Results are exactly the same in the two data cut-offs reported for the D2201 trial (9th July 2013 and 1st December 2014) and results using the latest data cut-off were used to inform the economic model
[b] Numbers and proportions with different categories of major response (complete remission, incomplete remission, pure clinical response) and partial response (good partial response and minor partial response) are presented in Table 14, Table 15 and Table 16 of the CS and Table 2 of the A2213 trial publication[31]
[c] Reasons to explain why patients were not evaluable for response in the D2201 trial were: concurrent use of high-dose glucocorticoids (n=9), not enough time receiving treatment (n=3), death (n=1), red-cell transfusion (n=1), and neutropenia (n=1)
ASM=aggressive systemic mastocytosis; CI=confidence interval; MCL=mast cell leukaemia; NR=not reported; ORR=overall response rate; PEP=primary efficacy population; SM-AHN=systemic mastocytosis with associated haematologic neoplasm;
Source: Extracted and adapted from CS; Table 14, Table 15, Table 16, Table 17 and Table 20; A2213 trial publication[31]

At the time of analysis in the PEP, the ORR in the D2201 trial was 60% (95% confidence interval [CI]: 49 to 70%) and in the A2213 trial was 69% (95% CI: 50 to 88%). The ORR in the full analysis set [FAS] of the D2201 trial (116 enrolled patients) was 46% (95% CI [calculated by the ERG]: 37 to 55%).

In the D2201 trial, patients with ASM had the highest response rate of 75% (95% CI: 48 to 93%) compared to 58% (95% CI: 44 to 71%) and 50% (95% CI: 25 to 75%) for patients with SM-AHN and patients with MCL, respectively. The company notes that, in contrast, patients

with ASM in the A2213 trial had the lowest response rate with an ORR of 33%, compared to 76% and 67% for patients with SM-AHN and patients with MCL, respectively.

The ERG considers that direct comparisons between the numerical results of ORR across the disease subtypes should not be made due to very small numbers of patients and uncertainty in ORR estimates (reflected in the wide CIs of ORR estimates in the D2201 trial and lack of reported CIs in the A2213 trial). As noted in Section 3.3 of this ERG report, the ERG also considers that direct comparisons between the numerical values of the efficacy results of the D2201 trial and the A2213 trial should be not made due to the different median duration of follow-up times in the two trials.

Other subgroup analyses

Aside from disease subtype, other subgroup analyses conducted in the PEP of the D2201 trial (data cut-off: 9th July 2013 and equivalent results for data cut-off 1st December 2014) for ORR based on *KIT* D816V mutation status (positive, negative or unknown) and number of prior therapies (0 or ≥1) are presented in Table 17 and Figure 19 of the CS. Additional subgroup analyses of ORR in the D2201 trial by C-findings present at baseline (data cut-off 9th July 2013) and by age, gender, MSAS category and SF-12 (data cut-off 1st December 2014) are presented in Appendix E to the CS.

Other subgroup analyses conducted in the PEP of the A2213 trial (data cut-off: 1st March 2017) for ORR based on *KIT* D816V mutation status (positive, negative or other), number of prior therapies (0 or ≥1), C-findings present at baseline (anaemia, thrombocytopenia, neutropenia or non-haematologic C-findings) and additional SM-related findings (pleural effusions and increased alkaline phosphatase) are presented in Table 20 of the CS.

Responses were observed in all pre-specified subgroups of the D2201 trial and in all pre-specified subgroups of the A2213 trial, except for transfusion-dependent thrombocytopenia, neutropenia and lytic lesions where the ORR was 0%.

3.3.2 Secondary outcome: OS

A summary of OS results in the trials of midostaurin is provided in Table 13.

Table 13 Summary of OS results for all patients in the trials of midostaurin: PEP and FAS

Population	Number of patients alive: n (%)	Median OS (95% CI): months	Survival rate: (95% CI)	
			3 years	5 years
D2201 trial (data cut-off 9th July 2013, median duration of follow-up 26 months [range 12 to 54 months])				
PEP (n=89)	48 (54%)	28.7 (18.1 to NE)	46% (32 to 58%)	Not reported
FAS (n=116)	48 (41%)	33.9 (20.3 to 45.5)	46% (35 to 57%)	Not reported
D2201 trial (data cut-off 1st December 2014, median duration of follow-up 43 months [range 29 to 70 months])				
PEP (n=89)	35 (39%)	26.8 (17.6 to 34.7)	38.2% (27.5 to 48.8%)	Not reported
FAS (n=116)	35 (30%)	29.9 (20.3 to 42.0)	42.4% (32.6 to 51.8%)	Not reported
D2201 trial (data cut-off 24th August 2017, median duration of follow-up 76 months [range 62 to 103 months])				
PEP (n=89)	[redacted]	[redacted]	[redacted]	[redacted]
FAS (n=116)	[redacted]	[redacted]	[redacted]	[redacted]
A2213 trial (data cut-off 1st March 2017, median duration of follow-up 124 months [range 82 to 140 months])				
PEP (n=26)[c]	4 (15%)	40.0 (27.3 to 52.7)	Not reported	Not reported

[a] 4 patients were known to be alive (ongoing without event), an additional 9 patients (10%) were lost to follow-up early in the trial and an additional 12 patients (13%) were lost to follow-up but known to be alive in the 5 months before data cut-off
[b] 6 patients were known to be alive (ongoing without event), an additional 14 patients (12%) were lost to follow-up early in the trial and an additional 16 patients (14%) were lost to follow-up but known to be alive in the 5 months before data cut-off
[c] The PEP and the FAS were equivalent in the A2213 trial
CI=confidence interval; FAS=full analysis set; NE=not estimated; OS=overall survival; PEP=primary efficacy population
Source: Extracted and adapted from CS: Section 2.6.1 (pp49-51), Section 2.6.2 (p58) and ERG calculation

At the time of the final D2201 trial OS analysis, after a median duration of follow-up of 76 months, the median OS (95% CI) was [redacted] months for the PEP and [redacted] months for the FAS. In the A2213 trial, after a median duration of follow-up of 124 months, the median OS (95% CI) was 40.0 (27.3 to 52.7) months for the PEP. The ERG emphasises that the different durations of median follow-up times in the D2201 and the A2213 trials should be considered when drawing conclusions from the OS trial results.

A summary of OS results in the PEP of the trials of midostaurin by disease subtype is provided in Table 14.

Table 14 Summary of OS results by disease subtype in the PEP of the trials of midostaurin

	Disease subtype			All patients
	ASM	SM-AHN	MCL	
D2201 trial (data cut-off 9th July 2013, median duration of follow-up 26 months [range 12 to 54 months])				
Number of patients	16	57	16	89
Median OS (95% CI), months	NR (28.7 to NE)	20.7 (16.0 to 44.4)	9.4 (7.5 to NE)	28.7 (18.1 to NE)
D2201 trial (data cut-off 1st December 2014, median duration of follow-up 43 months [range 29 to 70 months])				
Number of patients	16	57	16	89
Median OS (95% CI), months	51.1 (28.7 to NE)	20.7 (16.3 to 33.9)	9.4 (7.5 to NE)	26.8 (17.6 to 34.7)
D2201 trial (data cut-off 24th August 2017, median duration of follow-up 76 months [range 62 to 103 months])				
Number of patients	16	57	16	89
Median OS (95% CI), months	[redacted]	[redacted]	[redacted]	[redacted]
A2213 trial (data cut-off 1st March 2017, median duration of follow-up 124 months [range 82 to 140 months])				
Number of patients	3	17	6	26
Median OS (95% CI), months	NR (NR to NR)	40.0 (24.2 to 55.9)	18.5 (0.0 to 62.2)	40.0 (27.3 to 52.7)

ASM=aggressive systemic mastocytosis; CI=confidence interval; MCL=mast cell leukaemia; NE=not estimated; NR=not reached; OS=overall survival; PEP=primary efficacy population; SM-AHN=systemic mastocytosis with associated haematologic neoplasm;
Source: Extracted and adapted from CS: Table 18, Table 19, Table 21 and Section B.2.7.1 (p67)

The company notes that K-M data (CS, Figure 15, Figure 20 and Figure 23) indicate that OS was highest for patients with ASM. The ERG considers that direct comparisons between numerical results for OS across the disease subtypes should not be made due to very small numbers of patients and uncertainty in OS estimates (wide CIs and CIs not reached or not estimated for median OS).

Additional subgroup analyses of D2201 trial OS data by response (data cut-offs 9th July 2013 and 1st December 2014) and by *KIT* D816V mutational status (data cut-off 1st December 2014 and 24th August 2017) are presented in the CS, Appendix E.

3.3.3 Secondary outcomes: PFS and DoR

A summary of PFS and DoR results for all patients and by disease subtype in the PEP of the trials of midostaurin are provided in Table 15.

Table 15 Summary of PFS and DoR results for all patients and by disease subtype in the PEP of the trials of midostaurin

	Disease subtype			All patients
	ASM	SM-AHN	MCL	
D2201 trial (data cut-off 9th July 2013, median duration of follow-up 26 months [range 12 to 54 months])				
Number of patients	16	57	16	89
Median PFS (95% CI), months	28.7 (24.8 to NE)	11.0 (7.4 to 17.0)	11.3 (2.8 to NE)	14.1 (10.2 to 24.8)
Number of responders	12	33	8	53
Median DoR (95% CI), months[a]	NR (24.1 to NE)	12.7 (7.4 to 31.4)	NR (3.6 to NE)	24.1 (10.8 to NE)
D2201 trial (data cut-off 1st December 2014, median duration of follow-up 43 months [range 29 to 70 months])				
Number of patients	16	57	16	89
Median PFS (95% CI), months	NR (NR to NR)	11.0 (7.4 to 17.9)	11.3 (2.8 to NE)	17.0 (10.2 to 24.8)
Number of responders	12	33	8	53
Median DoR (95% CI), months[a]	NR (NR to NR)	12.7 (7.4 to 31.4)	Not reported	31.4 (10.8 to NE)
A2213 trial (data cut-off 1st March 2017, median duration of follow-up 124 months [range 82 to 140 months])				
Number of patients	3	17	6	26
Median PFS (95% CI), months	Not reported	Not reported	Not reported	41.0 (4.4 to 77.6)
Number of responders	1	13	4	18
Median DoR (95% CI), months[a]	Not reported	Not reported	Not reported	132 (NE to NE)

[a] DoR is measured only in those achieving an overall response
ASM=aggressive systemic mastocytosis; CI=confidence interval; DoR=duration of response; MCL=mast cell leukaemia; NE=not estimated; NR=not reached; OS=overall survival; PEP=primary efficacy population; PFS=progression free survival; SM-AHN=systemic mastocytosis with associated haematologic neoplasm;
Source: Extracted and adapted from CS: Table 18 and Table 19, Section 2.6.1 (pp51-53), Section 2.6.2 (pp58-60)

At a median duration of follow-up of 43 months, the median PFS (95% CI) was 17.0 (10.2 to 24.8) months in the D2201 trial; and for the 53 responders, the median DoR (95% CI) was 31.4 (10.8 to NE) months. At a median duration of follow-up of 124 months, the median PFS (95% CI) was 41.0 (4.4 to 77.6) months in the A2213 trial; and for the 18 responders, the median DoR (95% CI) was 132 (NE to NE) months. The company states (CS, Section 2.7) that PFS and DoR results are often highest for the ASM subgroup (where results are reached); the ERG considers that comparisons of numerical results for PFS and DoR across disease subtypes should not be made due to very small numbers of patients.

According to the definitions of OS and PFS used within the A2213 trial,[31] median OS should be longer than PFS. However, the ERG notes that the reported median PFS is longer than the reported median OS (41.0 months versus 40.0 months respectively). These results are reported in all published sources of the A2213 trial[23,31,56] and therefore are unlikely to be a typographical error. The ERG acknowledges that the company has access to only published sources of the A2213 trial data and therefore cannot explain this result. The ERG concludes that the inconsistency in median OS and PFS is likely due to the small numbers of patients enrolled within the A2213 trial as a single OS or PFS event could have a large impact on the survival probabilities, and therefore on the time taken for median OS or PFS to be reached. The uncertainty around these results is also reflected within the large 95% CIs around median OS (Table 13) and median PFS (Table 15).

3.3.4 Other outcomes

Histopathologic response outcomes based on mast cell infiltration and serum tryptase levels are reported in the CS (on pp53-54 for the D2201 trial, and on pp60-61 for the A2213 trial).

3.3.5 Post-hoc analysis of response by IWG criteria in the D2201 trial

A post-hoc analysis using data from the D2201 trial (data cut-off 1st December 2014) was conducted using the more stringent IWG[45] criteria to measure response. The response of patients without measurable C-findings who were excluded from the pre-specified analyses of ORR based on modified Valent[57] and Cheson[58,59] criteria adjudicated by the trial Steering Committee[28] could be assessed according to the IWG criteria. Within the post-hoc analysis using the IWG criteria,[45] the confirmation period for responses was 12 weeks and analyses excluded ascites as C-findings.

A summary of best overall response, ORR and DoR results for all patients and by disease subtype by IWG criteria in the D2201 trial are provided in Table 16.

Table 16 Summary of ORR and DoR results for all patients and by disease subtype by IWG criteria in the D2201 trial (data cut-off 1st December 2014)

	Disease subtype				All patients evaluated
	ASM	SM-AHN	MCL	Subtype unknown	
Number of patients	15	72	21	5	113
Overall response: n	9	15	7	1	32
Complete remission: n (%)[a]	0 (0%)	0 (0%)	1 (5%)	0 (0%)	1 (1%)
Partial remission: n (%)[b]	5 (33%)	8 (11%)	3 (14%)	1 (20%)	17 (15%)
Clinical improvement: n (%)[c]	4 (27%)	7 (10%)	3 (14%)	0 (0%)	14 (12%)
ORR (95% CI)	60% (32 to 84%)	21% (12 to 32%)	33% (15 to 57%)	20% (1 to 72%)	28% (20 to 38%)
Median DoR (95% CI), months	36.8 (10.4 to 36.8)	NR (17.3 to NR)	NR (4.1 to NR)	NR (NR to NR)	NR (27.0 to NR)

[a] Patients with all organ damages in complete remission
[b] Patients with at least one organ damage in partial remission AND no progression on any other organ damage
[c] Patients with at least one organ damage clinically improved AND patient not in complete remission AND patient not in partial remission. A clinical improvement cannot be considered if a progression started before confirmation of clinical improvement in partial remission AND no progression on any other organ damage
ASM=aggressive systemic mastocytosis; CI=confidence interval; DoR=duration of response; IWG=International Working Group; MCL=mast cell leukaemia; NR=not reached; ORR=overall response rate; SM-AHN=systemic mastocytosis with associated haematologic neoplasm;
Source: Extracted and adapted from the CS, Appendix E, Table E.1.9, Table E.1.12

The ERG notes that for all patients, and for all disease subtypes, the ORR was lower when measured by the IWG criteria compared to the original measurement of response based on modified Valent[57] and Cheson[58,59] criteria (see Table 12 of this ERG report). However, the ERG acknowledges that due to the differences in the definitions of response according to the IWG criteria[45] and modified Valent[57] and Cheson[58,59] criteria, numerical results of ORR of the original analysis and of the post-hoc analysis may not be directly comparable.

3.4 Patient reported outcomes from the D2201 trial of midostaurin

While the A2213 trial and the D2201 trial both provided clinical effectiveness evidence for midostaurin for advanced SM, only the D2201 trial included any patient reported outcomes.

During the D2201 trial, data about patients' symptoms were collected using the Memorial Symptom Assessment Scale (MSAS).[60,61] The MSAS provides information about the frequency, severity and distress caused by 32 symptoms commonly reported by patients with cancer.

In the CS (p54), the company presents the total MSAS score (TMSAS) as the average score, across the 32 symptoms, across three domains. The TMSAS thus provides an overall score of zero to four, with a minimally important difference of 0.20–0.45.[28] The company also

presents three subscale scores from the MSAS (CS, p54): i) the physical symptom subscale (PHYS), ii) the psychological symptom subscale (PSYCH), and iii) the global distress index (GDI).

HRQoL data were also collected during the D2201 trial using the Medical Outcomes Study 12-Item Short-Form Health Survey (SF-12).[62] The SF-12 questionnaire comprises 12 items that provide two component scores, a physical component summary (PCS) score and a mental component summary (MCS) score. The mental and the physical component summary scores of the SF-12 both have a range of 0–100 and a minimal important difference of 4 points. The SF-12 scores collected during the D2201 trial were mapped to EQ-5D values and used to inform the values used in the company's base case economic analysis.

Responses to the MSAS and SF-12 questionnaires were collected at baseline, the end of treatment cycles 1-12, every 3 cycles thereafter, and at the end of treatment in the D2201 trial. The patient-reported symptoms and HRQoL results reported in the CS are derived from the earliest data cut-off (9th July 2013).

3.4.1 Summary of MSAS data

Evaluable data were available for 79 patients. The baseline values for TMSAS, PHYS, PSYCH, and GDI were compared to the values obtained at the data point when the best reported total score (TMSAS) compared to baseline was achieved. The best reported TMSAS was selected from all available data points, collected prior to the 9th July 2013 data cut-off.

The most commonly reported symptoms at baseline (CS, p54) were lack of energy (n=68, 86%), feeling drowsy (n=57, 72%), and difficulty sleeping (n=47, 60%). The company showed that the frequency for 30 of the 32 symptoms decreased from baseline to the time of best reported TMSAS (CS, p55). The frequency of two symptoms, nausea and vomiting, increased from baseline to the time of best reported TMSAS; both symptoms are known AEs associated with treatment with midostaurin. The company reported that the median TMSAS and the median scores for all subscales (PHYS, PSYCH, and GDI) were significantly lower at the time of best reported TMSAS compared to baseline (Table 17).

The ERG considers that, in the absence of MSAS data for a comparator arm, and due to the open-label design of the D2201 trial, it is difficult to interpret the results of the MSAS questionnaires. Furthermore, none of other relevant studies, identified by the literature searches,[7,12,32-41] reported any HRQoL outcomes using the MSAS tool.

Table 17 Median best percentage change in MSAS scores from baseline to time of best reported total score in D2201

Median MSAS score	Number of patients included in the analysis	Median best percentage CfB	p-value*
TMSAS	77	-58%	<0.001
PHYS	76	-67%	<0.001
PSYCH	67	-80%	<0.001
GDI	73	-69%	<0.001

* p-values determined using two-sided Wilcoxon two-sample test (t approximation)
CfB=change from baseline; GDI=global distress index; MSAS=Memorial Symptom Assessment Scale; PHYS=physical subscore; PSYCH=psychological subscore; TMSAS=total score on Memorial Symptom Assessment Scale
Source: Adapted from CS, Figure 13

3.4.2 Summary of SF-12 data

Evaluable D2201 trial data were available from 81 patients for the PCS and 80 patients for the MCS. The baseline values for the PCS and MCS were compared to the best values achieved during treatment. The best values were selected from all available data points collected prior to the 9th July 2013 data cut-off.

The company demonstrates (CS, Figure 14) that the median best values for PCS and MCS during treatment were significantly higher than the median scores at baseline ($p<0.001$). The median best percentage change from baseline to treatment with midostaurin for PCS and MCS was were 29% and 26%, respectively.

The ERG considers that in the absence of a comparator arm, and due to the open-label design of the D2201 trial, it is difficult to interpret the relative percentage change in the PCS and MCS scores.

3.5 Safety and tolerability results from midostaurin studies

Safety and tolerability data are presented in the CS (Section B.2.10), with additional information provided in Appendix F. Safety data have been derived from the D2201 and A2213 trials. Data from the D2201 trial are from the Safety Evaluation Set (SES) final OS and safety analysis (24th August 2017 data-cut off). Safety data from the A2213 trial are derived from the 1st March 2017 data cut, or (in the absence of more recent data) the 3rd December 2012 data-cut off. AEs were monitored and graded according to Common Terminology Criteria of Adverse Events (CTCAE) version 3.0. In both trials, data were collected from the first day of midostaurin administration until 28 days after discontinuation of treatment.

The ERG cautions that the differences in patient numbers, trial treatment protocols and duration of follow up should be considered when making comparisons of the safety data from the D2201 and the A2213 trials.

Exposure to study treatment

The D2201 trial and A2213 trial treatment exposure data are summarised in the CS (Table 29). The median duration of treatment exposure was [redacted] in the D2201 trial ([redacted]) than in the A2213 trial (9.8 months).

3.5.1 Adverse events

A summary of the AEs from the D2201 and A2213 trials is presented in

Table 18. All patients in the D2201 and A2213 trials experienced at least one AE of any grade. The proportion of AEs considered to be related to treatment was similar in the D2201 and A2213 trials ([redacted] and 96.2% respectively).

The rates of Grade 3 or 4 AEs were greater in the D2201 trial ([redacted]) than in the A2213 trial (61.5%). Further, a higher proportion of patients in the D2201 trial experienced serious adverse events (SAEs) compared to the proportion of patients in the A2213 trial ([redacted] and 46.2%, respectively)

Table 18 Summary of AEs from the D2201 and A2213 trials

Adverse event, n (%)	D2201 (N=116)	A2213 (N=26)
All causality AEs	[redacted]	26 (100)
Grade 3 or 4	[redacted]	16 (61.5)
Suspected to be drug-related	[redacted]	25 (96.2)
SAEs	[redacted]	12 (46.2)
Grade 3/4	[redacted]	NR
Suspected to be drug-related	[redacted]	4 (15.4)
AEs leading to discontinuation	[redacted]	4 (15.4) | 6 (23.1)[a]
Suspected to be drug-related	[redacted]	1 (3.8)
AEs leading to dose adjustment/interruption	NR	13 (50.0)
AEs leading to dose reduction	[redacted]	NR
AEs leading to dose interruption	[redacted]	NR

[a] More recent data; analysis of A2213 data cut-off: 1st March 2017; Safety Evaluation Set (SES)
Final analysis of D2201 data cut-off: 24th August 2017; SES. Analysis of A2213 data cut-off: 3rd December 2012; SES
AE=adverse event; NR=not reported; SAE=serious adverse event
Source: CS, Table 30

Treatment related adverse events

Treatment-related AEs reported in ≥10% of patients participating in the D2201 and A2213 trials are presented in Table 19. Nausea, vomiting and diarrhoea were the most commonly reported AEs in the two trials. The ERG notes that high rates of nausea and vomiting were reported in both trials, even though prophylaxis for the prevention of nausea and vomiting was recommended to be given to all patients in the D2201 and A2213 trials (CS, p91).

Table 19 Treatment-related AEs in ≥10% patients from D2201 and A2213

Adverse event, n (%)	D2201 (N=116)		A2213 (N=26)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Nausea	[redacted]	[redacted]	24 (92.3)	0 (0.0)
Vomiting	[redacted]	[redacted]	19 (73.1)	0 (0.0)
Diarrhoea	[redacted]	[redacted]	7 (26.9)	0 (0.0)
Lipase increased	NA	NA	3 (11.5)	2 (7.7)
Thrombocytopaenia	NA	NA	4 (15.4)	1 (3.8)
Fatigue	NA	NA	4 (15.4)	1 (3.8)
Headache	NA	NA	6 (23.1)	0 (0.0)
Anaemia	NA	NA	4 (15.4)	2 (7.7)

Final analysis of D2201 data cut-off: 24th August 2017; SES. Analysis of A2213 data cut-off: 3rd December 2012; Safety Evaluation Set (SES)
NA=not applicable
Source: CS Appendix F, Table F2

Deaths

The [redacted] patient deaths in the D2201 trial (on treatment or within ≥28 days after treatment discontinuation) were attributed to disease progression ([redacted]), cardiac disorders (n=5), multiple organ dysfunction syndrome (n=3), sepsis (n=3), pneumonia (n=1) and acute myeloid leukaemia (n=1).

The 5 patient deaths in the A2213 trial, were attributed to disease progression (n=2), non-neutropenic sepsis (n=2) and bacterial urinary tract infection (n=1).

The company states that none of the deaths were considered to be related to treatment.

Serious adverse events regardless of study drug relationship

SAEs experienced by ≥1% patients in the D2201 and A2213 trials (regardless of study drug relationship) are presented in the CS (Table 32 and Table 33 respectively).

In the D2201 trial, pneumonia (any grade: [redacted]; Grade 3 or 4: [redacted]) and sepsis (any grade: [redacted]; Grade 3 or 4: [redacted]) were the most frequently reported SAEs. No Grade 5 SAEs were reported.

In the A2213 trial, sepsis (n=1), febrile neutropenia (n=1), facial bone fracture due to mechanical fall (n=1), elevated total bilirubin (n=1) and hypercalcaemia (n=1) were experienced as SAEs. Two patients (CS, Table 35) experienced Grade 5 sepsis.

Adverse events leading to treatment discontinuation

A slightly higher proportion of patients in the D2201 trial discontinued treatment due to AEs ([redacted]) compared to the proportion in the A2213 trial (23.1%). In the D2201 trial, nausea

([redacted]) and QT prolongation ([redacted]) were the most commonly reported AEs that caused patients to discontinue treatment.

In the A2213 trial, sepsis was the most common AE that caused patients to stop treatment. One patient experienced sepsis as a Grade 3 or 4 AE and two patients experienced it as a Grade 5 AE.

Adverse events of special interest

The company defined severe infections, leukopenia, pulmonary toxicity, cardiac dysfunction and reproductive and developmental toxicity as AEs of special interest (AESI) and presented data for those events from the D2201 trial.

Severe infection was the most common AESI with a frequency of [redacted] and included viral upper respiratory tract infection ([redacted]), urinary tract infection ([redacted]), pneumonia ([redacted]), and upper respiratory tract infection ([redacted]). Grade 3 or 4 infections occurred in [redacted] of patients and included sepsis ([redacted]) and pneumonia ([redacted]).

Leukopenia was reported in [redacted] of patients and [redacted] of events were categorised as Grade 3 or 4 AEs. Neutropenia was the most common leucopoenia event ([redacted]) and was a Grade 3 or 4 AE for [redacted] of patients.

Pulmonary toxicity was experienced by [redacted] of patients, with [redacted] considered to be Grade 3 or 4 AE. Pleural effusion of any grade was the most frequent AE ([redacted]).

Cardiac dysfunction was reported in [redacted] of patients, of these, [redacted]events were categorised as Grade 3 or 4 AEs. The most commonly reported AE was cardiac failure ([redacted]) and [redacted] were considered to be Grade 3 or 4 AEs.

Reproductive and developmental toxicity was reported in [redacted] of patients, with [redacted] considered to be Grade 3 or 4 AEs.

ERG summary of safety results

Overall, nausea and vomiting were the most frequently reported AEs experienced by patients treated with midostaurin in the D2201 and A2213 trials. The company states that nausea and vomiting events were generally manageable with antiemetics and by administering midostaurin with food.

The ERG agrees with the company (Section B.2.10.3) that it is difficult to establish whether the Grade 3 or 4 haematological AEs reported in the trials were related to treatment with midostaurin or to disease progression.

In the absence of a control arm, the safety and tolerability data from the D2201 and A2213 trials are difficult to interpret. Clinical advice to the ERG is that AEs arising from treatment with midostaurin, as with current unlicensed treatments, require careful monitoring by a specialist clinical team with the experience to provide early recognition and management of cytoreductive therapy-related AEs, and that this can place a high burden on NHS staff and systems.

3.6 ERG critique of the additional and indirect evidence

As described in Section 3.2.1 of this ERG report, the company identified eight studies (two single-arm trials,[33,38] two case-series[32,39] and four retrospective studies[34-37,63]) that provided clinical evidence for the five comparators listed in the final scope[1] issued by NICE (cladribine, interferon alpha, nilotinib, imatinib and dasatinib). Due to the absence of comparative RCT data for midostaurin versus comparators, an indirect treatment comparison was not possible.

The company concluded that the evidence for the comparators from single arm, mostly retrospective studies, is 'much weaker' than the evidence base for midostaurin (CS, p88). The ERG agrees with the company conclusions and also agrees that results from the comparator studies should not be used to inform a decision about the comparative effectiveness of midostaurin versus the comparators. A summary and ERG critique of clinical evidence for the comparators is provided in Appendix 7.1.1 to this ERG report.

In the absence of head-to-head RCTs or other prospective controlled studies, the only available evidence demonstrating the comparative efficacy of midostaurin versus SoC is provided by two historical control studies:

- Reiter et al[12,42] study: a pooled analysis of 89 patients from the D2201 (n=63) and A2213 (n=26) trials versus historical control data for 42 patients from a German registry
- Chandesris et al[40,41] studies: a prospective observational survey of 28 patients with mastocytosis treated with midostaurin in France under a compassionate use programme, compared with 44 historical controls.

The ERG considers that the best source of indirect evidence that is available for the comparison of midostaurin versus SoC is the Reiter et al[42] presentation. A summary and ERG critique of the Reiter et al[12,42] study is provided in Section 3.6.1 of this ERG report.

The ERG also considers that the results of the Chandesris et al[40,41] study should not be used to inform a decision about the comparative effectiveness of midostaurin versus SoC due to the small number of patients and a lack of published information regarding the methods employed leading to uncertainty around the validity of the results. A summary and ERG critique of the study by Chandesris et al[40,41] is provided in Appendix 7.1.2 to this ERG report.

3.6.1 Analysis of pooled data from the D2201 and A2213 trials compared to German registry data: Reiter et al study

The OS and baseline characteristics data from the D2201 and A2213 trials (from 89 patients with a known date of SM diagnosis) were pooled and compared to a historical control group of 42 patients from a German registry. Data from the German registry were described as being 'contemporary' with the trials of midostaurin (CS, p71).

Baseline characteristics of the midostaurin group and the control group are summarised in Table 22 of the CS. The ERG agrees with the company assessment that baseline patient characteristics were similar across the two groups, with the exceptions of age and time since diagnosis; the control group were older (71% diagnosed with SM over the age of 65 compared to 42% of the midostaurin group) and had a slightly longer time from diagnosis to start of treatment (median 7.3 months since diagnosis compared to 2.2 months since diagnosis in the midostaurin group). Despite differences in trial cut-off dates (pooled data cut-off 1st July 2016 for OS) and the German registry data (data cut-off 9th May 2017 for OS), the median duration of follow-up from time of diagnosis to the data cut-off were comparable; the median duration of follow-up was 79.5 months (range 51.4 to 234 months) in the trials of midostaurin and was 84.2 months (range 22.3 to 176.3 months) in the Germany registry (CS, p70).

Four comparative analyses of OS were conducted; a description and ERG critique of these analyses is provided in Table 20 and the results of these analysis are provided in Table 21.

In response to question A1 of the clarification letter, the company provided a statistical analysis plan (SAP) that described how the pooled D2201 and the A2213 trial data were compared to the German registry data.[64] The ERG is satisfied that outcome definitions, methods of pooling data from the D2201 and A2213 trials and the statistical approaches used in the comparative analyses of OS were appropriate and were mostly pre-specified in the SAP. The ERG notes that aspects of the multivariable OS analysis which were not pre-specified in the SAP (but are summarised in Table 20) do not impact the size of the HR. The ERG also notes that the OS subgroup analyses presented in Table 24 of the CS, with the exception of sex, were not described in the SAP.

Table 20 Comparative OS analyses reported by Reiter et al

Analysis	Description	ERG comment
Primary (unadjusted)	OS was defined as the time of diagnosis to death so only patients with known dates of diagnosis were included. Patients who were alive at the end of follow-up were censored at their last date of contact.	The analysis approach, including date of diagnosis of ASM, SM-AHN or MCL was pre-defined in the SAP (Section 6.1.1 and Section 6.2.1). The ERG considers the analysis approach to be appropriate.
Multivariable[a]	OS was defined as the time of diagnosis to death as in the primary analysis with multivariable adjustment for age group at diagnosis (≤65 years vs >65 years), sex, type of disease (ASM vs SM-AHN, MCL), AHN (Yes, No or unknown), *KIT* D816 mutation status (positive, negative, unknown) and prior lines of therapy (≤1 vs >1).	The analysis approach was pre-specified in the SAP (Section 6.2.2). The ERG considers the analysis approach to be appropriate but notes that the multivariable analyses were pre-defined to be 'exploratory' and that pre-specified analyses described that a Wald two-sided p-value would be presented (SAP, Section 6.2.2). However, a one-sided p-value calculated according to the methods described in response to question A1 of the clarification letter is presented in the CS for the multivariable analysis (Table 23). Results of the multivariable analysis were used within the base case economic analysis (CS, Section 3.3.2 and Section 3.3.6) as the results of the multivariable analysis were consistent with the primary (unadjusted) analysis while adjusting for multiple baseline characteristics.
Propensity score adjusted (matched pair)	OS was defined as the time of diagnosis to death as in the primary analysis in a propensity score matched subset of patients, matched based on age group at diagnosis (≤65 years vs >65 years), sex, type of disease (ASM vs SM-AHN, MCL) and prior lines of therapy (≤1 vs >1).	Analysis approach, including variables for propensity score matching and method of matching were pre-specified in the SAP (Section 6.2.5 to Section 6.2.7). The ERG considers the analysis approach to be appropriate. The ERG acknowledges that this propensity score adjusted analysis was based on a much smaller sample size than the other comparative OS analyses and excludes 53% of patients from the trials of midostaurin.
Sensitivity analysis	OS was defined as the start date of last treatment to death. Patients who were alive at the end of follow-up were censored at their last date of contact.	The analysis approach was pre-specified in the SAP (Section 6.2.4). The ERG considers the analysis approach to be appropriate. The ERG acknowledges that this analysis was conducted to compensate for bias in the selection of the patient populations and the ERG notes this analysis included the largest number of patients from the trials of midostaurin.
Subgroup analysis	Subgroup analyses of OS by age at diagnosis (≤65 years vs >65 years), sex, type of disease (ASM, SM-AHN or MCL and SM with or without AHN) and *KIT* D816 mutation positive. OS defined as in the primary (unadjusted analysis).	With the exception of sex, these subgroup analyses were not pre-specified in the SAP (Section 5).

[a] The comparative OS analyses which adjusted for baseline characteristics were pre-defined in the SAP and described in the CS as 'multivariate' analyses. The ERG considers that a more accurate term for these analyses is 'multivariable.'[65]
ASM=aggressive systemic mastocytosis; MCL=mast cell leukaemia; OS=overall survival; SM=systemic mastocytosis; SM-AHN=systemic mastocytosis with associated haematologic neoplasm;
Source: CS, Section 2.9.1 (pp72-74); Reiter et al;[12,42] statistical analysis plan of the pooled analysis compared to German registry data[64]

Table 21 Summary of OS results reported by Reiter et al

Analysis	Midostaurin group			Registry control group		
	Patients (n)	Events (n)	Median OS (95% CI), months	Patients (n)	Events (n)	Median OS (95% CI), months
Primary (unadjusted)	89	56	41.4 (31.0 to 49.1)	42	36	19.5 (13.0 to 35.3)
	HR (95% CI): 0.50 (0.33 to 0.76); p=0.0007					
Multivariable	89	56	41.4 (31.0 to 49.1)	42	36	19.5 (13.0 to 35.3)
	HR (95% CI): 0.52 (0.32 to 0.84); p=0.0075[a]					
Propensity score adjusted (matched pair)	42	31	27.8 (19.3 to 44.6)	42	36	19.5 (13.0 to 35.3)
	HR (95% CI): 0.64 (0.33 to 1.24); p=NR					
Sensitivity analysis	115	75	28.7 (19.2 to 34.7)	39[b]	33	5.7 (2.2 to 11.7)
	HR (95% CI): 0.44 (0.29 to 0.67); p<0.0001					

[a] One-sided p-value
[b] Three patients in the German registry were not treated.
CI=confidence interval; HR=hazard ratio; NR=not reported; OS=overall survival
Source: Extracted and adapted from the CS, Table 23

The ERG agrees with the company that the results from the multivariable analysis are consistent with results from the primary (unadjusted) analysis, and also benefit from including adjustments for multiple baseline characteristics. The ERG notes that the propensity score adjusted analysis excludes 53% of patients from the trials of midostaurin.

The ERG notes that very limited information is available regarding the Germany registry data (SAP, Section 3), including the source and recruitment methods of patients into the registry. The ERG also highlights concerns raised by the company as the rationale for not using the A2213 trial results in the model:

"Treatment and study not reflective of UK clinical practice in that per the study protocol, treatment was discontinued for non-responders." (CS, Table 7)

Due to these differences in study protocols, the ERG, therefore, questions whether the pooling of data from the D2201 trials and A2213 trials was appropriate. A comparative analysis based on the D2201 trial alone, which is reflective of UK practice, may have shown different results and may have been considered a more relevant comparison to inform UK practice.

3.6.2 ERG conclusions: indirect clinical evidence

The ERG considers that the most reliable source of evidence to inform a decision about the comparative effectiveness of midostaurin versus SoC is from the multivariable analysis reported in the Reiter et al[42] presentation.

However, the ERG emphasises the following uncertainties: very limited information is available regarding the historical German registry data and, therefore, the comparability of these patients with those in the trials of midostaurin is unknown; pooling of the data from the trials of midostaurin may have been inappropriate due to differences in study protocols; and all comparative analyses of OS are based on very small numbers of patients.

3.7 Conclusions of the clinical effectiveness section

3.7.1 Direct evidence

The company provided direct clinical evidence from two single arm, open label, phase II trials of midostaurin in patients with advanced SM, the D2201 trial and the A2213 trial. The D2201 and the A2213 trials appear to be of a higher methodological quality than the studies of the comparator treatments discussed in the CS.

The results from the D2201 and A2213 trials are available for patients with ASM, SM-AHN and MCL disease subtypes and for the overall advanced SM patient population. Neither of the midostaurin trials provides direct evidence comparing the effectiveness of midostaurin versus any of the comparators listed in the final scope[1] issued by NICE.

The outcomes available from the D2201 and A2213 trials match the outcomes specified in the final scope[1] issued by NICE; however, the results from the trials are difficult to interpret given the lack of a comparator arm, the open-label design of the trials, and the small numbers of patients within each disease subtype.

3.7.2 Indirect evidence

There is no randomised clinical evidence available for the use of any of the comparators listed in the final scope[1] issued by NICE for treating patients with advanced SM. The company identified eight studies[32-39] (observational or retrospective) that reported outcomes for patients treated with the comparators. The heterogeneous designs of the comparator studies and the small and heterogeneous patient populations meant that the company was unable to conduct indirect treatment comparisons.

The only available evidence demonstrating the comparative efficacy of midostaurin is provided by two historical control studies.[12,40-42] Reiter et al[12,42] compared pooled D2201 and A2213 trial data (n=89) with data from a German registry (n=42). The ERG considers that the most reliable source of evidence to inform a decision about the comparative effectiveness of midostaurin versus SoC is from the multivariable analysis reported in the Reiter et al[42] presentation. However, the ERG emphasises that there are several areas of uncertainty relating to the Reiter et al[12,42] methods and results.

Chandesris et al[40,41] compared data from a cohort of patients receiving midostaurin in a French compassionate programme (n=28) versus French registry data (n=44). The analysis methods used by Chandesris et al[40,41] are insufficiently described leading to uncertainty around the validity of the presented results; the ERG considers that these results should not be used as a basis for decision making.

4 COST EFFECTIVENESS EVIDENCE

This section provides a structured critique of the economic evidence submitted by the company in support of the use of midostaurin for treating advanced SM. The two key components of the economic evidence presented in the CS are (i) a systematic review of the relevant literature and (ii) a report of the company's de novo economic evaluation. The company has provided an electronic copy of its economic model, which was developed in Microsoft Excel.

4.1 Published cost effectiveness evidence

4.1.1 Objective of the company's literature searches

The company undertook systematic and targeted searches to identify studies evaluating the cost effectiveness of midostaurin and other relevant interventions for the treatment of advanced SM.

4.1.2 Search strategy

The searches were carried out on 30 October 2019 and were updated on 14 November 2019. Relevant electronic databases (MEDLINE, Embase, Health Technology Assessment Database [HTAD] and the National Health Service Economic Evaluations Database [NHS-EED]) were searched and the search terms used included combinations of index terms and free text words. Searches of conference abstracts were also conducted to identify relevant abstracts published during the 2 years prior to the database searches. Abstracts relating to the following organisations/conferences were searched:

- American Society of Clinical Oncology (ASCO)
- American Society of Haematology (ASH)
- Annual Congress of the European Haematology Association (EHA)
- European Organisation for Research and Treatment of Cancer (EORTC)
- European Society for Medical Oncology (ESMO)
- International Society of Pharmacoeconomic and Outcomes Research (ISPOR): European and International meetings.

In addition, the websites of UK and international health technology appraisal (HTA) agencies were searched to identify appraisals or assessments of relevant therapies used to treat advanced SM that included descriptions of cost effectiveness models.

4.1.3 Eligibility criteria used in study selection

The eligibility criteria were designed to identify cost effectiveness studies that had been developed to estimate the cost effectiveness of midostaurin, interferon alpha, cladribine, imatinib, nilotinib or dasatinib versus any comparator for the treatment of advanced SM.

Two researchers independently screened all publications according to their title and abstract content. Any discrepancies in terms of inclusion/exclusion decisions between the researchers were resolved through discussion or the involvement of a third researcher. The same procedure was repeated when determining eligibility of the full-length articles selected during the title and abstract screening process, and for the data extraction process.

4.1.4 Findings from the company's cost effectiveness review

The company's selection strategy identified two economic evaluations.[66,67] One publication contained details about a model-based evaluation, but details about costs were not provided.[66] The other publication presented the findings from a cost effectiveness analysis conducted from an Australian health care system perspective, but the company identified that the details reported about the model were too limited for that model to be relevant to this appraisal.[67]

4.1.5 ERG comments

The ERG has updated the company's searches and is satisfied with the company's cost effectiveness literature search, study selection methods and search results. The ERG also agrees with the company's conclusion that the information in the two publications[66,67] that were identified is not sufficient to inform the development of a model for this appraisal.

The searches used by the company to identify cost effectiveness models were also used to identify HRQoL, resource and cost information that could be used to populate the company economic model. The study selection process for identifying these types of data differed only slightly from those used to identify the cost effectiveness studies.

4.2 ERG critique of the company model

4.2.1 NICE Reference Case checklist

Table 22 NICE Reference Case checklist

Element of health technology assessment	Reference Case	Does the company model adhere to the Reference Case?
Definition of the decision problem	The scope developed by NICE	Yes
Comparator(s)	As listed in the scope issued by NICE (namely, current clinical management including but not limited to: interferon alpha, cladribine, imatinib, nilotinib and dasatinib)	Partly. A basket of drugs was used to represent current clinical management. Clinical advice to the company (which was reflected by clinical advice to the ERG) was that nilotinib and dasatinib were not relevant comparators, but that peg-interferon alpha and AML-like treatments were relevant comparators.
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes
Perspective on costs	NHS and PSS	Yes
Type of economic evaluation	Cost-utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes
Synthesis of evidence on health effects	Based on systematic review	Yes
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D-3L is the preferred measure of health-related quality of life in adults.	Yes
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Yes
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes

AML=acute myeloid leukaemia; EQ-5D=EuroQol-5 dimensions; EQ-5D-3L=EuroQol-5 dimensions-3 levels; PSS=Personal Social Services; QALYs=quality adjusted life years
Source: NICE Guide to the Methods of Technology Appraisal[46]

4.2.2 Drummond checklist

Table 23 Drummond checklist for the company's economic analysis completed by the ERG

Question	Critical appraisal	ERG comment
Was a well-defined question posed in answerable form?	Yes	-
Was a comprehensive description of the competing alternatives given?	Yes	-
Was the effectiveness of the programme or services established?	No	There is no direct evidence comparing the effectiveness of treatment with midostaurin versus current clinical management. The multivariable OS HR generated by comparing pooled data from two single-arm midostaurin trials (D2201 trial and A2213 trial) with historical German registry data [42] was a key driver of cost effectiveness.
Were all the important and relevant costs and consequences for each alternative identified?	Yes	-
Were costs and consequences measured accurately in appropriate physical units?	Yes	-
Were the cost and consequences valued credibly?	Yes	-
Were costs and consequences adjusted for differential timing?	Yes	-
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	-
Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	-
Did the presentation and discussion of study results include all issues of concern to users?	Yes	-

Source: Drummond checklist[68]

4.3 ERG summary of the company model

The company developed a de novo economic model to compare the cost effectiveness of midostaurin versus current clinical management (CCM) in the UK as a first-line treatment for advanced SM. The primary outcomes from the company model are incremental cost effectiveness ratios (ICERs) per quality adjusted life year (QALY) gained.

4.3.1 Populations

The modelled population is adults with advanced SM. The population comprises three disease subtypes (ASM, SM-AHN and MCL). The modelled population is consistent with the D2201 trial population and that described in the final scope[1] issued by NICE. Within the final scope[1] issued by NICE, it is stated that analysis for each subtype should be explored if there is sufficient relevant available evidence. The company has carried out analyses relating to the overall advanced SM population and to the combined SM-AHN+MCL combined subgroup.

4.3.2 Structure of the company model

The company model structure (a partitioned survival model) is shown in Figure 2. It comprises four mutually exclusive health states: progression-free with sustained response (PF-response) and progression-free with lack/loss of response (PF-no-response), progressed disease (PD) and death. The modelled population enters the model in either the PF-response health state or the PF-no-response health state depending on the presumed ORR. A fixed ORR is applied throughout the time horizon of the model. At the end of each 28-day cycle, patients in the PF-response and PF-no-response health states can remain in their respective health state or experience disease progression and move to the PD health state. In addition, patients in the PF-response health state can lose previously achieved response without having a progressed disease and thereby transit to the PF-no-response health state. Patients in the PD health state can, at the end of each cycle, remain in that health state but they cannot return to the PF-response health state or to the PF-no-response health state. Transitions to the death health state can occur from any of the other health states. Death is an absorbing health state from which transitions to other health states are not permitted.

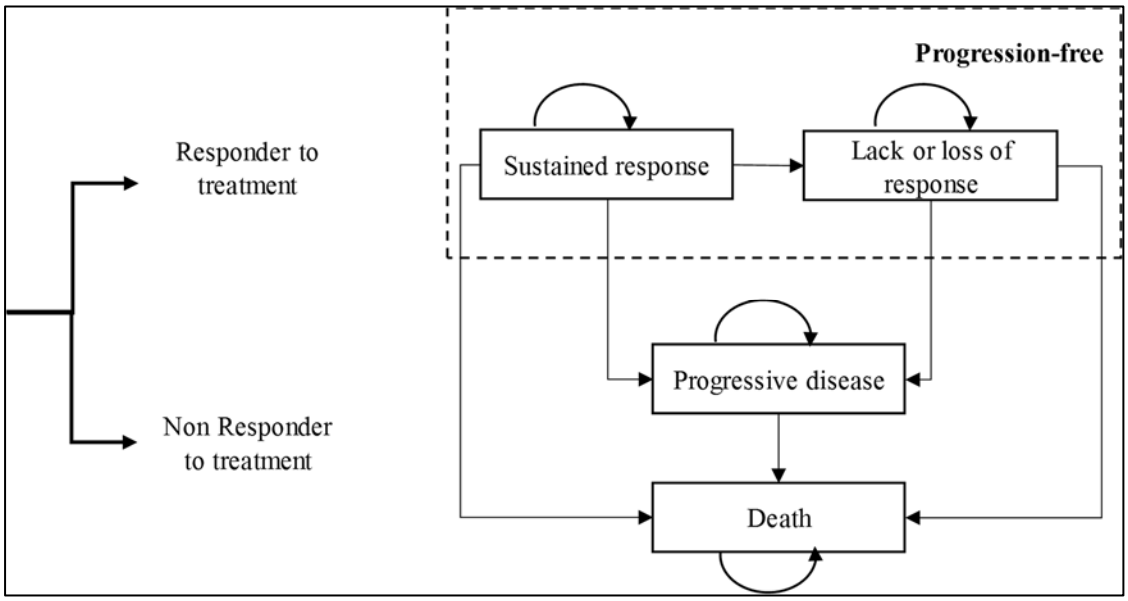

Figure 2 Structure of the company model

Source: CS, Figure 27

4.3.3 Interventions and comparators

Intervention

The intervention is midostaurin. In line with the summary of product characteristics (SmPC)[20] and the D2201 trial, the modelled dose was 100mg twice daily.

Comparator

There are no therapies licensed for the treatment of advanced SM in the UK. The comparator used in the model is CCM, which is costed as the weighted average of the five treatment options that the company considers are in use in the UK (Table 24). The weights for combining the treatment options are the proportions of patients receiving each treatment option (i.e., treatment mix), which the company estimated from discussions with five clinicians.

Table 24 Treatment mix of the five treatment options that constitute current clinical management in the model based on clinical advice to the company

Comparator	Dosing schedule	Clinical expert estimates of proportion used in the UK*	
		Advanced SM	SM-AHN+MCL
Listed in the final scope[1] issued by NICE			
Cladribine	0.14mg/kg at day 1 to day 5 of 28 day cycle[69]	[redacted]	[redacted]
Interferon alpha (Roferon-A)	3, 4, or 5 million units 3 times a week[70]	[redacted]	[redacted]
Imatinib	400mg daily[71]	[redacted]	[redacted]
Identified by UK clinical experts			
Peg-interferon alpha (Pegasys)	180 mcg per week[72]	[redacted]	[redacted]
AML-like treatments, defined as treatment typically used to treat AML	Based on TA552[73]	[redacted]	[redacted]

* Weights used to estimate costs
AML=acute myeloid leukaemia; CCM=current clinical management; kg=kilogram; mcg=microgram; MCL=mast cell leukaemia; mg=milligram; SM=systemic mastocytosis; SM-AHN=systemic mastocytosis with an associated haematological neoplasm; TA=technology appraisal
Source: CS, Table 40

Dasatinib and nilotinib are listed as relevant comparators in the final scope[1] issued by NICE. Clinical advice to the company is that these two treatments are rarely used in UK clinical practice due to the limited clinical evidence base available. The company has, therefore, not included these drugs as comparators in their base case analysis; however, the company model does include a switch that enables dasatinib and nilotinib to be included as treatment options.

4.3.4 Perspective, time horizon and discounting

The company states that costs were considered from the perspective of the NHS and Personal Social Services. The model cycle length was 28 days; a half-cycle correction was not applied as the company considered that this was not required given the cycle length. The model time horizon was set at 38.3 years and costs and outcomes were discounted at 3.5% per annum.

4.3.5 Treatment effectiveness and extrapolation in the base case

Treatment effectiveness was modelled using OS, PFS, ORR and DoR. The company fitted parametric functions to OS, PFS and DoR data from the D2201 trial to model the experience of patients treated with midostaurin. To obtain survival estimates for patients treated with CCM, the 'Reiter et al'[42] OS HR was applied to OS, PFS and DoR midostaurin data. For patients treated with midostaurin, the ORR estimate was obtained from the D2201 trial, whilst ORR estimates relating to treatment with CCM were calculated using values from the literature and assumptions.

Modelling overall survival for patients treated with midostaurin

The company fitted six parametric functions (exponential, gamma, Gompertz, log-normal, log-logistic and Weibull) and two spline hazard functions (one knot and two knots) to the OS K-M data from the D2201 trial (24th August 2017 data cut). The company identified the spline hazard one knot function as being the most appropriate function to use to represent OS. This conclusion was reached by examining goodness-of-fit statistics (Akaike Information Criterion and Bayesian Information Criterion), visual inspection and clinical opinion. In the company base case analysis, the spline hazard one knot function was used for the entire model time horizon to represent the experience of patients treated with midostaurin.

Modelling overall survival for patients receiving comparator treatments

The comparator treatment, CCM, comprised several different treatments (cladribine, interferon alpha, peg-interferon alpha, imatinib and AML-like treatments); however, in the company model there is a single representation of OS for patients receiving CCM (i.e., OS is the same irrespective of comparator treatment).

Reiter et al[42] reported results from OS analyses comparing pooled D2201 and A2213 trial data versus historical German registry data. Four different analyses were carried out:

- Unadjusted analysis (midostaurin: n=89, registry: n=42): HR=0.500 (95% CI:0.33 to 0.76)
- Propensity score matched-pair approach (midostaurin: n=42, registry: n=42): HR=0.636 (95% CI: 0.326 to 1.244)
- Multivariable approach (midostaruin: n=89, registry: n=42): HR=0.517 (95% CI: 0.319 to 0.839)
- Sensitivity analysis: time from last treatment to death (midostaurin: n=115, registry: n=39): HR=0.44 (95% CI: 0.29 to 0.67)

Chandesris et al[40,41] also reported HRs generated from the comparison of a historical cohort of patients that received treatments other than midostaurin (CEREMAST database, n=44) with

those who received midostaurin as part of a French compassionate use programme (n=28). The HRs generated by the approach taken by Chandesris et al[40,41] were lower than those reported by Reiter et al[42] (univariable [matched] approach HR=0.447, multivariable [matched] approach HR=0.333).

The company interpreted the clinical advice it received to mean that the multivariable OS HR from the study by Reiter et al[42] was the most appropriate for use in the base case analysis. This OS HR was applied to the midostaurin spline hazard one knot function OS estimates to generate OS estimates for patients treated with CCM.

Modelling progression-free survival for patients receiving midostaurin

The method used by the company to identify an appropriate parametric distribution for modelling PFS for patients receiving midostaurin was the same as the method used to identify an appropriate distribution for modelling OS. In brief, parametric functions and spline hazard functions were fitted to D2201 trial (1 December 2014 data cut) PFS K-M data. The suitability of these functions was assessed based on goodness-of-fit statistics, visual inspection and clinical opinion. Based on these assessments, the two-knot spline hazard function was selected to model the PFS experience of patients treated with midostaurin.

Modelling progression-free survival for patients receiving comparator treatments

The company did not identify any PFS data relating to patients treated with CCM. Clinical advice to the company was that, in the absence of any PFS data, it was reasonable to assume that, the OS HR used to adjust midostaurin OS estimates to represent the experience of patients treated with CCM, could be used to adjust midostaurin PFS data to represent the PFS experience of patients treated with CCM. As per the OS representation for patients receiving CCM, PFS is the same irrespective of comparator treatment.

Overall response rates

The ORR for patients treated with midostaurin (59.6%) was obtained directly from the D2201 trial, whilst the ORR for patients treated with CCM was calculated using published ORRs. Where available, subgroup (ASM, SM-AHN, MCL) ORRs were used in the model and weighted according to the population included in the D2201 trial. The ORRs used in the company model are presented in Table 25.

Table 25 Overall response rates used in the company model

Treatment	Overall response rate used in the economic model		Source		
	Overall advanced SM population	SM-AHN + MCL	ASM	SM-AHN	MCL
Midostaurin	59.5%	56.2%	D2201 trial[28]	D2201 trial[28]	D2201 trial[28]
Cladribine	[redacted]	[redacted]	Barete et al[34] Lim et al[35]	Barete et al[34]	Jawhar et al[39]
Interferon-based regimens	[redacted]	[redacted]	Lim et al[35] Hauswirth et al[32]	Hauswirth et al[32] Pardanani et al[37]	Derived from ASM and SM-AHN
Imatinib	[redacted]	[redacted]	Lim et al[35] Pardanani et al[37]	Lim et al[35] Pardanani et al[37]	Pardanani et al[37]
AML-like treatments	[redacted]	[redacted]	Assumption (same as cladribine)		

AML=acute myeloid leukaemia; ASM=aggressive systemic mastocytosis; MCL=mast cell leukaemia; SM=systemic mastocytosis; SM-AHN=systemic mastocytosis with an associated haematological neoplasm
Source: CS, Table 46

Duration of response

For treatment with midostaurin, the company obtained the DoR estimate used in the company model from the D2201 trial. The company noted that the DoR K-M data were flat for the first three cycles and, therefore, fitted parametric functions to the DoR K-M data after the third cycle. The method used to identify the most appropriate parametric distribution was the same as that used to identify the most appropriate OS and PFS distributions. The one-knot spline hazard function was selected as the preferred function. In the company model, a constraint was added to ensure than the extrapolation of DoR was consistent with that of PFS.

The company assumed that DoRs differed by comparator drug. To estimate the DoRs for the comparator drugs, the company applied the DoR HR for each drug to the parametric distribution that was used to reflect the DoR experience (one-knot hazard function) of patients receiving midostaurin. The DoR HRs for the comparator drugs were calculated from median DoRs reported in published studies (Table 26).

Table 26 Duration of response hazard ratios used in the company model

Comparator treatment	Median DoR for comparator	DoR probability for midostaurin when median reached	Derived HR	Source
Cladribine	11.0 months	[redacted]	[redacted]	Derived from Lim et al[35] and the D2201 trial
Interferon alpha/peg-interferon alpha	12.0 months	[redacted]	[redacted]	
TKIs (imatinib, nilotinib, dasatinib)	19.6 months	[redacted]	[redacted]	
AML-like treatments	11.0 months	[redacted]	[redacted]	Assumed to be the same as cladribine

AML=acute myeloid leukaemia; DoR=duration of response; HR=hazard ratio: TKI=tyrosine kinase inhibitor
Source: CS, Table 48

4.3.6 Time on treatment

Time on treatment (ToT) K-M data from the D2201 trial were used in the company model to calculate midostaurin treatment costs. As complete data were available there was no need to extrapolate the available ToT K-M data.

Based on the treatment regimen reported by Barete et al,[34] the company assumed that all patients treated with cladribine received 3.68 cycles of treatment and that 14.7% of these patients remained on treatment for an additional two cycles. The treatment cost for these cycles (3.68+0.29 cycles) was applied as a one-off cost to the first cycle.

Patients receiving interferon-based treatments (interferon alpha and peg-interferon alpha) and imatinib were assumed to be treated until disease progression, i.e., it was assumed that ToT could be modelled using PFS estimates.

4.3.7 Adverse events

Rates of Grade ≥3 AEs occurring in ≥5% of patients in the D2201 trial and A2213 trial were used to represent the experience of patients treated with midostaurin. Rates for those treated with CCM were obtained from the SmPC[69] for cladribine and from a published study[34] that evaluated the long term efficacy and safety of cladribine in patients with mastocytosis. The modelled AE rates and unit costs (obtained from previous NICE technology appraisals [TA400[74] and TA460[75]]) used in the company model are presented in Table 27.

Table 27 Adverse events (Grade 3/4) included in the company model: prevalence and unit costs

Adverse event	Unit cost		Midostaurin		CCM	
	Cost	Source	Prevalence	Source	Prevalence	Source
Nausea	£182.00	TA400[74]	[redacted]	Pooled D2201 trial and A2213 trial	16.50%	Cladribine SmPC[69]
Vomiting	£182.00	Assumed =nausea	[redacted]		7.00%	Cladribine SmPC[69]
Diarrhoea	£182.00	TA400[74]	[redacted]		7.50%	Cladribine SmPC[69]
Anaemia	£211.73	TA460[75]	[redacted]		14.00%	Cladribine SmPC[69]
Fatigue	£91.68	TA460[75]	[redacted]		25.00%	Cladribine SmPC[69]
Thrombocytopaenia	£280.28	TA460[75]	[redacted]		20.79%	Cladribine SmPC[69]
Dyspnoea	£422.41	TA460[75]	[redacted]		6.34%	Assumed same as midostaurin
Neutropenia	£808.28	TA460[75]	[redacted]		47.06%	Barete et al[34]
Infection	£517.68	TA460[75]	[redacted]	D2201 trial[28]	22.06%	Barete et al[34]
Lymphopenia	£808.28	Assumed =neutropenia	[redacted]		82.35%	Barete et al[34]

CCM=current clinical management; SmPC=Summary of Product Characteristics
Source: CS, Table 49 and Table 58

4.3.8 Health-related quality of life

Patients in the D2201 trial completed the SF-12 questionnaire[62] at baseline (on Day1, cycle 1) and then on the last day of each 28-day treatment cycle until cycle 12. Trial participants also completed the questionnaire at study completion or discontinuation if this occurred before cycle 12. Patient responses to the SF-12 questionnaire (MCS and PCS) were mapped onto EQ-5D-3L scores using the Gray et al algorithm.[76] This approach is consistent with the methods recommended in the NICE Reference Case.[46] A regression equation with progression status and response to midostaurin as covariates was then used to estimate health utility values. The equation accounted for multiple observations per patient and a manual adjustment was made to ensure that the utility value for the PF-response health state and the PF-no-response health state were higher than that the PD health state utility value. The health state utility values used in the economic model are shown in Table 28.

Table 28 Utility values used in the company model

Health state	Treatment arm	Utility value
PF-response	Midostaurin and CCM	[redacted]
PF-no-response	Midostaurin and CCM	[redacted]
Progressive disease	Midostaurin and CCM	[redacted]

CCM=current clinical management; PF=progression-free
Source: CS, Table 52

The company model also applied utility decrements to account for the discomfort associated with subcutaneous (interferon-based treatments), or intravenous (cladribine and AML-like treatments) administration routes, and the frequency of administration: cladribine (-0.041 applied to first cycle only), interferon alpha (-0.003 applied to every cycle), peg-interferon alpha (-0.002 applied to every cycle) and AML-like treatments (-0.041 applied to first cycle only). Midostaurin and imatinib were not associated with a utility decrement as these treatments are administered orally.

4.3.9 Resources and costs

Three main categories of costs were included in the company model (Section B.3.5):

- drug costs
- health state costs
- AEs.

Drug acquisition and administration costs

Confidential PAS discounts are available for midostaurin and azacitidine (an AML-like treatment). However, the PAS discount for azacitidine is not known to the company. In the CS, the company assumed that this PAS discount for azacitidine was 85%. The dosing schedules used in the company model for midostaurin and CCM drugs are reported in Section 4.3.3 of this report.

Midostaurin and imatinib are administered orally and do not have any administration costs. All other drugs are administered either subcutaneously or intravenously. Treatment with cladribine and AML-like treatments are assumed to have a one-off administration cost to the first cycle, in line with the method that was used to estimate ToT for these drugs. The administration costs associated with interferon-based treatments are applied to the ToT estimate to each model cycle. Details of intervention and comparator drug costs, including administration costs, are presented in Table 29.

The costs of AML-like treatments were applied as a one-off cost in the first cycle. These costs were obtained from the NICE STA of cytarabine+daunorubicin for previously untreated AML (TA552) and reflect use as a second-line treatment.[73]

Table 29 Drug acquisition costs (list price) and administration cost used in the company model

Drug	Vial/pack information (units per pack)	Cost per vial/pack	Vials/ packs per cycle	Cost per 28-day cycle	Admin cost	Source
Per cycle costs						
Midostaurin	25mg (56 tablets)	£5,609.94	4	£22,439.76	£0.00	D2201 trial[28]
Interferon alpha	6MU/0.5ml (1 vial)	£28.37	12	£340.44	£69.22	Lim et al[35] (single use syringe)
Peg-interferon alpha	90mcg/0.5ml (1 vial)	£76.51	4	£306.04	£23.07	Expert opinion (single use syringe)
Imatinib▲	400mg (30 tablets)	£172.29 (generic) £1,933.21 (Glivec)	1	£506.67	£0.00	eMIT (calculated)
One-off costs						
Cladribine	10mg/5ml (1 vial)	£159.50	N/A	£3,173.33	£8,634.10	Barete et al[34]
AML-like treatments (azacitidine)	-	-	-	£3,842.40*	£14,135	TA552[74]
AML-like treatments (others)	-	-	-	£6,8	£18,327	TA552[74]

▲ 79% receive generic drug and 21% receive branded drug
* 85% Patient Access Scheme discount assumed;
Admin=administration; eMIT=electronic market information tool; mcg=microgram; mg=milligram; ml=millilitre; MU=million unit
Source: CS, Table 55

The company model also included a one-off disease progression cost (of £11,807) to represent subsequent treatment costs. This cost was based on the cost of treatment with cladribine and, in the absence of evidence, this assumption was considered reasonable. In the company base case, 50% of patients were assumed to receive a subsequent therapy.

Resource use by health state

The company considered that the per-cycle cost incurred by patients who are progression-free varied over time. The company was unable to identify any UK cost study or NICE appraisal relating to advanced SM. The company, therefore, asked clinical experts (n=5) to estimate the resources used by patients. Unit costs were applied to the mean resource use estimates provided by these clinical experts. The company then calculated the per-cycle costs during the first 6 months ([redacted]). These costs were greater than the costs incurred during the following 6 months ([redacted]). The costs incurred after the first year of treatment were [redacted] per cycle. The per-cycle cost of the PD health state was estimated to be [redacted]. The resource use assumptions underpinning the health state cost calculations

are summarised in Table 30.

Table 30 Company resource use, unit costs and health state cost (per cycle)

Resource use	Unit cost	HRG code/Source	Health states resource use			
			Progression-free			PD
			0-6M	6-12M	>12M	
GP visit - surgery	£39.00	PSSRU (2019)[77]	[redacted]	[redacted]	[redacted]	[redacted]
GP visit - home visit	£100.62	PSSRU (2019)[77]	[redacted]	[redacted]	[redacted]	[redacted]
District nurse visit	£38.45	NHS Ref Cost (2017/2018)[78]: N02AF	[redacted]	[redacted]	[redacted]	[redacted]
Cancer nurse visit	£25.65	Assumed: 66.7% of community nurse cost (£38.45) as per TA400[74]	[redacted]	[redacted]	[redacted]	[redacted]
Pain and symptom management	£104.17	TA181[79] NHS Ref Cost (2017/2018)[78]: N21AF	[redacted]	[redacted]	[redacted]	[redacted]
Depression assessment and management	£81.31	TA181[79] NHS Ref Cost (2017/2018)[78]:A06A1	[redacted]	[redacted]	[redacted]	[redacted]
Outpatient visit	£194.39	NHS Ref Cost (2017/2018)[78]: face to face Clinical Oncology follow-up	[redacted]	[redacted]	[redacted]	[redacted]
ED use	£253.67	TA460[75] NHS Ref Cost (2017/2018)[78]: VB01Z, VB04Z, VB05Z, VB07Z, VB08Z	[redacted]	[redacted]	[redacted]	[redacted]
Hospitalisation days	£666.28	NHS Ref Cost (2017/2018)[78]: SA08G, SA08H, SA08J	[redacted]	[redacted]	[redacted]	[redacted]
ICU	£1,602.04	TA460[75] NHS Ref Cost (2017/2018)[78]: XC01Z - XC07Z	[redacted]	[redacted]	[redacted]	[redacted]
Bone marrow biopsy	£272.94	TA460.[75] NHS Ref Cost (2017/2018)[78]: SA33Z	[redacted]	[redacted]	[redacted]	[redacted]
ECG	£264.80	NHS Ref Cost (2017/2018)[78]: EY50Z	[redacted]	[redacted]	[redacted]	[redacted]
CT scan	£106.88	NHS Ref Cost (2017/2018)[78]: RD24Z	[redacted]	[redacted]	[redacted]	[redacted]
Chest X Ray	£106.88	Assume same as CT scan (assumption in TA400[74])	[redacted]	[redacted]	[redacted]	[redacted]
US scan	£89.08	NHS Ref Cost (2017/2018)[78]: RD24Z	[redacted]	[redacted]	[redacted]	[redacted]
MRI scan	£202.64	NHS Ref Cost (2017/2018)[78]: RD05Z	[redacted]	[redacted]	[redacted]	[redacted]
Blood test	£2.51	NHS Ref Cost (2017–2018): Directly Accessed Pathology Services, Haematology, DAPS05 (98)[78]	[redacted]	[redacted]	[redacted]	[redacted]
Bone densitometry	£71.72	NHS Ref Cost (2017/2018)[78]: RD50Z	[redacted]	[redacted]	[redacted]	[redacted]
Total cost per cycle			[redacted]	[redacted]	[redacted]	[redacted]

CT=computed tomography; ECG=electrocardiogram; ED=emergency department; GP=general practitioner; HRG=healthcare resource group; ICU=intensive care unit; MRI=magnetic resonance imaging; PD=progressed disease; PSSRU=Personal Social Services Research Unit; NHS Ref Cost=NHS Reference Cost; US=ultrasound
Source: CS, Table 57

Adverse event costs

The costs associated with AEs were obtained from recent NICE technology appraisals (TA400[74] and TA460[75]). The company estimated the cost of AEs for treatment with midostaurin and treatment with CCM to be £411 and £1,354 respectively. These costs were applied to the first cycle only.

4.3.10 Results

The company base case ICERs per QALY gained for the comparison of treatment with midostaurin versus CCM are shown in Table 31. The costs and QALYs associated with treatment with CCM were calculated using the weighted average (by treatment mix shown in Table 24) of the costs and QALYs associated with treatment with the five most common comparator drugs used in the NHS.

The company used a confidential PAS discount price when costing treatment with midostaurin and assumed that treatment with azacitidine had an 85% discount applied (azacitidine is an AML-like treatment that is available to patients in basket of comparator treatments). List prices have been used for all other treatments.

Table 31 Base cost effectiveness results for the overall advanced SM population (discounted prices for midostaurin and azacitidine)

Treatment	Total cost	Total LYG	Total QALYs	Incremental			Incremental cost per QALY gained
				Cost	LYG	QALYs	
Midostaurin	[redacted]	[redacted]	[redacted]				
CCM	£39,189	1.90	1.10	[redacted]	[redacted]	[redacted]	[redacted]

CCM=current clinical management; LYG=life years gained; QALY=quality adjusted life year; SM=systemic mastocytosis
Source: CS, Table 61

The company also presented results for treatment with midostaurin versus the individual treatment strategies that comprised CCM in scenario analyses (CS, Section B.3.8.3) as shown in Table 33 of this ERG report.

4.3.11 Subgroup analysis

The company conducted cost effectiveness analyses for the SM-AHN+MCL combined subgroup. The company base case cost effectiveness results for the comparison of treatment with midostaurin versus CCM for this subgroup are shown in Table 32.

Table 32 Base case cost effectiveness results for the SM-AHN+MCL combined subgroup (discounted prices for midostaurin and azacitidine)

Treatment	Total cost	Total LYG	Total QALYs	Incremental			Incremental cost per QALY gained
				Cost	LYG	QALYs	
Midostaurin	[redacted]	[redacted]	[redacted]				
CCM	£37,836	1.46	0.85	[redacted]	[redacted]	[redacted]	[redacted]

CCM=current clinical management; LYG=life years gained; QALY=quality adjusted life year; SM=systemic mastocytosis; SM-SM-AHN=systemic mastocytosis with an associated haematological neoplasm
Source: CS, Table 66

4.3.12 Sensitivity analyses

Deterministic sensitivity analyses

The company states that the choice of deterministic one-way sensitivity analyses (OWSAs) parameters was made a priori. Results from the company's OWSAs showed that variation (upper and lower 95% CI) of the OS HR had the greatest impact on the magnitude of the cost effectiveness results (see Figure 3).

Figure 3 Tornado diagram showing OWSA results for the comparison of treatment with midostaurin versus CCM in patients with advanced SM

CI=confidence interval; gen pop=general population; CCM=current clinical management; OS=overall survival; OWSA=one-way sensitivity analysis; PFS=progression-free survival; QALY: SM=systemic mastocytosis
Source: CS, Figure 39

Probabilistic sensitivity analyses

The results from the company's probabilistic sensitivity analysis are reproduced in Figure 4. Using the discounted price of midostaurin and azacitidine, the mean probabilistic ICER (£ per QALY gained) is the deterministic ICER (£ per QALY gained) for the comparison of treatment with midostaurin versus CCM. The company estimated that the probability of midostaurin being a cost effective treatment option at a willingness-to-pay threshold of £50,000 per QALY gained was % (see Figure 5).

Figure 4 Scatter plot of the cost effectiveness of treatment with midostaurin versus CCM in patients with advanced SM (1,000 iterations)

CCM=current clinical management; PSA=probabilistic sensitivity analysis; QALYs=quality adjusted life years; SM=systemic mastocytosis; WTP=willingness-to-pay threshold
Source: CS, Figure 37

Figure 5 Cost effectiveness acceptability curve of treatment with midostaurin versus CCM at a willingness-to-pay threshold of £50,000 per additional QALY gained in patients with advanced SM

CCM=current clinical management; QALYs=quality adjusted life years; SM=systemic mastocytosis; WTP=willingness-to-pay
Source: CS, Figure 38

The company highlights

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4.3.13 Scenario analyses

The company explored several alternative scenarios for the comparison of treatment with midostaurin versus CCM. Table 33 shows selected results relating to various approaches for extrapolation of OS and PFS data. None of the scenario analyses undertaken by the company generated ICERs below £100,000 per QALY gained.

Table 33 Selected scenario analysis results – with discounted prices for midostaurin and azacitidine and list prices for other drugs

Scenario	Incremental			ICER (£/QALY)
	Costs	Life years (undiscounted)	QALYs	
Base case	[redacted]	[redacted]	[redacted]	[redacted]
Individual comparators				
Comparator=cladribine	[redacted]	[redacted]	[redacted]	[redacted]
Comparator=interferon alpha	[redacted]	[redacted]	[redacted]	[redacted]
Comparator= peg-interferon	[redacted]	[redacted]	[redacted]	[redacted]
Comparator=imatinib	[redacted]	[redacted]	[redacted]	[redacted]
Comparator=AML-like treatments	[redacted]	[redacted]	[redacted]	[redacted]
Use of piecewise extrapolation				
K-M+extrapolation	[redacted]	[redacted]	[redacted]	[redacted]
Parametric extrapolation for OS				
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]
Loglogistic	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
Spline2	[redacted]	[redacted]	[redacted]	[redacted]
Parametric extrapolation for PFS				
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]
Loglogistic	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
Spline1	[redacted]	[redacted]	[redacted]	[redacted]
HR for OS for comparator				
Reiter et al[42] - Matched	[redacted]	[redacted]	[redacted]	[redacted]
Reiter et al[42]- Unmatched	[redacted]	[redacted]	[redacted]	[redacted]
Reiter et al[42]- From last treatment	[redacted]	[redacted]	[redacted]	[redacted]
Chandesris et al[40,41] - Univariable (matched)	[redacted]	[redacted]	[redacted]	[redacted]
Chandesris et al[40,41] - Multivariable (matched)	[redacted]	[redacted]	[redacted]	[redacted]
Barete et al[34] – derived	[redacted]	[redacted]	[redacted]	[redacted]

AML=acute myeloid leukaemia; HR=hazard ratio; ICER=incremental cost effectiveness ratio; OS=overall survival; PFS=progression-free survival; QALYs=quality adjusted life years; spline1=spline hazard model with one knot; spline2=spline hazard model with two knots
Source: CS, Table 65

4.3.14 Model validation

The company states that input from clinical experts was sought during model development. Additionally, an independent reviewer stress-tested the model, assessed the model for coding errors and validated the model.

4.4 ERG critique of the company models

4.4.1 Introduction

The company provided an MS Excel model that is easy to understand and accurately represents the model structure described in the CS. The company has made significant efforts to make the best use of the available data from the D2201 trial and other relevant trials to estimate the cost effectiveness of treatment with midostaurin versus CCM. The ERG confirms that the parameter values used in the company model match the values presented in the CS and that the model algorithms are error free. The approaches used by the company to value and incorporate utility weightings, estimate resource use for different health states and summarise the AEs associated with different treatments are appropriate for use in decision making.

Data to populate the midostaurin arm of the company model were available from two single arm, open label, phase II trials, the D2201 and A2213 trials. The ERG considers that both these trials were of reasonable methodological quality and clinical advice to the ERG is that the baseline characteristics of the patients included in these trials were similar to those of NHS patients. However, the A2213 trial was very small (n=26), and the trial protocol did not reflect NHS practice as treatment for non-responders was discontinued. The company, therefore, focused on using results from the D2201 in their model. The quality of the D2201 and A2213 trials is discussed in Section 3.2.2 of this ERG report and results from these trials are presented in Section 3.3 of this ERG report.

The company has generated model cost effectiveness results for the overall population with advanced SM and for the SM-AHN+MCL combined subgroup. The comparator arm of the model is CCM, which has been modelled to comprise the weighted average of the five treatment options that the company considered were used in the UK (cladribine, interferon alpha, imatinib, peg-interferon alpha and AML-like treatments). The weight applied to each treatment was equal to the proportion of patients receiving each treatment option (as estimated from discussions with five UK clinical experts [CS, Section B.3.2.3]).

In the company model, OS and PFS for patients treated with midostaurin was modelled by fitting curves to D2201 trial data. An OS HR was used to adjust the midostaurin OS and PFS data to model the experience of patients receiving CCM. This OS HR is the key driver of cost effectiveness. This parameter is so important to the company's base case cost effectiveness results that, without a level of certainty around this estimate, discussions about other model-related concerns are largely academic. Nevertheless, the ERG has identified three additional

major concerns relating to the parameter values that were used to populate the company model:

- PFS for midostaurin versus CCM
- Partitioning survival data
- Lifetime duration of the treatment effect of midostaurin.

The ERG cautions that any cost effectiveness results generated by making changes to model parameters relating to these areas of concern could be misleading as the magnitude of their impact might be very different if used in combination with a reliable OS HR. Therefore, the ERG has only indicated (where this has been possible) whether suggested changes to these parameter values would be likely to increase or decrease the company base case cost effectiveness results.

4.4.2 Overall survival hazard ratio

As midostaurin OS data were not available from the D2201 trial for the whole model time horizon, the company carried out standard procedures to fit a range of parametric curves to the trial data. The distribution selected by the company, which was used for the whole of the model time horizon, was the spline hazard one-knot distribution. The ERG is satisfied that the distribution selection process was carried out appropriately and, whilst there is always uncertainty around projections of OS data, the distribution chosen by the company provided a good visual fit to the D2201 trial OS K-M data.

The experience of patients receiving CCM was modelled by applying a HR to midostaurin OS estimates. The OS HRs considered by the company were generated by Reiter et al,[42] Chandesris et al[41] and, by the company, using data from the D2201 trial and Barete et al[34] (Table 34). The ERG has some concerns about the reliability of the Reiter et al[42] results; nevertheless, the ERG considers that given the limited options available to the company, the results generated by Reiter et al[42] provide the most reliable estimates. Summary details relating to the ERG's critiques of the Reiter et al[42] analyses, the Chandesris et al[41] analyses and the analyses undertaken using information published by Barete et al[34] are provided in Box 2. Full details of the ERG's critiques of the Reiter et al[42] and Chandesris et al[41] analyses are provided in Section 3.6.1 and Appendix 7.1.2 respectively.

Box 2 Summary of the ERG critique relating to the derivation of the overall survival hazard ratio analyses considered for inclusion in the company cost effectiveness analyses

ERG critique of Reiter et al[42] analyses

The ERG concerns:

- differences between the D2201 and A2213 trial treatment protocols (patients in the A2213 trial who did not respond, discontinued treatment) mean that it is unclear whether it was appropriate to pool data from these two trials
- small numbers of patients (the primary [unadjusted] and multivariable analyses included data from 89 patients receiving midostaurin [D2201 and A2213 trials] and 42 patients receiving treatment other than midostaurin)
- no information about the type of treatments received by German registry patients
- no details relating to the source or recruitment methods of patients into the German registry; nor is it known whether data from all German registry patients were included in the analyses
- the partial results reported in the abstract do not completely match those described in more detail in the powerpoint presentation (which does not appear to have been peer-reviewed), albeit the results provided in the unpublished study[42] and used in the company's base case are less favourable to the cost-effectiveness case than the published study.[12]

Given the limited options available to the company, the ERG considers it was appropriate for the company to use the multivariable OS HR in their base case analysis.

ERG critique of Chandesris et al[41] analyses

The ERG concerns:

- the small numbers of patients (French compassionate programme: n=28, French registry: n=44) included some patients with SM subtypes that were not relevant to the decision problem
- that the source and recruitment methods of patients were unclear
- that the process used to match intervention and control group patients was unclear (group sizes are not proportional)
- that no statistical methods for any of the OS analyses were reported
- the OS the univariate HR estimate calculated by the company relates to a single time point (20 years), rather than being a comparative measure relating to a period of time
- the methods used to estimate the HR were not reported in detail. This adds uncertainty to the reliability of the result.

The ERG considers that analysis methods were insufficiently described and that this had led to uncertainty around the validity of the presented results. The ERG, therefore, considers that these results should not be used to inform decision making.

ERG critique of analyses carried out using data reported by Barete et al[34]

The ERG concerns:

- the analysis only included data relating to patients with ASM, and numbers were very small (D2201 trial: 16 patients, cladribine: 14 patients)
- the HR estimate related to a specific time point rather than being a comparative measure over a period of time.

The ERG considers that this OR HR result should not be used to inform decision making.

ASM=aggressive systemic mastocytosis; CS=company submission; ERG=Evidence Review Group; HR=hazard ratio; OS=overall survival; SM=systemic mastocytosis. Source: ERG report Section 3.61 and Appendix 7.1.2

The company sought advice from clinical experts to help identify the most appropriate OS HR for the overall advanced SM population and for the SM-AHN+MCL combined subgroup. For both the overall advanced SM population and for the SM-AHN+MCL combined subgroup, clinical experts considered that the OS predictions generated by the Reiter et al[42] matched pair analysis OS HR (0.636) were optimistic, but that the OS HRs lying between this OS HR and the Chandesris et al[41] matched multivariable analysis OS HR (0.333) were reasonable. They also considered that the predictions generated by the Reiter et al[42] multivariable analysis OS HR (0.517) were the most plausible. Consequently, the multivariable OS HR of 0.517 reported by Reiter et al[42] was used in the company base case analysis to model relative effectiveness for both the overall advanced SM population and for the SM-AHN+MCL combined subgroup. The ERG highlights that the range over which clinical experts considered the OS HR might be plausible is very wide.

Table 34 Published overall survival hazard ratios considered for inclusion in the company economic analyses

Source	Analysis	Number		HR		
		Midostaurin	Registry	Mean	LCI	UCI
Reiter et al[42]*	Primary analysis (unmatched)	89	42	0.500	0.330	0.760
	Propensity scoring (matched pair)	42	42	0.636	0.326	1.244
	Multivariable	89	42	0.517	0.319	0.839
	From last treatment	115	39	0.440	0.290	0.670
Chandesris et al[41]	Univariable (matched)	28	44	0.447	NR	NR
	Multivariable (matched)	28	44	0.333	NR	NR
Barete et al[34]	Unmatched (derived)	16	14	0.22	NE	NE

* These numbers are from the unpublished presentation and not from the published abstract
HR=hazard ratio; LCI=lower confidence interval; NE=not estimated; NR=not reported; OS=overall survival; UCI=upper confidence interval
Source: CS, Table 44

Results from sensitivity analyses carried out by the company show that the company's cost effectiveness estimates are very sensitive to changes in the OS HR. The company's base case ICER per QALY gained for the comparison of the cost effectiveness of midostaurin versus CCM was £[redacted]. Results from the company's deterministic sensitivity analyses showed that using the upper and lower 95% CI OS HR estimates (0.319 and 0.839 respectively) generated ICERs per QALY gained for the comparison of the cost effectiveness of midostaurin versus CCM of £[redacted] and £[redacted] respectively. Company deterministic sensitivity analysis results demonstrated that the OS HR was the key driver of cost

effectiveness results. The ERG considers that without a robust and accurate OS HR estimate, it is not possible to produce reliable cost effectiveness results. The ERG has not been able to identify a reliable OS HR and, therefore, has not generated preferred cost effectiveness results.

4.4.3 Progression-free survival for midostaurin versus current clinical management

The company was not able to identify any comparative PFS data. Therefore, based on clinical advice, the company set the PFS HR equal to the OS HR. However, it is unclear whether this assumption is reasonable and, even if it were reasonable, there is no way of knowing if the uncertainty around the OS HR would extend to the PFS estimate. The ERG could not identify any clinical evidence to support the company's PFS HR estimate or identify an alternative estimate that would be more clinically plausible. It is not known whether setting the PFS HR equal to the OS HR leads to an under- or over-estimate of the true value. Therefore, the likely direction of the impact on the ICER per QALY gained from the uncertainty around the PFS HR is also not known. However, the results of the sensitivity analysis around the PFS HR undertaken by the company suggested that, even if the PFS HR was five times higher than had been assumed in the base case analysis, it would only reduce the ICER per QALY gained for the comparison of treatment with midostaurin versus CCM by 3.6% (CS, Table 65). As such, it is unlikely that even if the true PFS HR were known, it would make a big difference to the company's cost effectiveness results.

4.4.4 Partitioning survival data

The PF health state in the company model is partitioned into a PF-response health state and a PF-no-response health state to reflect the company assumption that HRQoL differs between responders and non-responders. The data provided by the company in response to the ERG's clarification request (question B1) suggest that, whilst the D2201 trial was not powered to show a difference in PFS or OS between responders and non-responders, PFS and OS results for responders differ to those for non-responders (Figure 6). As the decision was made to partition PFS, the ERG considers that it was inconsistent not to have also partitioned OS.

Figure 6 Overall survival and progression-free survival for responders and non-responders (D2201 trial)

PFS=progression-free survival; OS=overall survival SM=systemic mastocytosis
Source: Company clarification response question B1

The company used ORR and DoR estimates to partition the PFS health state into responders and non-responders. This approach effectively used DoR as a proxy for PFS in the responder group and led to an over-estimate of PFS after 18 cycles (Figure 7). However, the ERG has concerns about the reliability of the ORR and DoR estimates used in the company model and therefore considers that it was not appropriate to use these estimates to partition the PFS health state (nor would it have been appropriate to use them to partition OS). The ERG's critique of the sources for these estimates is provided in Section 3.6.1 of this ERG report. If the D2201 trial PFS K-M curves had been stratified by response status, the issues relating to the reliability of DoR and ORR results would have been avoided.

Figure 7 Progression-free survival and duration of response for responders and non-responders (D2201 trial)

DoR=duration of response; PFS=progression-free survival; SM=systemic mastocytosis
Source: Company clarification response question B1

The effect of removing partitioning from the company model on the cost effectiveness of treatment with midostaurin versus CCM is to decrease incremental QALYs, and thus increase the size of the ICER per QALY gained. For example, using the company model, the ERG has estimated that, if the average utility value across the PF-response and PF-no-response health states (0.652) were applied to both health states, the ICER per QALY gained for the comparison of midostaurin versus CCM would increase by £[redacted] to £[redacted] per QALY gained.

4.4.5 Lifetime duration of treatment effect of midostaurin

In the D2201 trial, the median time on treatment for patients receiving midostaurin was less than 1 year and only 19% of patients were still on treatment at 3 years, yet the treatment benefit attributed to midostaurin persisted for the whole 38-year model time horizon. The ERG considers that even if the OS and PFS HRs suggested by the company were reliable, it is unlikely that treatment with midostaurin would deliver a lifetime benefit (i.e., mortality and disease progression rates for patients treated with midostaurin would be lower than the same rates for patients treated with CCM for the whole of the model time horizon). The ERG considers that it is more likely that, at some point before 38 years, the progression and

mortality rates for patients initially receiving midostaurin and those initially receiving CCM would become equal.

The effect of equalising progression and mortality rates at some point during the model time horizon on the comparative cost effectiveness of midostaurin versus CCM would be to decrease incremental QALYs and thus increase the size of the ICER per QALY gained. For example, in an ERG scenario where the progression and mortality rates of treatment with midostaurin become equal to those of CCM after 3 years, the ICER per QALY gained for the comparison of treatment with midostaurin versus CCM would increase by £[redacted] to £[redacted] per QALY gained

4.5 Conclusions of the cost effectiveness section

Concerns around the reliability of the midostaurin clinical effectiveness data (the D2201 trial is a small, open label, single arm, trial) underpin the uncertainties around the company's cost effectiveness results. The key driver of cost effectiveness results is the uncertainty associated with the OS HR used to adjust midostaurin survival data to represent the experience of patients receiving CCM. Neither the company nor the ERG were able to generate reliable cost effectiveness results for this comparison. The assumption that the treatment effect of midostaurin on OS and PFS compared to the treatment effect of CCM would last a lifetime suggests that, whilst accurate cost effectiveness results cannot be calculated, the company base case ICER per QALY gained may be underestimated.

5 END OF LIFE CRITERIA

A technology meets NICE End of Life criteria[46] if (i) the treatment is indicated for patients with a short life expectancy, normally less than 24 months and (ii) there is sufficient evidence to indicate that the treatment offers an extension to life, normally of a least an additional 3 months compared with current NHS treatment.

The ERG considers that as the advanced SM subtypes can be determined at the time of treatment commencement, the End of Life criteria should be assessed, independently, for each subtype and not for the overall population with advanced SM. However, there are insufficient data to generate reliable survival estimates for each advanced SM subtype.

Short life expectancy

The company has generated model cost effectiveness results for the overall population with advanced SM and for the SM-AHN+MCL combined subgroup. The company base case model mean OS estimate for patients treated with CCM was [redacted] months for the overall advanced SM population and [redacted] months for the SM-AHN+MCL combined subgroup. The note of caution here is that these mean OS estimates depend on the validity of the OS HR in the company model, which is currently unknown.

The median OS for German registry patients (advanced SM population) who provided data included in the analysis carried out by Reiter et al[42] was 19.5 months. However, the company quotes published data (CS, p21) that suggest that median survival from diagnosis differs substantially between the different subtypes of advanced SM. Median survival is estimated to be between 41 months[7] and 11 years[14] for patients with ASM, between 24 months[7] and 4.4 years[4] for patients with SM-AHN, and between 2 months[7] and 9.2 months[13] for patients with MCL. The company advises that published life expectancy estimates for patients with SM-AHN may be too high as they include unknown proportions of patients with indolent SM. The ERG considers that, given the paucity of data, these estimates are reasonable and highlights that the only subtype for which the short life expectancy End of Life criterion is definitely met is patients with MCL, although it may also be met for patients with SM-AHN. Assessing short life expenctancy for the combined subgroup (SM-AHN+MCL) is, therefore, problematic.

Life extension

Company model base case results for the overall population with advanced SM, suggest that mean OS for patients treated with midostaurin is 31.8 months longer than that for patients treated with CCM. Company base case model results for the SM-AHN+MCL combined subgroup, suggest that mean OS for patients treated with midostaurin is 22.6 months longer than that for patients treated with CCM. However, these results are uncertain given the lack of robust clinical effectiveness data available to describe the size of the benefit of midostaurin over CCM.

Median OS results for the overall population with advanced SM presented by Reiter et al[42] suggest that, compared with the historical control group in that study, treatment with midostaurin extends life by 21.9 months. However, there is some uncertainty around the reliability of the OS results generated by Reiter et al.[42] This uncertainty relates to the inputs (midostaurin data and German registry data) and to the differences between the results presented in the published abstract[12] and those provided in the unpublished presentation.

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7 APPENDICES

7.1 Appendix 1: Additional evidence presented by the company

7.1.1 Summary of clinical evidence: comparators

Characteristics of the studies of the comparators

A summary of the disease subtypes of patients included in the trials of midostaurin and studies of comparators is provided in Table 35.

Table 35 Proportions of patients with different subtypes of SM in trials of midostaurin and studies of the comparators

Intervention	Study[b]	Disease subtype: n (% of total advanced SM)				Non-advanced SM
		ASM	SM-AHN[c]	MCL	Total advanced SM	
Midostaurin	D2201 (PEP)[28]	16 (18%)	57 (64%)	16 (18%)	89	0
	A2213[31]	3 (12%)	17 (65%)	6 (23%)	26	0
Cladribine	Barete et al[34]	14 (44%)	17 (53%)	1 (3%)	32	36
	Jawhar et al[39]	0 (0%)	0 (0%)	6 (100%)	6	0
	Lim et al[35,63]	3 (15%)	13 (85%)	0 (0%)	16	10
	Pagano et al[36]	NR[d]	NR[d]	NR[d]	3	0
	Pardanani et al[37]	0 (0%)	11 (100%)	0 (0%)	11	0
Interferon alpha[a]	Hausworth et al[32]	3 (60%)	2 (40%)	0 (0%)	5	0
	Lim et al[35,63]	14 (39%)	22 (61%)	0 (0%)	36	11
	Pagano et al[36]	NR[d]	NR[d]	NR[d]	8	0
	Pardanani et al[37]	0 (0%)	23 (100%)	0 (0%)	23	0
Imatinib	Lim et al[35,63]	4 (21%)	14 (74%)	1 (5%)	19	8
	Pagano et al[36]	NR[d]	NR[d]	NR[d]	17	0
	Pardanani et al[37]	0 (0%)	21 (100%)	0 (0%)	21	0
Nilotinib	Hochhaus et al[33]	37 (90%)	1 (2%)	3 (7%)	41	20
Dasatinib	Verstovsek et al[38]	9 (60%)	6 (40%)	0 (0%)	15	18

[a] Patients in Lim et al,[35,63] Pardanani et al[37] and four out of five patients in Hausworth et al[32] received interferon alpha plus prednisolone
[b] 'Some' patients (exact numbers not specified) in Lim et al,[35,63] Pagano et al[36] and Pardanani et al[37] received multiple treatments
[c] Unclear for studies of the comparators whether the SM-AHN disease subgroup also included patients with ISM, SSM or MCL with AHN
[d] Numbers of patients within each subtype receiving each intervention were not reported in Pagano et al.[36] For all 24 patients included in the study, 12 (50%) had ASM, 4 (17%) had SM-AHN and 8 (33%) had MCL
ASM=aggressive systemic mastocytosis; ISM=indolent systemic mastocytosis; MCL=mast cell leukaemia; NR=not reported; PEP=primary efficacy population; SM=systemic mastocytosis; SM-AHN=systemic mastocytosis with associated haematologic neoplasm; SSM=smouldering systemic mastocytosis
Source: Extracted and adapted from CS, Table 26

In terms of the total number of patients with advanced SM, data were available for 115 patients receiving midostaurin,[28,31] 72 patients receiving interferon alpha (63 of whom received interferon alpha plus prednisolone),[32,35-37,63] 68 patients receiving cladribine,[34-37,39,63] 57 patients receiving imatinib,[35-37,63] 41 patients receiving nilotinib[33] and 15 patients receiving

dasatinib.[38] Four of the studies included interventions which were not relevant comparators listed in the final scope[1] issued by NICE; midostaurin–cladribine 'mix',[39] hydroxyurea[35,37,63] and allogenic haematopoietic stem cell transplant, chemotherapy, steroids or radiotherapy.[36] Furthermore, within three of these studies,[35-37,63] it was reported that patients had received multiple interventions.

The proportion of patients with each disease subtype varied across the trials of midostaurin and across the comparator studies, and the number of patients receiving each of the comparator treatments was very small. Furthermore, four of the studies[33-35,38,63] included patients with non-advanced ASM and, within the comparator studies, it was unclear how the SM-AHN subgroup was defined. In particular, whether patients with non-advanced types of mastocytosis with AHN (such as ISM-AHN and SSM-AHN) were included within the SM-AHN disease subtype.

Characteristics of patients (age, gender and *KIT* D816V mutational status) within the comparator studies are reported in the CS (Table 26 and Appendix D, Table D.4.1.2). The company judges that, compared to the proportion in the D2201 trial, a similar proportion of *KIT* D816V positive patients was included in Barete et al[34] and Verstovsek et al.[38] Similarly, patients with a similar median age and gender distribution were included in Jawhar et al,[39] Lim et al,[35,63] Pagano et al,[36] and Pardanani et al.[37] The ERG agrees with this assessment but considers that direct comparisons between the study populations should not be made as characteristics were mostly reported only for the entire cohort of the study. The cohort may have included patients with non-advanced SM and/or patients receiving other interventions which are not relevant comparators listed within the final scope.[1]

Quality assessment of the studies of the comparators

Quality assessment of the comparator studies was undertaken using the Downs and Black checklist.[47] Assessments of each checklist item and an overview of study quality are presented in Table D.11.1 and Table D.11.2 (see CS, Appendix D).

The ERG agrees with the company assessments relating to characteristics of patients within the comparator studies and notes that the main findings of the studies and main outcome measures were clearly reported. The ERG also agrees with the company assessments that many items of the checklist were unclear or not present within the comparator studies; for example, very limited details of any individuals lost to follow-up were presented, limited adverse event results were available and for all of the studies of comparators, it is unclear how

the patients were recruited and whether the included patients within the studies were representative of the entire population from which they were recruited.

In the response to question A8 of the clarification letter (Table 2), the company explained that overall judgements of quality presented in Table 26 of the CS (good quality, reasonable quality, poor quality) were made 'crudely and qualitatively' based on the number of items marked 'yes', 'unclear' or 'no' on the checklists. It is unclear to the ERG how items marked as 'N/A' in Table 2 of the clarification letter contributed to the overall judgements, or how many items marked as 'yes' or 'no' corresponded to a judgement of good, reasonable or poor quality. Therefore, the ERG does not consider this qualitative assessment of overall quality to be appropriate.

Despite the ERG concerns regarding the assessment of overall quality, particularly relating to whether patients within the comparator studies were representative of the population of advanced SM, the ERG agrees with the company conclusion (CS, p88) that the evidence base provided by the comparator studies is weaker than the evidence provided by the trials of midostaurin.

Clinical efficacy results from the studies of comparators: overall response rate

A summary of the ORR results for all patients and by disease subtypes (where available) in the trials of midostaurin and studies of comparator treatments is provided in Table 36.

Table 36 Summary of ORR results in trials of midostaurin and studies of the comparators

Intervention	Study[b]	Overall response rate: responders / total patients, (%)			
		Disease subtype			Total advanced SM
		ASM	SM-AHN[d]	MCL	
Midostaurin	D2201 (PEP)[28]	12/16 ORR: 75%	33/57 ORR: 58%	8/16 ORR: 50%	53/89 ORR: 60%
	A2213[31]	1/3 ORR: 33%	13/17 ORR: 76%	4/6 ORR: 67%	18/26 ORR: 69%
Cladribine	Barete et al[34]	6/14 ORR: 43%	10/17 ORR: 59 %	0/1 ORR: 0%	16/32 ORR: 50%
	Jawhar et al[39]	No patients ORR: NA	No patients ORR: NA	1/6 ORR: 17%	1/6 ORR: 17%
	Lim et al[35,63]	1/2[c] ORR: 50%	6/11[c] ORR: 55%	No patients ORR: NA	NR/16[c] ORR: NR
	Pagano et al[36]	NR	NR	NR	3/3 ORR: 100%
	Pardanani et al[37]	No patients ORR: NA	6/11 ORR: 55%	No patients ORR: NA	6/11 ORR: 55%
Interferon alpha[a]	Hausworth et al[32]	1/3 ORR: 33%	2/2 ORR: 100%	No patients ORR: NA	3/5 ORR: 60%
	Lim et al[35,63]	6/10[c] ORR: 60%	9/20[c] ORR: 45%	No patients ORR: NA	NR/36[c] ORR: NR
	Pagano et al[36]	NR	NR	NR	3/8 ORR: 38%
	Pardanani et al[37]	No patients ORR: NA	11/23 ORR: 48%	No patients ORR: NA	11/23 ORR: 48%
Imatinib	Lim et al[35,63]	2/4[c] ORR: 50%	1/11[c] ORR: 9%	NR/1 ORR: NR	NR/19[c] ORR: NR
	Pagano et al[36]	NR	NR	NR	5/17 ORR: 29%
	Pardanani et al[37]	No patients ORR: NA	11/21 ORR: 52%	No patients ORR: NA	11/21 ORR: 52%
Nilotinib	Hochhaus et al[33]	8/37 ORR: 22%	NR	NR/3 ORR: NR	NR/41 ORR=NR
Dasatinib	Verstovsek et al[38]	3/9 ORR: 33%	2/6 ORR: 33%	No patients ORR: NA	5/15 ORR: 33%

[a] Patients in Lim et al,[35,63] Pardanani et al[37] and four out of five patients in Hausworth et al[32] received interferon alpha plus prednisolone

[b] 'Some' patients (exact numbers not specified) in Lim et al,[35,63] Pagano et al[36] and Pardanani et al[37] received multiple treatments

[c] ORR results are not reported for all patients in the ASM and SM-AHN subgroups and therefore ORR results are not available for the total number of patients with advanced SM in Lim et al[35,63]

[c] Unclear for studies of the comparators whether the SM-AHN disease subgroup also included patients with ISM, SSM or MCL with AHN.

ASM=aggressive systemic mastocytosis; ISM=indolent systemic mastocytosis; MCL=mast cell leukaemia; NA=not applicable; NR=not reported; ORR=overall response rate; PEP=primary efficacy population; SM=systemic mastocytosis; SM-AHN=systemic mastocytosis with associated haematologic neoplasm; SSM=smouldering systemic mastocytosis

Source: Extracted and adapted from CS, Table 27

ORR results reported in the CS were limited and varied across studies and interventions. For all patients with advanced SM, ORR ranged from 60% to 69% for midostaurin, 17% to 100% for cladribine, 38% to 60% for interferon alpha, 29% to 52% for imatinib, 33% for dasatinib and ORR for all patients with advanced SM were not reported within the study of nilotinib.[33] ORR results reported by disease subtype were also limited, particularly for the MCL disease subtype, and varied across studies and interventions.

The criteria used and the timepoints for response for the trials of midostaurin are summarised in Table 6 of this ERG report. Across the comparator studies and compared to the trials of midostaurin, the criteria used and the timepoints of response varied. Six studies used Valent criteria[33,34,36,37] or modified Valent criteria,[32,35,63] one study[39] used IWG-MRT and ECNM criteria[39] and one study[38] used Valent criteria to assess responses for patients with ASM and 'descriptive criteria' to assess responses for patients with SM-AHN. Five of the studies considered overall response as the timepoint,[32,34-37,63] one study[33] considered responses for a minimum of 4 weeks and another study[38] for a minimum of three treatment cycles, and one study[39] considered responses by month 6.

The ERG considers that direct comparisons between the ORR results for midostaurin and the comparators (and also between the comparators) should not be made:

- due to the uncertainty around the definitions of disease subtypes and the interventions patients received in the studies of the comparators (these are described in 'Characteristics of the studies of the comparators' section of this ERG report)
- due to variability of response criteria definitions and timepoints for response assessments
- due to very small numbers of patients contributing data to the ORR results, particularly for the disease subtypes.

Other clinical efficacy and safety evidence from the studies of the comparators

Other clinical efficacy and safety evidence reported in the studies of the comparators were very limited (CS, Table 27 and Table 28). In summary:

- Median (range) DoR was reported for one study[35,63] of cladribine, interferon alpha (plus prednisolone) and imatinib and the range of DoR was reported for one study of dasatinib.[38] Within these two studies, DoR results for each intervention was available only for a mixed population of patients with advanced SM and non-advanced SM.
- Very limited OS data for all patients with advanced SM or for the different disease subtypes were reported in the comparator studies. The company estimated median OS from graphical figures reported in the publications for three studies[34,36,37] of cladribine, interferon alpha (plus prednisolone) and imatinib and the number of deaths occurring were reported in two studies of nilotinib[33] and dasatinib[38] (CS, Table 28).

- None of the studies of the comparators reported PFS data. One study of cladribine reported relapse-free survival (RFS) and the company estimated the median RFS from graphical figures reported in the publication.[34]
- Adverse events (Grade 3 or 4 reported in at least 5% of patients, or events described as 'major toxicities'[32] or 'substantial side effects'[35,63]) were reported in five of the comparator studies. Adverse events were reported from mixed populations of patients with advanced SM and non-advanced SM.

The ERG considers that direct comparisons between other clinical and safety results for midostaurin and the comparators (and also between the comparators) should not be made as:

- numerical results are very limited or estimated,
- results are mainly based on mixed populations of patients with advanced SM and non-advanced SM who may be receiving multiple interventions
- results reflect very small numbers of patients.

7.1.2 Comparison of midostaurin with historical control data: the Chandesris et al study

The studies by Chandesris et al[40,41] were conducted by the French National Reference Centre for Mastocytosis; therefore, only published information relating to this study was available to the company.[40,41] Twenty-eight patients with advanced SM who received midostaurin 100mg twice daily (number of cycles unclear) under a compassionate transitory-use authorisation programme were included in the study. These midostaurin patients were compared to a control group of 44 patients who did not receive midostaurin, matched for age at diagnosis and subtype of mastocytosis via a 'logistic regression method' of propensity score matching. Patient characteristics of the midostaurin group and control group are summarised in Table 25 of the CS. A small number of patients included in the Chandesris et al[40,41] studies had subtypes of SM not relevant to the decision problem; mast-cell sarcoma (one patient in the midostaurin group and two patients in the control group) and progressive smouldering SM (two patients in each of the midostaurin and control groups). The control group were reported to have received a median of 2 (range 1 to 4) previous therapies. However, it is unclear what these therapies were and how many of the control group were receiving treatment when their data were included within the analysis compared to midostaurin patients.

The ERG considers that the source of the control group data is unclear; for example, it is not explicitly stated whether the control group patients were from the same hospital or clinic as the midostaurin treated patients and/or if they were recruited over the same time period. Furthermore, the ERG does not understand how the control group has been matched to the midostaurin group as matching should result in a control group size that is proportional to the

intervention group size. In other words, if one patient in the control group was matched to each midostaurin patient, the control group would comprise 28 patients, and if two patients in the control group were matched to each midostaurin patient then the control group would comprise 56 patients).

ORR and DoR, with treatment response assessed according to modified Valent and Cheson criteria, as in the D2201 trial, were only reported for the midostaurin group. The ORR for all midostaurin patients was 71% (median DoR 17 months, range 5 to 32 months). The ORR for the different disease subtypes were: three out of four patients with ASM (75%), thirteen out of eighteen patients with SM-AHN (72%) and two out of three patients with MCL (66%).

A comparative OS analysis was reported. The OS rate in the midostaurin group was 42.7% (95% CI: 18 to 100%) compared with 14.9% (95% CI: 6 to 36%) in the control group, corresponding to a two-fold higher hazard of death in the control group compared to the midostaurin group (HR 2.20, 95% CI: 1.08 to 4.47, p=0.02). The authors[40] also reported that in a multivariable analysis, age of diagnosis, signs of organ dysfunction and midostaurin treatment 'significantly affected OS' (p2026). However, the direction of these effects is unclear.

The findings from the Chandesris et al[40,41] studies also suggested that OS may be significantly higher for patients with ASM and MCL compared to the OS of patients with SM-AHN. The authors[41] note that the 'poor prognosis of MCL and ASM appears to be reversed by midostaurin' (p29). The ERG considers that this interpretation of the OS results is not appropriate due to the very small numbers of patients with each subtype and the lack of comparison with control data for this analysis of OS by disease subtype.

Furthermore, no statistical methods for any of the analysis of OS were reported for the Chandesris et al[40,41] studies. The ERG has been unable to verify whether the statistical approach to this comparative analysis of OS was appropriate. It is, therefore, not clear whether the results of the Chandesris et al[40,41] studies are reliable.

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

ERG report – factual accuracy check

Midostaurin for treating advanced systemic mastocytosis [ID1573]

You are asked to check the ERG report to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies, you must inform NICE by **5pm on Thursday 28 May** using the below comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

The factual accuracy check form should act as a method of detailing any inaccuracies found and how and why they should be corrected.

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28th May 2020

Dear Helen,

Midostaurin for treating advanced systemic mastocytosis [ID1573] – Response to ERG Report

Thank you for providing the ERG report for fact checking. The NICE pro-forma document for detailing factual inaccuracies has been completed and is presented at the end of this letter. We welcome the ERG's commentary on the significant efforts made by Novartis to make the best use of the available data to estimate the cost effectiveness of treatment with midostaurin versus current clinical management, despite the typical data limitations associated with ultra-rare conditions such as advanced systemic mastocytosis (advanced SM). Below are key points to note as part of Novartis' response to the ERG report.

- The pivotal trial for midostaurin (D2201) represents the largest ever study of advanced SM patients and midostaurin is the only licensed treatment for advanced SM. The D2201 trial demonstrated midostaurin to have significant disease-modifying activity, with a high and durable overall response rate. This was corroborated by a substantial decrease in the bone marrow mast cell burden, serum tryptase level and KIT D816V allele burden.

- We note that the ERG agrees with our conclusion that the evidence base provided by the comparator studies is weaker than the evidence provided by the trials of midostaurin. As highlighted during the scoping consultation and in other meetings with NICE, there are major challenges associated with appraising an ultra-rare condition such as advanced SM via the single technology appraisal (STA) rather than the highly specialised technology (HST) route. These challenges include the availability and quality of the evidence base, and the heterogeneity of the patient population; the key uncertainties highlighted in the ERG report arise from these challenges. Novartis aims to work collaboratively with NICE and NHSE to find solutions and we note NICE's undertaking (see scoping consultation response) to *"take into account the scarcity of the data in its decision making through the STA process"*

- Regarding how midostaurin in advanced SM is assessed against the end of life criteria, the ERG acknowledges that the "*life expectancy of patients with advanced SM varies significantly across disease subtypes"*. The wide range of published median survival times from diagnosis are symptomatic of the heterogeneity of systemic mastocytosis, and how non-advanced (e.g. indolent SM-AHN) and advanced subtypes have frequently been considered together in the literature. However, this appraisal is only concerned with advanced SM. Estimates are further complicated by the availability of midostaurin for advanced SM since September 2017.

- As noted in the company submission and the ERG report, median OS reported by Reiter et al for a cohort of patients with advanced SM, who received treatment other than midostaurin was 19.5 months. Furthermore clinical experts advised that in a world without midostaurin, patients with advanced SM would normally have a life expectancy of less than 24.

- We believe that midostaurin should therefore be considered an end-of-life treatment for patients with advanced SM. This should be considered in the context of a typical HST appraisal for an ultra-rare condition such as advanced SM, which applies a willingness to pay threshold of £100,000 to £300,000 per QALY, without factoring an end of life criteria.

- The current HST process was specifically designed for the evaluation of technologies for rare diseases, taking into consideration broader decision-making criteria in comparison to the conventional STA process. Advanced SM would be expected to meet the HST criteria. However, we acknowledge NICE's decision outlined in the NICE scoping consultation response: that the topic does not meet the criteria for HST because midostaurin is also used to treat FLT3-positive acute myeloid leukaemia, and because advanced SM is not currently managed in a highly specialised service even though treatment is concentrated in only a few centres.

Thank you for your time and please do not hesitate to contact me using the details below if you would like to discuss further

Yours sincerely,

Kevin Jameson

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Section 1: Major Comments

Issue 1

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 12, first sentence states: *"…….and notes the differences between the results presented in the published abstract and those provided in the unpublished presentation*" Page 24 states: *"and that some of these unpublished values differ from those reported in the published abstract"* Page 78 states: *"partial results reported in the abstract do not completely match those described in more detail in the powerpoint presentation"* Page 84, final sentence states: "*This uncertainty relates to the inputs (midostaurin data and German registry data) and to the differences between the results presented in the published*	Please change to "*…….and notes the differences between the results presented in the published abstract and those provided in the unpublished presentation - **albeit the results provided in the unpublished study and subsequently used in the company's base case are less favourable to the cost-effectiveness case than the published one***" Please include this statement wherever the discrepancy in values is highlighted in the ERG report.	The statement is subject to misinterpretation as the reader may come to the wrong conclusion that the company selectively chose a more favourable source of results.	Thank you for the observation. We have added the suggested text to page 24 and page 78 of the ERG report.

abstract and those provided in the unpublished presentation"			

Issue 2

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pages 12 and 49 state: *"Clinical advice to the ERG is that AEs arising from treatment with midostaurin require careful monitoring by a specialist clinical team with the experience to provide early recognition and management of cytoreductive therapy-related AEs, and that this can place a high burden on NHS staff and systems"*	Please change to: "*Clinical advice to the ERG is that* ***as with current unlicensed treatments for advanced systemic mastocytosis****, AEs arising from treatment with midostaurin require careful monitoring by a specialist clinical team with the experience to provide early recognition and management of cytoreductive therapy-related AEs, and that this can place a high burden on NHS staff and systems"*	This statement is factually inaccurate by omission and potentially misleading. Management of all cytoreductive therapies requires close specialist monitoring. This is not specific to midostaurin only.	Thank you. We have added the suggested text to pages 12 and 49 of the ERG report.

Issue 3

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 17 states: *"For patients with SM-AHN, life expectancy ranges from 24 months to 4.4 years, and for patients with ASM life expectancy ranges from 41 months to 11 years."*	Please include the following statement: "*For patients with SM-AHN, life expectancy ranges from 24 months to 4.4 years, and for patients with ASM life expectancy ranges from 41 months to 11 years.* ***However, the company has suggested that published life expectancy estimates for patients with SM-***	We appreciate that the ERG have acknowledged the uncertainty surrounding the life expectancy estimates for patients with SM-AHN. This context should be reported wherever the life	Thank you. We have added the suggested text to page 17 of the ERG report. We have added this text to page 84 of the ERG report:

Page 84 states: *"Median survival is estimated to be between 41 months and 11 years for patients with ASM, between 24 months and 4.4 years for patients with SM-AHN, and between 2 months and 9.2 months for patients with MCL"*	***AHN may be too high as they include unknown proportions of patients with indolent SM (ISM-AHN).**"*	expectancy estimates for SM-AHN patients are presented.	*The company advises that published life expectancy estimates for patients with SM-AHN may be too high as they include unknown proportions of patients with indolent SM.*

Section 2: Other Comments

Issue 4

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pages 22, Table 3, last row of the table contains the following text: *"Cost effectiveness results were generated for the overall population (ASM+SM-AHN+MCL) and for the combined AHN+MCL population*""	Please change to: "*Cost effectiveness results were generated for the overall population (ASM+SM-AHN+MCL) and for the combined **SM**-AHN+MCL population"*	Minor typographical error	Thank you. We have corrected the error as advised.

Issue 5

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 25, Section 2.10: *"Confidential Patient Access Scheme (PAS) discounts are in*	Please correct spelling of **azacitidine**.	Minor typographical error	Thank you. We have corrected the error as advised.

place for midostaurin and azactidine (the latter is used in the company's basket of comparator treatments). The PAS price of azactidine is not known to the company. The actual discounted price of midostaurin and an assumed discounted price of azactidine were used in the company model."			

Issue 6

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 29, Table 6, Patient population for D2201 does not include presence of ≥1 C-findings	This should be amended to include: "***Presence of ≥1 C-findings***" in line with A2213	Gotlib et al. (2016) states that patients with at least one measurable C-finding that was considered to be related to mastocytosis were eligible for the primary efficacy population of the D2201 trial. This should be reflected in Table 6, such that this does not appear to differ between the D2201 and A2213 trials.	Thank you. We have corrected the error as advised.

Issue 7

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 29, Table 6, median length of follow-up for ORR for A2213 is reported as: *"124 months (range 18 to 140)"*	This should be amended to: *"124 months (range **82** to 140)"*	Minor typographical error	Thank you. We have corrected the error as advised.

Issue 8

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 37, Table 12, ORR for all patients in A2213 is reported as: *"69% (50 to 89%)"* And in the following statement on page 37: *"At the time of analysis in the PEP, the ORR in the D2201 trial was 60% (95% confidence interval [CI]: 49 to 70%) and in the A2213 trial was 69% (95% CI: 50 to 89%)."*	This should be amended to: *"69% (50 to **88**%)"*	Minor typographical error	Thank you. We have corrected the error as advised.

Issue 9

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 40, Table 14, median OS for MCL patients in A2213 is reported as: *"1.5 (0.0 to 62.2)"*	This should be amended to: *"**18.5** (0.0 to 62.2)"*	Minor typographical error	Thank you. We have corrected the error as advised.

Issue 10

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 47, Table 19: a number of adverse events are marked as *"NR"* for the D2201 trial	These should be amended to *"**NA**"*, and a footnote should be added to the table to note that these adverse events were omitted as they did not occur in ≥10% of patients participating in the D2201 trial	Minor typographical error	Thank you. We have corrected the error as advised.

Issue 11

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 47 states: *"It is unclear from the CS if one patient (CS, p95) or two patients (CS, Table 35) experienced Grade 5 sepsis."*	This statement should be removed.	Data in Table 33 of the CS are reported for the first 12 cycles of treatment (main protocol), as reported in DeAngelo et al. (2018). Data in Table 35 of the CS are reported including the first 12	Thank you. We have amended the text on page 47 to: *Two patients (CS, Table 35) experienced Grade 5 sepsis*.

		cycles of treatment (main protocol) and the extension protocol. Therefore, 2 patients experienced Grade 5 sepsis – 1 as part of the main protocol and 1 as part of the extension protocol of the study.	

Issue 12

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 48: *"Leukopenia was reported in [redacted]% of patients and [redacted]% of events were categorised as Grade 3 or 4 AEs."*	This should be amended to: *"Leukopenia was reported in [redacted]% of patients and [redacted]% of events were categorised as Grade 3 or 4 AEs."*	Minor typographical error	Thank you. We have corrected the error as advised.

Issue 13

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 68, Table 29, vial/pack information for Peg-interferon alpha is reported as: *"90mcg/0.5m (1 vial)"*	This should be amended to: *"90mcg/0.5**mL** (1 vial)"*	Minor typographical error	Thank you. We have corrected the error as advised.

Issue 14

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 68: *"The per-cycle cost of the PD health state was estimated to be £[redacted]"*	This should be amended to: *"The per-cycle cost of the PD health state was estimated to be £[redacted]"*	Minor typographical error	Thank you. We have corrected the error as advised.

Issue 15

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 80: *"However, there is no way of knowing whether this assumption is reasonable and, even if it were reasonable, there is no way of knowing if the uncertainty around the OS HR would extend to the PFS estimate"*	Please could this wording be softened, for example: *"However, **it is unclear whether** this assumption is reasonable and, even if it were reasonable, there is no way of knowing if the uncertainty around the OS HR would extend to the PFS estimate"*	Whilst we acknowledge that this assumption is associated with uncertainty, it was considered reasonable by clinical experts (as stated in the CS and acknowledged in the ERG report).	Thank you for the observation. We have amended the text as requested.

Issue 16

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 84 states: *"The company base case model mean OS estimate for patients treated with CCM was **xxx** months for the overall advanced SM population*	This should be amended to: *"The company base case model mean OS estimate for patients treated with CCM was [redacted] months for the overall advanced SM population and [redacted]*	Minor typographical error and missing commercial in confidence highlighting	Thank you. We have corrected the errors as advised.

and [redacted] months for the SM-AHN+MCL combined subgroup"	*months for the SM-AHN+MCL combined subgroup"*		

Section 3: Confidentiality highlighting amendments

Issue 17

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pages 25 states: *"Outcomes were assessed over a [redacted] time horizon. Costs were considered from an NHS and a Personal Social Services perspective"* Page 61 states: *The model time horizon was set at [redacted] years and costs and outcomes were discounted at 3.5% per annum.*	Please remove the confidentiality highlighting here.	The model time horizon is not confidential.	Thank you. We have corrected the errors as advised.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technical report

Midostaurin for treating advanced systemic mastocytosis [ID1573]

This document is the technical report for this appraisal. It has been prepared by the NICE technical team.

The technical report and stakeholder's responses to it are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the appraisal committee meeting.

This report is based on:

- the evidence and views submitted by the company, consultees and their nominated clinical experts and patient experts and
- the evidence review group (ERG) report.

The technical report should be read with the full supporting documents for this appraisal.

1 Key issues summary

Issue	Summary	Technical Team Preliminary Judgement
1. Generalisibility of trial results	• The evidence for the clinical effectiveness of midostaurin comes from 2 single-arm, open-label, trials: D2201 (n=116) and A2213 (n=26). There are no randomised trials for midostaurin. • The trials included people with the following subtypes of advanced systemic mastocytosis: aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated haematological neoplasm (SM-AHN) or mast cell leukaemia (MCL). • Clinical expert advice to the company and NICE agreed that people with advanced systemic mastocytosis are a heterogenous group. They also agreed that patient characteristics in trials are similar to those of people seen in NHS clinical practice.	• The baseline characteristics of people in the D2201 and A2213 trials are generalisable to people seen in the NHS clinical practice. • It is unclear whether treatment practice in the trials is generalisable to the NHS setting.
2. Comparator treatments	• There are currently no licenced treatments for systemic mastocytosis in the UK. • The treatment pathway is complex and not well defined because of the heterogeneity of the disease. • Treatment may include interferon alpha, cladribine, imatinib (for disease without the KIT mutation), nilotinib or dasatinib. Treatment for systemic mastocytosis with an associated haematological disease will also include treatment for that disease. • The company's model includes a composite comparator including interferon alpha, cladribine, imatinib, pegylated interferon alpha and AML-like treatments. Clinical expert advice was used to estimate the proportion of use of each treatment in NHS clinical practice.	• The treatment pathway for advanced systemic mastocytosis is complex and not well defined. • The extent to which different treatments are used in clinical practice is uncertain. • It is unclear whether AML-like treatments are appropriate comparators. • Alternative scenarios using different compositions of comparators may be informative.

	• Clinical expert advice to the company, ERG and NICE agreed that nilotinib and dasatinib are not relevant comparators as they are rarely used in NHS practice. • NICE's clinical expert does not consider AML-like treatments to be relevant comparators as these treat the associated haematological neoplasm rather than advanced systemic mastocytosis.	
3. Subgroups	• Advanced systemic mastocytosis is a heterogeneous disease with varying clinical symptoms. There are 3 subgroups: aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated haematological neoplasm (SM-AHN) and mast cell leukaemia (MCL). • Clinical expert advice to the company, ERG and NICE agree that life expectancies vary substantially between the 3 subgroups. • Clinical expert advice to NICE suggest that treatment choice depends on the subgroup and the presentation of the disease. • The company presented an exploratory subgroup analysis including only people with SM-AHN and people with MCL.	• Systemic mastocytosis is a heterogenous disease with varying clinical symptoms. • People in the 3 subgroups have different life expectancies and might receive different treatment options depending on their symptoms. • It is unclear whether people with SM-AHN and people with MCL should be combined in 1 subgroup analysis. • If evidence is available separate analyses for each subgroup are preferable.
4. Comparative effectiveness data sources	• There are no randomised trials for the comparators. • The company identified 8 non-ranodmised comparator studies (single arm trials or observational studies). • The company identified 2 comparative studies that included midostaurin and an unspecified comparator: o Reiter et al. compared pooled D2201 and A2213 trial data (n=89) with data from a German registry (n=42). It included only people for whom the date of diagnosis was known. The authors presented several hazard ratios using different methods.	• It is unclear whether the Reiter and Chandesris data are generalisable to the NHS setting. Further clinical advice on the comparability of treatments and patients in Germany, France and the NHS in England would be informative. • Both comparative studies have methodological limitations, including that they are not randomised. • Ongoing registries might provide additional comparative effectiveness data.

	The ERG accepted that this study provided the best available source of comparative effectiveness data, but had concerns about the small sample size, generalisability of the German registry data to NHS practice, and whether the D2201 and A2213 trial data should have been pooled (section 3.6 of ERG report). o Chandesris et al. compared data from a cohort of patients receiving midostaurin in a French compassionate use programme (n=28) with French registry data (n=44). The ERG had concerns about the methodology used, small sample size, and differences in patient characteristics between the French cohorts and the patients recruited to the D2201 and A2213 trials (sections 3.6 and 4.4.2. of ERG report). • The company used the hazard ratio from the multivariable analysis from Reiter et al. in its base-case model. • The technical team is aware of additional registries for people with mastocytosis; such as the European Competence Network on Mastocytosis (ECNM) registry initiated in 2012.	
5. Overall survival estimates	• For midostaurin, the company used data from D2201. This trial had a median follow up of 76 months. The company fitted a spline model with 1 knot to the data to get overall survival estimates for the 38-year time horizon (see section 3.3.2 of company submission), based on statistical fit, visual fit and expert advice. It explored other distributions in scenario analyses. • The ERG was satisfied that the spline hazard one-knot model was selected appropriately. • For the standard of care, the base-case model included a hazard ratio from Reiter et al. (0.52) applied to the overall survival curve of midostaurin.	• The company's overall survival curve for midostaurin appears to be reasonable. • The overall survival hazard ratio is a key driver of cost effectiveness. • There are limitations with using the Reiter et al. study to inform comparative effectiveness, therefore the hazard ratio for midostaurin versus standard of care is highly uncertain. • It is unclear whether the company used the most appropriate hazard ratio in their model. • Further evidence on proportion of people still alive at 15 years on midostaurin may inform

	Clinical advice was used to select the base-case value.The ERG noted that the range clinical experts considered plausible was very wide (0.33 to 0.64). The company provided scenario analyses using hazard ratios from Reiter et al. and Chandesris et al. • The ERG questioned the reliability of the results from Reiter et al. (see section 4.4.2 of ERG report). It noted that the resulting hazard ratio is the key driver of cost-effectiveness results. The company's cost-effectiveness estimate varied by -24% to +137% in its deterministic sensivity analysis on this parameter (using its 95% confidence interval bounds of 0.32 and 0.84).	the appropriateness of the fit used by the company. • Further evidence on the proportion of people still alive at 5, 10, and 15 years with standard of care may inform the most appropriate hazard ratio.
6. Progression-free survival estimates	• For midostaurin, the company used a spline hazard two-knot distribution to model progression-free survival estimates (see section 3.3.3 of company submission), based on statistical fit, visual fit and expert advice. It explored other distributions in scenario analyses. • The company did not identify data on comparative progression-free survival. It used the same hazard ratio as for overall survival (see issue on overall survival estimates). • The ERG questioned the appropriateness of using the overall survival hazard ratio for progression-free survival (see section 4.4.3 of ERG report). It could not identify clinical evidence to support the company's approach or an alternative approach. • The company's deterministic sensitivity analysis showed that this parameter had little impact on cost-effectiveness estimates, between -8% and +3%.	• The company's progression-free survival curve for midostaurin appears to be reasonable. • There is no evidence to inform the progression-free survival of standard of care relative to midostaurin, and the appropriateness of using the overall survival hazard ratio is uncertain. However, the progression-free survival hazard ratio does not appear to be a key driver of cost-effectiveness estimates.
7. Partitioning survival data	• The company's partitioned survival model has 4 mutually exclusive health states: 2 progression-free states (sustained response, lack or loss of response), progressed disease and death. Clinical expert advice	• Because of the heterogenetiy of the disease and the limited evidence base, modelling disease evolution of advanced systemic mastocytosis is difficult.

	to the company and NICE supports 2 progression-free health states as quality of life differs depending on the treatment response. • The ERG acknowledged that progression-free and overall survival may be different for responders and non-responders, based on the trial data. However, it had concerns with the reliability of the response rate and duration data used by the company to partition the progression-free health states, and considered that they were not appropriate for this purpose. The ERG also felt it is not appropriate to partition progression-free survival without similarly partitioning overall survival. • The ERG noted that removing the partitioning of the progression-free health state (collapsing it from 2 states into 1 using an average utility value) increased the company's base-case cost-effectiveness estimate by 6%. It also noted that unreliable response data would not have been required to partition progression-free survival if the D2201 had been stratified by response status.	• Quality of life among people who are progression free may differ depending on their response to treatment. • However, without reliable data to inform a partitioned model, it may be more appropriate to use 1 progression-free health state with a weighted average utility value for progression-free patients and weighted average costs. Sensitivity analysis could explore the importance of the weights. • In a partitioned model, using D2201 data stratified by response status would be a more appropriate method than the company's approach. • In a partitioned model, overall survival should also be partitioned.
8. Utility values	• Health state utility values were informed by estimating EQ-5D values from SF-12 data collected in D2201. • The company used a mapping approach by Gray et al. (2006), but other approaches exist such as those mentioned by the company, as well as the approach by Conigliani et al. (2015). Different approaches may give different utility estimates. • The company adjusted the utility values used in the model, to restrict the values for progression-free disease to always be higher (i.e. better quality of life) than the value for progressed disease.	• To obtain EQ-5D values from SF-12 data, other approaches may be better than that by Gray et al. (2006). • Manually restricting health state utility values in the model is unlikely to be consistent with the data and may underestimate the uncertainty.

9. Duration of treatment effect	• In the company's model, the treatment benefit of midostaurin persisted for the whole 38-year model time horizon. • In D2201, most people had stopped treatment with midostaurin within 1 year. The median time on treatment with midostaurin was less than 1 year and 19% of patients were still on treatment at 3 years (see section 3.3.5 of company submission). • Clinical expert advice to NICE suggests that, based on 10-year follow up of the A2213 trial, responses to treatment appeared to be durable. • The ERG questioned whether this was appropriate, and suggests that it is likely the progression and survival rates for midostaurin and the composite comparator would become equal over time. Illustratively, assuming treatment benefit lasts for 3 years increases the midostaurin cost-effectiveness estimate by 19% (section 4.4.5 of ERG report).	• Response to treatment with midostaurin may be durable over time. However, it is unlikely that the relative benefit of midostaurin over standard of care lasts for 38 years, particularly as the median treatment duration is less than 1 year. • Further evidence on the duration of midostaurin's relative effectiveness over time would be informative. • Alternative scenarios using shorter durations of relative treatment benefit would be informative for decision making.
10. End of life criteria	• There are 3 subgroups of people with advanced systemic mastocytosis: aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated haematological neoplasm (SM-AHN) and mast cell leukaemia (MCL). The company provided evidence for 2 groups: the overall population, and an "exploratory" analysis in the combined SM-AHN and MCL subgroup. • Median survival from diagnosis with standard of care differs substantially between the different subtypes (section 5 of ERG report). The ERG advised that only people with MCL appear to meet the short life expectancy criterion (less than 24 months) with certainty. • The overall survival benefit of midostaurin is uncertain because of limited data, discussed above.	• End of life criteria should be assessed for each subgroup independently. • Only people with MCL meet the short life expectancy criterion (less than 24 months).

11. Cancer Drugs Fund	• If the technology is not recommended for routine use, but the committee thinks that there is plausible potential for the technology to be cost effective, the committee could recommend it for use in the Cancer Drugs Fund while additional data are collected that address the uncertainties in the evidence base. • There are no ongoing trials of midostaurin for treating advanced systemic mastocytosis.	• Additional data collection within the Cancer Drugs Fund would not reduce the uncertainty, because no data on comparator treatments would be collected.

2 Questions for engagement

Issue 1: Generalisibilty of trial results

1. Is clinical practice in the trials generalisable to the NHS setting?

Issue2: Comparator treatments

2. Are AML-like treatments used in the NHS in England to treat mastocytosis?

3. What are the most appropriate comparators in the UK? Please provide details of which are most used, e.g. treatment 1: 60% of people, treatment 2: 10% of people, and so on.

4. Is it appropriate to have a composite comparator?

Issue 3: Subgroups

5. Are the 3 subgroups, aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated haematological neoplasm (SM-AHN) and mast cell leukaemia (MCL), distinguishable in clinical practice?

6. Are people in the 3 subgroups offered different treatment options in the NHS in England? For each subgroup please provide details of which are most used, e.g. treatment 1: 60% of people, treatment 2: 10% of people, and so on.

7. Is it appropriate to combine people with SM-AHN and people with MCL in 1 subgroup?

Issue 4: Comparative effectiveness data sources

8. Is clinical practice for managing masotcytosis in France and Germany comparable to clinical practice in the NHS in England?

9. Is it appropriate to assume that outcomes from the studies in Germany and France are comparable to the NHS in England?

10. Is it appropriate to combine results from D2201 and A2213, as done in Reiter et al.?

Issue 5: Overall survival estimates

11. How many people would you expect to be still alive at 5, 10 and 15 years on midostaurin? At 15 years, is 5% to 10% an appropriate estimate?

12. How many people would you expect to be still alive at 5, 10, and 15 years on standard of care?

13. What is to most appropriate hazard ratio to estimate overall survival of the comparators? Is any of the hazard ratios in Reiter et al. appropriate? What is the clinically plausible range for this hazard ratio?

14. Is it appropriate to use the same hazard ratio for all comparators assuming similar effectiveness of comparators?

15. Is it appropriate to use the same hazard ratio for the subgroups?

Issue6: Progression-free survival

16. Is it appropriate to use the same hazard ratio for progression-free survival and overall survival?

17. What is to most appropriate hazard ratio to estimate progression-free survival of the comparators? Is any of the hazard ratios in Reiter et al. appropriate? What is the clinically plausible range for this hazard ratio?

Issue 7: Partitioning survival data

18. Are partitioned health states appropriate?

    a. Is the company's approach (progression-free survival partitioned based on response rates and durations) methodologically and clinically appropriate.

    b. What is the impact on cost-effectiveness estimates if both overall survival and progression-free survival are partitioned, using data from D2201 stratified by response status? Are such stratified data available?

Issue 8: Utility values

19. What is the impact of using alternative mapping approaches on the resulting utility values and cost-effectiveness estimates?

20. Is it appropriate to manually restrict utility values, potentially underestimating the overall parameter uncertainty?

Issue 9: Duration of treatment effect

21. Is it plausible that the effect of midostaurin on survival and progression, relative to current treatments, can be maintained for a person’s lifetime while on treatment?

22. If not, how long would you expect midostaurin’s treatment effect to last while on treatment? e.g. 5, 10, 15 years, or other.

23. If discontinued, how long would you expect midostaurin’s treatment effect to last? e.g. 5, 10, 15 years, or other.

Issue 10: End of life

24. In the overall population of people with advanced systemic mastocytosis, and in the 3 subgroups (ASM, SM-AHN and MCL):

    a. What is the life expectancy of a person with current treatments?

    b. Would you expect midostaurin to increase survival by at least 3 months?

Issue 10: Cancer Drugs Fund

25. Would additional data collection within the Cancer Drugs Fund reduce the uncertainty?

NICE National Institute for Health and Care Excellence

Technical engagement response form

Midostaurin for treating advanced systemic mastocytosis [ID1573]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments **5pm** on **Wednesday 29 July 2020**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential

information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	**Bemi Odunlami**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Novartis Pharmaceuticals UK Ltd**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

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Professor Stephen O'Brien
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29th July 2020

Dear Professor O'Brien,

Midostaurin for treating advanced systemic mastocytosis (advanced SM) [ID1573] – Response to Technical Report

Thank you for the opportunity to review and respond to the key issues identified by the NICE Technical Report: our response has been provided to NICE. However, there are broader issues related to this appraisal, including process issues which are not acknowledged in the technical report. Furthermore, based on discussions during the NICE technical engagement call with NICE and the ERG, we are not convinced that these broader issues have been adequately considered when interpreting the evidence base. Novartis would like to work collaboratively with NICE and NHS England to secure patient access to midostaurin, including through a potential confidential agreement [redacted], which makes midostaurin cost-effective in the licensed population. The rest of this letter details broader issues that we would like the committee to take into consideration when interpreting the evidence.

Advanced SM is an ultra-rare and heterogeneous condition with a very limited evidence base. Nevertheless, the midostaurin trial (D2201) is the largest ever trial conducted in this patient population. On the other hand, there is a very limited evidence base for the comparator, where the existing evidence is weaker than the evidence provided by the trials of midostaurin. Midostaurin is the only licensed treatment for advanced SM and was initially available to UK NHS patients via a compassionate use program.

The current highly specialised technology (HST) process was specifically designed for the evaluation of technologies for rare diseases such as advanced SM, and it is able to take into consideration broader decision-making criteria in comparison to the conventional single technology appraisal (STA) process. Advanced SM would be expected to meet the HST criteria. However, we acknowledge NICE's decision outlined in the NICE scoping consultation response: that the topic does not meet the criteria for HST because midostaurin is also used to treat FLT3-positive acute myeloid leukaemia, and because advanced SM is not currently managed in a highly specialised service, even though treatment is concentrated in only a few centres.

Notwithstanding this, and as highlighted during the scoping consultation and in other meetings with NICE, there are major challenges associated with appraising an ultra-rare condition such as advanced

SM via the STA rather than the HST route. These challenges include the availability and quality of the evidence base, and the heterogeneity of the patient population. Of note is that the key uncertainties highlighted in the ERG report arise from these challenges. Based on the stakeholder responses to the draft scope, it appears that patient groups and the clinical community were similarly concerned that sufficient flexibilities would not be afforded to this ultra-rare disease if the appraisal was routed via an STA. We welcome NICE's undertaking (see scoping consultation response) to "*take into account the scarcity of the data in its decision making through the STA process"*. On this basis, we provided our evidence submission to NICE for review through the STA process, and would like to bring this undertaking to the attention of the committee. We note some similarities between this appraisal and NICE TA588 (nusinersen [Spinraza®] for treating spinal muscular atrophy), during which the committee was "*mindful during its decision making of the need to consider whether any adjustments to its normal considerations were needed to take into account the rarity and severity of the disease*".

One area that merits further consideration by the committee is how the routing of the appraisal via STA instead of HST has brought about a major process issue – end of life. An HST appraisal for an ultra-rare condition such as advanced SM, can apply a willingness to pay threshold of £100,000 to £300,000 per QALY, without factoring in end of life criteria. This raises an inequality if a rigid consideration of the end of life criteria is applied. Nevertheless, advanced SM is expected to meet the end of life criteria as evidenced in the company submission.

Finally, we would like to re-state our commitment to working with NICE and NHS England to secure early access to midostaurin: given the resource constraints created by the COVID-19 situation, our intention is to resolve issues in as few committee meetings as possible – ideally a single meeting. To that end, we have introduced [redacted] that makes midostaurin cost-effective at the £50,000 per QALY threshold [redacted]

Thank you for your time and please do not hesitate to contact me using the details below if you would like to discuss further

Yours sincerely,

Kevin Jameson

Head of Health Economics and Outcomes Research
Phone: [redacted]
Email: [redacted]

CC Helen Knight
Jasdeep Hayre

Questions for engagement

Responses to the questions for engagement are provided below, and additional economic scenario analyses supporting our responses are presented in Appendix 1 at the end of the document.

Issue 1: Generalisability of trial results	
Is clinical practice in the trials generalisable to the NHS setting?	• In the D2201 trial, there were four patients enrolled across three centres in the UK (Glasgow, London & Liverpool).[1] In addition, as part of this submission, Novartis has sought feedback from five highly experienced clinicians from UK treatment centres, which is a substantial number in the context of a rare disease such as advanced systemic mastocytosis (advanced SM). Clinical expert feedback has confirmed that patients included in the pivotal D2201 trial are reflective of those treated in UK NHS practice. Novartis are pleased to see that clinical advice to NICE is in agreement with this position. • Clinical expert feedback has further confirmed that treatment practice in the pivotal D2201 trial is reflective of UK NHS practice and how midostaurin will be used. It should be noted that midostaurin was available in the UK NHS via a compassionate use programme and treatment practice in that setting was aligned with the D2201 trial. • The supportive A2213 trial includes patients with similar baseline characteristics to patients included in the pivotal D2201 trial.[1] As such, patients included in the A2213 trial are reflective of those treated in UK NHS practice and the A2213 trial provides valuable long-term data of the efficacy and safety of midostaurin. It should be noted that in the A2213 trial, treatment with midostaurin was stopped for patients who did not achieve a response after the first two treatment cycles.[1] Therefore, clinical practice in the supportive A2213 trial is less generalisable to the UK NHS setting. The economic analysis does not consider a stopping rule for midostaurin, and treatment is considered in the model as per the study D2201 protocol, and modelled as per the

<table>
<tr><td></td><td>expected use of midostaurin in clinical practice in the UK.</td></tr>
<tr><td colspan="2">Issue 2: Comparator treatment</td></tr>
<tr><td>Are AML-like treatments used in the NHS in England to treat mastocytosis?</td><td>• The inclusion of acute myeloid leukaemia (AML)-like treatments in the composite comparator for the treatment of advanced SM in the UK NHS was based on feedback from UK clinical experts with experience of managing patients with advanced SM.

• As part of this submission, Novartis has sought feedback from five clinicians from UK treatment centres, four of whom indicated that AML-like treatments form part of the treatment of advanced SM and should therefore be considered as relevant comparators. Page 11 of the ERG report confirms that clinical advice to the ERG supports this clinical advice provided to Novartis.</td></tr>
<tr><td>What are the most appropriate comparators in the UK? Please provide details of which are most used, e.g. treatment 1: 60% of people, treatment 2: 10% of people, and so on.</td><td>• The most appropriate comparators in the UK were determined based on feedback from five clinical experts with experience in the management of patients with advanced SM. Clinical experts each completed a questionnaire on the proportion of treatments received in the UK according to disease subgroup (aggressive SM [ASM], SM-AHN and MCL). The results (Table 1) were then pooled and used in the economic model associated with this submission.

Table 1: Treatment received in the UK used in the submission for the overall advanced SM population and the SM-AHN + MCL subgroup (excluding supportive care and clinical trial)
<table>
<tr><th>Comparator</th><th>Proportion used in the UK (overall advanced SM population)</th><th>Proportion used in the UK (SM-AHN + MCL)</th></tr>
<tr><td>Cladribine</td><td>53.65%</td><td>52.12%</td></tr>
<tr><td>Interferon alpha</td><td>2.05%</td><td>1.53%</td></tr>
<tr><td>Peg-interferon alpha</td><td>24.23%</td><td>23.74%</td></tr>
<tr><td>Imatinib</td><td>4.50%</td><td>3.64%</td></tr>
<tr><td>Dasatinib</td><td>-</td><td>-</td></tr>
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	<table><tr><td>Nilotinib</td><td>-</td><td>-</td></tr><tr><td>AML-like treatment (azacitidine)</td><td>7.53%</td><td>9.19%</td></tr><tr><td>AML-like treatment (other)</td><td>8.03%</td><td>9.78%</td></tr></table> **Abbreviations:** Advanced SM: advanced systemic mastocytosis; AML: acute myeloid leukaemia; ASM: aggressive systemic mastocytosis; MCL: mast cell leukaemia; peg-interferon alpha: pegylated interferon alpha; SM-AHN: systemic mastocytosis with associated haematologic neoplasm.
Is it appropriate to have a composite comparator?	• At present, there are no therapies other than midostaurin licensed for the treatment of advanced SM in the UK. There is no established treatment pathway for advanced SM in the UK and there are currently no UK-specific clinical guidelines. Therefore, patients with advanced SM are likely to receive a mix of treatments, as evidenced by clinical expert feedback (Table 1). Note that these treatments are all off-licence with very little, if any evidence of efficacy or safety. • In this context, a composite comparator was judged to be adequate for capturing the complexity of current treatment practice. • Nonetheless, whilst a composite comparator has been used in the base case economic analysis associated with this submission, the economic model has the functionality for each individual treatment to be assessed separately and scenario analyses where midostaurin was compared to each individual treatment were presented in the Company submission. It should be noted that assessment of each individual treatment separately results in incremental cost-effectiveness ratios (ICERs) which do not differ substantially to that presented in the base case analysis of the economic model.
Issue 3: Subgroups	
Are the 3 subgroups, aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated haematological neoplasm (SM-AHN) and	• Advanced SM is a highly heterogeneous disease. As there is no clear standard therapy, treatments are considered on an individual basis for each patient from a pool of treatment options which are broadly similar across the three subgroups (ASM, SM-AHN and MCL).[2, 3]

mast cell leukaemia (MCL), distinguishable in clinical practice?	
Are people in the 3 subgroups offered different treatment options in the NHS in England? For each subgroup please provide details of which are most used, e.g. treatment 1: 60% of people, treatment 2: 10% of people, and so on.	• Feedback from clinical experts with experience in the management of patients with advanced SM has indicated that patients in the three subgroups of advanced SM (ASM, SM-AHN and MCL) are offered broadly similar treatment options in the UK NHS, with treatments utilised in different proportions within each subgroup (Table 1). • This has been reflected in the economic model associated with this submission and utilisation of each treatment has further been weighted according to the proportion of patients in each of the three subgroups.
Is it appropriate to combine people with SM-AHN and people with MCL in 1 subgroup?	• The cost-effectiveness of midostaurin was assessed in the overall population of patients with advanced SM (ASM, SM-AHN and MCL) and in a subgroup of patients with SM-AHN or MCL only (SM-AHN + MCL). As discussed in the main body of the submission, patients with SM-AHN or MCL have a lower life expectancy and a greater unmet need, compared to patients with ASM. • In this context, it should be noted that advanced SM is a rare disease and, within the overall disease population, MCL is the subtype with the lowest prevalence.[4] Consequently, it was not possible to conduct a separate cost-effectiveness analysis for patients with MCL due to the very small sample size of patients included in the pivotal D2201 trial of midostaurin (n=16).[5] However, pooling the two subgroups together (SM-AHN + MCL) was considered reasonable by clinical experts on the basis of the shorter life expectancy and greater unmet need of patients in these subgroups. • Although the ASM subgroup has a relatively better prognosis compared to SM-AHN and MCL, patients with ASM still face a high unmet need, with no licensed treatment. Thus, patients would benefit from access to midostaurin in the full licensed population (ASM, SM-AHN and MCL).
Issue 4: Comparative effectiveness data sources	

Is clinical practice for managing masotcytosis in France and Germany comparable to clinical practice in the NHS in England?	• Treatment centres from France (n=1 and 0.6% of centres included in the study) and Germany (n=64 and 36.2% of centres included in the study) were included in the pivotal D2201 trial,[1] which is considered reflective of UK NHS clinical practice, as confirmed by clinical expert feedback discussed under Issue 1 of this document. Furthermore, clinical advice to the ERG has indicated that the management of patients with advanced SM in Europe is comparable to the management of patients with advanced SM in the UK NHS. Therefore, it is probable that clinical practice for managing advanced SM in France and Germany is comparable to clinical practice in the UK NHS.
Is it appropriate to assume that outcomes from the studies in Germany and France are comparable to the NHS in England?	• Yes, it is appropriate to assume that outcomes from the studies in Germany and France are comparable to the NHS in England. UK clinical experts have advised that overall response rate (ORR) (the primary outcome in the D2201 trial and subsequently used in the French – CEREMAST[6, 7] and German – Reiter *et al.* 2017[8] studies) aligns with UK NHS practice.[1]
Is it appropriate to combine results from D2201 and A2213, as done in Reiter et al.?	• The Reiter *et al.* (2017)[8] study reports on a pooled analysis of the D2201 trial and the A2213 trial compared with historical control data from a German registry. As discussed in the main body of the submission, there are some differences between the pivotal D2201 trial and the supportive A2213 trial, namely in eligibility criteria, duration and stopping of treatment, adjudication of response, study design and endpoint definition.[1] Nonetheless, the A2213 trial had a longer follow-up and could be considered conservative, as patients had to stop treatment if they had not demonstrated a response within the first 2 treatment cycles. Data from the A2213 trial provides valuable long-term evidence of the efficacy and safety of midostaurin and allows for an increase in sample size, when pooled together with data from the D2201 trial. Consequently, it was considered appropriate to combine results across the D2201 trial and the A2213 trial, as done by Reiter *et al.* (2017).[8] • Following the ERG's request, the latest data from the D2201 trial (final analysis of OS and safety data cut-off: 24th August 2017) has now been compared separately to the German historical control and the results are comparable to the pooled (D2201 and A2213) study results (Table 2).

- The updated economic model includes the option to run these scenarios and the results are presented in Appendix 1.

Table 2: Summary of updated results from the historical OS comparison study

Analysis	Results			
	Latest data from D2201 only versus German registry		Pooled latest data from D2201 and A2213 versus German registry	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Primary (from date of diagnosis), unadjusted comparisons	[redacted]	[redacted]	[redacted]	[redacted]
Sensitivity analysis (from start date of last treatment), unadjusted comparisons	[redacted]	[redacted]	[redacted]	[redacted]
Primary (from date of diagnosis), multivariate adjustment	[redacted]	[redacted]	[redacted]	[redacted]
Sensitivity analysis (from start date of last treatment), multivariate adjustment	[redacted]	[redacted]	[redacted]	[redacted]

Data cut-offs: D2201: 24th August 2017; A2213: 1st July 2016; German registry: 9th May 2017.
Abbreviations: CI: confidence interval; HR: hazard ratio.

Issue 5: Overall survival

How many people would you expect to be still alive at 5, 10 and 15 years on midostaurin? At 15 years, is 5% to 10% an appropriate estimate?

- It should be noted that the median follow-up in the D2201 trial was [redacted] months as of the 24th August 2017 data cut-off, not 26 months, as listed in the Technical report. Novartis would therefore like to raise this as a factual inaccuracy for the attention of NICE.
- The D2201 and A2213 trials provide direct evidence of OS at median [redacted] months ([redacted] years) and median 124 months (10.3 years) respectively – see Table 3 below (*nb – for D2201, the number of patients known to be alive at* [redacted] *years was* [redacted] *as explained in the footnote to the table*).

- OS extrapolations as presented in the submission were:

  (a) In line with the 5- and 10-year evidence from the D2201 and A2213 trials and

  (b) Validated by five UK clinical experts with experience of managing patients with advanced SM.

- In conclusion, an OS of 5% to 10% at 15 years can be considered an appropriate estimate for the overall advanced SM population.

Table 3: Summary of OS results based on the latest data cuts of the D2201 and A2213 trials

Population	Number of patients alive, n (%)	Median OS, months (95% CI)	Survival rate (95% CI)	
			3 years	5 years
D2201 trial (data cut-off: 24th August 2017, median duration of follow-up 76 months [range 62 to 103 months])				
PEP (n=89)	[redacted]	[redacted]	[redacted]	[redacted]
FAS (n=116)	[redacted]	[redacted]	[redacted]	[redacted]
A2213 trial (data cut-off: 1st March 2017, median duration of follow-up 124 months [range 82 to 140 months])				
PEP (n=26)[c]	4 (15%)	40.0 (27.3 to 52.7)	Not reported	Not reported

[a] [redacted] patients were known to be alive (ongoing without event), an additional [redacted] patients [redacted] were lost to follow-up early in the trial and an additional [redacted] patients ([redacted] were lost to follow-up but known to be alive in the 5 months before data cut-off

[b] [redacted] patients were known to be alive (ongoing without event), an additional [redacted] patients [redacted] were lost to follow-up early in the trial and an additional [redacted] patients [redacted] were lost to follow-up but known to be alive in the 5 months before data cut-off

[c] The PEP and the FAS were equivalent in the A2213 trial

Abbreviations: CI: confidence interval; FAS: full analysis set; NE: not estimated; OS: overall survival; PEP: primary efficacy population.

How many people would you expect to be still alive at 5, 10, and 15 years on standard of care?	• Please see response above
What is the most appropriate hazard ratio to estimate overall survival of the comparators? Is any of the hazard ratios in Reiter et al. appropriate? What is the clinically plausible range for this hazard ratio?	• The most appropriate hazard ratio (HR) to estimate OS for the comparators was selected on the basis of UK expert clinical feedback. Clinical experts consulted by Novartis considered the HR from the multivariate analysis from the Reiter *et al. (*2017)[8] study to be most appropriate in terms of the predictions generated for the comparator arm, as well as the nature of the analysis, which was judged to be more methodologically robust and allowed for the maximum evidence available to be used, as opposed to results from the propensity score matched analysis which excluded 2/3 of patients. It should be noted that this assessment is in agreement with feedback from the ERG.
Is it appropriate to use the same hazard ratio for all comparators assuming similar effectiveness of comparators?	• Advanced SM is a rare disease with a limited evidence base. The D2201 trial, which provides evidence of the effectiveness of midostaurin, is the largest and most robust trial conducted in the disease area.[5] However, evidence of the effectiveness of each comparator is very limited and of low quality. In the absence of alternative evidence, clinical experts judged it appropriate to assume similar effectiveness and use the same HR for all comparators across both the overall advanced SM population and the SM-AHN + MCL subgroup.
Is it appropriate to use the same hazard ratio for the subgroups?	• Advanced SM is a rare disease, and the prevalence of SM-AHN and MCL is particularly low.[4] As a result, evidence for each disease subgroup (ASM, SM-AHN and MCL) is very limited and based on a small number of patients. In this context, clinical experts indicated that sample sizes were too small to meaningfully argue a difference between subgroups and that it was appropriate to use the same HR for all disease subgroups (ASM, SM-AHN and MCL).
Issue 6: Progression-free survival	
Is it appropriate to use the same hazard ratio for progression-free survival and overall survival?	• In the absence of alternative data, it was not possible to model PFS in any other way, and therefore the same HR for PFS and OS was assumed. This approach was presented to clinical experts and they agreed that it would be appropriate in the absence of PFS evidence.

	• Novartis acknowledge the uncertainty around this approach. However, as described in the ERG report, the results of the sensitivity analyses around the PFS HR undertaken by Novartis suggested that, even if the PFS HR was five times higher than had been assumed in the base case analysis, it would only reduce the ICER per QALY gained for the comparison of midostaurin versus current clinical management by 3.6%. • As such, it is likely that even if the true PFS HR could be known, it would not make a material impact to the cost-effectiveness analysis results.
What is the most appropriate hazard ratio to estimate progression-free survival of the comparators? Is any of the hazard ratios in Reiter et al. appropriate? What is the clinically plausible range for this hazard ratio?	• As indicated above, in the absence of alternative data, it was not possible to model PFS in any other way, and therefore Novartis consider that the assumption of using the same HR for PFS and OS for current clinical management is the most appropriate approach.
Issue 7: Partitioning survival data	
Are partitioned health states appropriate? A. Is the company's approach (progression-free survival partitioned based on response rates and durations) methodologically and clinically appropriate. B. What is the impact on cost-effectiveness estimates if both overall survival and progression-free survival are partitioned, using data from D2201 stratified by response status? Are such stratified data available?	• In response to the ERG's concern with partitioning the PFS state based on response rates and durations, Novartis has now submitted a revised model with the flexibility to run the results based on a standard three state partitioned survival. The results are presented in Appendix 1 and demonstrate that the impact of removing partitioning is minimal, and results in a small (2%) increase from a base case ICER (with potential confidential agreement) of £44,878 • Please note that that we have used a regression model for utility (fitted to the D2201 trial) to calculate the PFS health state utility. The ERG conducted an analysis whereby the same utility value was assumed for the responder and non-responder health states, with the average utility value taken for both health states. Novartis do not consider this approach to be methodologically appropriate, but recognise that this was done as the ERG did not have access to the individual patient-level data from the midostaurin trials and could therefore not re-run the regression model to pool the PFS health state.

- A summary of the rationale for our initial approach is provided below. Whilst we believe the analysis to be appropriate, we acknowledge that there is uncertainty due to the very limited evidence base for this rare disease.

Summary of the rationale for partitioning the PFS state based on response rates

Response status was a primary endpoint in both the D2201 and A2213 trials and treatments for advanced SM are likely to be associated with different response rates. As such, Novartis decided to partition the PFS health state of the economic model to account for the differences in utility values between treatment responders and non-responders.

Typically, a simple approach can be taken by weighting the utility value based on response rates for each treatment. However, this approach does not account for differences in duration of response.

Novartis acknowledge that, given a distinct paucity of data on response rates and duration of response, estimates for these values may introduce uncertainty. However, similarly, assuming the same utility value for the PFS health state for midostaurin and current clinical management is considered to be a very conservative approach, given the distinct differences in mechanisms of action of midostaurin versus the treatments comprising current clinical management. It is important to note that midostaurin is a disease modifying therapy and therefore improves symptoms relative to standard of care.

There is no evidence to suggest that response rates may be used as a surrogate for OS or PFS, therefore response rates were not linked in the model to either PFS or OS, but only used to estimate quality of life. Partitioning of OS would imply building a response-based model which would not be appropriate as it would rely on (i) particularly uncertain parameters (response rates) as acknowledged by the ERG but also (ii) the strong assumption that response rates may be used as a surrogate for OS.

Issue 8: Utility values	
What is the impact of using alternative mapping approaches on the resulting utility values and cost-effectiveness estimates?	• Several alternative mapping algorithms were explored by Novartis when developing the Company Submission: Franks *et al.* (2003);[9] Franks *et al.* (2004);[10] Lawrence *et al.* (2004);[11] Gray *et al.* (2006),[12] and it was found that utility predictions were relatively similar between mapping algorithms. Consequently, in the base case, response mapping (using the physical health component summary scale [PCS] and mental health component summary scale [MCS] dimensions) using the Gray *et al.* (2006)[12] algorithm was selected as this was the most recent of these four algorithms, and the alternative mapping algorithms were explored in scenario analyses. • The Company Submission presents several scenario analyses using the alternative linear model mapping algorithms and the results of these scenario analyses demonstrate that the choice of mapping algorithm had a negligible impact on the ICER.
Is it appropriate to manually restrict utility values, potentially underestimating the overall parameter uncertainty?	• A constraint was applied in the economic model to ensure that pre-progression utility values were higher than post-progression utility values in the partitioned survival model as would be expected based on the course of the disease. Not applying such a constraint may have resulted in utility values that lacked face validity, thus Novartis believe this restriction is appropriate. Nevertheless, the constraint has now been removed and there is no impact on the ICER
Issue 9: Duration of treatment effect	
Is it plausible that the effect of midostaurin on survival and progression, relative to current treatments, can be maintained for a person's lifetime while on treatment?	• Midostaurin is a disease modifying therapy and therefore the length of treatment may not necessarily explain the duration over which the treatment effect should apply, and it is plausible that the treatment effect of midostaurin would continue beyond treatment discontinuation. Please note that, as described in the company submission, the treatment effect (the multivariate HR derived from the historical control comparison) is applied to the midostaurin curve to estimate outcomes for current clinical management. • Novartis acknowledge the uncertainty in long-term survival estimates and have therefore

	conducted additional scenario analyses in response to this question with different assumptions regarding the time point for equalising progression and mortality events for midostaurin versus the composite comparator. The results of these analyses are presented in Appendix 1.
If not, how long would you expect midostaurin's treatment effect to last while on treatment? e.g. 5, 10, 15 years, or other.	• Please refer to the response to Issue 5. Evidence from D2201 ([redacted] months follow-up)[13] and A2213 (124 months follow-up)[14] suggest that patients treated with midostaurin have a long duration of survival. Therefore, the time point for equalising progression and mortality events for midostaurin versus the composite comparator should be at least 10 years.
If discontinued, how long would you expect midostaurin's treatment effect to last? e.g. 5, 10, 15 years, or other.	• Feedback from clinical experts advised that only a small minority of patients would remain alive after 5 years using current clinical management, and therefore we believe that it is not appropriate to assume the treatment effect of midostaurin wanes before at least 10 years when looking at the tail generated for the comparator arm.
Issue 10: End of life	
In the overall population of people with advanced systemic mastocytosis, and in the 3 subgroups (ASM, SM-AHN and MCL): A. What is the life expectancy of a person with current treatments? B. Would you expect midostaurin to increase survival by at least 3 months?	**A. What is the life expectancy of a person with current treatments?** • The life expectancy of patients with advanced SM on current clinical management is less than 2 years as evidenced by: a. The Reiter *et al.* (2017) publication, which reports the median survival from diagnosis in a contemporary German registry of patients with advanced SM similar to those enrolled in D2201 and A2213 (patients with ASM or MCL ± AHN), who had not been treated with midostaurin (n=42) to be 19.5 months (95% CI 13.0–35.3).[8] b. The Company economic model, which predicted mean undiscounted life years of 1.90 for the overall advanced SM population and 1.46 for the subgroup of patients with SM-AHN + MCL

c. Clinical experts advised that in a world without midostaurin, patients with advanced SM would normally have a life expectancy of less than 2 years

- It is acknowledged that there is a wide range of published median survival estimates for patients with advanced SM. This is reflective of the heterogeneity of SM disease, and how non-advanced (e.g. indolent SM-AHN [ISM-AHN]) and advanced subtypes have frequently been analysed together in the literature.[15] For example, some published estimates of survival for patients with SM-AHN report a median survival of 24 months, but these studies included patients with ISM-AHN for whom survival is significantly longer, and therefore these studies are not reflective of the population considered in this appraisal (or the marketing authorisation for midostaurin).[16, 17] Estimates of survival are further complicated by the availability of midostaurin for advanced SM since September 2017. Importantly, this creates challenges when requesting clinicians to estimate the life expectancy of patients with advanced SM.

- The only published evidence for the survival of patients with SM-AHN (advanced) is from Reiter *et al.* (2017)[8] and therefore Novartis consider that the survival estimates from Reiter *et al.* (2017)[8] should be considered first and foremost by NICE in their considerations of midostaurin as an end-of-life treatment. As stated above these data are supported by the estimates from the Company economic model and feedback from UK clinical experts.

- The above considerations should also be made in the context of a typical highly specialised technology (HST) appraisal for an ultra-rare condition such as advanced SM, which can apply a willingness-to-pay threshold of £100,000 to £300,000 per QALY gained, *without factoring end-of-life criteria*.

B: Would you expect midostaurin to increase survival by at least 3 months?

- There are no direct comparisons between midostaurin and current clinical management; however, Reiter *et al.* (2017)[8] demonstrated a survival benefit of 21.9 months for patients treated with midostaurin (median OS 41.4 months) in the pooled analysis of D2201 and A2213 compared with current clinical management (median OS 19.5 months) observed in a German cohort which

	included similar patients. • Consequently, there is sufficient evidence to indicate that midostaurin offers an extension of life of at least an additional 3 months compared with current NHS treatment. This is further supported by the economic model, where the incremental life years gained (LYG) predicted by the model for midostaurin compared with current management was estimated to be [redacted] and [redacted] for the overall population and SM-AHN + MCL subgroup respectively, an increment that is considerably greater than 3 months.
Issue 11: Cancer Drugs Fund	
Would additional data collection within the Cancer Drugs Fund reduce the uncertainty?	• No further data cuts are planned for the D2201 and A2213 trials. The data from both trials already presented as part of the Company Submission represent 6 years of follow-up for D2201[13] and 10 years of follow-up for A2213,[14] the longest available follow-up time for any advanced SM trials. • Moreover, the rarity of the advanced SM means that,[4] even if further data were able to be collected, limited data would be available in 2 years on the CDF and therefore it would not be likely to resolve any uncertainty.

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Appendix 1: Additional economic analyses

Additional economic analyses have been conducted to explore the following:

Alternative HRs

1. HR based on pooled data using the latest D2201 data (latest D2201 + latest A2213 vs Historical control) – multivariate
2. HR based on pooled data using the latest D2201 data alone vs Historical control – multivariate

Alternative treatment effect assumptions

3. Treatment effect of midostaurin assumed to continue for 10 years (equal progression/mortality rates between midostaurin and current clinical management at 10 years)
4. Treatment effect of midostaurin assumed to continue for 5 years (equal progression/mortality rates between midostaurin and current clinical management at 5 years)
5. Treatment effect of midostaurin assumed to continue for 3 years (equal progression/mortality rates between midostaurin and current clinical management at 3 years)

Alternative model structure assumption

6. Removal of partitioning of progression-free state based on response (ERG approach)
7. Removal of partitioning of progression-free state based on response (regression)

Results are presented below for advanced SM (both including the **current PAS** for midostaurin as well as the potential confidential agreement [redacted], which makes midostaurin cost-effective in the full licensed population

Table 4: Results of alternative economic analyses (overall advanced SM population)

SM-AHN + MCL	Current PAS			Potential Confidential Agreement		
	Incremental Cost	Incremental QALY	ICER	Incremental Cost	Incremental QALY	ICER
Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£44,878
1. HR (pooled) - updated D2201* data - multivariate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£45,884
2. HR D2201 only - updated D2201* data - multivariate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£47,781
3. Treatment effect of midostaurin: 10 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£45,476
4. Treatment effect of midostaurin: 5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£48,048
5. Treatment effect of midostaurin: 3 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£51,775
6. Removal of progression-free state partition based on response (ERG approach)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£47,463
7. Removal of progression-free state partition based on response (New regression)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£45,851

Abbreviations: ERG: Evidence review group; HR: hazard ratio. * D2201 trial (data cut-off: 24th August 2017, median duration of follow-up 76 months [range 62 to 103 months])

Table 5: PSA results - overall advanced SM population (midostaurin at potential confidential agreement)

Technologies	Costs (£)	QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Probability of cost-effectiveness at £30,000 per QALY	Probability of cost-effectiveness at £50,000 per QALY
Current clinical management	[redacted]	[redacted]	-	-	-		-
Midostaurin	[redacted]	[redacted]	[redacted]	[redacted]	£47,743	[redacted]	[redacted]

Note: all results presented are discounted unless otherwise stated.
Abbreviations: ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years; PSA: probabilistic sensitivity analysis

Figure 1: PSA cost-effectiveness plane – overall advanced SM population (midostaurin at potential confidential agreement)

Figure 2: PSA cost-effectiveness acceptability curve – overall advanced SM population (midostaurin at potential confidential agreement)

Table 6: Results of alternative economic analyses (SM-AHN + MCL)

SM-AHN + MCL	Current PAS			Potential Confidential Agreement		
	Incremental Cost	Incremental QALY	ICER	Incremental Cost	Incremental QALY	ICER
Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£47,312
8. HR (pooled) - updated D2201* data - multivariate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£48,320
9. HR D2201 only - updated D2201* data - multivariate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£50,225
10. Treatment effect of midostaurin: 10 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£47,565
11. Treatment effect of midostaurin: 5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£49,103
12. Treatment effect of midostaurin: 3 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£51,861
13. Removal of progression-free state partition based on response (ERG approach)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£49,706
14. Removal of progression-free state partition based on response (New regression)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£48,061

Abbreviations: ERG: Evidence review group; HR: hazard ratio. * D2201 trial (data cut-off: 24th August 2017, median duration of follow-up 76 months [range 62 to 103 months])

Table 7: PSA results - SM-AHN + MCL (midostaurin at potential confidential agreement)

Technologies	Costs (£)	QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Probability of cost-effectiveness at £30,000 per QALY	Probability of cost-effectiveness at £50,000 per QALY
Current clinical management	[redacted]	[redacted]	-	-	-		-
Midostaurin	[redacted]	[redacted]	[redacted]	[redacted]	£49,540	[redacted]	[redacted]

Note: all results presented are discounted unless otherwise stated.
Abbreviations: ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years; PSA: probabilistic sensitivity analysis;

Figure 3: PSA cost-effectiveness plane – SM-AHN + MCL (midostaurin at potential confidential agreement)

Figure 4: PSA cost-effectiveness acceptability curve – SM-AHN + MCL (midostaurin at potential confidential agreement)

NICE National Institute for Health and Care Excellence

Technical engagement response form

Midostaurin for treating advanced systemic mastocytosis [ID1573]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments **5pm** on **Wednesday 29 July 2020**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential

information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	Dr Steven Knapper
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	Cardiff University / University Hospital of Wales (Nominated by Novartis, UK Mastocytosis Support Group and Leukaemia Care)
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nothing to disclose

Questions for engagement

Issue 1: Generalisibility of trial results	
Is clinical practice in the trials generalisable to the NHS setting?	Yes, I feel that the spectrum of patients represented in the 2 published clinical trials is generalisable to the NHS setting. Clearly this is a very heterogeneous disease group but the sub-groups represented in the trials reflect the spectrum (and relatives proportions in the different SM subgroups) of patients encountered in clinical NHS practice.
Issue 2: Comparator treatment	
Are AML-like treatments used in the NHS in England to treat mastocytosis?	'AML-like treatment' would cover a wide range of chemotherapy-based treatments ranging from intensive combination chemotherapy (eg. DA or FLAG-Ida) down to less intensive/palliative chemotherapy (principally low dose cytarabine or occasionally azacitidine). These types of treatment might be used sporadically in the management of SM, but mainly in the management of the subtype SM-AHN when treatment is primarily being aimed at the associated haematological neoplasm, for example intensive AML-type treatment might be used in a case of CMML (commonest form of SM-AHN) who was young/fit enough to be considered suitable for disease de-bulking prior to allogeneic stem cell transplant. I don't feel that that intensive type AML treatment is being used very often in ASM, but there might be some use in younger/fitter MCL patients who are felt to be suitable for a 'curative approach' through subsequent allogeneic stem cell transplant. Low dose cytarabine might also be considered for disease debulking as an alternative to cladribine in some cases of ASM/MCL. Overall, my feeling is that these treatments are used too sporadically to really be appropriate comparators for midostaurin.
What are the most appropriate comparators in the UK? Please provide details of which are most used, e.g. treatment 1: 60% of people, treatment 2: 10% of people, and so on.	I agree with the comparators that have been included in the report – and have to declare that I was one of the 'clinical experts' consulted by Novartis in drawing up this list of comparators. It is extremely difficult to answer this question in the form of percentage figures because treatments will be tailored to the subtype/extent of the SM and the age/fitness of individual patients – and this

	is a rare very heterogeneous disease so the denominators are small and will inevitably be influenced by the experience of individual clinicians. Across advanced systemic mastocytosis as a whole, the main comparators will be interferon and cladribine. Imatinib is only very rarely used (in cKIT neg cases) and nilotinib/dasatanib are virtually never used due to lack of evidence of efficacy and lack of funding. It should also be borne in mind that some patients, especially at a few of the larger centres, may be accessing treatments through entry into clinical trials (such as 'second generation' KIT inhibitors).
Is it appropriate to have a composite comparator?	Not ideal, but probably appropriate given that overall patient numbers are very small and that midostaurin is potentially being applied across all the 3 subgroups (ASM, MCL, SM-AHN) and that numbers for analysis become so small if the 3 subgroups (and potentially age / performance status groups within them) are sub-stratified. I agree, however, that application of comparator drugs might vary somewhat between the different SM subgroups – particularly in patients with SM-AHN where the clinical effects of the associated neoplasm predominate, interferon may be used less in MCL.
Issue 3: Subgroups	
Are the 3 subgroups, aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated haematological neoplasm (SM-AHN) and mast cell leukaemia (MCL), distinguishable in clinical practice?	Yes – generally patients will be clearly diagnosed as belonging to one or other of these groups through use of accepted diagnostic criteria (WHO 2017). SM-AHD will usually be particularly clinically evident as separate from the other two. Sometimes the boundaries between ASM and MCL will be more blurred, especially in cases where bone marrow trephine histology is being used to estimate whether abnormal mast cell numbers – this interpretation may be somewhat subjective and many reporting histopathologists have relatively little experience of this rare disease.
Are people in the 3 subgroups offered different treatment options in the NHS in England? For each subgroup please provide details of which are most used, e.g. treatment 1: 60% of people, treatment 2: 10% of people, and so on.	Again, I am reluctant to attempt to provide % figures here. As stated above, the management of SM-AHN will often be different and concentrate on management of the associated neoplasms – for example CMML: hydroxycarbamide, azacitidine, combination intensive chemotherapy / allograft in selected cases; Myelodysplastic syndromes: azacitidine, combination therapies in selected cases; Plasma cell neoplasms; myeloma-type therapes including combinations of steroids, bortezomib, 'Imids'. For ASM and MCL the comparator treatments (as above) will largely

	be interferon or cladribine – anecdotally I would expect the proportions receiving cladribine to be somewhat higher in MCL than in ASM (and vice versa for interferon).
Is it appropriate to combine people with SM-AHN and people with MCL in 1 subgroup?	I think this is a somewhat arbitrary sub-grouping. In my opinion the 3 subgroups should either be grouped into a composite comparator, or looked at completely separately from one another.
Issue 4: Comparative effectiveness data sources	
Is clinical practice for managing masotcytosis in France and Germany comparable to clinical practice in the NHS in England?	I don't feel sufficiently well-acquainted with clinical practice in France and Germany to be able to answer this question meaningfully. It is possible to gain some insight into French SM management by looking at the treatments used in the historical control groups Chandesris study: 49% of patients had received clardribine, 41% steroids, 18% thalidomide, 13% a TKI other than midostaurin, 8% interferon and 5% an mTOR inhibitor. From the published data, however, it is not possible to break these patients down by SM sub-group or determine which of these therapies might have been used for management of an associated haematological neoplasm. Overall, the use of cladribine looks a little higher than in the UK, interferon somewhat lower. Thalidomide is only rarely used in the UK – but again this might have been used in France for the management of an associated haematological neoplasm eg myeloma. The Reiter study (Germany) is only available to me in abstract form – this does not include any data on treatments received by their control registry group, so it's not possible to comment further.
Is it appropriate to assume that outcomes from the studies in Germany and France are comparable to the NHS in England?	It is difficult to give detailed comment on the German registry data which seem to have been presented in conference abstract form only (EHA 2017) – I don't have access to the conference presentation slides. From the limited information available from the abstract, the proportions of patients with the different SM subtypes in the German historical control group appear similar to that seen in the clinical trials and to that of the German compassionate use midostaurin group

	(and also to that expected in the NHS), but I have some concerns that the median age in the historical control group is higher than in the midostaurin group, but probably reflective of NHS practice. The French historical group does seem to have been broadly reflective of the clinical trial populations with similar median age, but here there is a possible over-representation of patients with SM-AHN.
Is it appropriate to combine results from D2201 and A2213, as done in Reiter et al.?	Again, it is difficult to formally comment on this without access beyond the abstract of the Reiter data. From the methods described within the abstract it appears that a statistical approach was taken that attempted to mitigate any inconsistencies. I'm not able to comment further.
Issue 5: Overall survival	
How many people would you expect to be still alive at 5, 10 and 15 years on midostaurin? At 15 years, is 5% to 10% an appropriate estimate?	I feel that the relevant data here (the Gotlib study and the longer-term follow-up data provided by the de Angelo study) have already been extensively reviewed as part of this process and it may be difficult to extract any further insights at this point. As the group knows, there are very limited published data to consider beyond this. The 10-year median follow information provided by the de Angelo study suggested that responses were generally durable in those achieving them. In that study, which only included 26 patients, the median duration of midostaurin therapy was 19 months with a range of 2-132 months (clearly only a tiny proportion of patients remained on midostaurin at the 10 year point) and the median OS was 40 months (95% CI 27-53 months) with a range of 1.2-134.6 months – again only a 1-2 patients can have still been alive at the 10 year mark. So, overall, I feel that 5% is probably a reasonable estimate for patients likely to be alive at the 15yr point. It is very difficult to dig deeper into this given that so few patients will have followed up for 15yrs which would have meant starting midostaurin prior to 2005.
How many people would you expect to be still alive at 5, 10, and 15 years on standard of care?	Conventional overall survival estimates for advanced SM vary according to the sub-category of disease with median expected survival quoted as 3.5yrs for patients with aggressive SM, 2 years

	for those with SM-AHN and under 6 months for those with mast cell leukaemia – although significant prognostic heterogeneity exists within each of these groups. I would have to extrapolate from those figures in order to estimate survival % at 5, 10 and 15 years with 'standard care treatment'. For MCL, only a tiny proportion of patients will be alive at 5,10 and 15 years (significantly below 5% - and some of these long-term survivors may be from the tiny minority of younger patients who undergo successful stem cell transplantation, although this is also complicated by the recognition of a chronic form of MCL that is characterised by a relative lack of organ damage and a more indolent course).
What is to most appropriate hazard ratio to estimate overall survival of the comparators? Is any of the hazard ratios in Reiter et al. appropriate? What is the clinically plausible range for this hazard ratio?	It seems important that OS should be matched with regards to age and SM sub-group of patients. Using the Reiter data, the differences in median age between the pooled midostaurin and registry control groups, mean that some caution needs to be applied with regards to the overall survival comparisons – although I can see from the abstract that 'multivariate Cox regression analysis adjusting for covariates' and 'propensity score for matched pairs' were applied – presumably this took into account the age discrepancies. Statistical significance was maintained with the regression analysis but not the matched pairs analysis (I'm afraid I don't have sufficient statistical knowledge to be able to critique these two approaches).
Is it appropriate to use the same hazard ratio for all comparators assuming similar effectiveness of comparators?	I'm not sure that I understand, or have sufficient statistical expertise, to answer this question. Others will be better qualified than me to comment.
Is it appropriate to use the same hazard ratio for the subgroups?	Ditto previous answer.
Issue 6: Progression-free survival	
Is it appropriate to use the same hazard ratio for progression-free survival and overall survival?	Ditto previous answer.
What is to most appropriate hazard ratio to estimate progression-free survival of the comparators? Is any of the hazard ratios in Reiter et al. appropriate?	Ditto previous answer.

What is the clinically plausible range for this hazard ratio?	
Issue 7: Partitioning survival data	
Are partitioned health states appropriate? A. Is the company's approach (progression-free survival partitioned based on response rates and durations) methodologically and clinically appropriate. B. What is the impact on cost-effectiveness estimates if both overall survival and progression-free survival are partitioned, using data from D2201 stratified by response status? Are such stratified data available?	In my opinion, the company has made a very reasonable attempt to partition different clinical response states and their approach with 4 'mutually exclusive health states' is probably appropriate. All individual patients are different – especially in such as a heterogeneous and challenging condition to model as advanced SM – and, when broken down according to individual patients' circumstances, these partitions can seem somewhat arbitrary – there are lots of 'shades of grey' rather than black vs white. Given that it has to be done, for purposes of these assessment though, I think it is probably as clinically appropriate as can be devised – and I can't think of a better approach to take. I agree that it might be helpful to stratify OS and PFS according to response status. In the Gotlib study, median OS was certainly longer among patients who had a response than those who did not (44.4m vs 15.4m – HR for death 0.42). This was particularly the case in patients with MCL (median survival not reached vs 7.6m). I am not aware whether similar data stratifying PFS by response are available.
Issue 8: Utility values	
What is the impact of using alternative mapping approaches on the resulting utility values and cost-effectiveness estimates?	I'm sorry but, again, I don't feel I have sufficient expertise in health economic modelling to provide any meaningful input on this question.
Is it appropriate to manually restrict utility values, potentially underestimating the overall parameter uncertainty?	Ditto previous answer
Issue 9: Duration of treatment effect	

Is it plausible that the effect of midostaurin on survival and progression, relative to current treatments, can be maintained for a person's lifetime while on treatment?	Given the mechanism of action of midostaurin I feel that it is reasonable to assume that patients who are maintaining a clinical response and staying on drug will continue to maintain benefits on survival and progression relative to current treatments. In the Gotlib study, only a minority of patients remained on treatment beyond 1 year, and 19% at 3 years. A small minority of patients do seem to maintain durable responses though – anecdotally we have certainly seen this in a several patients treated in Cardiff – I have one SM patient who has now been on midostaurin for >12yrs who continues to demonstrate a deep clinical response.
If not, how long would you expect midostaurin's treatment effect to last while on treatment? e.g. 5, 10, 15 years, or other.	See answer above.
If discontinued, how long would you expect midostaurin's treatment effect to last? e.g. 5, 10, 15 years, or other.	Again, according to mechanism of action of midostaurin, I would not normally expect sustained benefits following withdrawal of treatment – by definition, treatment discontinuation will generally be in the setting of lack of response or disease progression given that the drug is not often withdrawn due to patient intolerance. I would not therefore expect a sustained benefit to last beyond cessation of midostaurin. During the time while the patient *is* responding to midostaurin, however, their health status will generally be better maintained than for non-midostaurin-treated cases who will generally continue to progressively deteriorate – so at the point of cessation, many midostaurin-treated individual will be in a better clinical state than patients within a comparator group that have deteriorated – this gap is likely to be maintained a length of time that is really difficult to quantify and will probably vary according to the aggressiveness of an individual patient's disease from months to 2-3 years.
Issue 10: End of life	
In the overall population of people with advanced systemic mastocytosis, and in the 3 subgroups (ASM, SM-AHN and MCL):	As given in the answer to other questions, the conventional estimate of median survival for ASM with current treatments is 3.5yrs, SM-AHN 2 yrs and MCL 6 months. Clearly, this is massively variable between cases: ASM is much more aggressive in some patients than others and, even in MCL, there are subgroups of cases with more chronic/indolent disease.

A. What is the life expectancy of a person with current treatments? B. Would you expect midostaurin to increase survival by at least 3 months?	Based on the published data, with the caveats of phase 2 data and comparisons with registry data, I would certainly expect midostaurin to increase survival by at least 3 months. This will be especially true for patients in whom an objective clinical response to midostaurin therapy can be demonstrated.
Issue 11: Cancer Drugs Fund	
Would additional data collection within the Cancer Drugs Fund reduce the uncertainty?	I have very little personal experience with mechanisms for data collection within the Cancer Drugs Fund as this scheme has never been applicable to clinical practice in Wales.