Medicinrådet

Bilag til Medicinrådets vurdering af avapritinib til behandling af indolent systemisk mastocytose

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. avapritinib
2. Forhandlingsnotat fra Amgros vedr. avapritinib
3. Ansøgers endelige ansøgning vedr. avapritinib

26th February 2026

Blueprint Medicines response to Medicinrådets Udkast anbefaling vedr. avapritinib til behandling af indolent systemisk mastocytose

We are pleased to see the Danish Medicines Council has provided a fair and thorough assessment of our application, recognizing the value Ayvakyt® provides to patients with ISM with moderate to severe symptoms not adequately controlled with symptomatic therapies. Ayvakyt® remains the only approved, targeted treatment for patients with ISM, a condition with a high unmet medical need where only symptomatic treatments are currently available.

The introduction of Ayvakyt® to ISM patients will provide new hope by being able to more effectively control their symptoms. As shown in our application, Ayvakyt® is superior in being able to reduce severe, clinical symptomatic burden often experienced by these patients, which become progressively worse over time.

We are encouraged to see that the Danish Medicines Council has chosen to use our model and assumptions for the cost-effectiveness analysis. We acknowledge that the DMC has identified uncertainties associated with the model. As a company, we have made every effort to be data-driven and to validate our assumptions and model inputs to reflect Danish clinical practice. The reality of the Danish healthcare system, combined with the rarity of the disease, limits the possibility for extensive clinical expert validation. We consider the proposed modelling approach to be the most appropriate option under the given the clinical context.

We look forward to providing access to AYVAKYT® for ISM patients in need in Denmark.

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27.02.2026

MBA/LSC

Forhandlingsnotat

Dato for behandling i Medicinrådet	25.03.2026
Leverandør	Blueprint Medicines
Lægemiddel	Ayvakyt (avapritinib)
Ansøgt indikation	Behandling af voksne patienter med indolent systemisk mastocytose (ISM) med moderate til svære symptomer, der er utilstrækkeligt kontrolleret på symptomatisk behandling.
Nyt lægemiddel / indikationsudvidelse	Indikationsudvidelse

Prisinformation

Amgros har forhandlet følgende pris på Ayvakyt (avapritinib):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke (pakningsstørrelse)	AIP (DKK)	Nuværende SAIP, (DKK)	Nuværende rabat ift. AIP	Forhandlet SAIP (DKK)	Forhandlet rabat ift. AIP
Ayvakyt	25 mg (30 stk.)	211.200,00	[redacted]	[redacted]	[redacted]	[redacted]
Ayvakyt	50 mg (30 stk.)	211.200,00	[redacted]	[redacted]	[redacted]	[redacted]
Ayvakyt	100 mg (30 stk.)	211.200,00	[redacted]	[redacted]	[redacted]	[redacted]
Ayvakyt	200 mg (30 stk.)	211.200,00	[redacted]	[redacted]	[redacted]	[redacted]
Ayvakyt	300 mg (30 stk.)	211.200,00	[redacted]	[redacted]	[redacted]	[redacted]

Note: Det er udelukkende 25 mg styrken, som anvendes ved indolent systemisk mastocytose (ISM).

Prisen er betinget af Medicinrådets anbefaling. Det betyder, at hvis Medicinrådet ikke anbefaler Ayvakyt til ISM, indkøbes lægemidlet til nuværende SAIP.

Aftaleforhold

[redacted]

Konkurrencesituationen

Nuværende standard behandling er kun symptomatisk. Der findes ingen sygdomsmodificerende behandlinger for ISM. Ayvakyt er tillæg til best supportive care (BSC), og derfor inkluderes BSC ikke i nedenstående tabel, da den er identisk for både Ayvakyt + BSC og BSC alene.

Tabel 2: Lægemiddeludgifter pr. patient

Lægemiddel	Styrke (pakningsstørrelse)	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. behandling/år (SAIP, DKK)
Ayvakyt	25 mg (30 stk.)	25 mg dagligt, oral	[redacted]	[redacted]

Status fra andre lande

Tabel 3: Status fra andre lande

Land	Status	Link
Norge	Ikke anbefalet	Link til vurdering
England	Under vurdering	Link til status
Sverige	Ikke ansøgt	

Opsummering

[redacted]

Application for the assessment of avapritinib (Ayvakyt®) for the treatment of adult patients with indolent systemic mastocytosis (ISM) with moderate to severe symptoms inadequately controlled on symptomatic treatment

Color scheme for text highlighting	
Color of highlighted text	**Definition of highlighted text**
	Confidential information

Contact information

Contact information	
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Tables and Figures

Abbreviations

Abbreviation	Full name
AdvSM	Advanced systemic mastocytosis
AEs	Adverse events
AIP	Apotekets inkøbspris
ASM	Aggressive systemic mastocytosis
BM	Bone marrow
BMI	Body mass index
BSA	Body surface area
BSC	Best supportive care
C	Cycle
CDSR	Cochrane Database of Systematic Reviews
CEAC	Cost-effectiveness acceptability curves
CENTRAL	Cochrane Central Register of Controlled Trials
CFB	Change from baseline
CI	Confidence interval
CRD	Centre for Reviews and Dissemination
CT	Computed tomography
CXDX	Cycle X Day X
Dara	Daratumumab

DARE	Database of Abstracts of Reviews of Effects
DK	Danish Kroner
DMC	Danish Medicines Council
DRG	Diagnosis related group
EBM	Evidence-based Medicine
ECNM-AIM	European Competence Network of Mastocytosis and American Initiative in Mast Cell Diseases
ECOG	Eastern Cooperative Oncology Group
ECG	Electrocardiography
EconLit	American Economic Association's electronic database
EMA	European medicines agency
Embase	Excerpta Medica database
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EQ-5D-5L	EuroQoL Five-Dimension Five-Level
EQ-VAS	EuroQoL Visual Analogue Scale
FDA	Food and Drug Administration
GIST	Gastrointestinal stromal tumours
GI	Gastrointestinal
HCC	Half-cycle correction
HCRU	Healthcare resource utilisation
HR	Hazard ratio
HRQoL	Health-related quality of life
HSUVs	Health state utility values
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
IgE	Immunoglobin E
ISM	Indolent systemic mastocytosis
ISM-SAF TSS	Indolent Systemic Mastocytosis Symptom Assessment Form total symptom score
ITT	Intention-to-treat
IV	Intravenous
LS mean	Least squares mean
Max	Maximum
MCS/PCS	Mental and physical component scores
MCL	Mast cell leukaemia
Min	Minimum
MRI	Magnetic resonance imaging
MRR	Mortality rate ratio
N/A	Not applicable/not available
NCCN	National Comprehensive Cancer Network
NHS EED	National Health Service Economic Evaluation Database
NICE	National institute for health and care excellence

NL	Netherlands
NRS	Numeric rating scale
NSAIDs	Nonsteroidal anti-inflammatory drugs
OWSA	One-way sensitivity analysis
PDGFRA	Platelet-derived growth factor receptor alpha
PK	Pharmacokinetics
PRO	Patient reported outcome
PSA	Probabilistic sensitivity analysis
QALY	Quality adjusted life year
QD	Once daily
R	Randomised
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SIGN	Scottish Intercollegiate Guidelines Network
SLR	Systematic literature review
SM	Systemic mastocytosis
SF-12	12-Item Short Form Health Survey
SSM	Smouldering systemic mastocytosis
SM-AHN	Systemic mastocytosis with an associated haematological neoplasm
SSM	Smouldering systemic mastocytosis
TKI	tyrosine kinase inhibitor
TLR	Targeted literature review
ToT	Time on treatment
TSS	Total symptom score
UK	United Kingdom
VAF	Variant allele fraction
VAS	Visual analogue scale
WTP	Willingness to pay

1. Regulatory information on the medicine

Proprietary name	AYVAKYT
Generic name	Avapritinib
Therapeutic indication as defined by EMA	Avapritinib is indicated for the treatment of adult patients with indolent systemic mastocytosis (ISM) with moderate to severe symptoms inadequately controlled on symptomatic treatment (1).
Marketing authorization holder in Denmark	Blueprint Medicines (Netherlands) B.V.
ATC code	L01EX18 (1)
Combination therapy and/or co-medication	Avapritinib can be given in addition to best supportive care.
(Expected) Date of EC approval	EC approval received 11 December 2023 (2).
Has the medicine received a conditional marketing authorization?	No, conditional marketing authorisation is only based on the GIST indication.
Accelerated assessment in the European Medicines Agency (EMA)	No
Orphan drug designation (include date)	Yes, EMA declared avapritinib as orphan drug on 26 October 2018 for Mastocytosis (EU/3/18/2074) (3). The OD status was confirmed on 24 March 2022 (4) and 9 November 2023 (5).
Other therapeutic indications approved by EMA	• Avapritinib is indicated as monotherapy for the treatment of adult patients with unresectable or metastatic gastrointestinal stromal tumours (GIST) harbouring the platelet-derived growth factor receptor alpha (PDGFRA) D842V mutation (1). • Avapritinib is indicated as monotherapy for the treatment of adult patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated haematological neoplasm (SM-AHN) or mast cell leukaemia (MCL), after at least one systemic therapy (1).
Other indications that have been evaluated by the DMC (yes/no)	Yes, the two above listed indications have previously been evaluated and recommended by the DMC in May 2024.
Joint Nordic assessment (JNHB)	Are the current treatment practices similar across the Nordic countries (DK, FI, IS, NO, SE)? Yes. Is the product suitable for a joint Nordic assessment? No.

	Blueprint Medicines will launch avapritinib for ISM in the Nordics step by step similar to avapritinib for GIST and AdvSM.
Dispensing group	BEGR
Packaging – types, sizes/number of units and concentrations	AYVAKYT® (avapritinib) 25 mg; 30 x 25 mg film coated tablets (AYVAKYT 50, 100, 200 and 300 mg not approved for the treatment in ISM)

2. Summary table

Summary	
Indication relevant for the assessment	Avapritinib is indicated for the treatment of adult patients with indolent systemic mastocytosis (ISM) with moderate to severe symptoms inadequately controlled on symptomatic treatment (1).
Dosage regiment and administration	The recommended dose of avapritinib is 25 mg orally once daily on an empty stomach (1).
Choice of comparator	The comparator of choice for Danish clinical practice will be placebo + best supportive care (BSC). There are currently no approved disease-modifying treatments for ISM. In Denmark, there are no guidelines which define current Danish clinical practice for ISM. International guidelines which specify treatment for ISM such as the National Comprehensive Cancer Network (NCCN) (6), European Competence Network of Mastocytosis and American Initiative in Mast Cell Diseases (ECNM-AIM) (7) and the Swedish national guidelines for systematic mastocytosis (which includes treatment for ISM) (8) are very similar and commonly differentiate their recommendations based on the patient's symptom and comorbidity profile. It is expected that Danish clinical practice will be similar to that of Sweden since treatment does not vary and Sweden would be considered similar to Denmark in terms of treatment options. In ISM, BSC consists of symptomatic treatment and is individualised based on the symptoms experienced and comorbidities of the patient (8). This includes among others e.g., skin involvement (anti-H1/H2, antileukotrienes, corticosteroids, omalizumab), gastrointestinal symptoms (anti-H2, proton pump inhibitors), osteoporosis (vitamin D, calcium supplements, bisphosphonates) and anaphylaxis (anti-H1/H2, omalizumab) (8).
Prognosis with current treatment (comparator)	No therapies are available to treat the underlying cause of ISM. Therefore, the primary objectives in patients with ISM are to control symptoms and comorbidities, improve quality of life and reduce anaphylactic shock events and treatment side effects (9, 10). Despite treatment with standard-of-care

	symptomatic therapies, patients can progress to advanced forms of disease. Several risk factors can contribute to disease progression in patients with ISM. Increased serum tryptase levels, the presence of KIT D816V mutation and high symptom burden are risk factors for disease progression from ISM to more advanced forms of SM like SSM and advanced SM (11-13). Reported progression rates from ISM to advanced SM ranged from 2.9% (median follow-up: 4.2 years) (14) to 7% (median follow-up: 9 years) (13). Data also show that a considerable proportion of ISM patients (15%) with mild symptoms experienced disease worsening to ISM with more severe symptom burden within a timeframe of two years (12).
Type of evidence for the clinical evaluation	Head-to-head comparison.
Most important efficacy endpoints (Difference/gain compared to comparator)	Mean change from baseline in Indolent Systemic Mastocytosis Symptom Assessment Form total symptom score (ISM-SAF TSS) at week 24 Avapritinib: LS Mean: -15.58 (-18.61, -12.55) Placebo: LS Mean: -9.15 (-13.12, -5.18) Difference: LS Mean: –6.43 (–10.90, –1.96), p=0.003
Most important serious adverse events for the intervention and comparator	The safety profile of avapritinib was comparable to placebo and the majority of patients had Grade 1 and Grade 2 AEs. Serious adverse events occurred less frequently in the avapritinib arm (5.0%) vs placebo (11.3%), with no serious adverse events >5% occurring in either treatment arm.
Impact on health-related quality of life	Health economic model: Treatment with avapritinib in addition to BSC is associated with a QALY-gain compared to BSC, which is driven by an overall increase in HRQoL.
Type of economic analysis that is submitted	Cost-utility analysis based on a Markov cohort model.
Data sources used to model the clinical effects	The PIONEER study Part 2 provides direct a head-to-head comparison of efficacy between avapritinib plus BSC and placebo plus BSC over the 6 initial treatment cycles (24 weeks). For the avapritinib plus BSC arm, response evaluation was followed by maintenance treatment in Part 3 of the PIONEER trial. The modelled maintenance efficacy of the intervention is directly informed by patient distributions of the responders moving into Part 3 with continued treatment of avapritinib.
Data sources used to model the health-related quality of life	EQ-5D-5L data from the PIONEER trial PART 2 were used to derive utility values for the model's health states.
Life years gained	0.077 years

QALYs gained	0.482 QALY
Incremental costs	[redacted]
ICER (DKK/QALY)	[redacted]
Uncertainty associated with the ICER estimate	Deterministic: The most important uncertainty of the incremental cost-effectiveness ratio (ICER) estimate was the utilities for the mild disease severity.
Number of eligible patients in Denmark	Incidence: annually, approximately 6 patients Prevalence: approximately 141 patients
Budget impact (in year 5)	[redacted]

3. The patient population, intervention, choice of comparator(s) and relevant outcomes

3.1 The medical condition

Systemic mastocytosis (SM) is characterised by clonal proliferation of mast cells (MC) that accumulate either in the bone marrow or in one or more organ systems (15-17). It is broadly categorised into non-AdvSM (non-advanced SM) and advanced SM, both of which are characterised by the uncontrolled proliferation and activation of MCs (15, 16). The vast majority of SM patients are considered to have non-AdvSM, which primarily includes indolent systemic mastocytosis (ISM) (95% of patients with SM (18)) and a small subset of patients who have smoldering SM (SSM) (19). Advanced SM is classified into three subtypes: aggressive SM (ASM), SM with an associated haematological neoplasm (SM-AHN), and mast cell leukaemia (MCL) (17, 20).

3.1.1 The pathophysiology

MCs play a unique and important role in generating a healthy immune response to toxic environmental stimuli and infection. The functioning of normal MC depends on ligand-dependent KIT signalling for differentiation, growth, survival and homing (16).

Although the aetiology of ISM is not fully understood, an activating mutation of KIT, usually KIT D816V, is found in the MC in 95% of all ISM cases at diagnosis (13, 21, 22). This mutation results in constitutive activation of the KIT receptor tyrosine kinase leading to greater disease activity and the uncontrolled proliferation and activation of MC (13, 21,

22). The increased number of MCs are found in extracutaneous sites, such as, bone marrow, liver, spleen, lymph nodes, and GI tract, with or without skin involvement.

Additionally, activation of MCs leads to degranulation and secretion of numerous vasoactive and proinflammatory mediators, such as serum tryptase, which contribute to the multiple symptoms observed in patients with ISM. Increased total serum tryptase, recorded in the absence of acute MC mediator release episodes, has long been described in ISM,(23, 24) with serum tryptase levels >20 ng/mL used as a (minor) diagnostic criterion. High baseline levels of serum tryptase are associated with disease progression and worse prognosis (11).

3.1.2 The clinical presentation/symptoms of the condition.

Clinical manifestations of mastocytosis are the result of two different mechanisms: (i) mediator release from MCs, and (ii) growth and infiltration of the MCs in various organs.

The accumulation and hyperactivity of aberrant MCs leads to excessive release of vasoactive and inflammatory mediators, including histamines, leukotrienes, prostaglandins, heparin, and interleukins. These mediators contribute to a constellation of unpredictable, persistent and debilitating symptoms in ISM (17, 19, 25, 26). The triggers for mediator release can be unpredictable with patients sometimes reacting to triggers they have not reacted to in the past, making it difficult to avoid allergens. Potential triggers include exposure to food, infection, natural and chemical odours, physical stimuli (heat, cold, friction, sunlight, etc.), physical exertion, bacterial proteins, venom, medication (non-steroidal anti-inflammatory drugs, general anaesthetics) and stress (27).

There is substantial variation in ISM symptomatology, both in regard to symptom severity and type. Most patients experience symptoms that are moderate to severe in nature and impact across organ systems.

ISM symptoms include systemic symptoms (e.g., fatigue/tiredness, pain, headache, sweating), GI symptoms (e.g., abdominal pain diarrhoea, nausea, vomiting), skin symptoms (e.g., itching, flushing, spots), respiratory symptoms (e.g., nasal congestion, throat swelling, wheezing, dyspnoea), musculoskeletal symptoms (e.g., bone pain, muscle pain, osteoporosis/osteopenia) and neuropsychiatric symptoms (e.g., difficulty concentrating, memory loss, anxiety, depression, migraines) (25).

Extensive release of mediators from MCs can also cause unpredictable life-threatening anaphylactic reactions (28). In the PRISM study, 51% of all SM patients reported having experienced at least one anaphylactic reaction within the past year (29). Of the 237 patients with ISM, 189 (79.7%) reported having ever experienced anaphylaxis and 44.7% experienced an anaphylactic reaction that required treatment or immediate medical attention. A total of 13 (5%) ISM patients reported having had more than five anaphylactic reactions within one year (29).

The formal diagnosis of SM is based on pathologic and laboratory criteria established by the WHO (15, 16, 20, 30). A diagnosis of SM can be made with the documentation of multifocal dense infiltrates of tryptase- and/or CD117 positive mast cells (≥15 mast cells

in aggregates) detected in sections of bone marrow and/or other extracutaneous organ(s) (major criterion) and at least one of four minor criteria (17):

- In bone marrow biopsy or in section of other extracutaneous organs >25% of mast cells are spindle shaped or have an atypical immature morphology
- KIT D816V mutation or other activating KIT mutation detected in bone marrow, peripheral blood, or other extracutaneous organs
- Mast cells in bone marrow, peripheral blood or other extracutaneous organs express CD25, CD2, and/or CD30, in addition to mast cell markers
- Elevated serum tryptase level, persistently >20 ng/mL. In cases of SM-AMN an elevated tryptase does not count as a SM minor criterion

If the major criterion of mast cell infiltrates cannot be documented, a diagnosis of SM can also be made if at least three minor criteria are met. After the pathological criteria for SM are met, SM is sub-categorised based on the degree of organ infiltration and organ damage present, as well as the presence of adverse pathological features.

3.1.3 Patient prognosis

There are no therapies available to treat the underlying cause of ISM. Therefore, the primary treatment objectives in ISM patients are to control the symptoms and comorbidities associated with ISM, improve patients' quality of life, prevent acute life-threatening events like anaphylactic shock and reduce the side effects resulting from the long-term use of symptomatic treatment (9, 10). Due to the high symptom burden, patients often receive multiple medications simultaneously including off-label therapies to help manage their symptoms. Medication used to manage ISM symptoms comprise mainly antihistamines (anti-H1/H2), corticosteroids, PPIs, epinephrine injectors, cromolyn sodium and antileukotrienes. Despite the use of many symptomatic treatments, symptom relief is often not achieved as the pharmacodynamic effect of these drugs is only of short-term (31).

In patients diagnosed with ISM, despite treatment with standard-of-care symptomatic therapies, patients can progress to advanced forms of disease like SSM and advanced SM (11-13). Reported progression rates from ISM to advanced SM ranged from 2.9% (median follow-up: 4.2 years)(14) to 7% (median follow-up: 9 years) (13). Data also show that a considerable proportion of ISM patients (15%) with mild symptoms experienced disease worsening to ISM with more severe symptom burden within a timeframe of two years (13).

3.1.4 The influence of the condition on the patients' functioning and health-related quality of life.

The broad spectrum of persistent and debilitating symptoms in patients with ISM leads to a significant reduction in HRQoL. The majority of patients with ISM report that their daily activities, work life and/or mental health are substantially affected by the disease. A few studies have also shown that patients with SM had worse HRQoL than patients with other diseases such as cancer (e.g., colorectal cancer) or psoriasis (32, 33).

In the PRISM study, HRQoL was assessed via the 12-Item Short Form Health Survey (SF-12) mental and physical component scores (MCS/PCS), the EuroQol EQ-5D-5L and the EuroQol visual analogue scale (EQ-VAS). Across each of these scales, ISM patients showed impaired HRQoL compared to the general population. The SF-12 MCS and PCS scores of 39.9 and 42.2 respectively (higher scores indicate better HRQoL), are well below the average for healthy individuals (29, 32, 34).

A qualitative study from Denmark by Jensen et al (2019) interviewed seven patients with ISM about their HRQoL and concluded that the disease substantially affected activities of daily living and social relationships. For example, patients with ISM reported that the fear of anaphylactic shock is permanently present, which thus impairs participation in social activities (35). Episodes of anaphylaxis can also lead to patients seeking emergency care. In the PRISM study, a mean of 0.54 ER visits per patient (N=237) were reported over one year. ISM patients with moderate to severe symptoms visited the ER on average 1.3 times within one year compared with 0.29 ER visits in ISM patients with mild symptoms (29).

3.2 Patient population

Avapritinib is expected to be used within its label, which is adult patients with ISM with moderate to severe symptoms inadequately controlled on symptomatic treatment (1). No subgroups of patients are expected within this indication.

The incidence and prevalence of ISM in Denmark is best informed from the recent publication by Jørgensen et al., 2025 (36), which was a nationwide cohort study of mastocytosis conducted in Denmark from January 1, 1997 to December 31, 2021.

Based on estimated from Jørgensen et al., the prevalence rate of ISM as of January 1, 2022 is estimated at 9.36 per 100 000, while for the incidence, based on the average observed rate between 1997 -2021, the incidence rate is estimated at 0.43 per 100 000 (36). Using these estimates, and population data from Statistics Denmark (population in Denmark: 6 001 008, May 2025) (37), a conservative estimate for prevalence and incidence of ISM in Denmark is 562 and 26 patients, respectively.

For the estimates in Table 1, given the rare nature of ISM and that the incident estimates are based on an average between 1997-2021, it is assumed incidence is constant in the past 5 years. For prevalence, the 2022 estimate is used in the table below, and the remaining year are conservatively estimated using the incidence.

Table 1 Incidence and prevalence for ISM in the past 5 years

Year	2020	2021	2022	2023	2024
Incidence in Denmark	26	26	26	26	26
Prevalence in Denmark	510	536	562	588	614
Global prevalence *	9.6 and 13.0 cases per 100,000 persons in Europe (38)				

* For small patient groups, also describe the worldwide prevalence.

To best inform the number of ISM patients in Denmark who would be within the avapritinib label (adult patients with ISM with *moderate to severe symptoms inadequately controlled on symptomatic treatment*), a Swedish clinical expert was consulted for this dossier (39) as it is assumed that clinical practice between Denmark and Sweden are similar and thus, assumption in Sweden would be applicable to Danish clinical practice.

The clinical expert estimated that of the total ISM patients diagnosed, 22% of these patients would fall within the label of avapritinib and thus be eligible for treatment. Using the estimations from Table 1 (26 incident patients each year + prevalence) and assuming 22% of these patients fall within the label, patient number estimations from Year 1 -5 are provided below.

Table 2 Estimated number of patients eligible for treatment

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients in Denmark who are eligible for treatment in the coming years	141	147	153	159	165

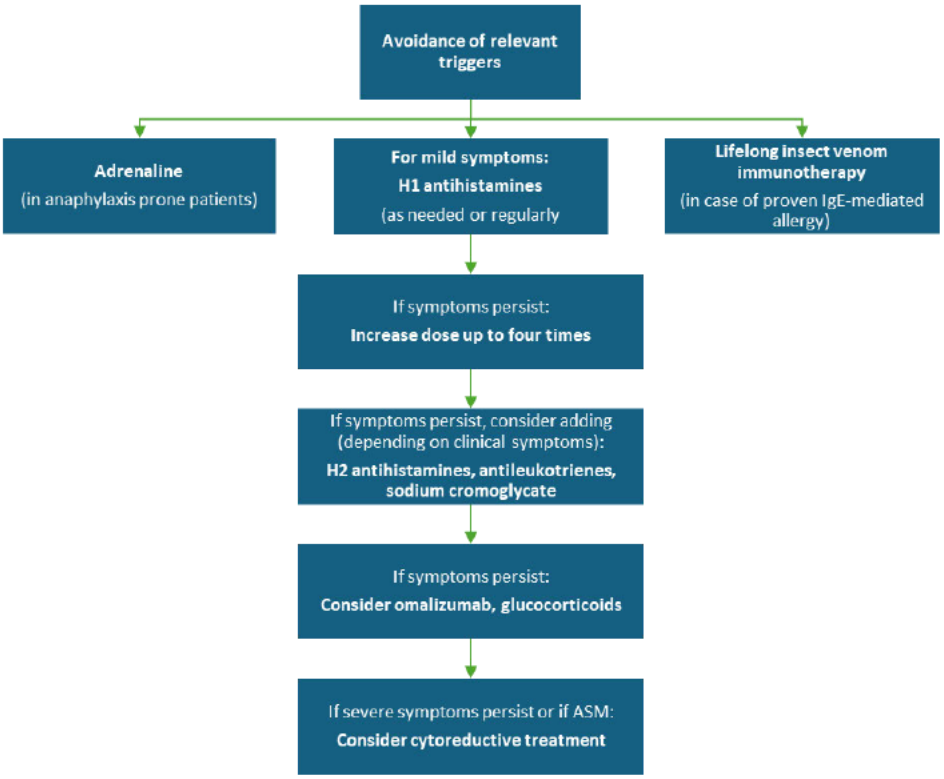
3.3 Current treatment options

There are currently no recommended treatments for ISM and in Denmark, there are no guidelines which define current clinical practice for ISM. International guidelines which specify treatment for ISM such as the National Comprehensive Cancer Network (NCCN) (6), European Competence Network of Mastocytosis and American Initiative in Mast Cell Diseases (ECNM-AIM) (7) and the Swedish national guidelines for systematic mastocytosis (which includes treatment for ISM) (8) are very similar and commonly differentiate their recommendations based on the patient's symptom and comorbidity profile. It is expected that Danish clinical practice will be similar to that of Sweden since treatment does not vary and Sweden would be considered similar to Denmark in terms of treatment options.

One of the principal symptom prevention approaches in the Swedish national guideline is to learn about the triggers that cause mediator release (e.g., heat/cold, stress, exercise, alcohol, or drugs like nonsteroidal anti-inflammatory drugs [NSAIDs]) and avoid them. However, there is large individual variation between patients in potential triggers, as such general advice to avoid all triggers should be avoided (8).

For the various symptoms associated with ISM, different symptomatic treatments are available. This includes skin involvement (anti-H1/H2, antileukotrienes, corticosteroids, omalizumab), gastrointestinal symptoms (anti-H2, proton pump inhibitors), osteoporosis (vitamin D, calcium supplements, bisphosphonates) and anaphylaxis (anti-H1/H2, omalizumab) (8). The stepwise and personalised approach recommended in the Swedish guidelines can be found in Figure 1.

Figure 1 Current treatment algorithm according to the Swedish national guidelines



Source: Klimkowska et al 2022 (8).

Abbreviations: ASM, advanced systemic mastocytosis; IgE, Immunoglobin E.

3.4 The intervention

Overview of intervention	
Indication relevant for the assessment	Avapritinib is indicated for the treatment of adult patients with indolent systemic mastocytosis (ISM) with moderate to severe symptoms inadequately controlled on symptomatic treatment (1).
ATMP	N/A
Method of administration	Oral
Dosing	The recommended dose of avapritinib is 25 mg orally once daily on an empty stomach (1).
Dosing in the health economic model (including relative dose intensity)	25 mg once daily.

Should the medicine be administered with other medicines?	No
Treatment duration / criteria for end of treatment	Treatment with avapritinib should be continued until disease progression or unacceptable toxicity occurs. For avapritinib a 5-year stopping rule applies (65 cycles), informed by a Swedish expert (39).
Necessary monitoring, both during administration and during the treatment period	Therapy should be initiated by a healthcare professional experienced in the diagnosis and treatment of ISM (1). Patients with ISM must notify their healthcare professional if they experience new or worsening cognitive symptoms (1). In patients with ISM, QT interval assessments by ECG should be considered, in particular in patients with concurrent factors that could prolong QT (e.g. age, pre-existing heart rhythm disorders, etc.) (1).
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	No
Package size(s)	AYVAKYT® (avapritinib) 25 mg; 30 x 25 mg film coated tablets

3.4.1 Description of ATMP

N/A

3.4.2 Mechanism of action

Avapritinib is a Type 1 kinase inhibitor that has demonstrated biochemical in vitro activity on the PDGFRA D842V and KIT D816V mutants associated with resistance to imatinib, sunitinib and regorafenib with half maximal inhibitory concentrations (IC50) of 0.24 nM and 0.27 nM, respectively, and greater potency against clinically relevant KIT exon 11, KIT exon 11/17 and KIT exon 17 mutants than against the KIT wild-type enzyme (1).

3.4.3 The intervention in relation to Danish clinical practice

Avapritinib is intended to be used for patients with moderate to severe symptoms that do not achieve adequate symptom control with symptomatic treatments. There are no specific tests needed prior to treatment with avapritinib (1).

3.5 Choice of comparator(s)

As there are currently no approved disease-modifying treatments for ISM in Denmark, and avapritinib is indicated as an add-on treatment to existing symptomatic treatments, the relevant comparator for this submission in placebo plus Danish BSC.

As outlined in Section 3.3, Danish standard of care consists of different symptomatic treatments targeting skin involvement (anti-H1/H2, antileukotrienes, corticosteroids, omalizumab), gastrointestinal symptoms (anti-H2, proton pump inhibitors), osteoporosis (vitamin D, calcium supplements, bisphosphonates) and anaphylaxis (anti-H1/H2, omalizumab) (8).

Overview of comparator	
Generic name	N/A
ATC code	N/A
Mechanism of action	N/A
Method of administration	N/A
Dosing	N/A
Dosing in the health economic model (including relative dose intensity)	N/A
Should the medicine be administered with other medicines?	N/A
Treatment duration/ criteria for end of treatment	N/A
Need for diagnostics or other tests (i.e. companion diagnostics)	N/A
Package size(s)	N/A

3.6 Cost-effectiveness of the comparator(s)

The symptomatic treatments within BSC have not been previously assessed by the DMC for ISM patients. According to the DMC methods guideline (40), if a comparator has not previously been assessed by the DMC, a comparison against placebo should be made, including cost-effectiveness. However, since BSC is a component of both the intervention and comparator arms in the PIONEER study design, we refer to the comparator arm as

placebo plus BSC for clarity. In practice, this represents a comparison of avapritinib against placebo.

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

Table 3 Efficacy outcome measures relevant for the application

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Indolent Systemic Mastocytosis Symptom Assessment Form (ISM-SAF) total symptom score (TSS) (ISM-SAF TSS) PIONEER	24 weeks	Mean change from baseline in TSS of the ISM-SAF	Measured by the trial investigator
ISM-SAF TSS PIONEER	24 weeks	Proportion of patients with ≥50% reduction in ISM-SAF TSS	Measured by the trial investigator
ISM-SAF TSS PIONEER	24 weeks	Proportion of patients with ≥30% reduction in ISM-SAF TSS	Measured by the trial investigator

* Time point for data collection used in analysis (follow up time for time-to-event measures)

Abbreviations: ISM-SAF TSS, Indolent systemic mastocytosis symptom assessment form total symptom score.

Validity of outcomes

The ISM-SAF is a 12-item daily diary that assesses the severity of 11 ISM symptoms namely bone pain, abdominal pain, headache, nausea, spots, itching, flushing, fatigue, dizziness, brain fog, and diarrhoea frequency over a 24-h recall period with an 11-point numeric rating scale (NRS), where 0 = No [symptom] and 10 = Worst imaginable [symptom]; the twelfth item assesses diarrhoea frequency by asking patients to enter a discrete numerical value.

The ISM-SAF was developed consistent with regulatory (41) and scientific guidelines (42) to evaluate clinical benefit hypotheses for use in product approval and labelling decisions. The ISM-SAF is a valid, sensitive tool that has been shown to distinguish patients with moderate to severe symptoms relative to those with less severe symptoms (43). The ISM-SAF is scored at an item level, domain level, and total score level. Insights can be drawn from the individual item scores (range 0 to 10) and from combined scores, the TSS (range 0 to 110; a ≥28-point threshold for moderate symptoms and a ≥42-point threshold for severe symptoms has been established), the GI Symptom Score (range 0 to 30), the Skin

Symptom Score (range 0 to 30) and the Neurocognitive Symptom Score (range 0 to 30). Higher scores indicate greater sign/symptom severity.

4. Health economic analysis

A cost-utility analysis was conducted based on a Danish adaptation of an Excel-based health economic model. The objective of the health economic model is to assess the cost-effectiveness of avapritinib plus BSC vs BSC for the treatment of adult patients with ISM with moderate to severe symptoms inadequately controlled on symptomatic treatment. The model outcomes include total and incremental costs and health outcomes expressed as quality-adjusted life years (QALYs) gained.

4.1 Model structure

A Markov state transition model with six health states is used to perform the cost-utility analysis of avapritinib plus BSC vs BSC only: initial treatment period, maintenance with avapritinib, maintenance with BSC, SSM, AdvSM, and death (see Figure 2).

Patients treated with avapritinib during the initial treatment phase were assessed at 24 weeks. Patients who show a response to treatment, defined as either a >30% TSS, move on to the maintenance phase with avapritinib while those that did not achieve a response move on to maintenance with BSC alone. Within the maintenance phase patients can continue to move between the mild, moderate and severe states until the trial period is over.

Patients who started on BSC in the initial treatment phase will continue BSC in the maintenance period. During this initial phase, patients are able to shift in either direction between severity states, and those that respond well to treatment may move into the mild state.

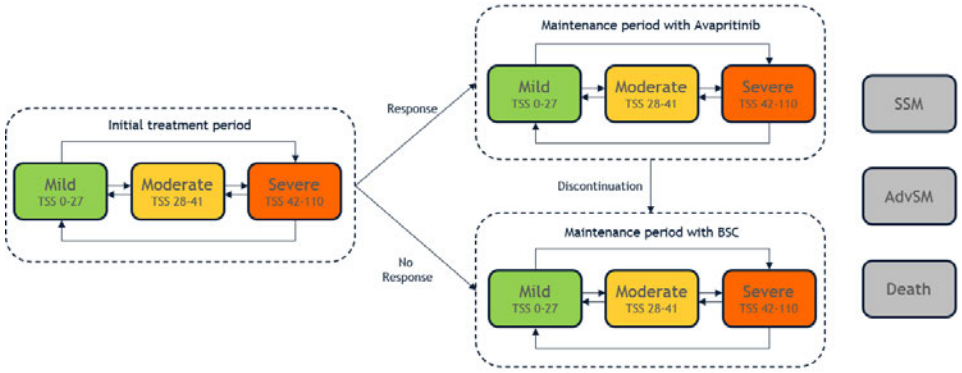


Figure 2 Illustration of the model structure of the Markov model.

Abbreviations: AdvSM, advanced systemic mastocytosis; BSC, best supportive care; SSM, smouldering systemic mastocytosis; TSS, total symptom score.

Within each of the treatment states, patients can be one of three disease severity states based on TSS with mild: 0-27, moderate: 28-41 and severe: 42-110. These thresholds are

based on the distribution of TSS scores in the PIONEER trial(44) and the clinical judgment of experts.

To take into account disease progression over time during any treatment phase patients can transition from mild, moderate or severe health states to SSM or AdvSM. The model assumes that patients in different treatment states also have different risks of progression to SSM and AdvSM. Patients in the SSM health state can transition to AdvSM, while patients in AdvSM remain in this state until death. From any disease health states, a transition to death is possible, which serves as an absorbing model state.

4.2 Model features

The model features are described in Table 4.

Table 4 Features of the economic model

Model features	Description	Justification
Patient population	Adult patients with ISM with moderate to severe symptoms inadequately controlled on symptomatic treatment.	Patient population according to EMA label (1).
Perspective	Limited societal perspective	According to DMC guidelines (40).
Time horizon	Lifetime (49 years)	To capture all health benefits and costs in line with DMC guidelines (40). The median age at baseline in PIONEER Part 2 was 51 years and the model extrapolates over lifetime. The median age at diagnosis of ISM in the adult (age >15 years) Danish population is 51.3 years (45).
Cycle length	28 days	Consistent with length of treatment cycle in the PIONEER trial.
Half-cycle correction	Yes	A half-cycle correction is applied to the patient distribution to increase accuracy of the health state occupancy estimates over time (44).
Discount rate	3.5 %	The DMC applies a discount rate of 3.5 % for all years (40).

Intervention	Avapritinib in addition to BSC	
Comparator(s)	BSC only	According to national treatment guideline in Sweden, validated by Swedish clinical expert and assumed to be valid in the Danish clinical practice (8).
Outcomes	Response (>30% reduction in TSS score), safety, HRQoL	Validated by Swedish clinical expert and assumed to be valid in the Danish clinical practice (8).

Abbreviations: BSC, best supportive care; DMC, Danish Medicines Council; EMA, ; HRQoL, Health-related quality of life; ISM, indolent systemic mastocytosis.

5. Overview of literature

5.1 Literature used for the clinical assessment

A systematic literature review was not conducted for this submission dossier, as the main trial, PIONEER (46, 47), provides head-to-head evidence of avapritinib plus BSC vs placebo plus BSC.

Table 5 Relevant literature included in the assessment of efficacy and safety [sample text in table for full paper, data on file and conference abstract]

Reference (Full citation incl. reference number)*	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
Gotlib J, Castells M, Elberink HO, et al. Avapritinib versus Placebo in Indolent Systemic Mastocytosis. *NEJM Evidence* 2023; **2**(6): EVIDoa2200339 (46) Clinical study report of PIONEER (47)	PIONEER	NCT03731260	Start: June 2020 Completion: 23/06/27 (primary completion) Data cut-off: 20/09/24 (Part 3) Future data cut-offs: 20 04/26 (estimated)	Avapritinib plus BSC vs. placebo plus BSC for adult patients with ISM with moderate to severe symptoms inadequately controlled on symptomatic treatment

Abbreviations: BSC, best supportive care; ISM, indolent systemic mastocytosis.
Note:* If there are several publications connected to a trial, include all publications used.

5.2 Literature used for the assessment of health-related quality of life

Health-related quality of life data for the estimation of health state utility values was obtained from the PIONEER head-to-head study. The EQ-5D-5L data from PIONEER trial with Danish preference weights was used to calculate the health state utility values for the disease categories *mild, moderate, and severe*. Utility values for the disease categories SSM

and AdvSM, as well as disutilities associated with adverse events, were derived from published literature. The references are presented in Table 6, and the literature search used to identify the inputs (including the latest available SLR conducted on 31 March 2025) is described in detail in Appendix I.

Table 6 Relevant literature included for (documentation of) health-related quality of life (See section 10)

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
Blueprint Medicines Corporation. Supplementary health-related quality of life data from the PATHFINDER study: NCT03580655 [Data on file. 2023] (48).	Utility value for AdvSM disease	Section 10.3.4.
Sullivan PW, Slejko JF, Sculpher MJ, Ghushchyan V. Catalogue of EQ-5D scores for the United Kingdom. Med Decis Making. 2011 Nov-Dec;31(6):800-4. doi: 10.1177/0272989X11401031. Epub 2011 Mar 21. PMID: 21422468 (49).	Disutility decrement for: • Headache • Flushing • Hair colour changes	Section 10.3.4.
Araújo A, Parente B, Sotto-Mayor R, Teixeira E, Almodôvar T, Barata F, Queiroga H, Pereira C, Pereira H, Negreiro F, Silva C. An economic analysis of erlotinib, docetaxel, pemetrexed and best supportive care as second or third line treatment of non-small cell lung cancer. Rev Port Pneumol. 2008 Nov-Dec;14(6):803-27. English, Portuguese. PMID: 19023496 (50).	Disutility decrement for: • Nausea • Diarrhoea	Section 10.3.4.
NICE. TA250: Eribulin for the treatment of locally advanced or metastatic breast cancer [Committee papers]. 2011. p. 110 (51).	Disutility decrement for: • Oedema peripheral • Periorbital oedema • Eyelid oedema • Face oedema	Section 10.3.4.
Lloyd A, Nafees B, Narewska J, Dewilde S, Watkins J. Health state utilities for metastatic breast cancer. Br J Cancer. 2006;95(6):683-90 (52).	Disutility decrement for: • Fatigue	Section 10.3.4.

NICE. TA124: PEMETREXED IN THE TREATMENT OF NON-SMALL-CELL LUNG CANCER. 2006: p. 114. (53)	Disutility decrement for: • Alopecia	Section 10.3.4.
NICE. Neuroendocrine tumours (metastatic, unresectable, progressive) - everolimus and sunitinib [ID858]. Commitee papers. GID-TA10024. 2017. p. 269 (54).	Disutility decrement for: • Aspartate aminotransferase increased • Alanine aminotransferase increased • Blood lactate dehydrogenase increased	Section 10.3.4.
NICE. CG173: Neuropathic pain – pharmacological management: appendix F 2020. p. 61 (55).	Disutility decrement for: • Dizziness	Section 10.3.4.
Farkouh RA WM, Tarrants ML, Castelli-Haley J, Armand C. . Cost-effectiveness of rasagiline compared with first-line early Parkinson disease therapies. 4(3): 99-107. 2012.(56)	Disutility decrement for: • Muscle spasms	Section 10.3.4.
Shaker M, Wallace D, Golden DBK, Oppenheimer J, Greenhawt M. Simulation of Health and Economic Benefits of Extended Observation of Resolved Anaphylaxis. JAMA Netw Open. 2019;2(10):e1913951.(57)	Disutility decrement for: • Anaphylaxis without complications	Section 10.3.4.

Abbreviations: AdvSM, Advanced systemic mastocytosis; NICE, national institute for health and care excellence.

5.3 Literature used for inputs for the health economic model

Besides data from PIONEER trial, ten additional references were identified to provide input to the health economic model (excluding cost sources, SmPCs, DRG tariffs etc), which are presented in Table 7. The literature search to identify the inputs is described in Appendix J.

Table 7 Relevant literature used for input to the health economic model

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied

Gotlib J, Castells M, Elberink HO, et al. Avapritinib versus Placebo in Indolent Systemic Mastocytosis. *NEJM Evidence* 2023; **2**(6): EVIDoa2200339 (46) Clinical study report of PIONEER (47) ClinicalTrials.gov. (PIONEER) Study to Evaluate Efficacy and Safety of Avapritinib (BLU-285), A Selective KIT Mutation-targeted Tyrosine Kinase Inhibitor, Versus Placebo in Patients With Indolent Systemic Mastocytosis [Available from: https://clinicaltrials.gov/study/NCT03731260].(44)	Efficacy response (>30% reduction in TSS score), observed TSS disease severity distribution, ToT, and adverse events rates	Trial of interest	Section 8 and 9.1
Blueprint Medicines Corporation. PRISM Partial Results (slide 13). 2023 (58) Blueprint Medicines Corporation. PRISM [data on file] (59)	Adverse events rate: • Anaphylaxis without complications • Anaphylaxis with complications	Targeted literature review	Section 9.2 and 11.4
Matito A, Morgado JM, Álvarez-Twose I, et al. Serum tryptase monitoring in indolent systemic mastocytosis: association with disease features and patient outcome. PLoS One. 2013;8(10):e76116. Published 2013 Oct 14. doi:10.1371/journal.pone.0076116 (11)	Probability of progression per cycle (severe and SSM)	Targeted literature review	Section 8.1.2
Trizuljak J, Sperr WR, Nekvindová L, et al. Clinical features and survival of patients with indolent systemic mastocytosis defined by the updated WHO classification. Allergy.	Probability of progression per cycle (severe and SSM)	Targeted literature review	Section 8.1.2

2020;75(8):1927-1938. doi:10.1111/all.14248 (14)			
Escribano L, Alvarez-Twose I, Sánchez-Muñoz L, et al. Prognosis in adult indolent systemic mastocytosis: a long-term study of the Spanish Network on Mastocytosis in a series of 145 patients. J Allergy Clin Immunol. 2009;124(3):514-521. doi:10.1016/j.jaci.2009.05.003 (60)	Probability of progression per cycle (severe and SSM)	Targeted literature review	Section 8.1.2
NICE. TA708: Budesonide for treating active eosinophilic oesophagitis [Comittee papers]. 2021. p. 75 (61)	Resource use activity (per health state): • Gastrointestinal domain: outpatient consultation	Targeted literature review	Section 11.4
NICE. TA534: Dupilumab for treating moderate to severe atopic dermatitis after topical treatments [Comittee papers]. 2018. p. 17 (62)	Resource use activity (per health state): • Skin domain: Dermatology outpatient consultation • Skin domain: Dermatologist nurse visit • Accident & Emergency visit • Hospitalization • Daycase admission	Targeted literature review	Section 11.4
NICE. TA753: Cenobamate for focal onset seizures in epilepsy [Comittee papers]. 2021. p. 138 (63)	Resource use activity (per health state): • Neurologic domain: outpatient consultation	Targeted literature review	Section 11.4
NICE. TA883: Tafasitamab with lenalidomide for treating relapsed or refractory diffuse large B-cell lymphoma [Comittee papers]. 2022. p. 130 (64)	Resource use activity (per health state): • Bone marrow biopsy • Coagulation test • Serum chemistry tests	Targeted literature review	Section 11.4

NICE. TA838: Slow-release potassium bicarbonate and potassium citrate for treating distal renal tubular acidosis [Comittee papers]. 2022. p. 149-150 (65)	Resource use activity (per health state): • Haematology visit • Biochemistry test: renal - Urin test • Computed tomography (CT) scan • Ultrasound scan • Bone densitometry	Targeted literature review	Section 11.4
NICE. TA814: Upadacitinib, abrocitinib and tralokinumab for dermatitis [Comittee papers]. 2022. p. 193 (66)	Resource use activity (per health state): • Photography • Full blood count	Targeted literature review	Section 11.4
Tefferi A, Shah S, Reichard KK, Hanson CA, Pardanani A. Smoldering mastocytosis: Survival comparisons with indolent and aggressive mastocytosis. *Am J Hematol*. 2019;94(1):E1-E2. doi:10.1002/ajh.25302 (67)	Mortality rate ratio (MRR) per Health State (SSM and AdvSM)	Targeted literature review	Section 8.1.2

Abbreviations: AdvSM, Advanced systemic mastocytosis; CT, computed tomography; MRR, mortality rate ratio; SSM, smouldering systemic mastocytosis; ToT, time on treatment.

6. Efficacy

6.1 Efficacy of avapritinib plus BSC compared to placebo plus BSC for patients with ISM with moderate to severe symptoms inadequately controlled on symptomatic treatment

6.1.1 Relevant studies

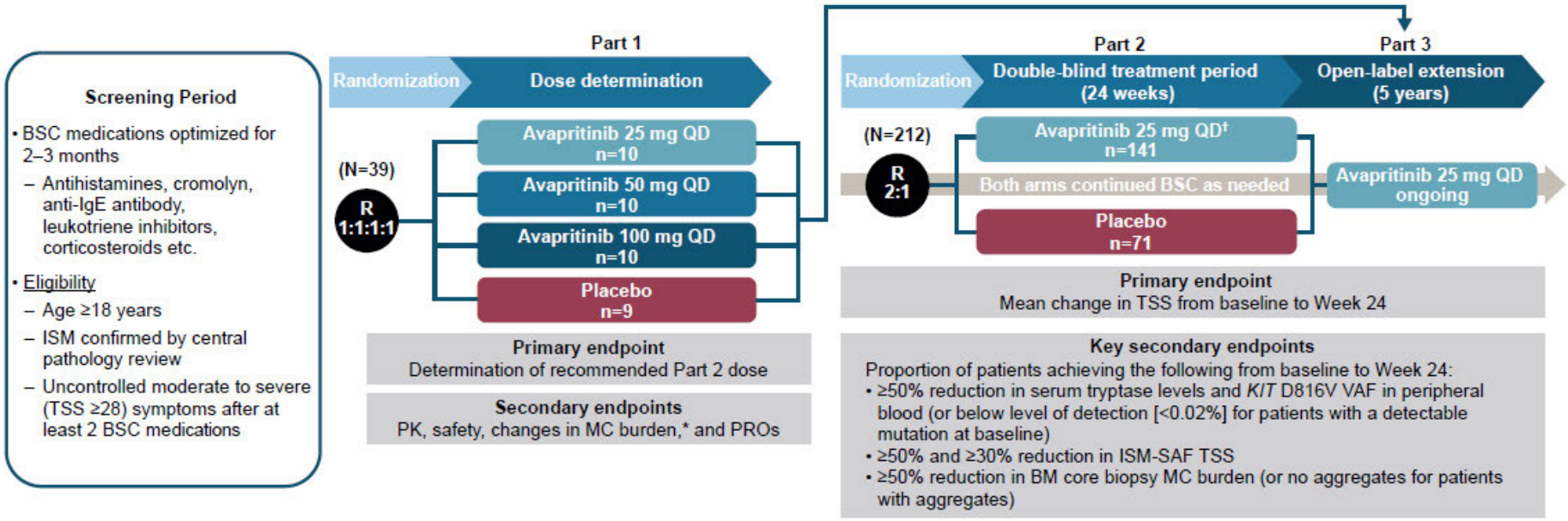
The efficacy and safety of avapritinib plus best supportive care (BSC) with placebo plus BSC in patients is being investigated in the three-part, phase 2, randomised, double-blind, placebo-controlled trial PIONEER (NCT03731260); this is the first randomised controlled trial in patients with ISM with a highly selective KIT D816V-targeting agent. The trial included adult patients with confirmed ISM and moderate to severe symptoms that were not adequately controlled with BSC. PIONEER was conducted in 42 sites, the majority of which were located in Europe (n=23), with 19 located in North America (46, 47). The trial was well-designed and robust.

In Part 1, the dose escalation phase of the PIONEER trial, the primary objective was to identify the RP2D of avapritinib in patients with ISM, which would be applied in Parts 2 and 3 of the study (Figure 3). Patients were allocated to either 25 mg avapritinib, 50 mg avapritinib, 100 mg avapritinib, or placebo. Subsequently, the efficacy and safety of 25 mg avapritinib QD was evaluated in the pivotal Part 2 of the study (47).

Patients who completed any treatment in Part 1 or Part 2 of the study were eligible to participate in Part 3. Part 3 of PIONEER is an open-label extension phase where all patients received 25 mg avapritinib QD in combination with BSC, regardless of prior treatment assignment. The primary objective was to assess the long-term safety and efficacy of avapritinib in ISM patients (47).

For the efficacy results of PIONEER, Part 2 and Part 3 will be reported in this dossier, as Part 1 was a dosing finding study with a small sample size, thus will not be presented. Part 2 efficacy results will be reported for the ITT population, which included patients who were randomised into avapritinib 25mg. For Part 3, the per protocol (PP) population will be presented as this included patients who only received avapritinib 25 mg in both Part 1 and Part 2 and continue to receive avapritinib 25mg in Part 3 since this best reflects the current EMA label within ISM.

Figure 3 Study design of PIONEER



Note:*Measured by reduction of serum tryptase, peripheral blood KIT D816V VAF and BM MCs; †The recommended dose of avapritinib for Part 2 and Part 3 was identified based on efficacy and safety results from Part 1.

Abbreviations: BM, bone marrow; BSC, best supportive care; IgE, immunoglobin E; ISM-SAF, Indolent Systemic Mastocytosis Symptom Assessment Form; MC, mast cell; PK, pharmacokinetics; PRO, patient reported outcome; QD, once daily; R, randomised; TSS, total symptom score; VAF, variant allele fraction.

Source: Blueprint Medicines Corporation. Adapted from CSR. Data on file, 2022; Gotlib et al (2023) (46, 47)

Table 8 Overview of study design for studies included in the comparison

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
PIONEER, NCT03731260 (46, 47)	A 3-Part, Randomized, Double-Blind, Placebo-Controlled Phase 2 Study	Part 2: 24 weeks (June 2022 DCO) Part 3: 2.5 years (September 2024 DCO)	Adult patients with ISM with moderate to severe symptoms and inadequately controlled on symptomatic treatment	Avapritinib, 25 mg daily	Best supportive care	Mean change in TSS of the ISM-SAF, from baseline to C7D1 (24 weeks of treatment), data cutoff: Part 2: June 2022 & Part 3: September 2024. Proportion of patients with a ≥50% reduction in ISM-SAF TSS from baseline to C7D1 (24 weeks of treatment), data cutoff: Part 2: June 2022 Proportion of patients with a ≥30% reduction in ISM-SAF TSS from baseline to C7D1 (24 weeks of treatment), data cutoff: Part 2: June 2022 Proportion of patients with a ≥50% reduction in peripheral blood KIT D816V allele fraction from baseline to C7D1 or undetectable (<0.02%) for patients with detectable mutation at baseline (24 weeks of treatment), data cutoff: Part 2: June 2022 Proportion of patients with a ≥50% reduction in bone marrow mast cells from baseline to C7D1 or no aggregates for patients with aggregates at baseline (24 weeks of treatment), data cutoff: Part 2: June 2022

6.1.2 Comparability of studies

6.1.2.1 Comparability of patients across studies

Patient demographics of the ITT/safety population enrolled in Part 2 were generally similar between treatment groups (Table 9). The majority of patients were female (73.5%) and below the age of 65 (89.1%). The mean age was 50.5 years. Moreover, 76% of patients were of non-Hispanic/Latino ethnicity and 81.6% were White. Height, weight and body mass index (BMI) at baseline were similar across groups (46, 47, 68, 69).

The characteristics of the patients who rolled over to Part 3 from Part 1 and Part 2 were in line with the individual demographic analyses in Part 1 and Part 2. The majority of the patients were female (72.7%) and below 65 years old (88.7%). In addition, most patients were White (85.3%) and of non-Hispanic/Latino ethnicity (77.3%). Height, weight and BMI measurements were similar across groups (47).

Table 9 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety

	PIONEER (Part 2)		PIONEER (Part 3)
	Avapritinib 25 mg N = 141	Placebo N = 71	Avapritinib, 25-mg starting dose and dose maintained N = 150
Age (years)*			
Mean (SD)	48.7 (11.70)	52.2 (12.52)	49.8 (12.9)
Median (Min, Max)	50.0 (18, 77)	54.0 (26, 79)	51.0 (18, 76)
Age group, n (%)			
<65 years	132 (93.6)	60 (84.5)	133 (88.7)
≥65 years	9 (6.4)	11 (15.5)	17 (11.3)
Sex, n (%)			
Female	100 (70.9)	54 (76.1)	109 (72.7)
Male	41 (29.1)	17 (23.9)	41 (27.3)
Ethnicity, n (%)			
Hispanic or Latino	6 (4.3)	1 (1.4)	5 (3.3)
Not Hispanic or Latino	99 (70.2)	58 (81.7)	116 (77.3)
Not reported	22 (15.6)	10 (14.1)	19 (12.7)

Unknown	14 (9.9)	2 (2.8)	10 (6.7)
Race, n (%)			
Asian	1 (0.7)	0	0
White	109 (77.3)	61 (85.9)	128 (85.3)
Unknown	27 (19.1)	8 (11.3)	18 (12.0)
Other	4 (2.8)	2 (2.8)	4 (2.7)
Height (cm)			
n	137	70	148
Mean (SD)	169.05 (9.726)	166.55 (9.073)	167.6 (9.8)
Median (Min, Max)	167.00 (152.4, 194.0)	165.00 (150.2, 195.0)	165.0 (150.2, 195.0)
Weight (kg)			
n	141	71	150
Mean (SD)	81.12 (17.915)	82.19 (17.796)	82.0 (19.8)
Median (Min, Max)	80.20 (45.0, 126.4)	80.70 (44.4, 134.8)	80.3 (44.1, 148.9)
BMI (kg/m2)			
n	137	70	148
Mean (SD)	28.31 (5.400)	29.46 (5.276)	29.1 (6.0)
Median (Min, Max)	27.84 (17.6, 42.0)	28.99 (19.7, 43.7)	28.3 (17.6, 51.4)

Abbreviations: BMI, body mass index; ITT, intention-to-Treat; Max, maximum; Min, minimum; SD, standard deviation.

Note:* at the time of informed consent

Source: Data on file. Table 16 (Part 2) and Table 2 (Part 3) from CSR. Blueprint Medicines Corporation, 2022 (46, 47)

6.1.3 Comparability of the study population(s) with Danish patients eligible for treatment

Table 10 Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population (Jørgensen et al., 2025 (36))	Value used in health economic model (PIONEER (47))

Age, years	49 (median)	51 (mean)
Gender, % female	53.9	72.8

6.1.4 Efficacy – results per PIONEER Part 2

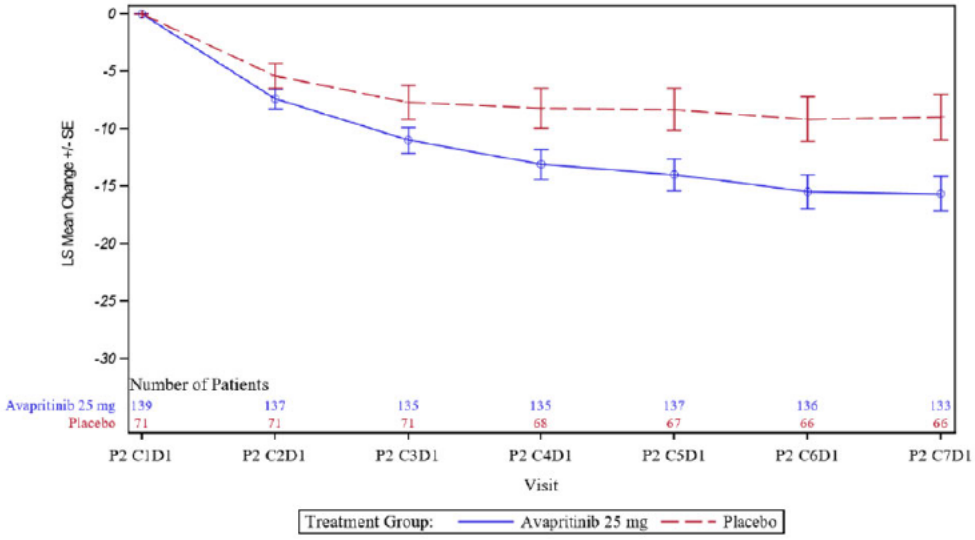
6.1.4.1 Primary endpoint

6.1.4.1.1 Mean change from baseline in ISM-SAF TSS

At Part 2 baseline (data cutoff: June 2022), the mean (SD) ISM-SAF TSS was 50.17 (19.145) points for the 25 mg avapritinib group and 52.43 (19.823) for the placebo group. During treatment, there was a reduction in the ISM-SAF TSS for both groups (46, 47, 68).

Avapritinib led to a significant reduction in symptom burden based on mean change in ISM-SAF TSS at C7D1 (Figure 4). The least squares (LS) mean change (standard error [SE]) from baseline was -15.58 (1.54) for the 25 mg avapritinib group and –9.15 (2.01) for the placebo group. The difference (95% CI) between treatment groups was –6.43 (–10.90, –1.96) points and statistically significant (P=0.003).

Figure 4 LS mean change from baseline in ISM-SAF TSS (ITT population)



Abbreviations: CXDX, Cycle X Day X; ISM-SAF, Indolent Systemic Mastocytosis Symptom Assessment Form; ITT, intention-to-treat; LS mean, least squares mean; SE, standard error; TSS, total symptom score.

Source: Data on file. Figure 4 from CSR. Blueprint Medicines Corporation, 2022(47).

Table 11 LS mean change from baseline in ISM-SAF TSS (ITT population)

Parameter	Avapritinib 25 mg N=141	Placebo N=71
Baseline		
n	139	71

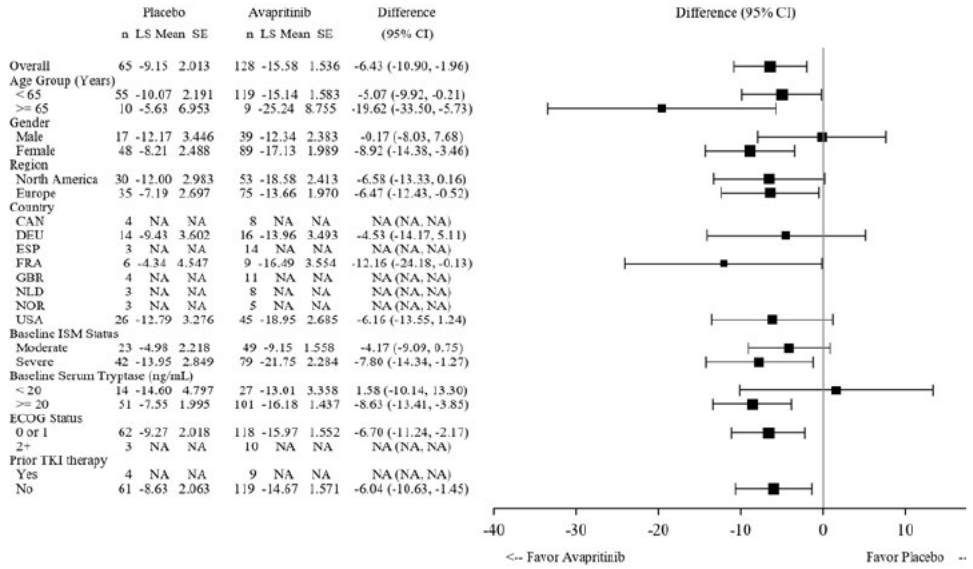
Mean (SD)	50.17 (19.145)	52.43 (19.823)
Median	47.86	47.79
Min, Max	12.1, 102.7	18.0, 104.4
C7D1		
n	130	65
Mean (SD)	33.48 (20.056)	42.32 (21.027)
Median	31.39	38.21
Min, Max	0.9, 103.5	5.5, 86.1
CFB		
n	128	65
LS Mean (SE)	–15.58 (1.536)	–9.15 (2.013)
95% CI	–18.61, –12.55	–13.12, –5.18
Difference (95% CI) in CFB	–6.43 (–10.90, –1.96)	
p-value	0.003	

Abbreviations: CFB, change from baseline; CI, confidence interval; CXDX, Cycle X Day X; ISM-SAF, Indolent Systemic Mastocytosis Symptom Assessment Form; ITT, intention-to-treat; LS mean, least squares mean; Max, maximum; Min, minimum; SD, standard deviation; SE, standard error; TSS, total symptom score.

Source: Data on file. Table 24 from CSR. Blueprint Medicines Corporation, 2022.(46, 47)

Results of the subgroup analyses for the primary endpoint are shown in Figure 5. Avapritinib was superior to placebo in all subgroups in terms of mean change in ISM-SAF TSS, aside for men and patients with baseline serum tryptase below 20 ng/mL (46, 47).

Figure 5 Subgroup analysis of the primary endpoint (ITT population)



Abbreviations: CXDX, Cycle X Day X; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; ISM-SAF, Indolent Systemic Mastocytosis Symptom Assessment Form; ITT, intention-to-treat; LS mean, least squares mean; NA, not applicable; SE, standard error; TKI, tyrosine kinase inhibitor; TSS, total symptom score.

Source: Data on file. Figure 7 from CSR. Blueprint Medicines Corporation, 2022.(47)

6.1.4.2 Key secondary endpoints

6.1.4.2.1 Patients with ≥50% reduction in TSS

ISM symptoms were reduced to a greater magnitude in patients receiving 25 mg avapritinib than in patients receiving placebo (Table 12, Figure 6). The proportion of patients who achieved a ≥50% reduction in ISM-SAF TSS at C7D1 was 24.8% (95% CI: 17.9-32.8) in the 25 mg avapritinib group and 9.9% (95% CI: 4.1-19.3) in the placebo group. The calculated odds ratio (OR) indicates threefold higher odds of symptom reduction for patients receiving avapritinib compared with placebo (OR, 3.10; 95% CI, 1.24-8.64), demonstrating that avapritinib substantially and statistically significantly reduced the ISM symptom burden of patients compared with placebo (P=0.005) (46, 47).

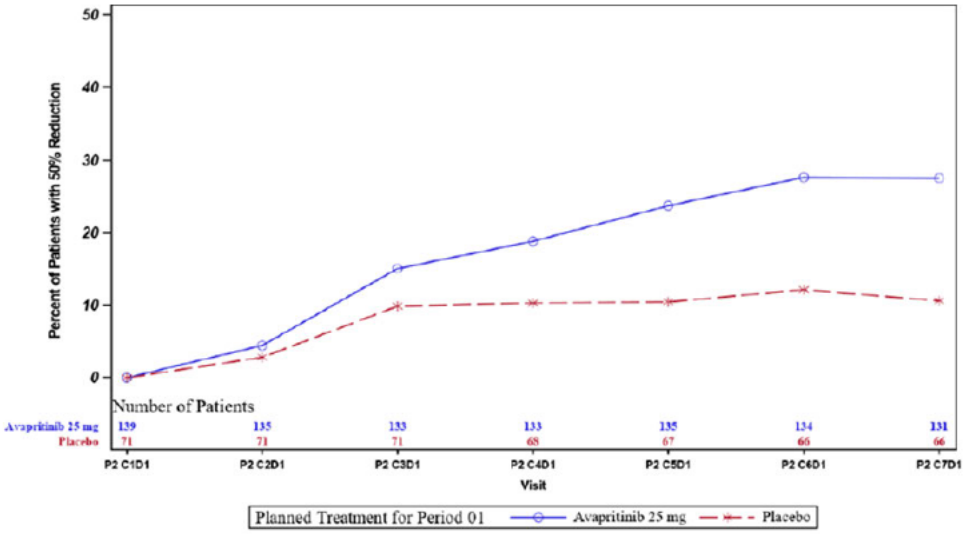
Table 12 Proportion of patients with ≥50% reduction in ISM-SAF TSS at C7D1 (ITT population)

Key secondary endpoints	Avapritinib 25 mg		Placebo		Odds ratio		
	n/N (%)	95% CI	n/N (%)	95% CI	Value	95% CIs	P-Value
Patients with ≥50% reduction in TSS	35/141 (24.8)	17.9-32.8	7/71 (9.9)	4.1-19.3	3.10	1.24-8.64	0.005

Abbreviations: CI: confidence interval; ISM-SAF: Indolent Systemic Mastocytosis Symptom Assessment Form; ITT: intention-to-treat; TSS: total symptom score.

Source: Data on file. Adapted from Table 25 from CSR. Blueprint Medicines Corporation, 2022 (47)

Figure 6 Percent of patients with ≥50% reduction in ISM-SAF TSS at C7D1 over time (ITT Population)



Abbreviations: CXDX: Cycle X Day X; ISM-SAF: Indolent Systemic Mastocytosis Symptom Assessment Form; ITT: intention-to-treat; TSS: total symptom score.

Source: Data on file. Figure 8 from CSR. Blueprint Medicines Corporation, 2022 (47)

6.1.4.2.2 Patients with ≥30% reduction in TSS

A reduction of ≥30% in ISM-SAF TSS was achieved by 45.4% (95% CI: 37.0-54.0) of the patients receiving 25 mg avapritinib and by 29.6% (95% CI: 19.3-41.6) of patients in the placebo group (Table 13, Figure 7). The OR showed a substantial and statistically significant reduction in symptom burden in the avapritinib arm compared with placebo (OR, 2.07; 95% CI, 1.08-3.99; p=0.009) (46, 47).

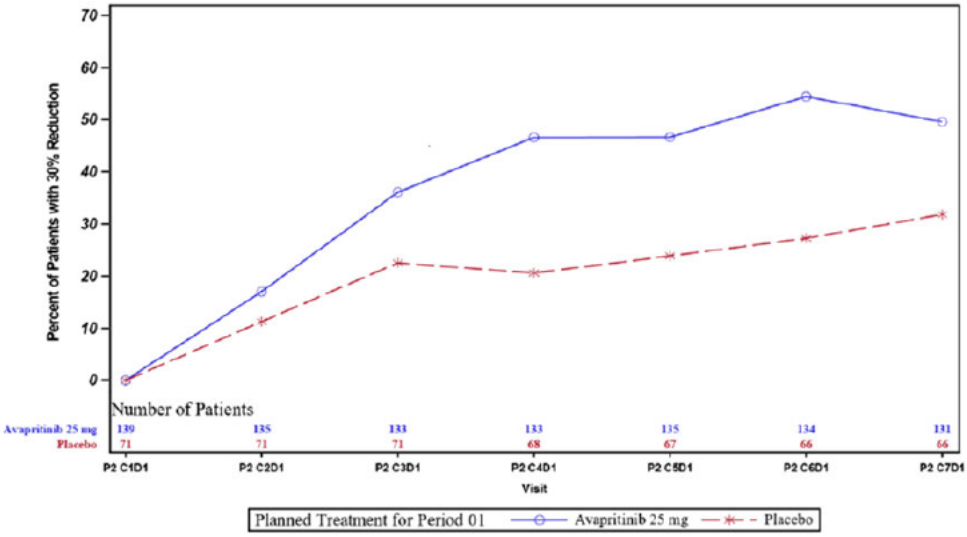
Table 13 Proportion of patients with ≥30% reduction in ISM-SAF TSS at C7D1 (ITT population)

Key secondary endpoints	Avapritinib 25 mg		Placebo		Odds ratio		
	n/N (%)	95% CI	n/N (%)	95% CI	Value	95% CIs	P-Value
Patients with ≥30% reduction in TSS	64/141 (45.4)	37.0-54.0	21/71 (29.6)	19.3-41.6	2.07	1.08-3.99	0.009

Abbreviations: CI: confidence interval; ISM-SAF: Indolent Systemic Mastocytosis Symptom Assessment Form; ITT: intention-to-treat; TSS: total symptom score.

Source: Data on file. Adapted from Table 25 from CSR. Blueprint Medicines Corporation, 2022 (47)

Figure 7 Percent of patients with ≥30% reduction in ISM-SAF TSS at C7D1 over time (ITT Population)



Abbreviations: CXDX: Cycle X Day X; ISM-SAF: Indolent Systemic Mastocytosis Symptom Assessment Form; ITT: intention-to-treat; TSS: total symptom score.

Source: Data on file. Figure 9 from CSR. Blueprint Medicines Corporation, 2022 (47)

6.1.4.2.3 Patients with ≥50% reduction in objective measures of mast cell burden

Treatment with 25 mg avapritinib decreased MC burden in patients based on serum tryptase, KIT 816V MAF and percent bone marrow MCs. The ORs were statically significant for all three endpoints (P<0.0001 for each outcome), supporting the superiority of avapritinib to reduce MC burden compared with placebo (Table 14) (46, 47, 68).

Table 14 Results in objective measures of mast cell burden (ITT Population)

Key secondary endpoints	Avapritinib 25 mg		Placebo		Odds ratio		
	n/N (%)	95% CI	n/N (%)	95% CI	Value	95% CIs	P-value
Proportion of patients with ≥50% reductions in serum tryptase	76/141 (53.9)	45.3-62.3	0/71 (0.0)	0.0-5.1	NE	30.59-NE	<0.0001
Proportion of patients with ≥50% reduction in KIT D816V MAF or undetectable (<0.02%) for patients with detectable mutation at baseline	80/118 (67.8)	58.6-76.1	4/63 (6.3)	1.8-15.5	39.34	10.93-140.56	<0.0001

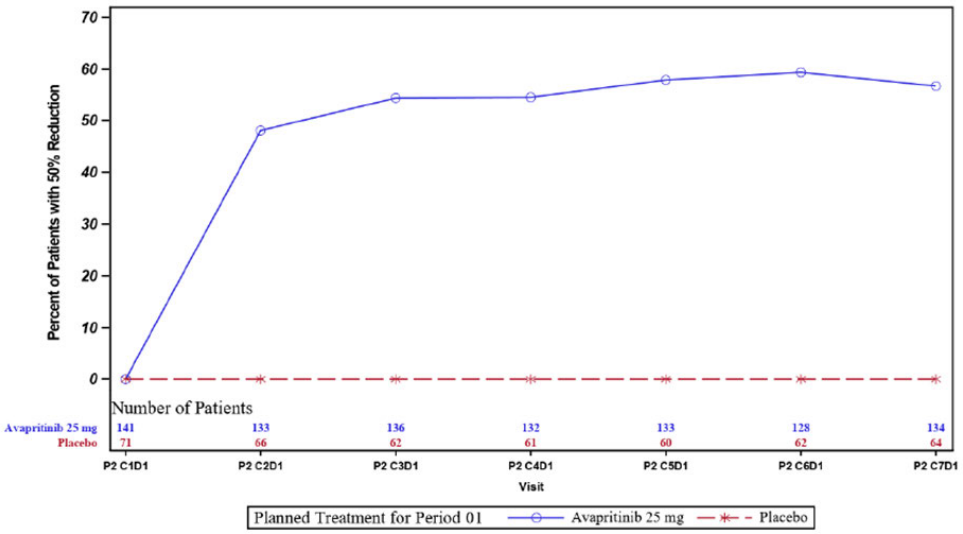
Proportion of patients with ≥50% reduction in bone marrow mast cells or no aggregates for patients with aggregates at baseline	56/106 (52.8)	42.9-62.6	13/57 (22.8)	12.7-35.8	4.74	2.06-11.45	<0.0001

Abbreviations: CI: confidence interval; ISM-SAF: Indolent Systemic Mastocytosis Symptom Assessment Form; ITT: intention-to-treat, MAF: mutant allele fraction; NE: not evaluable; TSS: total symptom score.

Source: Data on file. Table 26 from CSR. Blueprint Medicines Corporation, 2022 (47)

The proportion of patients that showed a ≥50% reduction in serum tryptase was 53.9% (95% CI: 45.3-62.3) in the 25 mg avapritinib group, whilst none (95% CI: 0.0-5.1) of the patients in the placebo group achieved a ≥50% reduction (Figure 8) (46, 47, 68, 69).

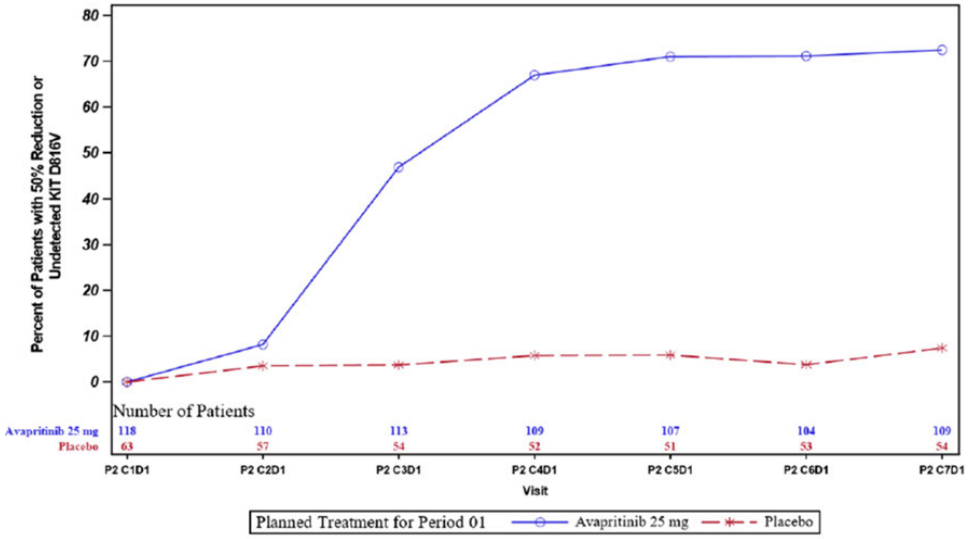
Figure 8 Proportion of patients achieving ≥50% reduction in serum tryptase at C7D1 (ITT Population)



Abbreviations: CXDX: Cycle X Day X; ITT: intention-to-treat.
Source: Source: Data on file. Adapted from Figure 12 from CSR. Blueprint Medicines Corporation, 2022 (47)

A ≥50% reduction in KIT D816V MAF or undetectable (<0.02%) was measured in 67.8% (95% CI: 58.6-76.1) of patients in the 25 mg avapritinib group and in 6.3% (95% CI: 1.8-15.5) of patients in the placebo group (Figure 9) (46, 47, 68, 69).

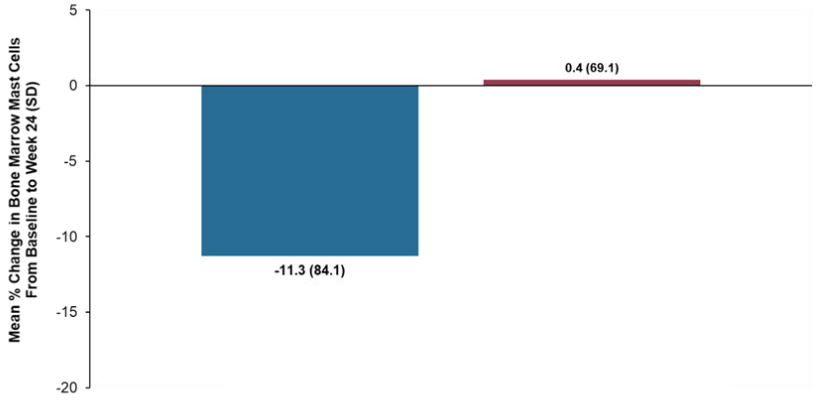
Figure 9 Proportion of patients achieving ≥50% reduction in KIT D816V MAF or undetectable at C7D1 (<0.02%; ITT Population)



Abbreviations: CXDX: Cycle X Day X; ITT: intention-to-treat
Source: Source: Data on file. Adapted from Figure 12 from CSR. Blueprint Medicines Corporation, 2022 (47)

The proportion of patients who had a ≥50% reduction in bone marrow MCs or no aggregates was higher in the 25 mg avapritinib group with 52.8% (95% CI: 42.9-62.6) compared with the placebo group with 22.8% (95% CI: 12.7-35.8). The mean (SD) change in bone marrow MCs from baseline was -11.3% (84.1%) in the 25 mg avapritinib group and +0.4% (69.1%) in the placebo group (Figure 10) (46, 47, 68, 69).

Figure 10 Proportion of patients achieving ≥50% reduction in bone marrow mast cells or no aggregates (ITT Population)



Blue: 25mg avapritinib group; red: placebo group
Abbreviations: ITT: intention-to-treat.
Source: Data on file. Adapted from Figure 12 from CSR. Blueprint Medicines Corporation, 2022 (47).

6.1.5 Efficacy – results per PIONEER Part 3

6.1.5.1 Primary endpoint

6.1.5.1.1 Mean change from baseline in ISM-SAF TSS

At Part 3 baseline (data cutoff: September 2024), avapritinib treatment was associated with substantial reductions in the severity of ISM-related symptoms (Table 15). Mean reductions from baseline of 22.2 points in TSS were observed in the Per Protocol population at 2.5 years (C31D1) of treatment with avapritinib (47).

Table 15 Change from baseline (time of avapritinib initiation) in ISM-SAF TSS (PP population)

Parameter	Avapritinib, 25-mg starting dose and dose maintained (N=150)
Baseline	
n	150
Mean (SD)	48.7 (18.0)
C31D1	
n	91
Mean (SD)	24.4 (19.1)
CFB	
Mean change from baseline (SD)	–22.2 (18.2)

Abbreviations: CxDx, Cycle x, Day x; ISM-SAF, Indolent Systemic Mastocytosis – Symptom Assessment Form; NR, not reported; SD, standard deviation; TSS, total symptom score.
Note: TSS is calculated as the average daily score from the 14-day period prior to the assessment time point. Patients who initiated avapritinib at a dose of 50 mg or 100 mg in Part 1 of PIONEER continued treatment with the recommended daily dose of 25 mg at the start of Part 3. The reported patient numbers were used in the calculation of mean TSS score.
Source: Data on file. Adapted from Table 9 from CSR. Blueprint Medicines Corporation (47)

7. Comparative analyses of efficacy

7.1.1 Differences in definitions of outcomes between studies

N/A

7.1.2 Method of synthesis

N/A

7.1.3 Results from the comparative analysis

Table 16 Results from the comparative analysis of avapritinib vs. placebo for patients with ISM with moderate to severe symptoms inadequately controlled on symptomatic treatment

	Part 2		
Outcome measure	**Avapritinib (N=141)**	**Placebo (N=71)**	**Result**
Mean change from baseline in ISM-SAF TSS (Part 2)	LS Mean: -15.58 (-18.61, -12.55)	LS Mean: -9.15 (-13.12, -5.18)	–6.43 (–10.90, –1.96), 0.003
Patients with ≥50% reduction in TSS	35 (24.8%; 17.9, 32.8)	7 (9.9%; 4.1, 19.3)	Odds ratio: 3.10 (1.24, 8.64), 0.005
Patients with ≥30% reduction in TSS	64 (45.4%; 37.0, 54.0)	21 (29.6%; 19.3, 41.6)	Odds ratio: 2.07 (1.08, 3.99), 0.009
Patients with ≥50% reduction in serum tryptase	76 (53.9%; 45.3, 62.3)	0 (0.0%; 0.0, 5.1)	Odds ratio: N/E (30.59, NE), <0.0001
Patients with ≥50% reduction in KIT D816V MAF or undetectable (<0.02%) for patients with detectable mutation at baseline	80 (67.8%; 58.6, 76.1)	4 (6.3%; 1.8, 15.5)	Odds ratio: 39.34 (10.93, 140.56), <0.0001
Patients with ≥50% reduction in bone marrow mast cells or no aggregates for patients with aggregates at baseline	56 (52.8%; 42.9, 52.8)	13 (22.8; 12.7, 35.8)	Odds ratio: 4.74 (2.06, 11.45), <0.0001
	Part 3		
	Avapritinib, 25-mg starting dose and dose maintained [redacted]		
Mean change from baseline in ISM-SAF TSS (Part 3)	[redacted]		

7.1.4 Efficacy – results per [outcome measure]

N/A

8. Modelling of efficacy in the health economic analysis

8.1 Presentation of efficacy data from the clinical documentation used in the model

As previously described in Section 6, the PIONEER study Part 2 provides direct a head-to-head comparison of efficacy between avapritinib plus BSC and placebo plus BSC over the 6 initial treatment cycles (24 weeks). The Part 2 informs the modelling of efficacy for both intervention and comparator. In the end of Part 2, patients on avapritinib plus BSC were assessed for response based on TSS score. Only the in-label population was considered, i.e., patients with moderate or severe disease at baseline (excluding patients with mild disease) and only receiving 25 mg dose of avapritinib (excluding patients that at any time of the study received the escalated dose of 50 mg avapritinib).

For the avapritinib plus BSC arm, response evaluation was followed by maintenance treatment in Part 3 of the PIONEER trial. The modelled maintenance efficacy of the intervention is directly informed by patient distributions of the responders moving into Part 3 with continued treatment of avapritinib.

The placebo plus BSC patients were allowed to cross over to avapritinib after Part 2, and there is no data available for placebo plus BSC efficacy beyond the initial 6 cycles.

In essence, the efficacy is modelled using the PIONEER Part 2 and 3 data directly, together with assumptions around time on treatment (ToT) and waning of treatment effect after treatment discontinuation. The Markov state transition feature is used for modelling transitions to SSM, AdvSM and death.

Modelling efficacy of the intervention

The patient distribution in the model is based on the proportion of patients in the PIONEER trial who are in each disease severity state in each 28-day cycle over the trial follow-up period.

After response assessment, all responding patients are moved to the avapritinib maintenance states. The distributions of patients in the maintenance states were informed by Part 3 of PIONEER trial, from cycle 7 (week 24) until available follow-up (DCO 20 September 2024) corresponding to model/treatment cycle 52 (week 204). In subsequent cycles, the base case assumption is that patients stay in their severity health state until treatment discontinuation, or transition to SSM, AdvSM or death. At the assumed treatment discontinuation, modelled as a stopping at maximum treatment time of 5 years (65 cycles), the patients are assumed to wane the efficacy back to the Part 2 baseline severity distribution of BSC over a waning period of 6 months. The expected time on treatment for responders at 5 years was informed by Swedish clinical expert.

The non-responders at week 24 are assumed to revert to the baseline severity distribution of BSC over a 6-cycle waning period.

Modelling efficacy of the comparator

Following the initial 24-week treatment phase, and in the absence of long-term placebo arm data, a return toward baseline symptom severity is assumed over the next 24 weeks. This assumption reflects a real-world context in which patients may not receive the same level of supportive care optimization, adherence support, or follow-up intensity as in a clinical trial setting. Beyond this period, symptom severity is assumed to stabilize at the baseline distribution for the remainder of the model.

8.1.1 Extrapolation of efficacy data

No extrapolation models were fitted to the efficacy data.

8.1.1.1 Extrapolation of [effect measure 1]

N/A

Table 17 Summary of assumptions associated with extrapolation of [effect measure]

Method/approach	Description/assumption
N/A	

Abbreviations: N/A, not applicable

8.1.1.2 Extrapolation of [effect measure 2]

N/A

8.1.2 Calculation of transition probabilities

Transitions from avapritinib initial treatment period were directly informed by the response rate and observed TSS disease severity distribution in the PIONEER trial (44). Responders were moved to avapritinib maintenance after response assessment at cycle 7 (week 24) and redistributed over TSS disease severity substates based on the PIONEER trial Part 3.

Time on avapritinib maintenance treatment was implemented as a set stopping at the expected time on treatment. In the PIONEER trial, few discontinuations were observed during the trial duration, and long-term treatment duration of avapritinib is unknown. The treatment duration parameter was therefore informed from expectations of clinical expert.

For patients in the BSC arm, all patients in the initial treatment period continued to BSC maintenance after the response assessment at cycle 7 (week 24). The distribution of patients between the TSS disease severity substate was directly informed by the PIONEER Part 2 trial, capturing the observed placebo effect in initial treatment period. Between cycle 7 and cycle 13, the placebo effect was assumed to wane back to the baseline

distribution of TSS disease severity substates. An overview of the transitions in the health economic model is presented in Table 18, while transition probabilities used in the base case analysis is presented in Table 19.

Table 18 Transitions in the health economic model

Health state (from)	Health state (to)	Description of method	Reference
Avapritinib initial treatment period	Avapritinib maintenance	After response assessment, all responders move to avapritinib maintenance	PIONEER trial (44)
	BSC maintenance	After response assessment, all non-responders move to BSC maintenance	PIONEER trial (44)
Avapritinib maintenance	BSC maintenance	Patients discontinuing avapritinib move to BSC maintenance	PIONEER trial (44)
BSC initial treatment period	BSC maintenance	After the initial 6 cycles, all patients move to BSC maintenance	PIONEER trial (44)
TSS severe substates	SSM	A weighted average of the per-cycle chance of progression taken from three publications	Trizuljak et al. 2020 (14), Escribano et al. 2009 (60), Matito et al. 2013 (11)
	AdvSM	A weighted average of the per-cycle chance of progression taken from three publications	Trizuljak et al. 2020 (14), Escribano et al. 2009 (60), Matito et al. 2013 (11)
TSS moderate substates	SSM	Half of severe to SSM	Assumption
	AdvSM	Half of severe to AdvSM	Assumption
TSS mild substates	SSM	Quarter of severe to SSM	Assumption

	AdvSM	Quarter of severe to AdvSM	Assumption
SSM	AdvSM	A weighted average of the per-cycle chance of progression taken from three publications	Trizuljak et al. 2020 (14), Escribano et al. 2009 (60), Matito et al. 2013 (11)
All	Death	General population mortality for ISM health state. Increased mortality for SSM and AdvSM.	Tefferi et al. 2019 (67, 70)

Abbreviations: AdvSM, advanced systemic mastocytosis; BSC, best supportive care; ISM, indolent systemic mastocytosis; SSM, smouldering systemic mastocytosis; TSS, total symptom score.

Table 19 Transition probabilities of disease progression per cycle

Health state (from)	Health state (to)	Transition probability (per cycle)	Reference / assumption
TSS severe substates	SSM	0.0314%	Trizuljak et al. 2020 (14), Escribano et al. 2009 (60), Matito et al. 2013 (11)
	AdvSM	0.0544%	Trizuljak et al. 2020 (14), Escribano et al. 2009 (60), Matito et al. 2013 (11)
TSS moderate substates	SSM	0.0157%	Half of severe to SSM
	AdvSM	0.0272%	Half of severe to AdvSM
TSS mild substates	SSM	0.0078%	Quarter of severe to SSM
	AdvSM	0.0136%	Quarter of severe to AdvSM
SSM	AdvSM	0.1682%	Trizuljak et al. 2020 (14), Escribano et al. 2009 (60), Matito et al. 2013 (11)

Abbreviations: AdvSM, advanced systemic mastocytosis; SSM, smouldering systemic mastocytosis; TSS, total symptom score.

For patients with ISM, mortality rates were assumed to be the same as general population. For patients that had progressed to SSM or AdvSM, a mortality rate ratio (MRR) of 5.5 was applied based on Tefferi et al. 2019 (67).

The transition probabilities derived from the PIONEER trial and supplementary literature are considered relevant for modelling disease progression in a Danish setting. The trial population is generally comparable to Danish patients, and the treatment protocol aligns with national guidelines, making the estimates likely to reflect real-world clinical outcomes in Denmark.

8.2 Presentation of efficacy data from [additional documentation]

Not relevant.

8.3 Modelling effects of subsequent treatments

Not relevant.

8.4 Other assumptions regarding efficacy in the model

Not relevant.

8.5 Overview of modelled average treatment length and time in model health state

An overview of the proportion of patients by health state in the avapritinib arm and the BSC arm are provided in Figure 11 and Figure 12, respectively.

Figure 11 Health states distribution over time in the avapritinib arm

Figure 12 Health states distribution over time in the BSC arm

OS and PFS are not states being modelled in this analysis; hence it is not applicable. An overview of the modelled average treatment length and time in the health states is provided in Table 21.

Table 20 Estimates in the model

	Modelled average [effect measure] (reference in Excel)	Modelled median [effect measure] (reference in Excel)	Observed median from relevant study
[Name of intervention]	N/A	N/A	N/A

[Name of comparator]	N/A	N/A	N/A

Abbreviations: N/A, not applicable.

Table 21 Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction

Treatment	Treatment length [years]	Mild [years]	Moderate [years]	Severe [years]	SMM [years]	AdvSM [years]
Avapritinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AdvSM, advanced systemic mastocytosis; BSC, best supportive care; N/A, not applicable; SSM, smouldering systemic mastocytosis.

Note:* BSC is given to all patients in all stages in both arms

9. Safety

9.1 Safety data from the clinical documentation

In Part 2, the safety population comprised all patients who received at least one dose of avapritinib (n=141) or placebo (n=71) and was identical with the ITT population (47). In Part 3, the safety population comprised all patients who initiated avapritinib in Parts 1, 2, or 3 of PIONEER at a dose of 25 mg and have continued to receive a 25-mg dose in Part 3 as of the time of the data cut (47).

Table 22 Overview of safety events. PIONEER (Part 2, Safety population, DCO June 2022; Part 3, Safety population, September 2024)

	Part 2		Part 3
	Avapritinib 25 mg N = 141	Placebo N = 71	Avapritinib, 25-mg starting dose and dose maintained [redacted]
Number of adverse events, n	N/A	N/A	[redacted]
Number and proportion of patients with ≥1 adverse events, n (%)	128 (90.8)	66 (93.0)	[redacted]
Number of serious adverse events*, n	N/A	N/A	[redacted]
Number and proportion of patients with ≥ 1 serious adverse events*, n (%)	7 (5.0)	8 (11.3)	[redacted]
Number of CTCAE grade ≥ 3 events, n	N/A	N/A	[redacted]
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events§, n (%)	30 (21.3)	15 (21.1)	[redacted]
Number of adverse reactions, n	N/A	N/A	[redacted]
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	N/R	N/R	[redacted]

Number and proportion of patients who had a dose reduction, n (%)	2 (1.4)	1 (1.4)	[redacted]
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	3 (2.1)	1 (1.4)	[redacted]
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	2 (1.4)	1 (1.4)	[redacted]

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).

§ CTCAE v. 5.0 must be used if available.

No SAE's with a frequency >5% occurred in Part 2 and Part 3 of PIONEER.

Table 23 Serious adverse events occurring in more than >5% of patients. PIONEER (Part 2, Safety population, DCO June 2022; Part 3, Safety population, September 2024)

	Part 2				Part 3	
Adverse events	**Avapritinib 25 mg N = 141**		**Placebo N = 71**		**Avapritinib, 25-mg starting dose and dose maintained (N=169)**	
	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events
Adverse event, n (%)	0	0	0	0	0	0

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).

The model accounts for AEs associated with avapritinib and BSC, based on the PIONEER clinical trial data (47). The model includes all treatment-related AEs reported in the trial. Table 24 shows the AE rates for each treatment.

For simplicity the model adjusts for AEs only in the first cycle. This is a simplifying assumption, as AEs have a minor impact on the model outcomes and most patients who experience AEs are likely to discontinue treatment. The model assigns once-off costs and

disutility values to each AE, based on literature sources. The model then multiplies the costs and disutility values by the AE incidence to obtain the total costs and disutility associated with AEs.

Table 24 Adverse events used in the health economic model

Adverse events	Avapritinib	BSC		
	Frequency used in economic model for intervention	Frequency used in economic model for comparator	Source	Justification
Adverse event, n (%)	N/A	N/A	N/A	N/A
Headache	7.8%	9.9%	PIONEER (71)	Treatment-Related Adverse Events by Preferred Term (n>=3)
Nausea	6.4%	8.5%	PIONEER (71)	
Oedema peripheral	6.4%	1.4%	PIONEER (71)	
Periorbital oedema	6.4%	2.8%	PIONEER (71)	
Fatigue	4.3%	2.8%	PIONEER (71)	
Flushing	4.3%	0.0%	PIONEER (71)	
Alopecia	3.5%	4.2%	PIONEER (71)	
Blood alkaline phosphatase increased	3.5%	0.0%	PIONEER (71)	
Contusion	3.5%	0.0%	PIONEER (71)	
Eyelid oedema	3.5%	1.4%	PIONEER (71)	
Face oedema	3.5%	0.0%	PIONEER (71)	
Aspartate aminotransferase increased	2.8%	1.4%	PIONEER (71)	
Diarrhoea	2.8%	2.8%	PIONEER (71)	
Dizziness	2.8%	7.0%	PIONEER (71)	

Hair colour changes	2.8%	1.4%	PIONEER (71)	
Photosensitivity reaction	2.8%	0.0%	PIONEER (71)	
Alanine aminotransferase increased	2.1%	1.4%	PIONEER (71)	
Blood lactate dehydrogenase increased	2.1%	0.0%	PIONEER (71)	
Dry mouth	2.1%	1.4%	PIONEER (71)	
Muscle spasms	2.1%	0.0%	PIONEER (71)	
Anaphylaxis without complications	12.3%	25.5%	PRISM (58)	51% report ≥1 anaphylaxis reaction per year. Assumed that results in 25.5% having anaphylaxis with complications, 25.5% without complications. Assumed incidence in Ava arm to be halved compared to BSC.
Anaphylaxis with complications	12.3%	25.5%	PRISM (58)	

Abbreviations: BSC, best supportive care.

9.2 Safety data from external literature applied in the health economic model

Where needed, AE data were supplemented by findings from the PRISM study (32), which was conducted in seven European countries. The PRISM study elicited experiences from both advanced and non-AdvSM patients, and incorporated perspectives from healthcare providers, thereby providing additional insights into the burden of AEs in clinical practice.

The PRISM-derived AE rates were used to inform the model in the same manner as described in Section 9.1, with costs and disutility values applied accordingly. AE incidence rates from the PRISM study are included in Table 24.

Table 25 Adverse events that appear in more than X % of patients

Adverse events	Intervention (N=x)			Comparator (N=x)			Difference, % (95 % CI)	
	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for intervention	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for comparator	Number of patients with adverse events	Number of adverse events
Adverse event, n	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Abbreviations: CI, confidence interval; N/A, not applicable.

10. Documentation of health-related quality of life (HRQoL)

HRQoL data were collected in the PIONEER trial Part 2. EQ-5D-5L questionnaires were completed at baseline (day 1 of cycle 1), then on day 1 of each cycle up to cycle 7.

Table 26 Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
EQ-5D-5L	PIONEER	Utilities for the ISM health states: mild, moderate and severe disease
EQ-VAS	PIONEER	Demonstrates that patients on the intervention maintains a comparable quality of life

Abbreviations: EQ-5D-5L, EuroQoL Five-Dimension Five-Level; EQ-VAS, EuroQoL Visual Analogue Scale; HRQoL, Health-related quality of life.

10.1 Presentation of the health-related quality of life

10.1.1 Study design and measuring instrument

The instrument EQ-5D-5L was considered to be the most transferable and informative for the decision problem, as this is a widely accepted measure of HRQoL and allows for direct estimation of Danish utility values in line with the DMC guidelines. EQ-5D-5L was analysed based on the ITT analysis set (N=212). As patients in the placebo plus BSC arm were allowed to cross over to avapritinib after Part 2 of the study, and QoL data continued to be collected beyond the initial six treatment cycles, only data from this population are presented here to ensure consistency and avoid confounding effects from treatment crossover.

Both VAS and EQ-5D-5L index were captured. For VAS, the patient is asked to mark on a scale from 0 to 100 (0 being worst health imaginable, and 100 best health imaginable), how their overall health is that day. To estimate the EQ-5D-5L index, the patient is asked to grade their perceived level on a 5-point scale across 5 domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). These health states were then converted into a Health Utility Index using a Danish value set (72) where 1 represents full health and 0 represents dead.

A priori, it was anticipated that changes in HRQoL would vary across different health states. Consequently, utility values were assessed for the ISM health states: mild, moderate, and severe disease. These utility values for these different states are assumed to be independent of the treatment administered to patients.

10.1.2 Data collection

HRQoL data were collected in the PIONEER trial Part 2. EQ-5D-5L questionnaires were completed at baseline (day 1 of cycle 1), then on day 1 of each cycle up to cycle 7 using an electronic tablet. In exceptional cases, data were collected using a paper form previously approved by the Institutional Review Board/Independent Ethics Committee.

Missing data and completion are reported in Table 27. No imputation for missing observation was conducted according to the PIONEER trial SAP (73). For the inclusion in the subsequent analyses, patients were required to have a baseline value as well as at least one follow-up value.

Table 27 Pattern of missing data and completion

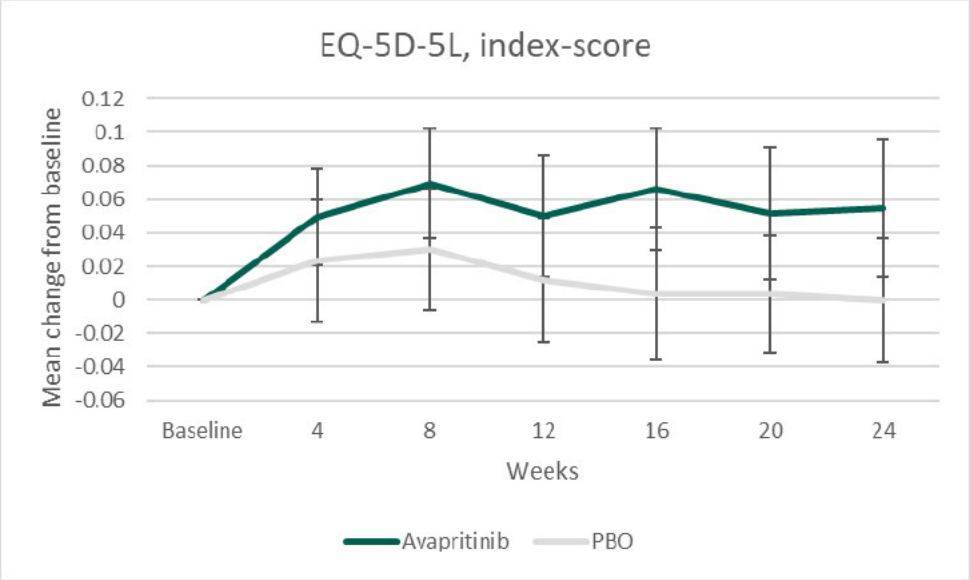
Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
C1D1, baseline	212	10 (4.7%)	212	202 (95.3%)
C2D1	212	7 (3.3%)	212	205 (96.7%)
C3D1	212	14 (6.6%)	209	195 (93.3%)
C4D1	212	19 (9.0%)	207	188 (90.8%)
C5D1	212	18 (8.5%)	207	189 (91.3%)
C6D1	212	15 (7.1%)	205	190 (92.7%)
C7D1	212	14 (6.6%)	203	189 (93.1%)

Abbreviations: C, cycle; D, day.

10.1.3 HRQoL results

The mean change from baseline for the EQ-5D-5L index-score and the EQ-5D-5L VAS are presented in Figure 13 and Figure 14, respectively. For the EQ-5D-5L index score, the analysis included all completed questionnaires that were correctly filled out by patients and had corresponding TSS severity score data available at the time of completion. As for the VAS score, the analysis population consisted of all randomized subjects (ITT) who received any amount of study treatment and completed at least one patient-reported outcome (PRO) assessment at baseline. The summary statistics are presented in Table 28 and Table 29, respectively.

Figure 13 Mean change from baseline, EQ-5D-5L index-scores, ITT population (part 2)



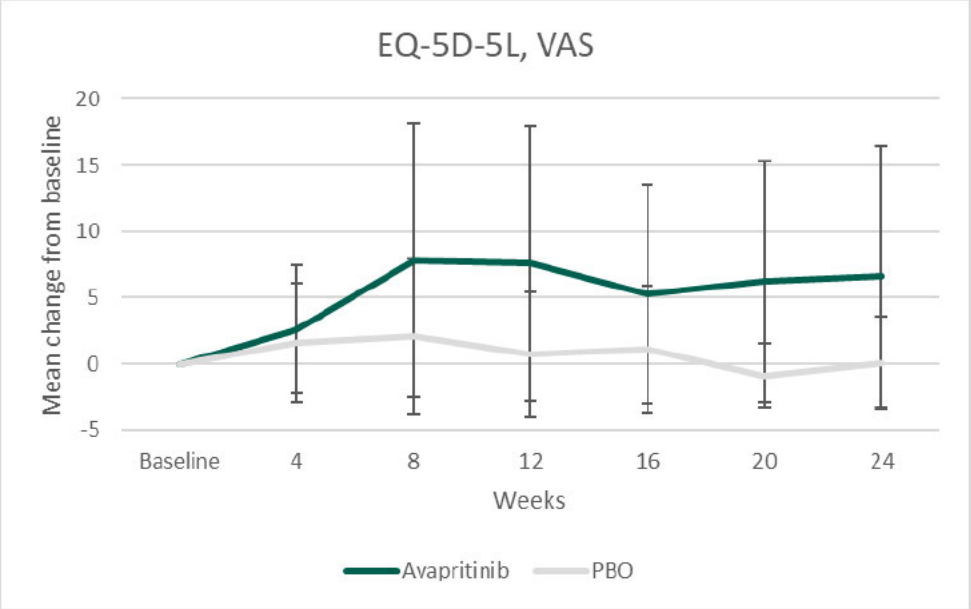
Abbreviations: EQ-5D-5L, EuroQol 5 Dimension 5 Level; ITT, itention to treat; PBO, BSC plus placebo

Table 28 HRQoL EQ-5D-5L summary statistics, utility index scores, ITT population (part 2) with patients for whom information on the TSS severity score was available at the time of completing the questionnaire

	Intervention		Comparator		Intervention vs. comparator
	N	Mean (SD)	N	Mean (SD)	Difference (95% CI) p-value
C1D1, baseline	122	0.61 (0.22)	60	0.63 (0.19)	N/A
C2D1	120	0.66 (0.22)	59	0.65 (0.19)	N/A
C3D1	116	0.67 (0.21)	58	0.65 (0.20)	N/A
C4D1	116	0.66 (0.23)	55	0.64 (0.18)	N/a
C5D1	115	0.67 (0.23)	59	0.63 (0.14)	N/A
C6D1	114	0.66 (0.25)	57	0.63 (0.24)	N/A
C7D1	122	0.66 (0.25)	60	0.63 (0.16)	N/A

Abbreviations: C, cycle; CI, confidence interval; D, day; N/A, not available; SD, standard deviation

Figure 14 Mean change from baseline, EQ-5D-5L VAS, ITT population (part 2)



Abbreviations: EQ-5D-5L, EuroQol 5 Dimension 5 Level; ITT, itention to treat; PBO, BSC plus placebo; VAS, visual analogue scale.

Table 29 HRQoL EQ-5D-5L summary statistic, VAS scores, ITT population (Part 2)

	Intervention		Comparator		Intervention vs. comparator
	N	Mean (SD)	N	Mean (SD)	Difference (95% CI) p-value
C1D1, baseline	135	57.2 (17.61)	67	55.9 (17.85)	N/A
C2D1	137	59.8 (18.01)	68	57.5 (16.77)	N/A
C3D1	128	63.9 (17.91)	67	57.9 (19.36)	N/A
C4D1	129	64.1 (18.27)	60	55.2 (18.13)	N/A
C5D1	125	62.3 (18.33)	64	56.8 (18.30)	N/A
C6D1	129	63.8 (18.60)	62	54.3 (18.94)	N/A
C7D1	127	63.8 (18.73)	62	56.1 (19.91)	N/A

Abbreviations: C, cycle; CI, confidence interval; D, day; EQ-5D-5L, EuroQoL Five-Dimension Five-Level; HRQoL, health-related quality of life; ITT, intention-to-treat; N/A, not available; SD, standard deviation; VAS, visual analogue scale.

10.2 Health state utility values (HSUVs) used in the health economic model

The utility calculations were based on all patients enrolled in Part 2 of the PIONEER trial. The collected EQ-5D-5L responses were pooled from the avapritinib (122 patients) and placebo (60 patients). As mentioned above, the analysis included all completed questionnaires that were correctly filled out by patients and had corresponding TSS severity score data available at the time of completion (N=2,685).

10.2.1 HSUV calculation

EQ-5D-5L with Danish preference weights were used to generate the utilities (74). A linear regression model approach was used to calculate utility values, using the lm() function in R. The regression outputs are presented in Table 30.

Table 30: Utility regression outputs

Effect	Estimate	Standard error	T value
Intercept (mild)	0.853	0.006828	124.979
Moderate	-0.105	0.010947	-9.571
Severe	-0.273	0.010235	-26.684

The health state utilities are calculated based on disease severity, where the intercept gives the utility for mild disease, and the coefficients gives the change in utility values in moderate and severe disease, respectively.

$$Utility = \beta_0 + \beta_1 \times Moderate + \beta_2 \times Severe$$

Since the obtained Danish utility value of mild ISM was slightly higher than expected in general population, a base case assumption was selected with the mild health state equating the age specific general population value in Denmark (75), i.e. the value 0.839. The unadjusted utility value for mild disease is explored in the scenario analysis.

Based on the definition of the mild, moderate and severe health states it is possible for patients to respond to treatment but not change health states. However, a drop in symptoms by 30% would likely lead to an increase in the HRQoL experienced by a patient. As such the base case analysis allows for a proportion of patients to experience an improvement in their health state utility if they have responded and not changed health states. In the base case it is assumed 10% of patients who are in the moderate and severe health states after cycle 6 are responders, and their utility is increased by 5%.

The utility values are applied for each cycle spent in each health and disease severity state and quality-adjusted life years (QALYs) are calculated by multiplying the time patients spent in each disease severity category by the utility value associated with that category.

10.2.1.1 Mapping

No utilities were derived from mapping.

10.2.2 Disutility calculation

Disutilities are included in the model but as they are derived from the literature, they are presented in section 10.3.4.

10.2.3 HSUV results

The utility values for the moderate and severe health states were derived using the linear regression analysis described above in section 10.2.1. The mild health state was set to align with the age-specific utility value of the general population in Denmark (75).

Table 31 Overview of health state utility values [and disutilities]

	Results [SE]	Number of observations	Instrument	Tariff (value set) used	Comments
HSUVs base case, adjusted for age based on Danish general population					
Mild	0.839 [N/A]	1,101	EQ-5D-5L	DK	Age specific general population value in Denmark (75)
Moderate	0.734 [N/A]	701	EQ-5D-5L	DK	Estimate from linear regression model, both trial arms pooled.
Severe	0.566 [N/A]	883	EQ-5D-5L	DK	Estimate from linear regression model, both trial arms pooled.
HSUV scenario, unadjusted for age based on Danish general population					
Mild	0.853 [0.004]	1,101	EQ-5D-5L	DK	Estimate from linear regression model, both trial arms pooled.
Moderate	0.749 [0.008]	701	EQ-5D-5L	DK	Estimate from linear regression model, both trial arms pooled.
Severe	0.580 [0.010]	883	EQ-5D-5L	DK	Estimate from linear regression model, both trial arms pooled.

Abbreviations: DK, danish kroner; HSUVs, health state utility values; N/A, not applicable; SE, standard error.

10.3 Health state utility values measured in other trials than the clinical trials forming the basis for relative efficacy

In the PIONEER trial EQ-5D data was not collected for SSM and AdvSM. Therefore, a TLR was conducted to inform the model, which is reported in detail in Appendix I. Based on the findings of the TLR, one citation (i.e., PATHFINDER) was used inform the HSUV associated with AdvSM. Specifically, the HSUV associated with AdvSM was informed by the post-progression HSUV for first-line treatment from the PATHFINDER trial.

No published studies were identified that provided utility estimates for the SSM health state. Given that there was no alternative source to obtain an estimate, the middle point between the HSUV associated with severe disease (i.e., 0.532) and the HSUV associated with AdvSM (i.e., 0.531), was used as a proxy to inform the utility associated with SSM (i.e. 0.531), calculated using Dutch tariffs. This assumption was endorsed as a second-best approach by clinical experts during the Dutch advisory board meeting on July 1st, 2024. The experts concluded that the impact of the SSM health state on patient quality of life is at least comparable to that of the ISM severe health state, but less severe than the impact associated with the advanced SM health state.

The disutility values associated with AEs were derived from published sources and informed by previous submissions to NICE as informed by the TLR.

For study design of the PATHFINDER trial refer to below.

10.3.1 Study design

QoL in PATHFINDER were measured by means of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (QLQ-C30- Questionnaire). The EORTC QLQ-C30 questionnaire is a commonly used instrument for the measurement of QoL. It assesses a patient's perception of disease symptoms at a point in time. The EORTC QLQ-C30 has been widely used to evaluate a patient's overall sense of whether a treatment has been beneficial. The data included from PATHFINDER represent patients who received avapritinib for AdvSM 1L treatment.

A mapping algorithm published by Hagiwara et al. (76) was used to convert QLQ-C30 scores into EQ-5D-5L values, which were subsequently transformed into health utility values using the Dutch tariff.

10.3.2 Data collection

Details on data collection are not available for the HSUV derived from the literature.

10.3.3 HRQoL Results

Details on HRQoL results are not available for the HSUV derived from the literature.

10.3.4 HSUV and disutility results

The utility value for the SSM health state informed by the Dutch Advisory Board is reported Table 32. Both the utility value for AdvSM and the associated disutilities are summarised in Table 33.

Table 32 Overview of health state utility values [and disutilities]

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
SSM	0.531	EQ-5D-5L	DK	EQ-5D-5L was informed by a Dutch Advisory Board convened on July 1st, 2024. Estimate based on the middle point between the utility estimate associated with the severe disease health state (i.e., 0.532) and the HSUV associated with AdvSM (i.e., 0.531).

Abbreviations: CI, confidence interval; DK, danish kroner; EQ-5D-5L, EuroQoL Five-Dimension Five-Level; SSM, smouldering systemic mastocytosis.

Table 33 Overview of literature-based health state utility values [and disutilites]

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
AdvSM	0.530 [N/A]	EQ-5D-5L	NL	EQ-5D-5L data was collected in PATHFINDER trial. Estimate is based on mean of both trial arms.
Disutilities				
Headache	0.027	EQ-5D	UK	Source: Sullivan PW et al. (49). Assumed duration of 14 days
Nausea	0.136	EQ-5D	UK	Source: Araújo et al. (50) Assumed duration of 14 days
Oedema peripheral	0.124	EQ-5D	UK	Assumed disutility for oedema derived from NICE TA250 (51). Assumed duration of 14 days
Periorbital oedema	0.124	EQ-5D	UK	Assumed disutility for oedema derived from NICE TA250 (51). Assumed duration of 14 days
Fatigue	0.115	EQ-5D	UK	Source: Lloyd et al. (52). Assumed duration of 14 days

Flushing	0.067	EQ-5D	UK	Source: Sullivan PW et al. (49). Assumed duration of 14 days
Alopecia	0.040	N/A	N/A	Source: NICE TA124 (53). Assumed duration of 14 days
Blood alkaline phosphatase increased	0.090	EQ-5D	UK	Source: NICE TA10924 (54). Assumed duration of 14 days
Eyelid oedema	0.124	EQ-5D	UK	Assumed disutility for oedema derived from NICE TA250 (51). Assumed duration of 14 days
Face oedema	0.124	EQ-5D	UK	Assumed disutility for oedema derived from NICE TA250 (51). Assumed duration of 14 days
Aspartate aminotransferase increased	0.090	EQ-5D	UK	Source: NICE TA10924 (54). Assumed duration of 14 days
Diarrhoea	0.126	EQ-5D	UK	Source: Araújo et al. (50) Assumed duration of 14 days
Dizziness	0.120	EQ-5D	UK	Source: NICE CG173 (55) Assumed duration of 14 days
Hair colour changes	0.067	EQ-5D	UK	Source: Sullivan PW et al. (49). Assumed duration of 14 days
Alanine aminotransferase increased	0.090	EQ-5D	UK	Source: NICE TA10924 (54). Assumed duration of 14 days
Blood lactate dehydrogenase increased	0.090	EQ-5D	UK	Source: NICE TA10924 (54). Assumed duration of 14 days
Muscle spasms	0.070			Source: Farkouh et al. (56) (based on dykinesia for parkinsons) Assumed duration of 14 days
Anaphylaxis without complications	0.090	N/A	US	Shaker et al. (57) (based on disutility resulting from a severe allergic reaction) Assumed duration of 14 days
Anaphylaxis with complications	0.180			Assumed double anaphylaxis without complications Assumed duration of 14 days

Abbreviations: AdvSM, advanced systemic mastocytosis; CI, confidence interval; EQ-5D-5L, EuroQoL Five-Dimension Five-Level; N/A, not applicable; NL, Netherland; UK, United Kingdom.

11. Resource use and associated costs

Resource use and costs were chosen to reflect the expected key cost components related to the treatment, the management and monitoring of mild, moderate and severe ISM patients. The model includes direct medical costs, as well as patient and transportation cost, consistent with the restricted societal perspective as described in the DMC guidelines (40). All costs were valued in 2025 Danish Krone (DKK). When 2025 prices were unavailable, prices were adjusted to 2025 price levels using the consumer price index without energy from Statistics Denmark (77).

11.1 Medicines - intervention and comparator

The medicines used in the model are presented in Table 34.

Table 34 Medicines used in the model

Medicine	Dose	Relative dose intensity / % of patients using	Frequency	Vial sharing
Avapritinib	25 mg	100%	Once daily	No
BSC				
Desloratadine	5 mg	25%*	Once daily	No
Fexofenadine	180 mg	25%*	Once daily	No
Levocetirizine	5 mg	25%*	Once daily	No
Hydroxyzine	25 mg	25%*	Once daily	No
Omeprazole	20 mg	40%	Once daily	No
Omalizumab	150 mg	5%	Every four weeks	No

Abbreviations: BSC, best supportive care.

Note: *It is assumed that 100% of the patients on BSC receives a H1-blocker, evenly distributed over the four available H1-blockers in Denmark: desloratidine, fexofenadine, levocetrizine, hydroxizine.

Avapritinib

Avapritinib is an oral therapy provided as tablets containing 300, 200, 100, 50, or 25 mg, all with the same list price of 211,200 DKK per pack of 30 tablets, informed by Medicinpriser.dk (78). The dosing regimen of avapritinib is 25 mg once daily and is aligned with the recommended dose of avapritinib for ISM and the PIONEER trial (1, 44).

Best supportive care (BSC)

BSC consists of H1-blockers, proton-pump inhibitor (omeprazole), leukotriene inhibitor (montelukast), corticosteroid (prednisolone), and monoclonal anti IgE inhibitor (omalizumab).

The proportion of patients receiving each therapy was taken from Swedish expert opinion, adjusted with availability of the specific treatments in Denmark in Table 34. The acquisition cost of BSC is presented in Table 35. The dosing regimen of BSC is based on Medicin.dk (79), and reported in Section 3.

Table 35 Pack prices for best supportive care (BSC)

Medicine	Strength	Units per pack	AIP (DKK)	Nordic number
Desloratadine	5 mg	100	240.00	116009
Fexofenadine	180 mg	100	51.75	511322
Levocetirizine	5 mg	30	49.00	537454
Hydroxyzine	25 mg	100	20.80	085609
Omeprazole	20 mg	100	16.45	585692
Omalizumab	150 mg / 1 ml	1	1,937.53	385816

Abbreviations: AIP, Apotekets inkøbspris; BSC, best supportive care; DKK, Danish kroner.

Source: Medicinpriser.dk(78).

11.2 Medicines– co-administration

Not applicable.

11.3 Administration costs

The cost of administration was derived from the DRG tariff system (80). Oral administration was assumed to not incur any cost. For subcutaneous administration a cost were only applied for the first administration, as it was assumed that the patient could learn to self-administrate at the first visit. Cost per administration for each pharmaceutical is presented in Table 36. All treatments included in the model are administered orally, except for omalizumab, which is given subcutaneously. The administration cost of omalizumab is applied to both arms equally and has therefore no impact on the results.

Table 36 Administration costs used in the model

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference

Subcutaneous	One-off in first model cycle	2,136.00	17MA98	DRG 2025, IV infusion (80)

Abbreviations: DKK, Danish kroner; DRG, diagnosis related group; IV, intravenous.

11.4 Disease management costs

Disease management resource use as well as disease monitoring diagnostic tests were estimated with the support of a Nordic clinical expert, through validation and adaptation of estimates to the Danish setting from a global cost-effectiveness analysis in a UK setting. The selection of resources is based on disease severity in non-responders in the PIONEER trial. The frequency of use is sourced from relevant literature. It is assumed that resource use is reduced by 50% for responders on avapritinib.

Patients within different disease health states (responder, non-responder) and TSS health states (mild, moderate, severe) are expected to utilize different amounts of healthcare resources. To reflect this variation, the resource use frequencies applied in the model are adjusted accordingly.

Example: Patients experiencing gastrointestinal symptoms are assumed to require one outpatient consultation every 12 weeks (Table 37), equivalent to 0.33 consultations per model cycle (Table 37). 77% of non-responders with mild disease are expected to experience any symptom. Health state-specific resource use frequencies are calculated by multiplying the proportion of symptomatic non-responders by the unadjusted resource use frequency (i.e. $\mathbf{0.33 * 0.77 = 0.26}$ $\boldsymbol{outpatient\ visits\ per\ model\ cycle}$ for non-responders with mild disease).

The resource use for responders is assumed to be half that of the amount required by non-responders with a multiplier of 0.5 is applied. This information is used to calculate the cost of care per cycle for each health state (mild, moderate, or severe) for responders and non-responders.

The average percentage of patients experiencing any symptoms, which are used in the calculation of the health state-specific resource use frequencies applied in the health economic model are presented per health state in Table 24. All adjusted model inputs are detailed in Table 89, Appendix K. The unadjusted resource use frequencies, which are applicable for the subset of the population experiencing a specific event are presented in Table 37 and Table 38 below.

Table 37 Disease management activities and costs used in the model

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
Gastrointestinal domain: outpatient consultation	Every third months	1,073.70[1]	N/A	Frequency: NICE TA708 [Digestive tract conditions] (61) Cost: Værdisætning af enhedsomkostninger version

				1.8, Ledende overlæger/ professorer, hourly rate (81)
Skin domain: Dermatology outpatient consultation	Every second months	1,073.70[1]	N/A	Frequency: NICE TA534 [Eczema] (62) Cost: Værdisætning af enhedsomkostninger version 1.8, Ledende overlæger/ professorer, hourly rate (81)
Skin domain: Dermatologist nurse visit	Approximately every second years	470.64[1]	N/A	Frequency: NICE TA534 [Eczema] (62) Cost: Værdisætning af enhedsomkostninger version 1.8, Sygeplejersker, hourly rate (81)
Neurologic domain: outpatient consultation	Approximately every fifth week	1,073.70[1]	N/A	Frequency: NICE TA753 [Epilepsy] (63) Cost: Værdisætning af enhedsomkostninger version 1.8, Ledende overlæger/ professorer, hourly rate (81)
Accident & Emergency visit	Approximately every 11 years	2,012.00	01MA98	Frequency: NICE TA534 [Eczema] (62) Cost: DRG 2025 (80)
Hospitalization	Approximately every 8 years	2,926.64	17MA04	Frequency: NICE TA534 [Eczema] (62) Cost: DRG 2025 (80)
Daycase admission	Approximately every 5 years	2,012.00	01MA98	Frequency: NICE TA534 [Eczema] (62) Cost: DRG 2025 (80)
Anaphylaxis without complications	Approximately twice yearly	5,193.00	21MA01	Frequency: PRISM study, data on file (59) Cost: DRG 2025 (80)
Anaphylaxis with complications	Approximately twice yearly	13,784.00	21MA05	Frequency: PRISM study, data on file (59) Cost: DRG 2025 (80)
EpiPen use	Once yearly	346.00	N/A	Frequency: Assumption Cost: Medicinpriser.dk, EpiPen (VNR 520068) (78)

Abbreviations: DKK, Danish kroner; DRG, diagnosis related group; N/A, not applicable.
Note: [1] Price is adjusted to 2025 price levels using the consumer price index from Statistics Denmark (77).

Table 38 Disease monitoring diagnostic tests and costs used in the model

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
Bone marrow biopsy	Approximately every 10 weeks	16,156.00	17PR01	Frequency: NICE TA883 [Blood and bone marrow cancer - B-cell lymphoma] (64) Cost: DRG 2025 (80)
ECG	Twice yearly	2,136.00	17MA98	Frequency: Assumed same as CT scan Cost: DRG 2025 (80)
Haematology visit	Four visits every year	1,073.70[1]	N/A	Frequency: NICE TA838 [Blood condition – distal renal tubular acidosis] (65) Cost: Værdisætning af enhedsomkostninger version 1.8, Ledende overlæger/professorer, hourly rate (81)
Biochemistry test: renal - Urine test	4 visits every year	30.60	N/A	Frequency: NICE TA838 [Blood condition – distal renal tubular acidosis] (65) Cost: Takstkort 29A Laboratorieundersøgelser, Urin, steril (82)
Coagulation test	Approximately every 10 weeks	61.00	N/A	Frequency: NICE TA883 [Blood and bone marrow cancer - B-cell lymphoma] (64) Cost: Rigshospitalets Labportal, FIB (83)
Serum chemistry tests	Approximately every 10 weeks	22.95	N/A	Frequency: NICE TA883 [Blood and bone marrow cancer - B-cell lymphoma] (64) Cost: Takstkort 29A Laboratorieundersøgelser, Blod (82)
Photography	Approximately every 17 years	2,136.00	17MA98	Frequency: NICE TA814 [Eczema] (66) Cost: DRG 2025 (80)

CT scan	Twice yearly	2,701.00	30PR06	Frequency: NICE TA838 [Blood condition – distal renal tubular acidosis] (65) Cost: DRG 2025 (80)
Chest X-ray	Once yearly	1,731.00	30PR18	Frequency: Assumed to be same as ultrasound Cost: DRG 2025 (80)
Ultrasound scan	Once yearly	2,136.00	17MA98	Frequency: NICE TA838 [Blood condition – distal renal tubular acidosis] (65) Cost: DRG 2025 (80)
MRI scan	Twice yearly	2,603.00	30PR02	Frequency: Assumed same as CT scan Cost: DRG 2025 (80)
Full blood count	Four times every year	22.95	N/A	Frequency: NICE TA814 [Eczema] (66) Cost: Takstkort 29A Laboratorieundersøgelser, Blod (82)
Bone densitometry	Every second year	1,811.00	30PR07	Frequency: NICE TA838 [Blood condition – distal renal tubular acidosis] (65) Cost: DRG 2025 (80)

Abbreviations: CT, computed tomography; DKK, Danish kroner; DRG, diagnosis-related group; N/A, not applicable.
Note: [1] Price is adjusted to 2025 price levels using the consumer price index from Statistics Denmark.(77)

Costs associated with SSM and AdvSM

For each subsequent cycle in SSM and AdvSM there are additional resource use and monitoring costs. For both resource use and monitoring costs are assumed to be equal to the severe ISM health state (i.e., 18,788 DKK).

11.5 Costs associated with management of adverse events

The costing codes and unit costs associated with the management of AEs included within the CEM were sourced from interaktiv.drg (84) and DRG-takster (80). The cost of managing AEs was applied once during the first model cycle, as described in section 9.1. The costs associated with the management of each AE were multiple by the frequency reported in Table 24. The costs of treating AEs are summarised in Table 39.

Table 39 Cost associated with management of adverse events

	DRG code	Unit cost (DKK)/DRG tariff (84)
Headache	DRG: 23MA03 (DR519/DQ822)	5,271.00
Nausea	DRG: 06MA11 (DR119B/DQ822)	4,977.00
Oedema peripheral	DRG: 23MA03 (DR600/DQ822)	5,271.00
Periorbital oedema	DRG: 23MA03 (DR600/DQ822)	5,271.00
Fatigue	DRG: 23MA03 (DR539C/DQ822)	5,271.00
Flushing	DRG: 23MA03 (DR232/DQ822)	5,271.00
Alopecia	DRG: 09MA98 (DL631/DQ822)	1,578.00
Blood alkaline phosphatase increased	DRG: 07MA98 (DR748B/DQ822)	2,072.00
Contusion	DRG: 09MA98 (DT140B/DQ822)	1,578.00
Eyelid oedema	DRG: 23MA03 (DR600/DQ822)	5,271.00
Face oedema	DRG: 23MA03 (DR600/DQ822)	5,271.00
Aspartate aminotransferase increased	DRG: 07MA98 (DR748/DQ822)	2,072.00
Diarrhoea	DRG: 06MA11 (DK529B/DQ822)	4,977.00
Dizziness	DRG 03MA02, Svimmelhed	8,274.00
Hair colour changes	DRG: 09MA98 (DL671/DQ822)	1,578.00
Photosensitivity reaction	DRG: 09MA98 (DL561/DQ822)	1,578.00

Alanine aminotransferase increased	DRG: 07MA98 (DR748/DQ822)	2,072.00
Blood lactate dehydrogenase increased	DRG: 07MA98 (DR748/DQ822)	2,072.00
Dry mouth	DRG: 03MA09 (DR682/DQ822)	1,286.00
Muscle spasms	DRG: 08MA17 (DR252C/DQ822)	2,267.00
Anaphylaxis without complications	DRG: 21MA01 (DT782/DQ822)	5,193.00
Anaphylaxis with complications	DRG: 21MA01 (DT782/DQ822)	5,193.00

Abbreviations: DKK, Danish kroner; DRG, diagnosis related group.

11.6 Subsequent treatment costs

N/A

Table 40 Medicines of subsequent treatments

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
[Name of the intervention]	N/A	N/A	N/A	N/A

11.7 Patient costs

Patient costs were calculated for three types of healthcare activities based on the activities detailed in Table 37: planned visits (i.e. outpatient visits), unplanned visits (i.e. accident and emergency visits), and unplanned inpatient visits (i.e. hospitalisation). For each activity type, costs were estimated by multiplying the assumed time spent (in hours, Table 41) by an hourly rate of DKK 191.50, to which a fixed transportation cost of DKK 142.60 was added. Patient costs were estimated based on the DMC's catalogue of unit costs.(81)

As described in Section 11.4, patients within different disease and TSS health states are expected to utilize different amounts of healthcare resources and thus incur different costs. Therefore, the patient costs applied in the model are adjusted by applying the same logic as presented in Section 11.4.

Example: Non-responders with mild disease are expected to use 0.26 gastrointestinal outpatient consultations, 0.36 dermatology outpatient consultations, 0.03 dermatology nurse visits and 0.66 neurologic outpatient consultations per model cycle. Health state-specific resource use frequencies are calculated by summing these frequencies (i.e. **0.26** +

$0.36 + 0.03 + 0.66 = 1.31$ *planned visits per model cycle* for non-responders with mild disease).

Table 41 Patient costs used in the model

Activity	Time spent [minutes, hours, days]
Planned visit	0.5 hours
Unplanned visit	2.0 hours
Unplanned inpatient visit	16.0 hours

11.8 Other costs (e.g. costs for home care nurses, out-patient rehabilitation and palliative care cost)

Palliative care costs were assumed to be similar for the treatment arms and were thus excluded from the model.

12. Results

12.1 Base case overview

The base case overview is presented in Table 42 with the results of the base case presented in Table 43.

Table 42 Base case overview

Feature	Description
Comparator	BSC
Type of model	Markov model
Time horizon	49 years (lifetime)
Treatment line	1st line. Subsequent treatment lines not included.
Measurement and valuation of health effects	Health-related quality of life measured with EQ-5D-5L in the PIONEER trial (44). Danish population weights were used to estimate health-state utility values (85). Hvidberg et al. (75) provided the basis for the mild HSUV.
Costs included	Drug acquisition costs Drug administration costs

	Disease monitoring costs Costs associated with management of adverse events Patient and transportation costs
Dosage of medicine	Fixed dosage of avapritinib (25 mg)
Average time on treatment	Avapritinib 2.65 years (summary estimate of initial treatment period and maintenance period) BSC is given to all patients in all stages in both arms
Treatment duration	Avapritinib: 5 years for responders
Mortality	General population mortality for mild, moderate and severe disease states (86). Mortality rate ratio 5.5 for SSM and AdvSM (70).
Inclusion of waste	No
Average time in model health state (undiscounted, no HCC)	
Mild	Avapritinib: [redacted] / BSC: [redacted]
Moderate	Avapritinib: [redacted] / BSC: [redacted]
Severe	Avapritinib: [redacted] / BSC: [redacted]
SSM	Avapritinib: [redacted] / BSC: [redacted]
AdvSM	Avapritinib: [redacted] / BSC: [redacted]

Abbreviations: AdvSM, advanced systemic mastocytosis; BSC, best supportive care; EQ-5D-5L, EuroQoL Five-Dimension Five-Level; HCC, half-cycle correction; SSM, smouldering systemic mastocytosis.

12.1.1 Base case results

Table 43 present the discounted base-case results for treatment of ISM with avapritinib plus BSC versus BSC. The comparison indicates a net QALY gain of 0.482 at an incremental cost of [redacted] Results suggest that avapritinib plus BSC is more effective but also more costly compared to BCS, with [redacted] per QALY.

Table 43 Base case results, discounted estimates (discounted)

	Avapritinib	BSC	Difference
Medicine costs	[redacted]	35,438	[redacted]
Administration	2,136	2,136	0
Disease management costs*	2,176,939	2,893,531	-716,592

Cost associated with management of adverse events	4,361	4,919	-558
Patient costs	174,223	231,573	-57,350
Total costs	[redacted]	**3,167,596**	[redacted]
Life years gained (Mild)	2.892	1.094	1.798
Life years gained (Moderate)	4.841	5.279	-0.438
Life years gained (Severe)	9.532	10.654	-1.121
Life years gained (SSM)	0.341	0.390	-0.049
Life years gained (AdvSM)	0.731	0.844	-0.113
Total life years	**18.337**	**18.261**	**0.077**
QALYs (Mild)	2.366	0.887	1.479
QALYs (Moderate)	3.415	3.725	-0.310
QALYs (Severe)	5.134	5.742	-0.608
QALYs (SSM)	0.222	0.254	-0.032
QALYs (AdvSM)	0.434	0.502	-0.068
QALYs (adverse reactions)	0.004	0.004	0.000
Total QALYs	**11.833**	**11.351**	**0.482**
Incremental costs per life year gained	[redacted]		
Incremental cost per QALY gained (ICER)	[redacted]		

Abbreviations: AdvSM, advanced systemic mastocytosis; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; SSM, smouldering systemic mastocytosis; QALY, quality-adjusted life year.
Note:*Including monitoring cost for SSM and AdvSM.

12.2 Sensitivity analyses

12.2.1 Deterministic sensitivity analyses

A one-way sensitivity analysis (OWSA) was performed to identify key model drivers based on their relative influence on results. Parameters were varied one at a time between their upper and lower 95% confidence intervals, which were determined using SEs when available or using SEs estimated based on ±20% variation around the mean where measures of variance around the base case values were not available. Pairwise one-way sensitivity analyses were performed separately for each arm and are reported for the 10 most influential parameters on the ICER. OWSA results for avapritinib in addition to BSC and BSC are presented in [redacted] and Table 44. The OWSA showed that the parameters with the greatest influence on the ICER were the utilities for during mild disease.

Table 44 One-way sensitivity analyses results

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case			[redacted]	**0.482**	[redacted]
Lower bound					
Utilities Mild	0.644	Parameter uncertainty	[redacted]	0.130	[redacted]
Utilities Severe	0.454	Parameter uncertainty	[redacted]	0.607	[redacted]
Utilities Moderate	0.579	Parameter uncertainty	[redacted]	0.549	[redacted]
From Severe to AdvSM	0.000	Parameter uncertainty	[redacted]	0.468	[redacted]
Treatment waning (cycles)	4.000	Parameter uncertainty	[redacted]	0.472	[redacted]
Utilities AdvSM	0.425	Parameter uncertainty	[redacted]	0.494	[redacted]
From Severe to SSM	0.000	Parameter uncertainty	[redacted]	0.474	[redacted]
Responders that do not move health state	0.064	Parameter uncertainty	[redacted]	0.476	[redacted]
Adjust utility for response	0.033	Parameter uncertainty	[redacted]	0.476	[redacted]

Average ToT (Responders)	[redacted]	Parameter uncertainty	[redacted]	0.327	[redacted]
Upper bound					
Utilities Mild	0.964	Parameter uncertainty	[redacted]	0.709	[redacted]
Utilities Severe	0.675	Parameter uncertainty	[redacted]	0.360	[redacted]
Utilities Moderate	0.864	Parameter uncertainty	[redacted]	0.425	[redacted]
From Severe to AdvSM	0.001	Parameter uncertainty	[redacted]	0.498	[redacted]
Treatment waning (cycles)	9.000	Parameter uncertainty	[redacted]	0.497	[redacted]
Utilities AdvSM	0.663	Parameter uncertainty	[redacted]	0.470	[redacted]
From Severe to SSM	0.000	Parameter uncertainty	[redacted]	0.491	[redacted]
Responders that do not move health state	0.142	Parameter uncertainty	[redacted]	0.489	[redacted]
Adjust utility for response	0.072	Parameter uncertainty	[redacted]	0.498	[redacted]
Average ToT (Responders)	[redacted]	Parameter uncertainty	[redacted]	0.690	[redacted]

Abbreviations: AdvSM, advanced systemic mastocytosis; BSC, best supportive care; DK, Danish kroner; ICER, incremental cost-effectiveness ratio; SSM, smouldering systemic mastocytosis; ToT, time on treatment; QALY, quality-adjusted life year.

Figure 15 One way sensitivity analyses – tornado diagram

12.2.1.1 Scenario analysis

Scenario analyses were performed to test the impact of change in key inputs and assumptions on the CE estimates. Table 45 lists scenarios conducted around the base case analysis presented above. These scenarios included alternative discount rates, time horizons, treatment duration and other assumptions. The highest impact on the ICER was observed applying a [redacted]

Table 45 Scenario analyses

Scenario	Incremental cost	Incremental benefit (QALYs)	ICER
Base case	[redacted]	**0.482**	[redacted]
[redacted]	[redacted]	0.482	[redacted]
Discount rate - Costs: 0%, QALYs: 0%	[redacted]	0.583	[redacted]
Discount rate - Costs: 0%, QALYs: 6%	[redacted]	0.438	[redacted]
Discount rate - Costs: 6%, QALYs: 6%	[redacted]	0.438	[redacted]
Discount rate - Costs: 6%, QALYs: 0%	[redacted]	0.583	[redacted]
Time horizon: 5 years	[redacted]	0.406	[redacted]
Time horizon: 10 years	[redacted]	0.431	[redacted]
Time horizon: 20 years	[redacted]	0.451	[redacted]
Time horizon: 30 years	[redacted]	0.471	[redacted]
Time horizon: 40 years	[redacted]	0.481	[redacted]
No treatment stopping	[redacted]	2.057	[redacted]
Treatment discontinuation: After 2 years	[redacted]	0.482	[redacted]
Treatment discontinuation: After 5 years	[redacted]	0.482	[redacted]
Treatment discontinuation: After 10 years	[redacted]	0.925	[redacted]

No age-adjusted utilities	[redacted]	0.484	[redacted]
RUs are equal for responders and non-responders	[redacted]	0.482	[redacted]
Background therapy is equal for responders and non-responders	[redacted]	0.482	[redacted]
Reduction of background therapy for responders: 20%	[redacted]	0.482	[redacted]
Reduction of background therapy for responders: 80%	[redacted]	0.482	[redacted]
Expected advanced disease cost	[redacted]	0.482	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year.

12.2.2 Probabilistic sensitivity analyses

The variables included in the PSA are listed in the "PSA inputs" sheet in the model. From this sheet, the variables to include/exclude from the analysis and which distribution to select for each parameter can be set. For values not empirically estimated, an arbitrary uncertainty of +/- 20% was applied. The probabilistic base case as well as the convergence plot for the estimated mean were run with 5,000.

For event rates and utilities, a beta distribution is used to restrict draws to the 0-1 space for probabilities such as the progression to SSM or AdvSM. For costs and resource use estimates, a gamma distribution is fitted to prevent values less than zero. For correlated parameters, such as the parameters defining the utility values per disease severity category, a Cholesky decomposition of the variance-covariance matrix is used in order to capture the joint uncertainty. For the health state distributions, a Dirichlet distribution is applied so that they vary in relation to each other. The assumption of 20% variance is used the distribution.

The probabilistic results [redacted] align well with the deterministic results [redacted] The scatterplot of all the PSA iterations is presented in [redacted], while [redacted] while presents the cost-effectiveness acceptability curves (CEAC). The scatter plot confirms that avapritinib in addition to BSC is associated with higher QALYs but also incurs greater total costs compared to BSC. [redacted]

Figure 16 Cost-effectiveness scatterplot

Figure 17 Cost-effectiveness acceptability curve

Figure 18 Convergence plot

13. Budget impact analysis

The budget impact model was developed to estimate the expected financial impact of recommending avapritinib for the treatment of adult patients with ISM with moderate to severe symptoms inadequately controlled on symptomatic treatment in Denmark. This analysis is integrated within the cost-effectiveness model, meaning that any changes to the cost per patient model settings will directly influence the budget impact results. The budget impact result is representative of the populations in the cost per patient model. Thes costs included in the budget impact model are undiscounted, and patient cost and transportation cost have not been included as per the guidelines by the DMC (40).

The analysis compares the budgetary consequences of a scenario where avapritinib is recommended against the scenario where avapritinib is NOT recommended.

Number of patients (including assumptions of market share)

Number of patients are based on Table 2. As described in Section 3, it is assumed that approximately 141 patients receive treatment for ISM. Of these, in case avapritinib will be introduced, 10% will receive avapritinib the first year. Informed by experience from more mature markets such as Germany, the share is assumed to grow up to approximately 50% in year 2 to 5 (Table 46).

Table 46 Number of new patients expected to be treated over the next five-year period if the medicine is introduced (adjusted for market share)

	Year 1	Year 2	Year 3	Year 4	Year 5
			Recommendation		
Avapritinib	14	29	45	62	79

BSC	127	118	108	97	86
			No recommendation		
Avapritinib	0	0	0	0	0
BSC	141	147	153	159	165

Abbreviations: BSC, best supportive care.

Budget impact

Budget impact was calculated based on the expected number of patients. Budget impact is presented in Table 47.

Table 47 Expected budget impact of recommending the medicine for the indication

	Year 1 [DKK]	Year 2 [DKK]	Year 3 [DKK]	Year 4 [DKK]	Year 5 [DKK]
Avapritinib is recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Avapritinib is NOT recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact of the recommendation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DKK, Danish kroner.

14. List of experts

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Appendix A. Main characteristics of studies included

Table 48 Main characteristic of studies included

Trial name: PIONEER	NCT number: NCT03731260
Objective	To assess the efficacy and safety of avapritinib vs placebo in patients with ISM who have moderate to severe symptoms inadequately controlled on symptomatic treatment.
Publications – title, author, journal, year	Gotlib J, Castells M, Elberink HO, et al. Avapritinib versus Placebo in Indolent Systemic Mastocytosis. NEJM Evidence 2023; 2(6): EVIDoa2200339. (46) Castells M, Gotlib J, Giannetti M, et al. Efficacy and Safety of Avapritinib in Indolent Systemic Mastocytosis: Results From the Double Blinded Placebo-Controlled PIONEER Study. Eastern Allergy Conference (EAC); 2023. (68) Gotlib J, Castells M, Oude Elberink H, et al. Reductions in indolent systemic mastocytosis biomarker burden with avapritinib in the registrational, double-blind placebo-controlled PIONEER trial. European Hematology Association Annual Meeting. Frankfurt; 2023. (69)
Study type and design	This is a Phase 2, randomized, double-blind, placebo-controlled study comparing the efficacy and safety of avapritinib + best supportive care (BSC) with placebo + BSC in patients with indolent systemic mastocytosis (ISM) whose symptoms are not adequately controlled by BSC. The study will be conducted in 3 parts. All patients will receive treatment with avapritinib during Part 3 including those rolling over from the placebo group.
Sample size (n)	Part 2 (ITT population): avapritinib = 141, placebo = 71 Part 3 (PP population): avapritinib = 150
Main inclusion criteria	• Patient must have SM, confirmed by Central Pathology Review of BM biopsy, and central review of B- and C-findings by WHO diagnostic criteria. • Patient must have moderate-to-severe symptoms based on minimum mean total symptom score (TSS) of the ISM Symptom Assessment Form (ISM-SAF) over the 14-day eligibility screening period. • Patient must have failed to achieve adequate symptom control for 1 or more Baseline symptoms. • For patients receiving corticosteroids, the dose must be ≤ 20 mg/d prednisone or equivalent, and the dose must be stable for ≥ 14 days. • Patient must have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 2.

Main exclusion criteria	• Patient has been diagnosed with any of the following WHO SM subclassifications: cutaneous mastocytosis only, smoldering SM, SM with associated hematologic neoplasm, aggressive SM, mast cell leukemia, or mast cell sarcoma. • Patient must not have received prior treatment with avapritinib. • Patient must not have had any cytoreductive therapy including but not limited to masitinib and midostaurin, or investigational agent for < 14 days or 5 half-lives of the drug (whichever is longer), and for cladribine, interferon alpha, pegylated interferon, or antibody therapy < 28 days or 5 half-lives of the drug (whichever is longer), before beginning the 14-day ISM-SAF eligibility TSS assessment. • Patient must not have received radiotherapy or psoralen and ultraviolet A (PUVA) therapy < 14 days before beginning the 14-day ISM-SAF eligibility TSS assessment. • Patient must not have received any hematopoietic growth factor the preceding 14 days before beginning the 14-day ISM-SAF eligibility TSS assessment. • Patient must not have a QT interval corrected using Fridericia's formula (QTcF) of > 480 msec
Intervention	Avapritinib 25mg daily
Comparator(s)	Placebo
Follow-up time	Part 2: 24 weeks of treatment. Part 3: 2.5 years of treatment (maximum follow-up of 5 years).
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** • Mean change in TSS of the ISM-SAF, from baseline to C7D1 • Proportion of patients with a ≥50% reduction in serum tryptase from baseline to C7D1 • Proportion of patients with a ≥50% reduction in peripheral blood KIT D816V allele fraction from baseline to C7D1 or undetectable (<0.02%) for patients with detectable mutation at baseline • Proportion of patients with a ≥50% reduction in ISM-SAF TSS from baseline to C7D1 • Proportion of patients with a ≥30% reduction in ISM-SAF TSS from baseline to C7D1

	• Proportion of patients with a ≥50% reduction in bone marrow mast cells from baseline to C7D1 or no aggregates for patients with aggregates at baseline **Other endpoints:** • Change in measures of mast cell burden from baseline to C7D1: serum tryptase, KIT D816V allele burden in blood, bone marrow mast cells • Change in BSC usage • Change in gastrointestinal and skin domains, neurocognitive symptom cluster (brain fog, headache and dizziness), and individual symptom scores of ISM-SAF • Change in "lead (most severe) symptom" and "lead (most severe) domain/symptom cluster" score of ISM-SAF • Change in Mastocytosis Quality of Life Questionnaire (MC-QoL), Patient's Global Impression of Symptom Severity (PGIS), 12-Item Short Form Health Survey (SF-12), Patients' Global Impression of Change (PGIC), and EQ-5D-5L • Safety and tolerability of avapritinib, as assessed by adverse events (AEs), vital signs, electrocardiograms (ECGs), and laboratory tests • Pharmacokinetics of avapritinib • Correlations between avapritinib exposure and safety and efficacy endpoints
Method of analysis	Efficacy data was assessed from baseline until C7D1. Data cutoff for the efficacy analysis was on 23 June 2022. The primary endpoint mean change in TSS was calculated as the difference between TSS at C7D1 and TSS at baseline. The analysis was based on the intention-to-treat (ITT) population. Sensitivity analyses were conducted using a per protocol (PP) population.
Subgroup analyses	• age (< 65 years, ≥ 65 years) • sex (male, female) • region (North America, Europe) • country • baseline • ISM status (moderate, severe) • baseline serum tryptase level (< 20 ng/mL, ≥ 20 ng/mL) • ECOG PS (0 or 1, 2+) • prior TKI therapy (yes, no)
Other relevant information	N/A

Appendix B. Efficacy results per study

Results per study

Table 49 Results per study

Results of PIONEER (NCT03731260)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Mean change from baseline in ISM-SAF TSS (Part 2)	Avapritinib	141	LS Mean: -15.58 (-18.61, -12.55)	–6.43	–10.90, –1.96	0.003	N/A	N/A	N/A	Change in TSS from baseline to C7D1 was defined as C7D1 TSS minus baseline TSS. Any patients with high-dose steroid use within 7 days before C7D1 or > 14 consecutive days at any point from C1D1 to C7D1 and patients with either missing baseline or C7D1 TSS were excluded from the analysis. An ANCOVA controlling for randomization stratification factor (serum tryptase < 20 ng/mL vs ≥ 20 ng/mL) and baseline ISM status (moderate vs severe) was performed to compare avapritinib and placebo. If < 5 patients were in 1 of the combinations of tryptase and baseline ISM status under each arm, the corresponding stratification factor was	
	Placebo	71	LS Mean: -9.15 (-13.12, -5.18)								
Mean change from baseline in ISM-SAF TSS (Part 3)	Avapritinib	[redacted]	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								

Results of PIONEER (NCT03731260)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										removed from analysis. Avapritinib was deemed as superior in reducing SM symptoms compared to placebo if the 1-sided p-value was < 0.025.	
Patients with ≥50% reduction in TSS	Avapritinib	141	35 (24.8%; 17.9, 32.8)	N/A	N/A	N/A	Odds ratio: 3.10	1.24 – 8.64	0.005	Analysis was done on the ITT population	
	Placebo	71	7 (9.9%; 4.1, 19.3)								
Patients with ≥30% reduction in TSS	Avapritinib	141	64 (45.4%; 37.0, 54.0)	N/A	N/A	N/A	Odds ratio: 2.07	1.08 – 3.99	0.009		
	Placebo	71	21 (29.6%; 19.3, 41.6)								
Patients with ≥50% reduction in serum tryptase	Avapritinib	141	76 (53.9%; 45.3, 62.3)	N/A	N/A	N/A	Odds ratio: N/E	30.59-NE	<0.0001	If C7D1 serum tryptase was missing, the patient was deemed as not achieving ≥ 50% reduction. The proportion of patients with ≥ 50% reduction, including frequency, percentage, and 95% CI was calculated in each treatment arm. A Cochran-Mantel-Haenszel test controlling for	
	Placebo	71	0 (0.0%; 0.0, 5.1)								

Results of PIONEER (NCT03731260)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										randomization stratification factor (serum tryptase < 20 ng/mL vs ≥ 20 ng/mL) and baseline ISM status (moderate vs severe) was used to compare avapritinib and placebo.	
Patients with ≥50% reduction in KIT D816V MAF or undetectable (<0.02%) for patients with detectable mutation at baseline	Avapritinib	118	80 (67.8%; 58.6, 76.1)	N/A	N/A	N/A	Odds ratio: 39.34	10.93 – 140.56	<0.0001	If C7D1 KIT D816V MAF value was missing, the patient was deemed as not achieving ≥ 50% reduction. The proportion of patients with ≥ 50% reduction, including frequency, percentage, and 95% CI was calculated in each treatment arm. A Cochran-Mantel-Haenszel test controlling for randomization stratification factor (serum tryptase < 20 ng/mL vs ≥ 20 ng/mL) and baseline ISM status (moderate vs severe) was used to compare avapritinib and placebo.	
	Placebo	63	4 (6.3%; 1.8, 15.5)								
Patients with ≥50%	Avapritinib	106	56 (52.8%; 42.9, 52.8)	N/A	N/A	N/A	Odds ratio: 4.74	2.06 – 11.45	<0.0001	The percent change was calculated as (C7D1 bone marrow mast cells minus	

Results of PIONEER (NCT03731260)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
reduction in bone marrow mast cells or no aggregates for patients with aggregates at baseline	Placebo	57	13 (22.8; 12.7, 35.8)							baseline bone marrow mast cells) divided by baseline bone marrow mast cells. If baseline or C7D1 bone marrow mast cells value was missing, the patient was deemed as not achieving ≥ 50% reduction. The proportion of patients with ≥ 50% reduction, including frequency, percentage, and 95% CI was calculated in each treatment arm. A Cochran-Mantel-Haenszel test controlling for randomization stratification factor (tryptase) and baseline ISM status (moderate vs severe) was used to compare avapritinib and placebo.	

Appendix C. Comparative Analysis of efficacy

N/A

Appendix D. Extrapolation

No extrapolation models were fitted to the efficacy data.

D.1 Extrapolation of [effect measure 1]

D.1.1 Data input

N/A

D.1.2 Model

N/A

D.1.3 Proportional hazards

N/A

D.1.4 Evaluation of statistical fit (AIC and BIC)

N/A

D.1.5 Evaluation of visual fit

N/A

D.1.6 Evaluation of hazard functions

N/A

D.1.7 Validation and discussion of extrapolated curves

N/A

D.1.8 Adjustment of background mortality

N/A

D.1.9 Adjustment for treatment switching/cross-over

N/A

D.1.10 Waning effect

N/A

D.1.11 Cure-point

N/A

D.2 Extrapolation of [effect measure 2]

N/A

Appendix E. Serious adverse events

Table 50 Serious Adverse Events by Preferred Term (Part 2 Safety Population)

Preferred Term	Avapritinib (N=150)	Placebo (N=71)
Patients with at least 1 SAE	7 (5.0)	8 (11.3)
Abdominal pain	1 (0.7)	0
Acute myeloid leukaemia	1 (0.7)	0
Anaphylactic reaction	1 (0.7)	1 (1.4)
Bacteraemia	1 (0.7)	0
COVID-19 pneumonia	1 (0.7)	1 (1.4)
Chest pain	1 (0.7)	0
Pelvic haematoma	1 (0.7)	0
Adenovirus infection	0	1 (1.4)
Allergy to vaccine	0	1 (1.4)
COVID-19	0	1 (1.4)
Foot deformity	0	1 (1.4)
Hypertension	0	1 (1.4)
Mastocytosis	0	1 (1.4)
Mental status changes	0	1 (1.4)
Tachycardia	0	1 (1.4)
Patients with any related SAEs	0	0

Table 51 SAEs that occurred in ≥2 patients (Part 3 Safety population, September 20, 2024, data cut)

Preferred Term	Avapritinib, 25-mg starting dose and dose maintained [redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Appendix F. Health-related quality of life

N/A

Appendix G. Probabilistic sensitivity analyses

The parameters used for the probabilistic sensitivity analysis (PSA) can be found in Table 52. These parameters include point estimates, probability distributions and upper and lower bound.

Table 52 Overview of Parameters used in the PSA

Input Parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Avapritinib proportion of patients				
Avapritinib Proportion of patients in Mild Cycle 1	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Mild Cycle 2	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Mild Cycle 3	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Mild Cycle 4	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Mild Cycle 5	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Mild Cycle 6	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Mild Cycle 7	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Mild Cycle 8	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Mild Cycle 9	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Mild Cycle 10	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Mild Cycle 11	[redacted]	[redacted]	[redacted]	Dirichlet

Avapritinib Proportion of patients in Mild Cycle 12	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Mild Cycle 13	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Mild Cycle 14	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Mild Cycle 15	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Mild Cycle 16	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Mild Cycle 17	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Mild Cycle 18	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Mild Cycle 19	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Mild Cycle 20	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Mild Cycle 21	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Mild Cycle 22	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Mild Cycle 23	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Mild Cycle 24	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Mild Cycle 25	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Mild Cycle 26	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Mild Cycle 27	[redacted]	[redacted]	[redacted]	Dirichlet

Avapritinib Proportion of patients in Mild Cycle 28	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Mild Cycle 29	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Mild Cycle 30	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Mild Cycle 31	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Mild Cycle 32	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Mild Cycle 33	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Mild Cycle 34	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Mild Cycle 35	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Mild Cycle 36	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Mild Cycle 37	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Mild Cycle 38	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Mild Cycle 39	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Mild Cycle 40	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Mild Cycle 41	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Mild Cycle 42	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Mild Cycle 43	[redacted]	[redacted]	[redacted]	Dirichlet

Avapritinib Proportion of patients in Mild Cycle 44	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Mild Cycle 45	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Mild Cycle 46	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Mild Cycle 47	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Mild Cycle 48	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Mild Cycle 49	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Mild Cycle 50	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Mild Cycle 51	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Mild Cycle 52	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Moderate Cycle 1	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Moderate Cycle 2	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Moderate Cycle 3	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Moderate Cycle 4	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Moderate Cycle 5	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Moderate Cycle 6	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Moderate Cycle 7	[redacted]	[redacted]	[redacted]	Dirichlet

Avapritinib Proportion of patients in Moderate Cycle 8	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Moderate Cycle 9	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Moderate Cycle 10	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Moderate Cycle 11	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Moderate Cycle 12	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Moderate Cycle 13	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Moderate Cycle 14	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Moderate Cycle 15	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Moderate Cycle 16	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Moderate Cycle 17	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Moderate Cycle 18	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Moderate Cycle 19	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Moderate Cycle 20	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Moderate Cycle 21	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Moderate Cycle 22	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Moderate Cycle 23	[redacted]	[redacted]	[redacted]	Dirichlet

Avapritinib Proportion of patients in Moderate Cycle 24	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Moderate Cycle 25	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Moderate Cycle 26	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Moderate Cycle 27	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Moderate Cycle 28	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Moderate Cycle 29	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Moderate Cycle 30	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Moderate Cycle 31	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Moderate Cycle 32	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Moderate Cycle 33	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Moderate Cycle 34	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Moderate Cycle 35	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Moderate Cycle 36	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Moderate Cycle 37	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Moderate Cycle 38	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Moderate Cycle 39	[redacted]	[redacted]	[redacted]	Dirichlet

Avapritinib Proportion of patients in Moderate Cycle 40	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Moderate Cycle 41	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Moderate Cycle 42	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Moderate Cycle 43	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Moderate Cycle 44	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Moderate Cycle 45	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Moderate Cycle 46	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Moderate Cycle 47	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Moderate Cycle 48	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Moderate Cycle 49	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Moderate Cycle 50	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Moderate Cycle 51	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Moderate Cycle 52	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Severe Cycle 1	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Severe Cycle 2	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Severe Cycle 3	[redacted]	[redacted]	[redacted]	Dirichlet

Avapritinib Proportion of patients in Severe Cycle 4	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Severe Cycle 5	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Severe Cycle 6	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Severe Cycle 7	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Severe Cycle 8	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Severe Cycle 9	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Severe Cycle 10	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Severe Cycle 11	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Severe Cycle 12	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Severe Cycle 13	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Severe Cycle 14	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Severe Cycle 15	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Severe Cycle 16	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Severe Cycle 17	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Severe Cycle 18	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Severe Cycle 19	[redacted]	[redacted]	[redacted]	Dirichlet

Avapritinib Proportion of patients in Severe Cycle 20	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Severe Cycle 21	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Severe Cycle 22	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Severe Cycle 23	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Severe Cycle 24	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Severe Cycle 25	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Severe Cycle 26	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Severe Cycle 27	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Severe Cycle 28	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Severe Cycle 29	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Severe Cycle 30	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Severe Cycle 31	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Severe Cycle 32	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Severe Cycle 33	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Severe Cycle 34	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Severe Cycle 35	[redacted]	[redacted]	[redacted]	Dirichlet

Avapritinib Proportion of patients in Severe Cycle 36	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Severe Cycle 37	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Severe Cycle 38	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Severe Cycle 39	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Severe Cycle 40	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Severe Cycle 41	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Severe Cycle 42	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Severe Cycle 43	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Severe Cycle 44	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Severe Cycle 45	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Severe Cycle 46	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Severe Cycle 47	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Severe Cycle 48	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Severe Cycle 49	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Severe Cycle 50	[redacted]	[redacted]	[redacted]	Dirichlet
Avapritinib Proportion of patients in Severe Cycle 51	[redacted]	[redacted]	[redacted]	Dirichlet

Avapritinib Proportion of patients in Severe Cycle 52	[redacted]	[redacted]	[redacted]	Dirichlet
BSC proportion of patients				
BSC Proportion of patients in Mild Cycle 1	[redacted]	[redacted]	[redacted]	Dirichlet
BSC Proportion of patients in Mild Cycle 2	[redacted]	[redacted]	[redacted]	Dirichlet
BSC Proportion of patients in Mild Cycle 3	[redacted]	[redacted]	[redacted]	Dirichlet
BSC Proportion of patients in Mild Cycle 4	[redacted]	[redacted]	[redacted]	Dirichlet
BSC Proportion of patients in Mild Cycle 5	[redacted]	[redacted]	[redacted]	Dirichlet
BSC Proportion of patients in Mild Cycle 6	[redacted]	[redacted]	[redacted]	Dirichlet
BSC Proportion of patients in Mild Cycle 7	[redacted]	[redacted]	[redacted]	Dirichlet
BSC Proportion of patients in Mild Cycle 8	[redacted]	[redacted]	[redacted]	Dirichlet
BSC Proportion of patients in Mild Cycle 9	[redacted]	[redacted]	[redacted]	Dirichlet
BSC Proportion of patients in Mild Cycle 10	[redacted]	[redacted]	[redacted]	Dirichlet
BSC Proportion of patients in Mild Cycle 11	[redacted]	[redacted]	[redacted]	Dirichlet
BSC Proportion of patients in Mild Cycle 12	[redacted]	[redacted]	[redacted]	Dirichlet
BSC Proportion of patients in Mild Cycle 13	[redacted]	[redacted]	[redacted]	Dirichlet
BSC Proportion of patients in Moderate Cycle 1	[redacted]	[redacted]	[redacted]	Dirichlet

BSC Proportion of patients in Moderate Cycle 2	[redacted]	[redacted]	[redacted]	Dirichlet
BSC Proportion of patients in Moderate Cycle 3	[redacted]	[redacted]	[redacted]	Dirichlet
BSC Proportion of patients in Moderate Cycle 4	[redacted]	[redacted]	[redacted]	Dirichlet
BSC Proportion of patients in Moderate Cycle 5	[redacted]	[redacted]	[redacted]	Dirichlet
BSC Proportion of patients in Moderate Cycle 6	[redacted]	[redacted]	[redacted]	Dirichlet
BSC Proportion of patients in Moderate Cycle 7	[redacted]	[redacted]	[redacted]	Dirichlet
BSC Proportion of patients in Moderate Cycle 8	[redacted]	[redacted]	[redacted]	Dirichlet
BSC Proportion of patients in Moderate Cycle 9	[redacted]	[redacted]	[redacted]	Dirichlet
BSC Proportion of patients in Moderate Cycle 10	[redacted]	[redacted]	[redacted]	Dirichlet
BSC Proportion of patients in Moderate Cycle 11	[redacted]	[redacted]	[redacted]	Dirichlet
BSC Proportion of patients in Moderate Cycle 12	[redacted]	[redacted]	[redacted]	Dirichlet
BSC Proportion of patients in Moderate Cycle 13	[redacted]	[redacted]	[redacted]	Dirichlet
BSC Proportion of patients in Severe Cycle 1	[redacted]	[redacted]	[redacted]	Dirichlet
BSC Proportion of patients in Severe Cycle 2	[redacted]	[redacted]	[redacted]	Dirichlet
BSC Proportion of patients in Severe Cycle 3	[redacted]	[redacted]	[redacted]	Dirichlet
BSC Proportion of patients in Severe Cycle 4	[redacted]	[redacted]	[redacted]	Dirichlet

BSC Proportion of patients in Severe Cycle 5	[redacted]	[redacted]	[redacted]	Dirichlet
BSC Proportion of patients in Severe Cycle 6	[redacted]	[redacted]	[redacted]	Dirichlet
BSC Proportion of patients in Severe Cycle 7	[redacted]	[redacted]	[redacted]	Dirichlet
BSC Proportion of patients in Severe Cycle 8	[redacted]	[redacted]	[redacted]	Dirichlet
BSC Proportion of patients in Severe Cycle 9	[redacted]	[redacted]	[redacted]	Dirichlet
BSC Proportion of patients in Severe Cycle 10	[redacted]	[redacted]	[redacted]	Dirichlet
BSC Proportion of patients in Severe Cycle 11	[redacted]	[redacted]	[redacted]	Dirichlet
BSC Proportion of patients in Severe Cycle 12	[redacted]	[redacted]	[redacted]	Dirichlet
BSC Proportion of patients in Severe Cycle 13	[redacted]	[redacted]	[redacted]	Dirichlet
Probability of progression				
From Cycle 34 to SSM	0%	0.000	0.000	Beta
From Cycle 35 to SSM	0%	0.000	0.000	Beta
From Cycle 36 to SSM	0%	0.000	0.000	Beta
From Cycle 34 to AdvSM	0%	0.000	0.000	Beta
From Cycle 35 to AdvSM	0%	0.000	0.000	Beta
From Cycle 36 to AdvSM	0%	0.000	0.001	Beta
From Cycle 37 to AdvSM	0%	0.001	0.002	Beta
From Cycle 37 to 2	0%	0.000	0.000	Beta
From AdvSM to 2	0%	0.000	0.000	Beta

Long-term treatment efficacy				
Average ToT (Responders)	[redacted]	[redacted]	[redacted]	Lognormal
Treatment waning (cycles)	6.0000	4.000	9.000	Lognormal
Utility values				
Utilities Mild	0.8390	0.644	0.964	Beta
Utilities Moderate	0.7342	0.579	0.864	Beta
Utilities Severe	0.5659	0.454	0.675	Beta
Utilities SSM	0.5306	0.426	0.634	Beta
Utilities AdvSM	0.5297	0.425	0.633	Beta
Response adjustment to utility values				
Adjust utility for response	0.0500	0.033	0.072	Lognormal
Responders that do not move health state	0.1000	0.064	0.142	Beta
Resource use activity unit costs				
Abdominal pain: unit cost	4977.0000	3220.852	7109.166	Gamma
Nausea: unit cost	4977.0000	3220.852	7109.166	Gamma
Diarrhea: unit cost	4977.0000	3220.852	7109.166	Gamma
Brain fog: unit cost	2571.0000	1663.816	3672.426	Gamma
Dizziness: unit cost	8274.0000	5354.497	11818.614	Gamma
Headache: unit cost	5271.0000	3411.113	7529.117	Gamma

Flushing: unit cost	5271.0000	3411.113	7529.117	Gamma
Itiching : unit cost	1578.0000	1021.198	2254.021	Gamma
Spots: unit cost	1578.0000	1021.198	2254.021	Gamma
Gastrointestinal domain: outpatient consultation: unit cost	1073.7000	694.842	1533.677	Gamma
Skin domain: Dermatology outpatient consultation: unit cost	1073.7000	694.842	1533.677	Gamma
Skin domain: Dermatologist nurse visit: unit cost	470.6400	304.573	672.264	Gamma
Neurologic domain: outpatient consultation: unit cost	1073.7000	694.842	1533.677	Gamma
Accident & Emergency visit: unit cost	2012.0000	1302.060	2873.949	Gamma
Hospitalization: unit cost	2926.6429	1893.969	4180.428	Gamma
Daycase admission: unit cost	2012.0000	1302.060	2873.949	Gamma
Anaphylaxis without complications: unit cost	5193.0000	3360.636	7417.701	Gamma
Anaphylaxis with complications: unit cost	13784.0000	8920.278	19689.119	Gamma
Epipen use: unit cost	321.0000	207.734	458.518	Gamma
Bone marrow biopsy: unit cost	16156.0000	10455.311	23077.293	Gamma
ECG: unit cost	2136.0000	1382.307	3051.071	Gamma
Haematology visit : unit cost	1073.7000	694.842	1533.677	Gamma

Biochemistry test: renal - Urea and electrolytes test (UE test): unit cost	30.6000	19.803	43.709	Gamma
Coagulation test: unit cost	61.0000	39.476	87.133	Gamma
Serum chemistry tests: unit cost	22.9500	14.852	32.782	Gamma
Phototherapy: unit cost	2136.0000	1382.307	3051.071	Gamma
CT scan: unit cost	2701.0000	1747.945	3858.119	Gamma
Chest X-ray: unit cost	1731.0000	1120.212	2472.567	Gamma
Ultrasound scan: unit cost	2136.0000	1382.307	3051.071	Gamma
MRI scan: unit cost	2603.0000	1684.524	3718.135	Gamma
Full blood count: unit cost	22.9500	14.852	32.782	Gamma
Bone densitometry: unit cost	1811.0000	1171.984	2586.839	Gamma
Symptoms by severity				
Mild: Average % of patients experiencing any symptoms	0.7719	0.409	0.981	Beta
Moderate: Average % of patients experiencing any symptoms	0.9197	0.274	1.000	Beta
Severe: Average % of patients experiencing any symptoms	0.9649	0.965	0.965	Beta
Frequency resource use activity: Non-responders				
Mild: Gastrointestinal domain: outpatient consultation	0.2573	0.163	0.364	Beta
Mild: Skin domain: Dermatology outpatient consultation	0.3604	0.226	0.507	Beta

Mild: Skin domain: Dermatologist nurse visit	0.0325	0.021	0.046	Beta
Mild: Neurologic domain: outpatient consultation	0.6639	0.383	0.891	Beta
Mild: Accident & Emergency visit	0.0053	0.003	0.008	Beta
Mild: Hospitalization	0.0071	0.005	0.010	Beta
Mild: Daycase admission	0.0124	0.008	0.018	Beta
Mild: Anaphylaxis without complications	0.1213	0.078	0.173	Beta
Mild: Anaphylaxis with complications	0.1213	0.078	0.173	Beta
Mild: Epipen use	0.0592	0.038	0.084	Beta
Mild: Bone marrow biopsy	0.2933	0.186	0.414	Beta
Mild: ECG	0.1184	0.076	0.168	Beta
Mild: Haematology visit	0.2367	0.151	0.335	Beta
Mild: Biochemistry test: renal - Urin test	0.2367	0.151	0.335	Beta
Mild: Coagulation test	0.3088	0.195	0.436	Beta
Mild: Serum chemistry tests	0.3088	0.195	0.436	Beta
Mild: Photography	0.0036	0.002	0.005	Beta
Mild: CT scan	0.1184	0.076	0.168	Beta
Mild: Chest X-ray	0.0592	0.038	0.084	Beta
Mild: Ultrasound scan	0.0592	0.038	0.084	Beta
Mild: MRI scan	0.1184	0.076	0.168	Beta
Mild: Full blood count	0.2367	0.151	0.335	Beta
Mild: Bone densitometry	0.0296	0.019	0.042	Beta

Moderate: Gastrointestinal domain: outpatient consultation	0.3066	0.194	0.433	Beta
Moderate: Skin domain: Dermatology outpatient consultation	0.4293	0.266	0.601	Beta
Moderate: Skin domain: Dermatologist nurse visit	0.0388	0.025	0.055	Beta
Moderate: Neurologic domain: outpatient consultation	0.7909	0.408	0.990	Beta
Moderate: Accident & Emergency visit	0.0063	0.004	0.009	Beta
Moderate: Hospitalization	0.0085	0.005	0.012	Beta
Moderate: Daycase admission	0.0148	0.010	0.021	Beta
Moderate: Anaphylaxis without complications	0.1445	0.093	0.206	Beta
Moderate: Anaphylaxis with complications	0.1445	0.093	0.206	Beta
Moderate: Epipen use	0.0705	0.045	0.101	Beta
Moderate: Bone marrow biopsy	0.3495	0.220	0.492	Beta
Moderate: ECG	0.1410	0.090	0.201	Beta
Moderate: Haematology visit	0.2820	0.179	0.399	Beta
Moderate: Biochemistry test: renal - Urin test	0.2820	0.179	0.399	Beta
Moderate: Coagulation test	0.3679	0.230	0.517	Beta
Moderate: Serum chemistry tests	0.3679	0.230	0.517	Beta
Moderate: Photography	0.0042	0.003	0.006	Beta
Moderate: CT scan	0.1410	0.090	0.201	Beta
Moderate: Chest X-ray	0.0705	0.045	0.101	Beta
Moderate: Ultrasound scan	0.0705	0.045	0.101	Beta

Moderate: MRI scan	0.1410	0.090	0.201	Beta
Moderate: Full blood count	0.2820	0.179	0.399	Beta
Moderate: Bone densitometry	0.0353	0.023	0.050	Beta
Severe: Gastrointestinal domain: outpatient consultation	0.3216	0.203	0.454	Beta
Severe: Skin domain: Dermatology outpatient consultation	0.4505	0.278	0.629	Beta
Severe: Skin domain: Dermatologist nurse visit	0.0407	0.026	0.058	Beta
Severe: Neurologic domain: outpatient consultation	0.8298	0.399	0.999	Beta
Severe: Accident & Emergency visit	0.0067	0.004	0.010	Beta
Severe: Hospitalization	0.0089	0.006	0.013	Beta
Severe: Daycase admission	0.0155	0.010	0.022	Beta
Severe: Anaphylaxis without complications	0.1516	0.097	0.216	Beta
Severe: Anaphylaxis with complications	0.1516	0.097	0.216	Beta
Severe: Epipen use	0.0740	0.048	0.105	Beta
Severe: Bone marrow biopsy	0.3667	0.230	0.516	Beta
Severe: ECG	0.1479	0.095	0.210	Beta
Severe: Haematology visit	0.2959	0.187	0.418	Beta
Severe: Biochemistry test: renal - Urin test	0.2959	0.187	0.418	Beta
Severe: Coagulation test	0.3859	0.241	0.542	Beta
Severe: Serum chemistry tests	0.3859	0.241	0.542	Beta
Severe: Photography	0.0044	0.003	0.006	Beta

Severe: CT scan	0.1479	0.095	0.210	Beta
Severe: Chest X-ray	0.0740	0.048	0.105	Beta
Severe: Ultrasound scan	0.0740	0.048	0.105	Beta
Severe: MRI scan	0.1479	0.095	0.210	Beta
Severe: Full blood count	0.2959	0.187	0.418	Beta
Severe: Bone densitometry	0.0370	0.024	0.053	Beta
Frequency resource use activity: Responders				
Mild: Gastrointestinal domain: outpatient consultation	0.1287	0.083	0.183	Beta
Mild: Skin domain: Dermatology outpatient consultation	0.1802	0.115	0.256	Beta
Mild: Skin domain: Dermatologist nurse visit	0.0163	0.011	0.023	Beta
Mild: Neurologic domain: outpatient consultation	0.3319	0.209	0.468	Beta
Mild: Accident & Emergency visit	0.0027	0.002	0.004	Beta
Mild: Hospitalization	0.0036	0.002	0.005	Beta
Mild: Daycase admission	0.0062	0.004	0.009	Beta
Mild: Anaphylaxis without complications	0.0607	0.039	0.086	Beta
Mild: Anaphylaxis with complications	0.0607	0.039	0.086	Beta
Mild: Epipen use	0.0296	0.019	0.042	Beta
Mild: Bone marrow biopsy	0.1467	0.094	0.209	Beta
Mild: ECG	0.0592	0.038	0.084	Beta
Mild: Haematology visit	0.1184	0.076	0.168	Beta

Mild: Biochemistry test: renal - Urin test	0.1184	0.076	0.168	Beta
Mild: Coagulation test	0.1544	0.099	0.219	Beta
Mild: Serum chemistry tests	0.1544	0.099	0.219	Beta
Mild: Photography	0.0018	0.001	0.003	Beta
Mild: CT scan	0.0592	0.038	0.084	Beta
Mild: Chest X-ray	0.0296	0.019	0.042	Beta
Mild: Ultrasound scan	0.0296	0.019	0.042	Beta
Mild: MRI scan	0.0592	0.038	0.084	Beta
Mild: Full blood count	0.1184	0.076	0.168	Beta
Mild: Bone densitometry	0.0148	0.010	0.021	Beta
Moderate: Gastrointestinal domain: outpatient consultation	0.1533	0.098	0.218	Beta
Moderate: Skin domain: Dermatology outpatient consultation	0.2147	0.137	0.304	Beta
Moderate: Skin domain: Dermatologist nurse visit	0.0194	0.013	0.028	Beta
Moderate: Neurologic domain: outpatient consultation	0.3954	0.247	0.555	Beta
Moderate: Accident & Emergency visit	0.0032	0.002	0.005	Beta
Moderate: Hospitalization	0.0042	0.003	0.006	Beta
Moderate: Daycase admission	0.0074	0.005	0.011	Beta
Moderate: Anaphylaxis without complications	0.0723	0.047	0.103	Beta
Moderate: Anaphylaxis with complications	0.0723	0.047	0.103	Beta
Moderate: Epipen use	0.0353	0.023	0.050	Beta

Moderate: Bone marrow biopsy	0.1747	0.112	0.248	Beta
Moderate: ECG	0.0705	0.045	0.101	Beta
Moderate: Haematology visit	0.1410	0.090	0.201	Beta
Moderate: Biochemistry test: renal - Urin test	0.1410	0.090	0.201	Beta
Moderate: Coagulation test	0.1839	0.118	0.261	Beta
Moderate: Serum chemistry tests	0.1839	0.118	0.261	Beta
Moderate: Photography	0.0021	0.001	0.003	Beta
Moderate: CT scan	0.0705	0.045	0.101	Beta
Moderate: Chest X-ray	0.0353	0.023	0.050	Beta
Moderate: Ultrasound scan	0.0353	0.023	0.050	Beta
Moderate: MRI scan	0.0705	0.045	0.101	Beta
Moderate: Full blood count	0.1410	0.090	0.201	Beta
Moderate: Bone densitometry	0.0176	0.011	0.025	Beta
Severe: Gastrointestinal domain: outpatient consultation	0.1608	0.103	0.229	Beta
Severe: Skin domain: Dermatology outpatient consultation	0.2252	0.143	0.319	Beta
Severe: Skin domain: Dermatologist nurse visit	0.0203	0.013	0.029	Beta
Severe: Neurologic domain: outpatient consultation	0.4149	0.258	0.581	Beta
Severe: Accident & Emergency visit	0.0033	0.002	0.005	Beta
Severe: Hospitalization	0.0044	0.003	0.006	Beta
Severe: Daycase admission	0.0078	0.005	0.011	Beta

Severe: Anaphylaxis without complications	0.0758	0.049	0.108	Beta
Severe: Anaphylaxis with complications	0.0758	0.049	0.108	Beta
Severe: Epipen use	0.0370	0.024	0.053	Beta
Severe: Bone marrow biopsy	0.1833	0.117	0.260	Beta
Severe: ECG	0.0740	0.048	0.105	Beta
Severe: Haematology visit	0.1479	0.095	0.210	Beta
Severe: Biochemistry test: renal - Urin test	0.1479	0.095	0.210	Beta
Severe: Coagulation test	0.1930	0.123	0.274	Beta
Severe: Serum chemistry tests	0.1930	0.123	0.274	Beta
Severe: Photography	0.0022	0.001	0.003	Beta
Severe: CT scan	0.0740	0.048	0.105	Beta
Severe: Chest X-ray	0.0370	0.024	0.053	Beta
Severe: Ultrasound scan	0.0370	0.024	0.053	Beta
Severe: MRI scan	0.0740	0.048	0.105	Beta
Severe: Full blood count	0.1479	0.095	0.210	Beta
Severe: Bone densitometry	0.0185	0.012	0.026	Beta
Adverse events incidence				
Avapritinib: Headache	0.0780	0.050	0.111	Beta
Avapritinib: Nausea	0.0640	0.041	0.091	Beta
Avapritinib: Oedema peripheral	0.0640	0.041	0.091	Beta
Avapritinib: Periorbital oedema	0.0640	0.041	0.091	Beta
Avapritinib: Fatigue	0.0430	0.028	0.061	Beta

Avapritinib: Flushing	0.0430	0.028	0.061	Beta
Avapritinib: Alopecia	0.0350	0.023	0.050	Beta
Avapritinib: Blood alkaline phosphatase increased	0.0350	0.023	0.050	Beta
Avapritinib: Contusion	0.0350	0.023	0.050	Beta
Avapritinib: Eyelid oedema	0.0350	0.023	0.050	Beta
Avapritinib: Face oedema	0.0350	0.023	0.050	Beta
Avapritinib: Aspartate aminotransferase increased	0.0280	0.018	0.040	Beta
Avapritinib: Diarrhoea	0.0280	0.018	0.040	Beta
Avapritinib: Dizziness	0.0280	0.018	0.040	Beta
Avapritinib: Hair colour changes	0.0280	0.018	0.040	Beta
Avapritinib: Photosensitivity reaction	0.0280	0.018	0.040	Beta
Avapritinib: Alanine aminotransferase increased	0.0210	0.014	0.030	Beta
Avapritinib: Blood lactate dehydrogenase increased	0.0210	0.014	0.030	Beta
Avapritinib: Dry mouth	0.0210	0.014	0.030	Beta
Avapritinib: Muscle spasms	0.0210	0.014	0.030	Beta
Avapritinib: Anaphylaxis without complications	0.1225	0.079	0.174	Beta
Avapritinib: Anaphylaxis with complications	0.1225	0.079	0.174	Beta
Avapritinib: Placeholder	0.0000	0.000	0.000	Beta
Avapritinib: Placeholder	0.0000	0.000	0.000	Beta
BSC: Headache	0.0990	0.064	0.141	Beta

BSC: Nausea	0.0850	0.055	0.121	Beta
BSC: Oedema peripheral	0.0140	0.009	0.020	Beta
BSC: Periorbital oedema	0.0280	0.018	0.040	Beta
BSC: Fatigue	0.0280	0.018	0.040	Beta
BSC: Flushing	0.0000	0.000	0.000	Beta
BSC: Alopecia	0.0420	0.027	0.060	Beta
BSC: Blood alkaline phosphatase increased	0.0000	0.000	0.000	Beta
BSC: Contusion	0.0000	0.000	0.000	Beta
BSC: Eyelid oedema	0.0140	0.009	0.020	Beta
BSC: Face oedema	0.0000	0.000	0.000	Beta
BSC: Aspartate aminotransferase increased	0.0140	0.009	0.020	Beta
BSC: Diarrhoea	0.0280	0.018	0.040	Beta
BSC: Dizziness	0.0700	0.045	0.100	Beta
BSC: Hair colour changes	0.0140	0.009	0.020	Beta
BSC: Photosensitivity reaction	0.0000	0.000	0.000	Beta
BSC: Alanine aminotransferase increased	0.0140	0.009	0.020	Beta
BSC: Blood lactate dehydrogenase increased	0.0000	0.000	0.000	Beta
BSC: Dry mouth	0.0140	0.009	0.020	Beta
BSC: Muscle spasms	0.0000	0.000	0.000	Beta
BSC: Anaphylaxis without complications	0.2550	0.162	0.361	Beta
BSC: Anaphylaxis with complications	0.2550	0.162	0.361	Beta

AE Disutility

Headache	0.0266	0.017	0.038	Gamma
Nausea	0.1360	0.088	0.194	Gamma
Oedema peripheral	0.1240	0.080	0.177	Gamma
Periorbital oedema	0.1240	0.080	0.177	Gamma
Fatigue	0.1150	0.074	0.164	Gamma
Flushing	0.0669	0.043	0.096	Gamma
Alopecia	0.0400	0.026	0.057	Gamma
Blood alkaline phosphatase increased	0.0900	0.058	0.129	Gamma
Contusion	0.0000	0.000	0.000	Gamma
Eyelid oedema	0.1240	0.080	0.177	Gamma
Face oedema	0.1240	0.080	0.177	Gamma
Aspartate aminotransferase increased	0.0900	0.058	0.129	Gamma
Diarrhoea	0.1260	0.082	0.180	Gamma
Dizziness	0.1200	0.078	0.171	Gamma
Hair colour changes	0.0669	0.043	0.096	Gamma
Photosensitivity reaction	0.0000	0.000	0.000	Gamma
Alanine aminotransferase increased	0.0900	0.058	0.129	Gamma
Blood lactate dehydrogenase increased	0.0900	0.058	0.129	Gamma
Dry mouth	0.0000	0.000	0.000	Gamma
Muscle spasms	0.0700	0.045	0.100	Gamma
Anaphylaxis without complications	0.0900	0.058	0.129	Gamma
Anaphylaxis with complications	0.1800	0.116	0.257	Gamma

AE Duration (days)				
Headache	14.0000	9.060	19.998	Gamma
Nausea	14.0000	9.060	19.998	Gamma
Oedema peripheral	14.0000	9.060	19.998	Gamma
Periorbital oedema	14.0000	9.060	19.998	Gamma
Fatigue	14.0000	9.060	19.998	Gamma
Flushing	14.0000	9.060	19.998	Gamma
Alopecia	14.0000	9.060	19.998	Gamma
Blood alkaline phosphatase increased	14.0000	9.060	19.998	Gamma
Contusion	0.0000	0.000	0.000	Gamma
Eyelid oedema	14.0000	9.060	19.998	Gamma
Face oedema	14.0000	9.060	19.998	Gamma
Aspartate aminotransferase increased	14.0000	9.060	19.998	Gamma
Diarrhoea	14.0000	9.060	19.998	Gamma
Dizziness	14.0000	9.060	19.998	Gamma
Hair colour changes	14.0000	9.060	19.998	Gamma
Photosensitivity reaction	0.0000	0.000	0.000	Gamma
Alanine aminotransferase increased	14.0000	9.060	19.998	Gamma
Blood lactate dehydrogenase increased	14.0000	9.060	19.998	Gamma
Dry mouth	0.0000	0.000	0.000	Gamma
Muscle spasms	14.0000	9.060	19.998	Gamma
Anaphylaxis without complications	14.0000	9.060	19.998	Gamma
Anaphylaxis with complications	14.0000	9.060	19.998	Gamma

Adverse events cost (per event)

Headache	5271.0000	3411.113	7529.117	Gamma
Nausea	4977.0000	3220.852	7109.166	Gamma
Oedema peripheral	5271.0000	3411.113	7529.117	Gamma
Periorbital oedema	5271.0000	3411.113	7529.117	Gamma
Fatigue	5271.0000	3411.113	7529.117	Gamma
Flushing	5271.0000	3411.113	7529.117	Gamma
Alopecia	1578.0000	1021.198	2254.021	Gamma
Blood alkaline phosphatase increased	2072.0000	1340.889	2959.653	Gamma
Contusion	1578.0000	1021.198	2254.021	Gamma
Eyelid oedema	5271.0000	3411.113	7529.117	Gamma
Face oedema	5271.0000	3411.113	7529.117	Gamma
Aspartate aminotransferase increased	2072.0000	1340.889	2959.653	Gamma
Diarrhoea	4977.0000	3220.852	7109.166	Gamma
Dizziness	0.0000	0.000	0.000	Gamma
Hair colour changes	1578.0000	1021.198	2254.021	Gamma
Photosensitivity reaction	1578.0000	1021.198	2254.021	Gamma

Alanine aminotransferase increased	2072.0000	1340.889	2959.653	Gamma
Blood lactate dehydrogenase increased	2072.0000	1340.889	2959.653	Gamma
Dry mouth	1286.0000	832.231	1836.927	Gamma
Muscle spasms	2267.0000	1467.083	3238.192	Gamma
Anaphylaxis without complications	5193.0000	3360.636	7417.701	Gamma
Anaphylaxis with complications	5193.0000	3360.636	7417.701	Gamma
Mortality rate ratio (MRR) per health state				
MRR SSM	5.5000	7.951	4.459	Lognormal
MRR AdvSM	5.5000	7.951	6.430	Lognormal
Number of planned visits per cycle				
Responder mild	0.6571	0.425	0.939	Gamma
Responder moderate	0.7828	0.507	1.118	Gamma
Responder severe	0.8213	0.531	1.173	Gamma
Non-responder mild	1.3141	0.850	1.877	Gamma
Non-responder moderate	1.5656	1.013	2.236	Gamma
Non-responder severe	1.6426	1.063	2.346	Gamma
SSM	1.6426	1.063	2.346	Gamma
AdvSM	1.6426	1.063	2.346	Gamma
Number of unplanned visits w/o hospitalization per cycle				
Responder mild	0.0695	0.045	0.099	Gamma

Responder moderate	0.0828	0.054	0.118	Gamma
Responder severe	0.0869	0.056	0.124	Gamma
Non-responder mild	0.1391	0.090	0.199	Gamma
Non-responder moderate	0.1657	0.107	0.237	Gamma
Non-responder severe	0.1738	0.112	0.248	Gamma
SSM	0.1738	0.112	0.248	Gamma
AdvSM	0.1738	0.112	0.248	Gamma
Number of unplanned visits w hospitalization per cycle				
Responder mild	0.0642	0.042	0.092	Gamma
Responder moderate	0.0765	0.050	0.109	Gamma
Responder severe	0.0803	0.052	0.115	Gamma
Non-responder mild	0.1284	0.083	0.183	Gamma
Non-responder moderate	0.1530	0.099	0.219	Gamma
Non-responder severe	0.1605	0.104	0.229	Gamma
SSM	0.1605	0.104	0.229	Gamma
AdvSM	0.1605	0.104	0.229	Gamma

Abbreviations: AdvSM, advanced systemic mastocytosis; AE, adverse event; BSC, best supportive care; CT, computed tomography; ECG, electrocardiography; MMR, mortality rate ratio; MRI, magnetic resonance imaging; PSA, probabilistic sensitivity analysis; SSM, smouldering systemic mastocytosis; ToT, time on treatment.53

Appendix H. Literature searches for the clinical assessment

Head-to-head trial. Not relevant.

Appendix I. Literature searches for health-related quality of life

I.1 Health-related quality-of-life search

Objective

An economic SLR was conducted to identify all available economic evidence for avapritinib in patients with non-AdvSM to communicate the value of avapritinib in non-AdvSM to stakeholders, specifically to HTA agencies globally, and to identify potential economic and utility inputs for the cost-effectiveness model comparing avapritinib with existing treatments. The original SLR was conducted on 25 November 2022 and was updated on 29 November 2023. To satisfy the economic SLR objective, the following research questions were considered:

Cost-effectiveness:

- What is the cost-effectiveness of treatments available for non-AdvSM?
    - Which types of economic models have been developed for non-AdvSM?
    - What is the design of these models?
    - What model assumptions were made?
    - What input data (e.g., costs, utilities) was used for these models?
    - What are the cost/quality-adjusted life year (QALY) and cost/life year gained (LYG) results?
    - What are the quality and limitations of the included studies based on the NICE-recommended quality assessment checklist (i.e., Drummond Checklist)?

Resource use and costs:

- What resource use and cost are associated with treatment for non-AdvSM?
    - Which studies investigate the resource use and costs associated with non-AdvSM?
    - What is the design of these studies?
    - How much resource use and costs are associated with drug use, hospitalisation, outpatient visits, adverse events (AEs), workdays missed, productivity loss, and disease and caregiver burden?

Utilities and HRQoL:

- What is the impact of non-AdvSM and its treatment on patients' HRQoL?
    - Which studies investigate the utilities and HRQoL values associated with non-AdvSM?
    - What is the design of these studies?
    - Which HRQoL and utility values have been reported for patients with non-AdvSM?

The SLR was subsequently modified and updated on 31 March 2025, during which the economic SLR was split into separate HRQoL and HCRU searches. The 2025 update for HCRU is described in Appendix J. The primary aim of the 2025 SLR in this section was to identify HRQoL outcomes and utility values associated with non-AdvSM.

I.1.1 Information sources

Covering multiple European countries, this SLR was conducted according to European health authority submission requirements, the strictest of which are NICE requirements (87). These requirements include searching electronic databases, performing selection and extraction with two independent reviewers, completing quality assessment checklists for clinical and economic studies, and ensuring that the literature review is conducted at latest six months prior to submission; this SLR is compliant with NICE guidelines (87).

For the economic SLR, the Embase, Medline, and EconLit databases were searched by means of the ProQuest search engine to identify economic evidence for non-AdvSM published in peer-reviewed journals (Table 54). In the 2025 update, the following electronic databases were included as standard evidence sources for HRQoL and utility data:

- Embase® (via Ovid.com)
- MEDLINE® and MEDLINE® In-Process (via Ovid.com)
- Evidence-based Medicine (EBM) Reviews (via Ovid.com), including the following:
    - Cochrane Database of Systematic Reviews (CDSR)
    - Cochrane Central Register of Controlled Trials (CENTRAL)
- Econlit (via Ovid.com)
- CRD Database:
    - Database of Abstracts of Reviews of Effects (DARE)
    - National Health Service Economic Evaluation Database (NHS EED)
    - Health Technology Assessment (HTA)

Details of the bibliographic databases included in the literature search for the 2025 update are provided in Table 55.

Table 54 Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
Embase	ProQuest	1947 to present	29.11.2023
Medline	ProQuest	1946 to present	29.11.2023
EconLit	ProQuest	1886 to present	29.11.2023

Abbreviations: EconLit, American Economic Association's electronic database; Embase, Excerpta Medica database.

Table 55 Bibliographic databases included in the literature search (2025 update)

Database	Platform	Relevant period for the search	Date of search completion

Embase	Ovid	01.01.2023 – 31.03.2025	31.03.2025
Medline	Ovid	01.01.2023 – 31.03.2025	31.03.2025
EBM	Ovid	01.01.2023 – 31.03.2025	31.03.2025
EconLit	Ovid	01.01.2023 – 31.03.2025	31.03.2025
CRD Database	www.york.ac.uk	01.01.2023 – 31.03.2025	31.03.2025

Abbreviations: CRD, Centre for Reviews and Dissemination; EBM, Evidence-based Medicine; EconLit, American Economic Association's electronic database; Embase, Excerpta Medica database.

For the economic SLR, additional searches were performed on the websites of HTA authorities to retrieve critical appraisals and key learnings from previous assessments. The searches were limited to the last five years (2018 to 2022 for the original SLR, 2022 to 2023 for the first update, and 2023 to 2025 for the second update), except for UK HTA agencies, where no time restriction was applied. Relevant articles were identified using systemic mastocytosis-specific search terms, as outlined in Section I.1.2. The complete list of sources consulted is presented in Table 56.

Table 56 Other sources included in the literature search

Source name	Location/source	Date of search
Agencia Española de Medicamentos y Productos Sanitarios	www.aemps.gob.es	25.11.2022, 29.11.2023 and 31.03.2025
Agencia Española de Medicamentos y Productos Sanitarios	www.aemps.gob.es	
Canadian Agency for Drugs and Technologies in Health	www.cda-amc.ca	
Gemeinsamer Bundesausschuss	www.g-ba.de	
Haute Autorité De Santé	www.has-sante.fr	
National Institute for Health and Care Excellence	www.nice.org.uk	
National Centre for Pharmacoeconomics	www.ncpe.ie	
Rijksinstituut voor ziekte- en invaliditeitsverzekering	www.riziv.fgov.be/nl	
Scottish Medicines Consortium	www.scottishmed.org.uk	
Zorginstituut Nederland	www.zorginstituut.nl	
Agenzia Italiana del Farmaco*	www.aifa.gov.it	

All Wales Medicines Strategy Group*	www.awttc.nhs.wales	31.03.2025

Note: * Was only searched in the second update in 2025

For the economic SLRs, a search for conference abstracts was conducted to complement the search for peer-reviewed publications. Proceedings from the conferences, in Table 57, were searched from the last three years (2020 to 2022 for the original SLR, 2022 to 2023 for the first update and 2023 to 2025 in the second update). The searches for conference proceedings were independent of the search conducted for peer-reviewed publications. Conference proceedings that were indexed in Embase were searched electronically with the same search strategy as was used the peer-reviewed publications (Section I.1.2). Conferences that were not indexed in Embase were hand-searched using SM search terms in whatever format was provided by the conference (e.g., PDF booklet, online search portal).

Table 57 Conference material included in the literature search

Conference	Source of abstracts	Date of search
American Academy of Allergy, Asthma, and Immunology	www.aaaai.org	25.11.2022, 29.11.2023 and 31.03.2025
American Academy of Dermatology	www.aad.org	
American College of Allergy, Asthma and Immunology	www.acaai.org	
American College of Gastroenterology	www.gi.org	
American Neurogastroenterology and Motility Society	www.motilitysociety.org	
American Society of Clinical Oncology	www.asco.org	
American Society of Hematology	www.hematology.org	
Digestive Disease Week	www.ddw.org	
European Academy of Allergy and Clinical Immunology	www.eaaci.org	
European Academy of Dermatology and Venereology	www.eadv.org	
European Hematology Association	www.ehaweb.org	
European Society for Medical Oncology	www.esmo.org	
International Conference on Clinical Immunology and Allergy	www.icia.com	

International Conference on Immunological Aspects of Diseases	www.icad.com
Society of Hematologic Oncology	www.sohoonline.org
The European Competence Network on Mastocytosis	www.ecnm-conference.com
The Professional Society for Health Economics and Outcomes Research	www.ispor.org
United European Gastroenterology	www.ueg.eu
World Allergy Congress	www.worldallergy.org
World Congress of Dermatology	www.wcd.org
World Congress of Gastroenterology	www.wcg.org

Searches of conference proceedings and clinical trials registries were performed by a single reviewer and checked by a second reviewer. Conference abstracts and HTA reports that met the eligibility criteria were collated in a Microsoft Excel database and matched up to included peer-reviewed publications where relevant to determine if any additional information was provided. If the data presented in a conference abstract were available from a peer-reviewed publication, the conference abstract was excluded. Where duplicate data were presented in multiple conference abstracts, only the most recent abstract was included.

I.1.2 Search strategies

Search terms for cost-effectiveness studies were based on the filters provided by the Scottish Intercollegiate Guidelines Network (SIGN) (88) and the Canadian Agency for Drugs and Technologies in Health (CADTH) (89, 90). The economic search strategy for November 2022, the first update in November 2023 and the second update in 2025 is provided below.

I.1.2.1 Original SLR: November 2022

Table 58 Economic search strategy [MEDLINE, Embase, and EconLit] (November 25, 2022)

No.	Query	Results
#1	MESH.EXACT.EXPLODE("Mastocytosis, Systemic") OR MESH.EXACT.EXPLODE("Leukemia, Mast-Cell") OR EMB.EXACT.EXPLODE("systemic mastocytosis") OR EMB.EXACT.EXPLODE("indolent systemic mastocytosis") OR	6439*

	TI,AB(“systemic mastocytosis” OR “indolent systemic mastocytosis” OR “indolent mastocytosis”)	
#2	EMB.EXACT("Cost effectiveness analysis")	178672*
#3	MESH.EXACT("Cost-benefit analysis")	91119*
#4	MESH.EXACT("Economics")	467406*
#5	AB(cost NEAR/1 effectiveness) AND AB(costs or cost)	163285*
#6	TI(cost NEAR/1 effectiveness)	65145*
#7	EMB.EXACT("Cost benefit analysis")	95469*
#8	EMB.EXACT("Economic aspect")	132743*
#9	EMB.EXACT("Socioeconomics")	166571*
#10	MESH.EXACT("Economics, pharmaceutical")	3077°
#11	EMB.EXACT("Health economics")	42406*
#12	MESH.EXACT("Costs and cost analysis")	50973*
#13	MESH.EXACT("Value of life")	5795*
#14	TI,AB(Economic* OR pharmacoeconomic* OR price* OR pricing)	1397883*
#15	TI,AB,IF(monte carlo)	145641*
#16	EMB.EXACT("Probability")	147627*
#17	MESH.EXACT("Decision Theory" OR "Decision Trees")	12983*
#18	EMB.EXACT("Decision Tree")	19962*
#19	MESH.EXACT("Markov chains")	15841*
#20	EMB.EXACT("Statistical Model")	203109*
#21	MESH.EXACT("Monte carlo method")	31722*
#22	EMB.EXACT("Decision Theory")	2831°
#23	EMB.EXACT("Monte carlo method")	49586*
#24	TI,AB,IF(markov)	79994*
#25	AB,IF(cost* NEAR/2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes))	689645*

#26	TI,AB,IF(value NEAR/2 (money or monetary))	9999*
#27	TI,AB,IF(Decision* NEAr/2 (tree* or analy* or model*))	130554*
#28	TI,IF(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed)	2683361*
#29	MESH.EXACT.EXPLODE("Costs and cost analysis")	261238*
#30	EMB.EXACT("Economics")	252005*
#31	EMB.EXACT("Cost")	66297*
#32	AB,IF(economic model*)	255697*
#33	MESH.EXACT("Models, economic")	11037*
#34	EMB.EXACT("Cost utility analysis")	12084*
#35	TI,AB(cost NEAR/2 effectiveness)	180523*
#36	TI,AB(cost NEAR/2 utility)	20884*
#37	TI,AB(cost NEAR/2 benefit)	76277*
#38	S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37	4484528*
#39	S1 AND S38	42°
#40	MESH.EXACT("Economics")	467406*
#41	EMB.EXACT("Economic aspect")	132743*
#42	EMB.EXACT("Socioeconomics")	166571*
#43	MESH.EXACT("Economics, pharmaceutical")	3077°
#44	EMB.EXACT("Health economics")	42406*
#45	MESH.EXACT("Costs and cost analysis")	50973*
#46	MESH.EXACT("Value of life")	5795*
#47	TI,AB(Economic* OR pharmacoeconomic* OR price* OR pricing)	1397883*
#48	MESH.EXACT("Hospital costs")	11893*

#49	MESH.EXACT("Employer health costs")	1096°
#50	MESH.EXACT("Cost savings")	12649*
#51	MESH.EXACT("Direct service costs")	1213°
#52	EMB.EXACT("Financial management")	127699*
#53	EMB.EXACT("Health care financing")	14288*
#54	MESH.EXACT.EXPLODE("Budgets")	14053*
#55	MESH.EXACT.EXPLODE("Economics, medical")	14373*
#56	TI,AB(Low NEAR/1 cost)	250169*
#57	MESH.EXACT("Drug costs")	17278*
#58	MESH.EXACT("Deductibles and Coinsurance")	1835°
#59	EMB.EXACT("Health care cost")	221917*
#60	MESH.EXACT("Health expenditures")	23462*
#61	TI,AB(Cost NEAR/1 variable)	5030*
#62	EMB.EXACT("Cost of illness")	21468*
#63	MESH.EXACT("Capital expenditures")	1999°
#64	MESH.EXACT("Cost allocation")	2016°
#65	EMB.EXACT("Hospital cost")	25656*
#66	MESH.EXACT("Cost control")	21654*
#67	MESH.EXACT.EXPLODE("Economics, hospital")	25650*
#68	MESH.EXACT("Cost sharing")	2692°
#69	MESH.EXACT("Cost of illness")	31090*
#70	TI,AB((Healthcare OR health*care) NEAR/1 cost*)	47027*
#71	TI,AB(Fiscal OR funding OR financial OR finance)	682557*
#72	MESH.EXACT.EXPLODE("Fees and charges")	33764*
#73	EMB.EXACT("Cost minimization analysis")	3981°
#74	TI,AB(Cost NEAR/1 estimate*)	49620*

#75	MESH.EXACT("Health care costs")	43652*
#76	MESH.EXACT("Economics, Nursing")	3980°
#77	MESH.EXACT("Medical savings accounts")	544°
#78	EMB.EXACT("Cost control")	78391*
#79	TI,AB(High NEAR/1 cost)	139313*
#80	TI,AB(Unit NEAR/1 cost*)	13543*
#81	TI,IF(Economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed)	2683361*
#82	MESH.EXACT.EXPLODE("Costs and cost analysis")	261238*
#83	EMB.EXACT("Economics")	252005*
#84	EMB.EXACT("Cost")	66297*
#85	AB,IF(economic model*)	255697*
#86	MESH.EXACT("Models, economic")	11037*
#87	MESH.EXACT("Economics, Dental")	1896°
#88	EMB.EXACT("Budget")	37663*
#89	TI,AB,IF(budget*)	142246*
#90	TI,AB(Productivit*)	219255*
#91	TI,AB("Health care" AND cost*)	158111*
#92	TI,AB("Length of stay")	212233*
#93	TI,AB(Health AND resource)	338385*
#94	TI,AB(Resource NEAR/2 utili*ation)	47961*
#95	TI,AB(Hospitali*ation NEAR/2 (rate OR frequency))	37153*
#96	EMB.EXACT("Productivity")	60390*
#97	TI,AB(Resource NEAR/3 use)	75581*
#98	TI,AB(Visit NEAR/3 (inpatient OR outpatient OR ER OR emergency OR GP))	89719*

#99	TI,AB(Lost AND work* AND day*)	8934*
#100	S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50 OR S51 OR S52 OR S53 OR S54 OR S55 OR S56 OR S57 OR S58 OR S59 OR S60 OR S61 OR S62 OR S63 OR S64 OR S65 OR S66 OR S67 OR S68 OR S69 OR S70 OR S71 OR S72 OR S73 OR S74 OR S75 OR S76 OR S77 OR S78 OR S79 OR S80 OR S81 OR S82 OR S83 OR S84 OR S85 OR S86 OR S87 OR S88 OR S89 OR S90 OR S91 OR S92 OR S93 OR S94 OR S95 OR S96 OR S97 OR S98 OR S99	4993484*
#101	S1 AND S100	55°
#102	MESH.EXACT("Quality-Adjusted Life Years") OR EMB.EXACT("quality adjusted life year")	49333*
#103	TI,AB,IF(quality adjusted OR adjusted life year*)	168039*
#104	TI,AB,IF(qaly* OR qald* OR qale* OR qtime*)	39535*
#105	TI,AB,IF(illness state[*1] OR health state[*1])	1409207*
#106	TI,AB,IF(hui OR hui1 OR hui2 OR hui3)	6933*
#107	TI,AB,IF(multiattribute* OR multi attribute*)	17663*
#108	TI,AB,IF(utility NEAR/3 (score[*1] OR valu* or health* OR cost* OR measur* OR disease* OR mean OR gain or gains OR index*))	78732*
#109	TI,AB,IF(utilities)	662124*
#110	TI,AB,IF(eq-5d OR eq5d OR eq-5 OR eq5 OR euro qual OR euroqual OR euro qual5d OR euroqual5d OR euro qol OR euroqol OR euro qol5d OR euroqol5d OR euro quol OR euroquol OR euro quol5d OR euroquol5d OR eur qol OR eurqol OR eur qol5d OR eur qol5d OR eur?qul OR eur?qul5d OR euro* quality of life OR european qol)	84756*
#111	TI,AB,IF(euro* NEAR/3 (5*d OR 5d OR 5*dimension* OR 5dimension* OR 5*domain* OR 5domain*))	10966*
#112	TI,AB(sf6 OR sf 6 OR sf6d OR sf 6d OR sf six OR sfsix OR sf8 OR sf 8 OR sf eight OR sfeight)	86022*
#113	TI,AB(sf12 OR sf 12 OR sf twelve OR sftwelve)	45966*
#114	TI,AB(15D OR 15-D OR 15 dimension)	53404*
#115	TI,AB(sf16 OR sf 16 OR sf sixteen OR sfsixteen)	17218*
#116	TI,AB(sf20 OR sf 20 OR sf twenty OR sftwenty)	25994*
#117	TI,AB,IF(sf36* OR sf 36* OR sf thirtysix OR sf thirty six)	76659*

#118	S102 OR S103 OR S104 OR S105 OR S106 OR S107 OR S108 OR S109 OR S110 OR S111 OR S112 OR S113 OR S114 OR S115 OR S116 OR S117	2425826*
#119	S1 AND S118	143°
#120	TI,AB(standard gamble* OR sg)	34007*
#121	TI,AB,IF(time trade off[*1] OR time tradeoff[*1] OR tto OR timetradeoff[*1])	27681*
#122	TI,AB(rating scal*)	248595*
#123	TI,AB(linear scal*)	120565*
#124	TI,AB(linear analog*)	28861*
#125	TI,AB(visual analog* OR "VAS")	253414*
#126	(MESH.EXACT("Quality of Life") OR EMB.EXACT("quality of life")) AND TI,AB,IF(quality of life OR qol NEAR (score[*1] or measure[*1]))	644277*
#127	(MESH.EXACT("Quality of Life") OR EMB.EXACT("quality of life")) AND TI,AB,IF(health NEAR/3 status)	65350*
#128	TI,AB,IF(quality of life OR qol) AND (MESH.EXACT("Cost-Benefit Analysis") OR EMB.EXACT("cost benefit analysis"))	24255*
#129	TI,AB("Functional Assessment of Chronic Illness Therapy" OR "Functional Assessment of Cancer Therapy")	9529*
#130	TI,AB("EORTC QLQ-C30" OR "EORTC-QLQ-C30" OR "EORTC QLQ C30" OR "European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire")	11909*
#131	TI,AB("Indolent Systemic Mastocytosis Symptom Assessment Form" OR "ISM-SAF")	13°
#132	TI,AB("Mastocytosis Quality of Life Questionnaire" OR "MC-QoL")	14°
#133	S120 OR S121 OR S122 OR S123 OR S124 OR S125 OR S126 OR S127 OR S128 OR S129 OR S130 OR S131 OR S132	1284093*
#134	S1 AND S133	95°
#135	S39 OR S101 OR S119 OR S134	276°
#136	TI,AB(case NEAR/1 (stud* OR report))	2105231*
#137	EMB.EXACT("Case study")	145380*
#138	EMB.EXACT("Abstract report" OR "Letter")	1263950*

#139	RTYPE("Case reports")	2304248*
#140	RTYPE("Letter")	2451364*
#141	RTYPE("Historical article")	368879*
#142	PSTYPE("Conference proceedings")	4328°
#143	DTYPE("Conference review") OR DTYPE("Conference abstract") OR DTYPE("Conference Paper") OR RTYPE("Conference abstract")	5399253*
#144	RTYPE("Editorial")	1374994*
#145	RTYPE("Note")	918583*
#146	S136 OR S137 OR S138 OR S139 OR S140 OR S141 OR S142 OR S143 OR S144 OR S145	14066152*
#147	S135 NOT S146	116°

Abbreviations: EconLit, American Economic Association's electronic database; Embase; Excerpta Medica database.
Note: * Duplicates are removed from the search, but included in the result count; ° Duplicates are removed from the search and from the result count.

Table 59 Conference proceedings [Embase] (November 25, 2022)

No.	Query	Results
#1	MESH.EXACT.EXPLODE("Mastocytosis, Systemic") OR MESH.EXACT.EXPLODE("Leukemia, Mast-Cell") OR EMB.EXACT.EXPLODE("systemic mastocytosis") OR EMB.EXACT.EXPLODE("indolent systemic mastocytosis") OR TI,AB("systemic mastocytosis" OR "indolent systemic mastocytosis" OR "indolent mastocytosis")	4009°
#2	EMB.EXACT("avapritinib") OR TI,AB(avapritinib OR ayvakit OR ayvakyt OR "blu 112317" OR "blu 285" OR "BLU-263")	360°
#3	EMB.EXACT("imatinib") OR MESH.EXACT("Imatinib Mesylate") OR TI,AB(imatinib OR egitinib OR gleevac OR gleevec OR glipox OR glivec OR glivic OR imagerolan OR imakrebin OR imanivec OR imaniver OR imarem OR imatek OR "imatinib mesylate")	49174*
#4	EMB.EXACT("masitinib") OR TI,AB(masitinib or "ab 1010" or "ab1010" or "kinaction" or "masatinib" or "masatinib mesilate" or "masatinib mesylate" or "masican" or "masipro" or "masitinib mesilate" or "masitinib mesylate" or "masivet" or "masiviera")	723°
#5	EMB.EXACT("midostaurin") OR TI,AB(midostaurin OR rydapt OR "n benzoylstaurosporine" OR "pkc 412" OR pkc412)	3282°
#6	EMB.EXACT("bezuclastinib") OR TI,AB(bezuclastinib OR "cgt 9486" OR cgt9486 OR "plx 9486" OR plx9486)	15°

#7	EMB.EXACT("ripretinib") OR TI,AB(ripretinib OR qinlock)	212°
#8	EMB.EXACT("lirentelimab") OR TI,AB(lirentelimab OR "AK002" OR "AK 002")	101°
#9	EMB.EXACT("HT-KIT") OR TI,AB(HT-KIT)	9°
#10	EMB.EXACT.EXPLODE("protein tyrosine kinase inhibitor")	387031*
#11	TI,AB(H1-antihistamine OR ranitidine OR famotidine OR "leukotriene receptor antagonist" OR "proton pump inhibitor" OR "sodium cromoglycate" OR omalizumab OR "allogeneic stem cell transplantation" OR chlorodeoxyadenosine OR Cladribine OR 2-CdA OR Interferon-α OR INF-α)	66481*
#12	EMB.EXACT.EXPLODE("cromoglycate disodium") OR EMB.EXACT.EXPLODE("proton pump inhibitor") OR EMB.EXACT.EXPLODE("alpha interferon") OR EMB.EXACT.EXPLODE("antihistaminic agent") OR EMB.EXACT.EXPLODE("stem cell transplantation") OR EMB.EXACT.EXPLODE("leukotriene receptor blocking agent") OR EMB.EXACT.EXPLODE("cladribine") OR EMB.EXACT.EXPLODE("omalizumab")	729375*
#13	MESH.EXACT.EXPLODE("Proton Pump Inhibitors") OR MESH.EXACT.EXPLODE("Cromolyn Sodium") OR MESH.EXACT.EXPLODE("Interferon-alpha") OR MESH.EXACT.EXPLODE("Histamine H1 Antagonists") OR MESH.EXACT.EXPLODE("Stem Cell Transplantation") OR MESH.EXACT.EXPLODE("Leukotriene Antagonists") OR MESH.EXACT.EXPLODE("Cladribine") OR MESH.EXACT.EXPLODE("Omalizumab")	0°
#14	S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13	1096036*
#15	S1 AND S14	1816°
#16	CF(AACR 2021)	4020°
#17	CF(AACR 2020)	6330*
#18	CF(American Society of Clinical Oncology Annual Meeting, ASCO 2022)	5149*
#19	CF(American Society of Clinical Oncology Annual Meeting, ASCO 2021)	3712°
#20	CF(American Society of Clinical Oncology Annual Meeting, ASCO 2020)	5291*
#21	CF(ASH 2022)	40°
#22	CF(ASH 2021)	8725*

#23	CF(ASH 2020)	8339*
#24	CF(EHA 2022)	2231°
#25	CF(EHA 2021)	1708°
#26	CF(EHA 2020)	2322°
#27	CF(ESMO Congress 2022)	1964°
#28	CF(ESMO Congress 2021)	2701°
#29	CF(ESMO Congress 2020)	3142°
#30	CF(Society of Hematologic Oncology 2021 Annual Meeting)	446°
#31	CF(Society of Hematologic Oncology 2020 Annual Meeting)	337°
#32	CF(2022 AAAAI Annual Meeting)	737°
#33	CF(2021 AAAAI Annual Meeting)	602°
#34	CF(2020 AAAAI Annual Meeting)	852°
#35	CF(EAACI 2021)	1200°
#36	CF(DDW 2022 Digestive Disease Week)	896°
#37	CF(DDW 2021 Digestive Disease Week)	640°
#38	CF(DDW 2020 Digestive Disease Week)	5103*
#39	CF(19th American Neurogastroenterology and Motility Society Annual Scientific Meeting)	113°
#40	CF(Annual Scientific Meeting of the American College of Gastroenterology, ACG 2021)	3710°
#41	CF(Annual Scientific Meeting of the American College of Gastroenterology, ACG 2020)	3593°
#42	CF(30th United European Gastroenterology Week)	1714°
#43	CF(29th United European Gastroenterology Week)	1094°
#44	CF(28th United European Gastroenterology Week, UEG)	1536°
#45	CF(ISPOR 2022)	1526°
#46	CF(ISPOR 2021)	1242°

#47	CF(ISPOR 2020)	4284°
#48	CF(ISPOR Europe 2021)	1225°
#49	CF(Virtual ISPOR Europe 2020)	1588°
#50	CF(AAD Annual Meeting 2022)	851°
#51	CF(2021 AAD VMX Vertual Meeting)	801°
#52	CF(AAD Annual Meeting 2020)	888°
#53	CF(World Congress of Gastroenterology 2022)	0°
#54	S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50 OR S51 OR S52 OR S53	88249*
#55	S15 AND S54	70°

Abbreviations: Embase; Excerpta Medica database.

Note:* Duplicates are removed from the search but included in the result count; ° Duplicates are removed from the search and from the result count.

Table 60 Conference proceedings – Hand search (November 25, 2022)

Conference	Search terms	# Hits
AACR 2022	Mastocytosis	0
SOHO 2022	Mastocytosis	10
ECNM 2020-2022	Mastocytosis	0
AAAAI 2022	Mastocytosis	0
EAACI 2020	Systemic mastocytosis	5
IWA 2020-2022	Mastocytosis	0
ICCIA 2020-2022	Mastocytosis	0
ACAAI 2021-2022	Mastocytosis	1
ICIAD 2020-2022	Mastocytosis	N/A
EDC 2020-2022	Mastocytosis	0
WDC 2020-2022	Mastocytosis	0

WCOG 2020 and 2022	Mastocytosis	0
EADV 2021-2022	Mastocytosis	7
Total		**26**

Abbreviation: N/A, not available/not applicable.

Table 61 HTA database search (November 15, 2022)

Conference	Search terms	# Hits
NICE	Systemic mastocytosis	3
CADTH	Systemic mastocytosis	4
HAS	Systemic mastocytosis	1
GBA	Systemic mastocytosis	18
SMC	Systemic mastocytosis	1
NCPE	Systemic mastocytosis	1
AIFA	Systemic mastocytosis	46
ZinL	Systemic mastocytosis	0
RIZIV	Systemic mastocytosis	0
AEMPS	Systemic mastocytosis	0
Total		**74**

I.1.2.2 Updated SLR: November, 2023

Table 62 Economic search strategy [MEDLINE, Embase, and EconLit] (November 29, 2023)

No.	Query	Results
#1	MESH.EXACT.EXPLODE("Mastocytosis, Systemic") OR MESH.EXACT.EXPLODE("Leukemia, Mast-Cell") OR EMB.EXACT.EXPLODE("systemic mastocytosis") OR EMB.EXACT.EXPLODE("indolent systemic mastocytosis") OR TI,AB("systemic mastocytosis" OR "indolent systemic mastocytosis" OR "indolent mastocytosis")	6842*

#2	EMB.EXACT("Cost effectiveness analysis")	189524*
#3	MESH.EXACT("Cost-benefit analysis")	93427*
#4	MESH.EXACT("Economics")	468012*
#5	AB(cost NEAR/1 effectiveness) AND AB(costs or cost)	175176*
#6	TI(cost NEAR/1 effectiveness)	69297*
#7	EMB.EXACT("Cost benefit analysis")	98408*
#8	EMB.EXACT("Economic aspect")	137064*
#9	EMB.EXACT("Socioeconomics")	173342*
#10	MESH.EXACT("Economics, pharmaceutical")	3102°
#11	EMB.EXACT("Health economics")	43464*
#12	MESH.EXACT("Costs and cost analysis")	51632*
#13	MESH.EXACT("Value of life")	5816*
#14	TI,AB(Economic* OR pharmacoeconomic* OR price* OR pricing)	1496407*
#15	TI,AB,IF(monte carlo)	154642*
#16	EMB.EXACT("Probability")	160356*
#17	MESH.EXACT("Decision Theory" OR "Decision Trees")	13096*
#18	EMB.EXACT("Decision Tree")	23380*
#19	MESH.EXACT("Markov chains")	16037*
#20	EMB.EXACT("Statistical Model")	205780*
#21	MESH.EXACT("Monte carlo method")	32487*
#22	EMB.EXACT("Decision Theory")	2861°
#23	EMB.EXACT("Monte carlo method")	53329*
#24	TI,AB,IF(markov)	85380*
#25	AB,IF(cost* NEAR/2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes))	734218*
#26	TI,AB,IF(value NEAR/2 (money or monetary))	10675*

#27	TI,AB,IF(Decision* NEAr/2 (tree* or analy* or model*))	146112*
#28	TI,IF(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed)	2805322*
#29	MESH.EXACT.EXPLODE("Costs and cost analysis")	267214*
#30	EMB.EXACT("Economics")	252368*
#31	EMB.EXACT("Cost")	68036*
#32	AB,IF(economic model*)	277552*
#33	MESH.EXACT("Models, economic")	11094*
#34	EMB.EXACT("Cost utility analysis")	13040*
#35	TI,AB(cost NEAR/2 effectiveness)	193103*
#36	TI,AB(cost NEAR/2 utility)	22619*
#37	TI,AB(cost NEAR/2 benefit)	80028*
#38	S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37	4725711*
#39	S1 AND S38	50°
#40	MESH.EXACT("Economics")	468012*
#41	EMB.EXACT("Economic aspect")	137064*
#42	EMB.EXACT("Socioeconomics")	173342*
#43	MESH.EXACT("Economics, pharmaceutical")	3102°
#44	EMB.EXACT("Health economics")	43464*
#45	MESH.EXACT("Costs and cost analysis")	51632*
#46	MESH.EXACT("Value of life")	5816*
#47	TI,AB(Economic* OR pharmacoeconomic* OR price* OR pricing)	1496407*
#48	MESH.EXACT("Hospital costs")	11984*
#49	MESH.EXACT("Employer health costs")	1096°

#50	MESH.EXACT("Cost savings")	12759*
#51	MESH.EXACT("Direct service costs")	1213°
#52	EMB.EXACT("Financial management")	131029*
#53	EMB.EXACT("Health care financing")	14532*
#54	MESH.EXACT.EXPLODE("Budgets")	14150*
#55	MESH.EXACT.EXPLODE("Economics, medical")	14407*
#56	TI,AB(Low NEAR/1 cost)	275809*
#57	MESH.EXACT("Drug costs")	17485*
#58	MESH.EXACT("Deductibles and Coinsurance")	1860°
#59	EMB.EXACT("Health care cost")	234602*
#60	MESH.EXACT("Health expenditures")	24334*
#61	TI,AB(Cost NEAR/1 variable)	5257*
#62	EMB.EXACT("Cost of illness")	21964*
#63	MESH.EXACT("Capital expenditures")	2000°
#64	MESH.EXACT("Cost allocation")	2017°
#65	EMB.EXACT("Hospital cost")	26884*
#66	MESH.EXACT("Cost control")	21675*
#67	MESH.EXACT.EXPLODE("Economics, hospital")	25761*
#68	MESH.EXACT("Cost sharing")	2744°
#69	MESH.EXACT("Cost of illness")	31825*
#70	TI,AB((Healthcare OR health*care) NEAR/1 cost*)	52362*
#71	TI,AB(Fiscal OR funding OR financial OR finance)	749521*
#72	MESH.EXACT.EXPLODE("Fees and charges")	33902*
#73	EMB.EXACT("Cost minimization analysis")	4146°
#74	TI,AB(Cost NEAR/1 estimate*)	52668*
#75	MESH.EXACT("Health care costs")	44501*

#76	MESH.EXACT("Economics, Nursing")	3980°
#77	MESH.EXACT("Medical savings accounts")	546°
#78	EMB.EXACT("Cost control")	80726*
#79	TI,AB(High NEAR/1 cost)	152863*
#80	TI,AB(Unit NEAR/1 cost*)	14222*
#81	TI,IF(Economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed)	2805322*
#82	MESH.EXACT.EXPLODE("Costs and cost analysis")	267214*
#83	EMB.EXACT("Economics")	252368*
#84	EMB.EXACT("Cost")	68036*
#85	AB,IF(economic model*)	277552*
#86	MESH.EXACT("Models, economic")	11094*
#87	MESH.EXACT("Economics, Dental")	1897°
#88	EMB.EXACT("Budget")	39117*
#89	TI,AB,IF(budget*)	148718*
#90	TI,AB(Productivit*)	236537*
#91	TI,AB("Health care" AND cost*)	165313*
#92	TI,AB("Length of stay")	232097*
#93	TI,AB(Health AND resource)	371727*
#94	TI,AB(Resource NEAR/2 utili*ation)	52976*
#95	TI,AB(Hospitali*ation NEAR/2 (rate OR frequency))	40989*
#96	EMB.EXACT("Productivity")	63769*
#97	TI,AB(Resource NEAR/3 use)	81088*
#98	TI,AB(Visit NEAR/3 (inpatient OR outpatient OR ER OR emergency OR GP))	98744*
#99	TI,AB(Lost AND work* AND day*)	9443*

#100	S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50 OR S51 OR S52 OR S53 OR S54 OR S55 OR S56 OR S57 OR S58 OR S59 OR S60 OR S61 OR S62 OR S63 OR S64 OR S65 OR S66 OR S67 OR S68 OR S69 OR S70 OR S71 OR S72 OR S73 OR S74 OR S75 OR S76 OR S77 OR S78 OR S79 OR S80 OR S81 OR S82 OR S83 OR S84 OR S85 OR S86 OR S87 OR S88 OR S89 OR S90 OR S91 OR S92 OR S93 OR S94 OR S95 OR S96 OR S97 OR S98 OR S99	5310654*
#101	S1 AND S100	67°
#102	MESH.EXACT("Quality-Adjusted Life Years") OR EMB.EXACT("quality adjusted life year")	52861*
#103	TI,AB,IF(quality adjusted OR adjusted life year*)	184746*
#104	TI,AB,IF(qaly* OR qald* OR qale* OR qtime*)	42886*
#105	TI,AB,IF(illness state[*1] OR health state[*1])	1469930*
#106	TI,AB,IF(hui OR hui1 OR hui2 OR hui3)	7446*
#107	TI,AB,IF(multiattribute* OR multi attribute*)	19810*
#108	TI,AB,IF(utility NEAR/3 (score[*1] OR valu* or health* OR cost* OR measur* OR disease* OR mean OR gain or gains OR index*))	84904*
#109	TI,AB,IF(utilities)	710531*
#110	TI,AB,IF(eq-5d OR eq5d OR eq-5 OR eq5 OR euro qual OR euroqual OR euro qual5d OR euroqual5d OR euro qol OR euroqol OR euro qol5d OR euroqol5d OR euro quol OR euroquol OR euro quol5d OR euroquol5d OR eur qol OR eurqol OR eur qol5d OR eur qol5d OR eur?qul OR eur?qul5d OR euro* quality of life OR european qol)	93151*
#111	TI,AB,IF(euro* NEAR/3 (5*d OR 5d OR 5*dimension* OR 5dimension* OR 5*domain* OR 5domain*))	11817*
#112	TI,AB(sf6 OR sf 6 OR sf6d OR sf 6d OR sf six OR sfsix OR sf8 OR sf 8 OR sf eight OR sfeight)	91750*
#113	TI,AB(sf12 OR sf 12 OR sf twelve OR sftwelve)	49172*
#114	TI,AB(15D OR 15-D OR 15 dimension)	56901*
#115	TI,AB(sf16 OR sf 16 OR sf sixteen OR sfsixteen)	18473*
#116	TI,AB(sf20 OR sf 20 OR sf twenty OR sftwenty)	27724*
#117	TI,AB,IF(sf36* OR sf 36* OR sf thirtysix OR sf thirty six)	80903*
#118	S102 OR S103 OR S104 OR S105 OR S106 OR S107 OR S108 OR S109 OR S110 OR S111 OR S112 OR S113 OR S114 OR S115 OR S116 OR S117	2566075*

#119	S1 AND S118	155°
#120	TI,AB(standard gamble* OR sg)	37117*
#121	TI,AB,IF(time trade off[*1] OR time tradeoff[*1] OR tto OR timetradeoff[*1])	30106*
#122	TI,AB(rating scal*)	266600*
#123	TI,AB(linear scal*)	133026*
#124	TI,AB(linear analog*)	30351*
#125	TI,AB(visual analog* OR "VAS")	272605*
#126	(MESH.EXACT("Quality of Life") OR EMB.EXACT("quality of life")) AND TI,AB,IF(quality of life OR qol NEAR (score[*1] or measure[*1]))	702873*
#127	(MESH.EXACT("Quality of Life") OR EMB.EXACT("quality of life")) AND TI,AB,IF(health NEAR/3 status)	68530*
#128	TI,AB,IF(quality of life OR qol) AND (MESH.EXACT("Cost-Benefit Analysis") OR EMB.EXACT("cost benefit analysis"))	25572*
#129	TI,AB("Functional Assessment of Chronic Illness Therapy" OR "Functional Assessment of Cancer Therapy")	10470*
#130	TI,AB("EORTC QLQ-C30" OR "EORTC-QLQ-C30" OR "EORTC QLQ C30" OR "European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire")	13081*
#131	TI,AB("Indolent Systemic Mastocytosis Symptom Assessment Form" OR "ISM-SAF")	14°
#132	TI,AB("Mastocytosis Quality of Life Questionnaire" OR "MC-QoL")	18°
#133	S120 OR S121 OR S122 OR S123 OR S124 OR S125 OR S126 OR S127 OR S128 OR S129 OR S130 OR S131 OR S132	1392175*
#134	S1 AND S133	110°
#135	S39 OR S101 OR S119 OR S134	312°
#136	TI,AB(case NEAR/1 (stud* OR report))	2249384*
#137	EMB.EXACT("Case study")	153335*
#138	EMB.EXACT("Abstract report" OR "Letter")	1307754*
#139	RTYPE("Case reports")	2368562*

#140	RTYPE("Letter")	2533131*
#141	RTYPE("Historical article")	369394*
#142	PSTYPE("Conference proceedings")	4328°
#143	DTYPE("Conference review") OR DTYPE("Conference abstract") OR DTYPE("Conference Paper") OR RTYPE("Conference abstract")	5770331*
#144	RTYPE("Editorial")	1458683*
#145	RTYPE("Note")	965013*
#146	S136 OR S137 OR S138 OR S139 OR S140 OR S141 OR S142 OR S143 OR S144 OR S145	14798684*
#147	S135 NOT S146	128°
#148	S147 AND pd(>20221125)	12°

Abbreviations: EconLit, American Economic Association's electronic database; Embase; Excerpta Medica database.
Note:* Duplicates are removed from the search but included in the result count; ° Duplicates are removed from the search and from the result count.

Table 63 Conference proceedings [Embase] (November 29, 2023)

No.	Query	Results
#1	MESH.EXACT.EXPLODE("Mastocytosis, Systemic") OR MESH.EXACT.EXPLODE("Leukemia, Mast-Cell") OR EMB.EXACT.EXPLODE("systemic mastocytosis") OR EMB.EXACT.EXPLODE("indolent systemic mastocytosis") OR TI,AB("systemic mastocytosis" OR "indolent systemic mastocytosis" OR "indolent mastocytosis")	4299°
#2	EMB.EXACT("avapritinib") OR TI,AB(avapritinib OR ayvakit OR ayvakyt OR "blu 112317" OR "blu 285" OR "BLU-263")	525°
#3	EMB.EXACT("imatinib") OR MESH.EXACT("Imatinib Mesylate") OR TI,AB(imatinib OR egitinib OR gleevac OR gleevec OR glipox OR glivec OR glivic OR imagerolan OR imakrebin OR imanivec OR imaniver OR imarem OR imatek OR "imatinib mesylate")	51476*
#4	EMB.EXACT("masitinib") OR TI,AB(masitinib or "ab 1010" or "ab1010" or "kinaction" or "masatinib" or "masatinib mesilate" or "masatinib mesylate" or "masican" or "masipro" or "masitinib mesilate" or "masitinib mesylate" or "masivet" or "masiviera")	811°
#5	EMB.EXACT("midostaurin") OR TI,AB(midostaurin OR rydapt OR "n benzoylstaurosporine" OR "pkc 412" OR pkc412)	3738°

#6	EMB.EXACT("bezuclastinib") OR TI,AB(bezuclastinib OR "cgt 9486" OR cgt9486 OR "plx 9486" OR plx9486)	28°
#7	EMB.EXACT("ripretinib") OR TI,AB(ripretinib OR qinlock)	319°
#8	EMB.EXACT("lirentelimab") OR TI,AB(lirentelimab OR "AK002" OR "AK 002")	147°
#9	EMB.EXACT("HT-KIT") OR TI,AB(HT-KIT)	14°
#10	EMB.EXACT.EXPLODE("protein tyrosine kinase inhibitor")	423243*
#11	TI,AB(H1-antihistamine OR ranitidine OR famotidine OR "leukotriene receptor antagonist" OR "proton pump inhibitor" OR "sodium cromoglycate" OR omalizumab OR "allogeneic stem cell transplantation" OR chlorodeoxyadenosine OR Cladribine OR 2-CdA OR Interferon-α OR INF-α)	69353*
#12	EMB.EXACT.EXPLODE("cromoglycate disodium") OR EMB.EXACT.EXPLODE("proton pump inhibitor") OR EMB.EXACT.EXPLODE("alpha interferon") OR EMB.EXACT.EXPLODE("antihistaminic agent") OR EMB.EXACT.EXPLODE("stem cell transplantation") OR EMB.EXACT.EXPLODE("leukotriene receptor blocking agent") OR EMB.EXACT.EXPLODE("cladribine") OR EMB.EXACT.EXPLODE("omalizumab")	772049*
#13	MESH.EXACT.EXPLODE("Proton Pump Inhibitors") OR MESH.EXACT.EXPLODE("Cromolyn Sodium") OR MESH.EXACT.EXPLODE("Interferon-alpha") OR MESH.EXACT.EXPLODE("Histamine H1 Antagonists") OR MESH.EXACT.EXPLODE("Stem Cell Transplantation") OR MESH.EXACT.EXPLODE("Leukotriene Antagonists") OR MESH.EXACT.EXPLODE("Cladribine") OR MESH.EXACT.EXPLODE("Omalizumab")	0°
#14	S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13	1172481*
#15	S1 AND S14	1988°
#16	CF(American Society of Clinical Oncology Annual Meeting, ASCO 2023)	47°
#17	CF(ESMO Congress 2023)	2880°
#18	CF(2023 AAAAI Annual Meeting)	776°
#19	CF(DDW 2023 Digestive Disease Week)	956°
#20	CF(ISPOR 2023)	1898°
#21	CF(AAD Annual Meeting)	4100°

#22	S16 OR S17 OR S18 OR S19 OR S20 OR S21	11692*
#23	S15 AND S22	5°

Abbreviations: Embase; Excerpta Medica database.
Note:* Duplicates are removed from the search but included in the result count; ° Duplicates are removed from the search and from the result count.

Table 64 Conference proceedings – Hand search (November 29, 2023)

Conference	Search terms	# Hits
AACR 2023	Mastocytosis	0
ASH 2023	Mastocytosis	24
ISPOR Europe 2023	Mastocytosis	6
SOHO 2023	Mastocytosis	1
ACG 2023	Mastocytosis	2
ECNM 2021-2023	N/A	N/A
EHA 2023	N/A	N/A
AAAAI 2023	Mastocytosis	1
EAACI 2023	Systemic mastocytosis	N/A
IWA 2021-2023	N/A	N/A
ICIA 2021-2023	N/A	N/A
ACAAI 2022	Mastocytosis	0
ICIAD 2021-2023	N/A	N/A
EDC 2021-2023	N/A	N/A
WDC 2021-2023	N/A	N/A
WCOG 2023	N/A	N/A
ANMS 2023	Mastocytosis	0
EADV 2023	Mastocytosis	0
UEG 2023	Mastocytosis	0
Total		**34**

Abbreviation: N/A, not available/not applicable.

Table 65 HTA database search (November 29, 2023)

Conference	Search terms	# Hits
NICE	Systemic mastocytosis	6
CADTH	Systemic mastocytosis	5
HAS	Systemic mastocytosis	2
GBA	Systemic mastocytosis	29
SMC	Systemic mastocytosis	1
NCPE	Systemic mastocytosis	0
AIFA	Systemic mastocytosis	58
ZinL	Systemic mastocytosis	0
RIZIV	Systemic mastocytosis	0
AEMPS	Systemic mastocytosis	1
Total (November 2022)		74
Total (November 2023)		**102**

I.1.2.3 Updated SLR: March 2025

Table 66 HRQoL search strategy [Embase] (March 31, 2025)

No.	Query	Results
#1	exp systemic mastocytosis/	3,904
#2	exp mast cell leukemia/	1,870
#3	exp indolent systemic mastocytosis/	470
#4	("systemic mastocytosis" or "indolent systemic mastocytosis" or "indolent mastocytosis").ti,ab.	3,828
#5	(systemic mastocytosis or NonAdvSM or ISM or SSM).ti,ab.	9,721
#6	1 or 2 or 3 or 4 or 5	11,904

#7	exp "quality of life"/	749,521
#8	(quality of life or qol).ti,ab.	684,260
#9	exp quality adjusted life year/	39,852
#10	(quality adjusted or adjusted life year*).ti,ab.	39,583
#11	(qaly* or qald* or qale* or qtime*).ti,ab.	30,064
#12	(illness state* or health state*).ti,ab.	16,299
#13	(hui or hui1 or hui2 or hui3).ti,ab.	3,525
#14	(multiattribute* or multi attribute*).ti,ab.	1,676
#15	(utility adj3 (score* or valu* or health* or cost* or measur* or disease* or mean or gain or gains or index*)).ti,ab.	35,202
#16	utilities.ti,ab.	16,485
#17	(eq-5d or eq5d or eq-5 or eq5 or euro qual or euroqual or euro qual5d or euroqual5d or euro qol or euroqol or euro qol5d or euroqol5d or euro quol or euroquol or euro quol5d or euroquol5d or eur qol or eurqol or eur qol5d or eur qol5d or eur?qul or eur?qul5d or euro* quality of life or european qol).ti,ab.	35,872
#18	(euro* adj3 (5*d or 5d or 5*dimension* or 5dimension* or 5*domain* or 5domain*)).ti,ab.	5,971
#19	(sf6 or sf 6 or sf6d or sf 6d or sf six or sfsix or sf8 or sf 8 or sf eight or sfeight).ti,ab.	5,827
#20	(sf12 or sf 12 or sf twelve or sftwelve).ti,ab.	11,507
#21	(15D or 15-D or 15 dimension).ti,ab.	8,164
#22	(sf16 or sf 16 or sf sixteen or sfsixteen).ti,ab.	70
#23	(sf20 or sf 20 or sf twenty or sftwenty).ti,ab.	400
#24	(sf36* or sf 36* or sf thirtysix or sf thirty six).ti,ab.	48,659
#25	(standard gamble* or sg).ti,ab.	23,804
#26	(time trade off* or time tradeoff* or tto or timetradeoff*).ti,ab.	3,854
#27	rating scal*.ti,ab.	121,702
#28	linear scal*.ti,ab.	1,853

#29	linear analog*.ti,ab.	1,472
#30	(visual analog* or "VAS").ti,ab.	173,861
#31	((quality of life or qol) adj (score* or measure*)).ti,ab.	43,028
#32	(health adj3 status).ti,ab.	123,258
#33	exp "cost benefit analysis"/	99,138
#34	("Functional Assessment of Chronic Illness Therapy" or "Functional Assessment of Cancer Therapy").ti,ab.	7,596
#35	("EORTC QLQ-C30" or "EORTC-QLQ-C30" or "EORTC QLQ C30" or "European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire").ti,ab.	10,942
#36	("Indolent Systemic Mastocytosis Symptom Assessment Form" or "ISM-SAF").ti,ab.	27
#37	("Mastocytosis Quality of Life Questionnaire" or "MC-QoL").ti,ab.	23
#38	exp socioeconomics/	1,658,235
#39	exp Nottingham Health Profile/	702
#40	exp Sickness Impact Profile/	2,359
#41	exp health survey/	300,353
#42	exp disability assessment/	62,510
#43	exp economic model/	4,821
#44	exp questionnaire/	1,050,202
#45	exp visual analog scale/	145,392
#46	7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45	3,880,204
#47	6 and 46	987
#48	limit 47 to yr="2023 -Current"	236

Abbreviations: Embase; Excerpta Medica database.

Table 67 HRQoL search strategy [Medline] (March 31, 2025)

No.	Query	Results
#1	exp Mastocytosis, Systemic/	1,419
#2	exp Leukemia, Mast-Cell/	255
#3	indolent systemic mastocytosis.mp.	224
#4	("systemic mastocytosis" or "indolent systemic mastocytosis" or "indolent mastocytosis").ti,ab.	2,243
#5	(systemic mastocytosis or NonAdvSM or ISM or SSM).ti,ab.	6,598
#6	1 or 2 or 3 or 4 or 5	6,969
#7	exp "Quality of Life"/	303,294
#8	(quality of life or qol).ti,ab.	438,513
#9	exp Quality-Adjusted Life Years/	17,629
#10	(quality adjusted or adjusted life year*).ti,ab.	27,573
#11	(qaly* or qald* or qale* or qtime*).ti,ab.	16,441
#12	(illness state* or health state*).ti,ab.	9,382
#13	(hui or hui1 or hui2 or hui3).ti,ab.	2,181
#14	(multiattribute* or multi attribute*).ti,ab.	1,500
#15	(utility adj3 (score* or valu* or health* or cost* or measur* or disease* or mean or gain or gains or index*)).ti,ab.	22,569
#16	utilities.ti,ab.	10,393
#17	(eq-5d or eq5d or eq-5 or eq5 or euro qual or euroqual or euro qual5d or euroqual5d or euro qol or euroqol or euro qol5d or euroqol5d or euro quol or euroquol or euro quol5d or euroquol5d or eur qol or eurqol or eur qol5d or eur qol5d or eur?qul or eur?qul5d or euro* quality of life or european qol).ti,ab.	20,515
#18	(euro* adj3 (5*d or 5d or 5*dimension* or 5dimension* or 5*domain* or 5domain*)).ti,ab.	3,824
#19	(sf6 or sf 6 or sf6d or sf 6d or sf six or sfsix or sf8 or sf 8 or sf eight or sfeight).ti,ab.	4,309
#20	(sf12 or sf 12 or sf twelve or sftwelve).ti,ab.	6,991
#21	(15D or 15-D or 15 dimension).ti,ab.	6,547

#22	(sf16 or sf 16 or sf sixteen or sfsixteen).ti,ab.	37
#23	(sf20 or sf 20 or sf twenty or sftwenty).ti,ab.	370
#24	(sf36* or sf 36* or sf thirtysix or sf thirty six).ti,ab.	28,700
#25	(standard gamble* or sg).ti,ab.	16,351
#26	(time trade off* or time tradeoff* or tto or timetradeoff*).ti,ab.	2,632
#27	rating scal*.ti,ab.	82,827
#28	linear scal*.ti,ab.	2,005
#29	linear analog*.ti,ab.	1,199
#30	(visual analog* or "VAS").ti,ab.	116,684
#31	((quality of life or qol) adj (score* or measure*)).ti,ab.	26,206
#32	(health adj3 status).ti,ab.	96,680
#33	exp Cost-Benefit Analysis/	97,305
#34	("Functional Assessment of Chronic Illness Therapy" or "Functional Assessment of Cancer Therapy").ti,ab.	4,457
#35	("EORTC QLQ-C30" or "EORTC-QLQ-C30" or "EORTC QLQ C30" or "European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire").ti,ab.	5,373
#36	("Indolent Systemic Mastocytosis Symptom Assessment Form" or "ISM-SAF").ti,ab.	5
#37	("Mastocytosis Quality of Life Questionnaire" or "MC-QoL").ti,ab.	8
#38	exp Health Surveys/	649,357
#39	exp "Value of Life"/	5,834
#40	exp Disability Evaluation/	58,260
#41	exp Models, Economic/	16,796
#42	exp "Surveys and Questionnaires"/	1,302,225
#43	exp Visual Analog Scale/	4,216
#44	7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43	2,063,043

#45	6 and 44	372
#46	limit 45 to yr="2023 -Current"	69

Abbreviations: HRQoL, Health-related quality of life.

Table 68 HRQoL search strategy [CDSR] (March 31, 2025)

No.	Query	Results
#1	("systemic mastocytosis" or "mast cell leukemia" or "indolent systemic mastocytosis" or NonAdvSM or ISM or SSM).mp. [mp=title, short title, abstract, full text, keywords, caption text]	11
#2	limit 1 to last 3 years	0

Abbreviations: CDSR, cochrane database of systematic reviews; HRQoL, Health-related quality of life.

Table 69 HRQoL search strategy [CENTRAL] (March 31, 2025)

No.	Query	Results
#1	exp Mastocytosis, Systemic/	18
#2	exp Leukemia, Mast-Cell/	2
#3	indolent systemic mastocytosis.mp.	56
#4	("systemic mastocytosis" or "indolent systemic mastocytosis" or "indolent mastocytosis").ti,ab.	99
#5	(systemic mastocytosis or NonAdvSM or ISM or SSM).ti,ab.	319
#6	1 or 2 or 3 or 4 or 5	323
#7	limit 6 to yr="2023 -Current"	47

Abbreviations: HRQoL, Health-related quality of life.

Table 70 HRQoL search strategy [Econlit] (March 31, 2025)

No.	Query	Results
#1	("systemic mastocytosis" or "mast cell leukemia" or "indolent systemic mastocytosis" or NonAdvSM or ISM or SSM).mp. [mp=heading words, abstract, title, country as subject]	317
#2	limit 1 to yr="2023 -Current"	27

Abbreviations: EconLit, American Economic Association's electronic database; HRQoL, Health-related quality of life.

Table 71 HRQoL search strategy [NHS EED] (March 31, 2025)

No.	Query	Results

#1	(systemic mastocytosis) OR (mast cell leukemia) OR (NonAdvSM OR ISM OR SSM) IN DARE, NHSEED, HTA FROM 2023 TO 2025	0

Abbreviations: HRQoL, Health-related quality of life; NHS EED, National Health Service Economic Evaluation Database.

Note: Inception to 1st Quarter 2016 (Database no longer updated after this point).

Table 72 HRQoL grey literature search strategy (March 31, 2025)

Source	Link	Search strategy and hits from each term	Number included
American Academy of Allergy, Asthma, and Immunology	2023: https://www.sciencedirect.com/journal/journal-of-allergy-and-clinical-immunology/vol/151/issue/2/suppl/S#article-3 2024: https://www.sciencedirect.com/journal/journal-of-allergy-and-clinical-immunology/vol/153/issue/2/suppl/S?page=9#article-832 2025: https://www.jacionline.org/programs_abstracts	2023 to 2025: Systemic mastocytosis: 55 Non-advanced systemic mastocytosis: 8 Non advanced systemic mastocytosis: 8 non-AdvSM: 5 non AdvSM: 3 Indolent systemic mastocytosis: 33 ISM: 29 Smoldering systemic mastocytosis: 3 SSM: 0	2
American Academy of Dermatology	2023: https://eposters.aad.org/archives/AM2023 2024: https://eposters.aad.org/archives/AM2024 2025: https://eposters.aad.org/	2023 to 2025: Searched the abstract book manually	0
American College of Allergy, Asthma and Immunology	2023: https://www.annallergy.org/issue/S1081-1206(23)X0002-7#OralAbstracts1315 2024: https://www.sciencedirect.com/journal/annals-of-allergy-asthma-and-immunology/vol/133/issue/6/suppl/S	2023 to 2024: Systemic mastocytosis: 44 Non-advanced systemic mastocytosis: 3 Non advanced systemic mastocytosis: 3 non-AdvSM: 1 non AdvSM: 1 Indolent systemic mastocytosis: 17 ISM: 16 Smoldering systemic mastocytosis: 5 SSM: 0	0

	2025: Conference not held		
American College of Gastroenterology	2023: https://journals.lww.com/ajg/toc/2023/10001 2024: https://journals.lww.com/ajg/toc/2024/10001 2025: Conference not held	2023 to 2024: Searched the abstract book manually	0
American Neurogastroenterology and Motility Society	2023: https://onlinelibrary.wiley.com/doi/10.1111/nmo.14642 2024: Abstract link was not found 2025: Abstract link was not found	2023: Searched the abstract book manually	0
American Society of Clinical Oncology	2023: https://meetings.asco.org/abstracts-presentations/search?q=*&filters=%7B%22meetingTypeName%22:%5B%7B%22key%22:%22ASCO%20Annual%20Meeting%22%7D%5D,%22meetingYear%22:%5B%7B%22key%22:%222023%22%7D%5D%7D 2024: https://meetings.asco.org/abstracts-presentations/search?q=*&filters=%7B%22meetingTypeName%22:%5B%7B%22key%22:%22ASCO%20Annual%20Meeting%22%7D%5D,%22meetingYear%22:%5B%7B%22key%22:%222024%22%7D%5D%7D 2025: https://meetings.asco.org/abstracts-presentations/search?query=*&q=2025%20ASCO%20Annual%20Meeting&sortBy=Relevancy&filters=%7B%22meetingTypeName%22:%5B%7B%22key%22:%22ASCO%20Annual%20M	2023 to 2025: Systemic mastocytosis: 4 Non-advanced systemic mastocytosis: 0 Non advanced systemic mastocytosis: 0 non-AdvSM: 0 non AdvSM: 0 Indolent systemic mastocytosis: 0 ISM: 0 Smoldering systemic mastocytosis: 0 SSM: 23	0

	eeting%22%7D%5D,%22mediaType%22:%5B%7B%22key%22:%22Abstracts%22%7D%5D,%22meetingYear%22:%5B%7B%22key%22:%222025%22%7D%5D%7D&pageNumber=1		
American Society of Hematology	2023: https://ash.confex.com/ash/2023/webprogram/start.html 2024: https://ash.confex.com/ash/2024/webprogram/start.html 2025: Conference not held	2023 to 2024: Systemic mastocytosis: 42 Non-advanced systemic mastocytosis: 3 Non advanced systemic mastocytosis: 0 non-AdvSM: 1 non AdvSM: 0 Indolent systemic mastocytosis: 14 ISM: 10 Smoldering systemic mastocytosis: 5 SSM: 13	1
Digestive Disease Week	2023: https://www.gastrojournal.org/issue/S0016-5085(23)X6001-6# 2024: https://www.gastrojournal.org/issue/S0016-5085(24)X6001-1 2025: Conference not held	2023 to 2024: Searched the abstract book manually	0
European Academy of Allergy and Clinical Immunology	2023: https://onlinelibrary.wiley.com/toc/13989995/2023/78/S112 2024: https://onlinelibrary.wiley.com/toc/13989995/2024/79/S113 2025: Conference not held	2023 to 2024: Searched the abstract book manually	0
European Academy of Dermatology and Venereology	2023: https://eadv.org/scientific/abstract-books/?utm 2024: https://eadv.org/scientific/abstract-books/?utm 2025: Conference not held	2023 to 2024: Searched the abstract book manually	0
European Dermatology Congress	2023: Abstract link was not found 2024: Abstract link was not found	Systemic mastocytosis: NA Non-advanced systemic mastocytosis: NA Non advanced systemic mastocytosis: NA	NA

	2025: Abstract link was not found	non-AdvSM: NA non AdvSM: NA Indolent systemic mastocytosis: NA ISM: NA Smoldering systemic mastocytosis: NA SSM: NA	
European Hematology Association	2023: https://onlinelibrary.wiley.com/toc/25729241/2023/7/S3 2024: https://onlinelibrary.wiley.com/toc/25729241/2024/8/S1 2025: Conference not held	2023 to 2024: Systemic mastocytosis: 7 Non-advanced systemic mastocytosis: 4 Non advanced systemic mastocytosis: 4 non-AdvSM: 2 non AdvSM: 2 Indolent systemic mastocytosis: 1 ISM: 4 Smoldering systemic mastocytosis: 0 SSM: 3	0
European Society for Medical Oncology	2023: https://oncologypro.esmo.org/meeting-resources/esmo-congress-2023 2024: https://oncologypro.esmo.org/meeting-resources/esmo-congress-2024 2025: Conference not held	2023 to 2024: Systemic mastocytosis: 0 Non-advanced systemic mastocytosis: 0 Non advanced systemic mastocytosis: 0 non-AdvSM: 0 non AdvSM: 0 Indolent systemic mastocytosis: 0 ISM: 0 Smoldering systemic mastocytosis: 0 SSM: 0	0
International Conference on Clinical Immunology and Allergy	2023: Abstract link was not found 2024: Abstract link was not found 2025: Abstract link was not found	Systemic mastocytosis: NA Non-advanced systemic mastocytosis: NA Non advanced systemic mastocytosis: NA non-AdvSM: NA non AdvSM: NA Indolent systemic mastocytosis: NA ISM: NA Smoldering systemic mastocytosis: NA SSM: NA	NA
International Conference on Immunological Aspects of Diseases	2023: Abstract link was not found 2024: Abstract link was not found 2025: Abstract link was not found	Systemic mastocytosis: NA Non-advanced systemic mastocytosis: NA Non advanced systemic mastocytosis: NA non-AdvSM: NA non AdvSM: NA Indolent systemic mastocytosis: NA ISM: NA Smoldering systemic mastocytosis: NA SSM: NA	NA

Society of Hematologic Oncology	2023: https://www.sciencedirect.com/journal/clinical-lymphoma-myeloma-and-leukemia/vol/23/suppl/S1 2024: https://www.sciencedirect.com/journal/clinical-lymphoma-myeloma-and-leukemia/vol/24/suppl/S1 2025: Conference not held	2023 to 2024: Systemic mastocytosis: 52 Non-advanced systemic mastocytosis: 16 Non advanced systemic mastocytosis: 16 non-AdvSM: 13 non AdvSM: 13 Indolent systemic mastocytosis: 15 ISM: 4 Smoldering systemic mastocytosis: 2 SSM: 2	0
The European Competence Network on Mastocytosis	2023: Abstract link was not found 2024: Abstract link was not found 2025: Conference not held	Systemic mastocytosis: NA Non-advanced systemic mastocytosis: NA Non advanced systemic mastocytosis: NA non-AdvSM: NA non AdvSM: NA Indolent systemic mastocytosis: NA ISM: NA Smoldering systemic mastocytosis: NA SSM: NA	NA
The Professional Society for Health Economics and Outcomes Research	2023: https://www.ispor.org/heor-resources/presentations-database/search 2024: https://www.ispor.org/heor-resources/presentations-database/search 2025: Conference not held	2023 to 2024: Systemic mastocytosis: 3 Non-advanced systemic mastocytosis: 2 Non advanced systemic mastocytosis: 2 non-AdvSM: 0 non AdvSM: 0 Indolent systemic mastocytosis: 2 ISM: 2 Smoldering systemic mastocytosis: 1 SSM: 0	0
United European Gastroenterology	2023: https://onlinelibrary.wiley.com/toc/20506414/2023/11/S8 2024: https://onlinelibrary.wiley.com/toc/20506414/2024/12/S8 2025: Conference not held	2023 to 2024: Searched the abstract book manually	0
World Allergy Congress	2023: Abstract link was not found 2024: Abstract link was not found	Systemic mastocytosis: NA Non-advanced systemic mastocytosis: NA Non advanced systemic mastocytosis: NA non-AdvSM: NA	NA

	2025: Abstract link was not found	non AdvSM: NA Indolent systemic mastocytosis: NA ISM: NA Smoldering systemic mastocytosis: NA SSM: NA	
World Congress of Dermatology	2023: https://www.wcd2023singapore-abs.org/abstract_topics.php This conference helds after every 4 years. Last conference was held on 2023, and the next will be held on 2027	2023: Systemic mastocytosis: 4 Non-advanced systemic mastocytosis: 0 Non advanced systemic mastocytosis: 0 non-AdvSM: 0 non AdvSM: 0 Indolent systemic mastocytosis: 0 ISM: 546 Smoldering systemic mastocytosis: 0 SSM: 490	0
World Congress of Gastroenterology	This conference was last held on 2022, and next conference will be held on 19-22 September 2025	Systemic mastocytosis: NA Non-advanced systemic mastocytosis: NA Non advanced systemic mastocytosis: NA non-AdvSM: NA non AdvSM: NA Indolent systemic mastocytosis: NA ISM: NA Smoldering systemic mastocytosis: NA SSM: NA	NA
Canadian Agency for Drugs and Technologies in Health (CADTH)/)/Common Drug Review (CDR)	https://www.cadth.ca/search?keywords	2023 to 2025: Systemic mastocytosis: 6 Non-advanced systemic mastocytosis: 0 Non advanced systemic mastocytosis: 3 non-AdvSM: 0 non AdvSM: 1 Indolent systemic mastocytosis: 1 ISM: 1 Smoldering systemic mastocytosis: 1 SSM: 3	0
National Institute for Health and Care Excellence (NICE)	http://www.nice.org.uk/	2023 to 2025: Systemic mastocytosis: 6 Non-advanced systemic mastocytosis: 2 Non advanced systemic mastocytosis: 2 non-AdvSM: 0 non AdvSM: 0 Indolent systemic mastocytosis: 1 ISM: 0 Smoldering systemic mastocytosis: 0 SSM: 0	0
Scottish Medicines Consortium (SMC)	https://www.scottishmedicines.org.uk/	2023 to 2025: Systemic mastocytosis: 1 Non-advanced systemic mastocytosis: 0 Non advanced systemic mastocytosis: 0 non-AdvSM: 0 non AdvSM: 0 Indolent systemic mastocytosis: 0	0

		ISM: 0 Smoldering systemic mastocytosis: 0 SSM: 0	
All Wales Medicines Strategy Group (AWMSG)	http://www.awmsg.org/	2023 to 2025: Systemic mastocytosis: 51 Non-advanced systemic mastocytosis: 0 Non advanced systemic mastocytosis: 226 non-AdvSM: 0 non AdvSM: 0 Indolent systemic mastocytosis: 54 ISM: 0 Smoldering systemic mastocytosis: 51 SSM: 0	0
Haute Autorité De Santé (HAS)	https://www.has-sante.fr/	2023 to 2025: Systemic mastocytosis: 2 Non-advanced systemic mastocytosis: 2 Non advanced systemic mastocytosis: 2 non-AdvSM: 1 non AdvSM: 0 Indolent systemic mastocytosis: 1 ISM: 4 Smoldering systemic mastocytosis: 1 SSM: 6	1
Gemeinsamer Bundesausschuss (GBA)	https://www.g-ba.de/	2023 to 2025: Systemic mastocytosis: 57 Non-advanced systemic mastocytosis: 3 Non advanced systemic mastocytosis: 1096 non-AdvSM: 3 non AdvSM: 16 Indolent systemic mastocytosis: 42 ISM: 25 Smoldering systemic mastocytosis: 22 SSM: 49	1
National Centre for Pharmacoeconomics (NCPE)	https://www.ncpe.ie/	2023 to 2025: Systemic mastocytosis: 2 Non-advanced systemic mastocytosis: 0 Non advanced systemic mastocytosis: 0 non-AdvSM: 0 non AdvSM: 0 Indolent systemic mastocytosis: 1 ISM: 3 Smoldering systemic mastocytosis: 0 SSM: 2	0
Agenzia Italiana del Farmaco (Italian Medicines Agency) (AIFA)	https://www.aifa.gov.it/en/	2023 to 2025: Systemic mastocytosis: 69 Non-advanced systemic mastocytosis: 62 Non advanced systemic mastocytosis: 62 non-AdvSM: 1 non AdvSM: 0 Indolent systemic mastocytosis: 0	0

		ISM: 16 Smoldering systemic mastocytosis: 0 SSM: 0	
National Health Care Institute (Zorginstituut Nederland) (ZinL)	https://english.zorginstituutnederland.nl/publications?utm	2023 to 2025: Systemic mastocytosis: 0 Non-advanced systemic mastocytosis: 0 Non advanced systemic mastocytosis: 0 non-AdvSM: 0 non AdvSM: 0 Indolent systemic mastocytosis: 0 ISM: 0 Smoldering systemic mastocytosis: 0 SSM: 0	0
Rijksinstituut voor ziekte- en invaliditeitsverzekering (National Institute for Health and Disability Insurance) (RIZIV)	https://www.sciensano.be/en/partners/national-institute-health-and-disability-insurance-inami-riziv?utm	2023 to 2025: Systemic mastocytosis: 8 Non-advanced systemic mastocytosis: 5 Non advanced systemic mastocytosis: 6 non-AdvSM: 0 non AdvSM: 0 Indolent systemic mastocytosis: 0 ISM: 94 Smoldering systemic mastocytosis: 0 SSM: 48	0
Agencia Española de Medicamentos y Productos Sanitarios (Spanish Agency for Medicines and Health Products) (AEMPS)	https://www.aemps.gob.es/?lang=en	2023 to 2025: Systemic mastocytosis: 0 Non-advanced systemic mastocytosis: 0 Non advanced systemic mastocytosis: 0 non-AdvSM: 0 non AdvSM: 0 Indolent systemic mastocytosis: 0 ISM: 9 Smoldering systemic mastocytosis: 0 SSM: 9	0
American Academy of Allergy, Asthma, and Immunology	2023: https://www.sciencedirect.com/journal/journal-of-allergy-and-clinical-immunology/vol/151/issue/2/suppl/S#article-3 2024: https://www.sciencedirect.com/journal/journal-of-allergy-and-clinical-immunology/vol/153/issue/2/suppl/S?page=9#article-832 2025: https://www.jacionline.org/programs_abstracts	2023 to 2025: Systemic mastocytosis: 55 Non-advanced systemic mastocytosis: 8 Non advanced systemic mastocytosis: 8 non-AdvSM: 5 non AdvSM: 3 Indolent systemic mastocytosis: 33 ISM: 29 Smoldering systemic mastocytosis: 3 SSM: 0	2

American Academy of Dermatology	2023: https://eposters.aad.org/archives/AM2023 2024: https://eposters.aad.org/archives/AM2024 2025: https://eposters.aad.org/	2023 to 2025: Searched the abstract book manually	0

Abbreviations: AdvSM, advanced systemic mastocytosis; HRQoL, health-related quality of life; ISM, indolent systemic mastocytosis; NA, not applicable; SSM, smouldering systemic mastocytosis.

I.1.2.4 Eligibility criteria

The scope of this SLR was defined by the criteria for relevant population, intervention, comparators, outcomes, and study design (PICOS) is presented in Table 73 for the 2022 and 2023 SLR, and in Table 74 for the 2025 update. Only studies that met all the PICOS components were included.

Table 73 Inclusion/exclusion criteria for economic SLR (2022 and 2023)

Criteria	Inclusion Criteria	Exclusion Criteria
Population	• Patients ≥18 years with non-advanced SM ○ Indolent SM • Smouldering SM	• Patients with advanced SM • Individuals <18 years of age
Intervention	• Not applicable	• Not applicable
Comparators	• Not applicable	• Not applicable
Outcomes	**Economic evaluations** • (Incremental) QALYs • (Incremental) LY • Cost/QALY • Cost/LY • Cost-benefit Resource use and costs • Direct and indirect medical costs • Direct and indirect non-medical costs • Productivity losses Patient-reported and QoL outcomes from QoL questionnaires including: • ISM-SAF TSS • MC-QoL • EQ-5D (3L and 5L)	Studies that do not report any of the outcomes of interest specified in the inclusion criteria

	• SF-12	
Study design	Economic evaluations • Cost-effectiveness analysis • Cost-utility analysis • Cost-benefit analysis • Budget impact analysis Resource use and costs & utilities/HRQoL Economic evaluations • Cost-effectiveness analysis • Cost-utility analysis • Cost-benefit analysis • Budget impact analysis Observational studies • Cohort • Case-control • Cross-sectional	• Editorials • Commentaries • Letters • Systematic literature reviews and meta-analyses**
Time restriction	• Peer-reviewed publications: no time restriction • Conference proceedings: 2020 to 2022 for the original SLR and 2022 to 2023 for the update • HTA websites: 2018 to 2022 for the original SLR and 2022 to 2023 for the update	• Conference proceedings: <2020
Language	• No language restrictions	• Not applicable

Abbreviations: HRQoL, health-related quality of life; HTA, health technology assessment; ISM-SAF TSS, Indolent Systemic Mastocytosis Symptom Assessment Form Total Symptom Score; LY, life-year; MC-QoL, Mastocytosis Quality of Life Questionnaire; QALY, quality-adjusted life-year; QoL, quality of life; SF-12, 12-Item Short Form Health Survey; SLR, systematic literature review.

Note: **Systematic literature reviews and meta-analyses will not be included for data extraction, but references of the five most recent/relevant (impact factor journal) will be screened to check for any missed references.

Table 74 Inclusion/exclusion criteria for HRQoL and utility SLR (2025)

Criteria	Inclusion Criteria	Exclusion Criteria

Population	• Adult (age ≥18 years) patients with non-advanced systemic mastocytosis (non-AdvSM)[a] which includes:
	  ○ Indolent systemic mastocytosis (ISM)
	• Smoldering systemic mastocytosis (SSM)
		• Any other population, including, but not limited to:
		  ○ Advanced systemic mastocytosis (AdvSM)
		  ○ Aggressive systemic mastocytosis (ASM)
		  ○ Mast cell leukemia (MCL)
		  ○ SM with an associated hematologic neoplasm (SM-AHN)

		• Patients with diseases other than non-AdvSM • Paediatric population • Healthy volunteers
Intervention	• No restrictions	• None
Comparators	• No restrictions	• None
Outcomes	• Health-related quality of life (HRQoL) data • All types of utilities data including health state utility data, disutilities, mapping from QoL (i.e., SF-36), etc	• Studies not reporting HRQoL and utility values
Study design	• Studies reporting HRQoL and utility data • Economic evaluations reporting patient utility values • Systematic reviews and meta-analysis[b]	• Letters, comments, and editorials • Case series or case reports or case studies
Time restriction	• Peer-reviewed publications: no time restriction • Conference proceedings: 2020 to 2022 for the original SLR and 2022 to 2023 for the update • HTA websites: 2018 to 2022 for the original SLR and 2022 to 2023 for the update	• Letters, comments, and editorials • Case series or case reports or case studies
Language	• No limits	• None
Countries	• No limits	• None
Time limit	• Studies published 2023 onwards	• Studies published before 2023

Abbreviations: HRQoL, health-related quality of life; ISM, indolent systemic mastocytosis; non-AdvSM, non-advanced systemic mastocytosis; SF-36, 36-item short form; SLR, systematic liertaure review; SSM, smoldering systemic mastocytosis.

Notes: [a] Studies assessing mixed population of SM were included at the abstract/ title screening stage. At the full text screening stage, studies were only included if data is reported separately for non-AdvSM types: ISM and SSM.

[b] Bibliographies of systematic review articles were screened to ensure that all relevant studies are identified in the SLR.

I.1.3 Systematic selection of studies

A total of 151 publications were identified from the search of the electronic databases on 25 November 2022. After the removal of duplicates, the title and abstract of 114 publications were screened for eligibility. After excluding 103 publications based on title and abstract screening, 11 full-text publications were assessed for full-text eligibility based on the pre-specified criteria. Of these, five studies were eligible for inclusion. A further two publications were included from conference proceedings.

A total of seven publications were included and extracted within the scope of the economic SLR. Of these, four publications reported on HRQoL outcomes, and three publications reported on resource use and costs. No publication reporting on economic evaluations and utilities was identified in this review. The PRISMA diagram is provided in Figure 19.

All database searches for the first update were conducted on 29 November 2023. For the economic SLR update, a total of 21 publications were identified from the search of the electronic databases (Embase, MEDLINE and EconLit). The title and abstract of 12 publications were examined for eligibility following the removal of duplicates. Finally, one publication was included for extraction. One conference abstract was identified from hand search of conferences, and one journal article was identified from additional hand search. This resulted in the inclusion of a total of three publications. All three publications reported on HRQoL outcomes. The PRISMA diagram is provided in Figure 19.

Systematic database searches for the second update SLR were conducted on March 31, 2025, and the results were limited to studies published after January 1, 2023. Of the 379 publications initially identified and screened from multiple databases, 339 were excluded, leaving 40 publications for further evaluation. Of these, 27 publications were excluded during second screening. Five relevant publications were identified from grey literature search. Therefore, a total of 18 publications were included in the review. As some studies were associated with multiple publications, secondary publications were combined. Hence, the evidence comprised nine studies from 18 publications. Figure 21 presents a PRISMA flow diagram illustrating the study selection process for the second update SLR.

Table 75 presents a summary of all the included publications. A list of publications excluded during full-text screening from the 2023 and 2025 update, with exclusion reasons are reported in Table 76.

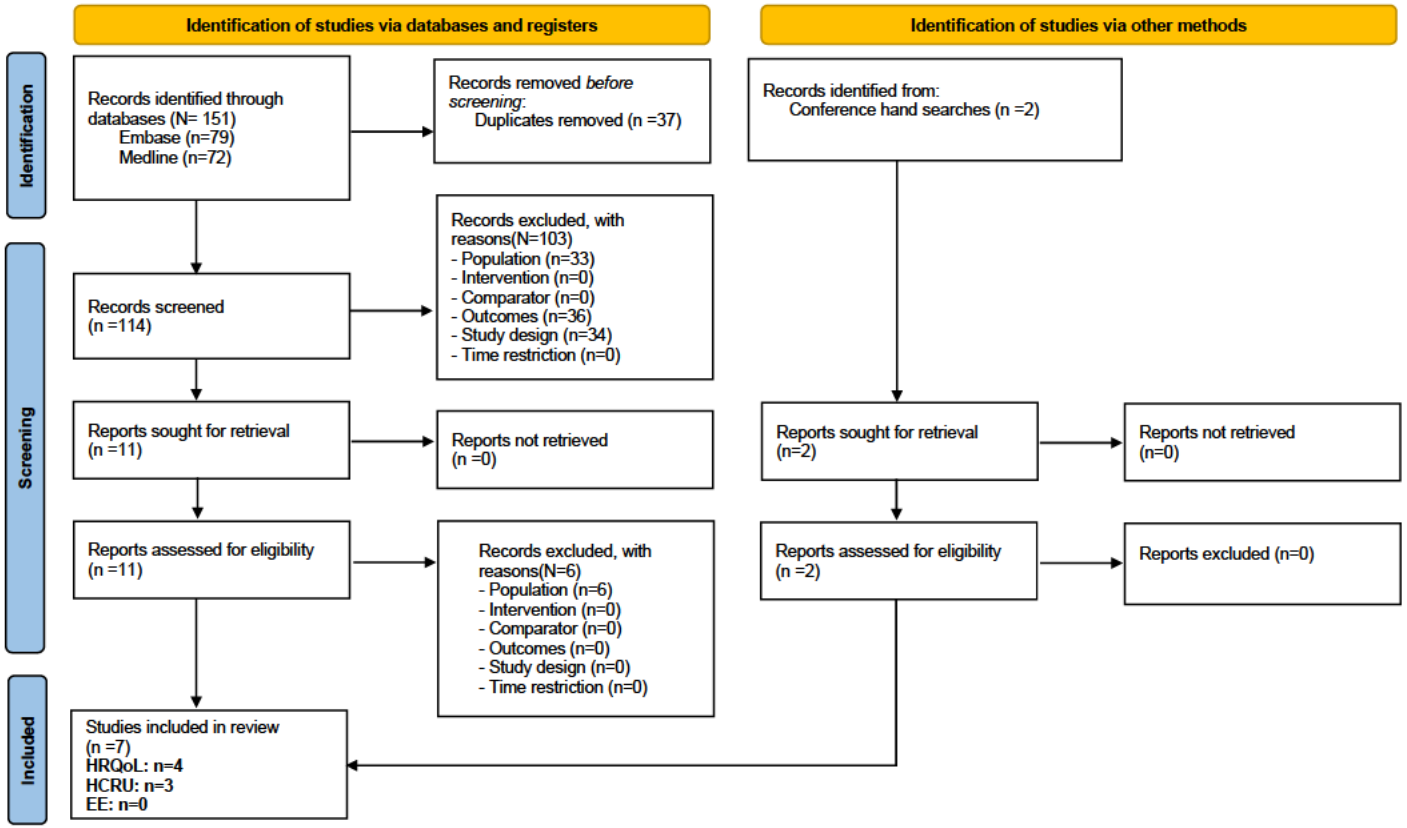

Figure 19 Study selection flow diagram for economic studies (original SLR: November 2022)

Abbreviations: Embase, Excerpta Medica database; HCRU, healthcare resource utilisation; HRQoL, health-related quality of life; SLR, systematic literature review.

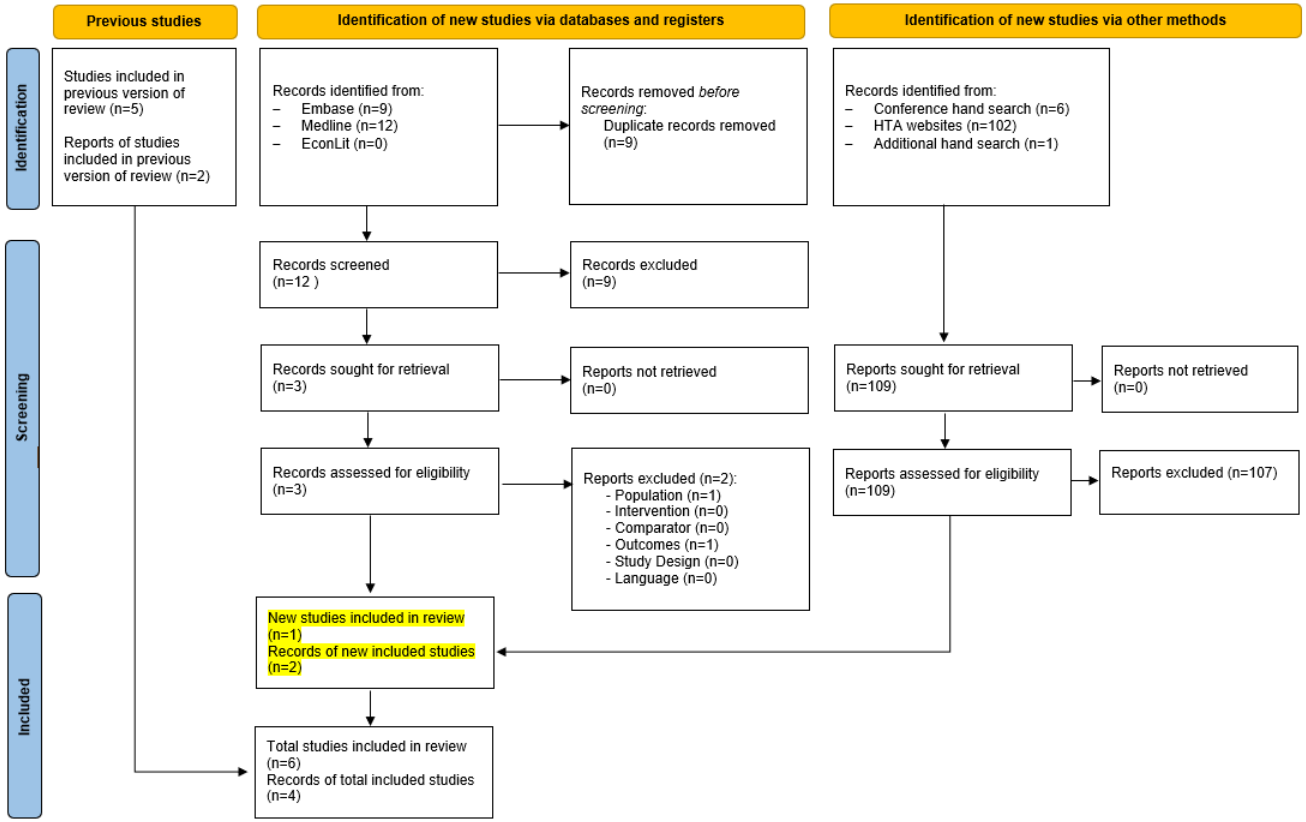

Figure 20 Study selection flow diagram for economic studies (First update SLR: November 2023)

Abbreviations: Embase, Excerpta Medica database; HTA, health technology assessment; SLR, systematic literature reviw.

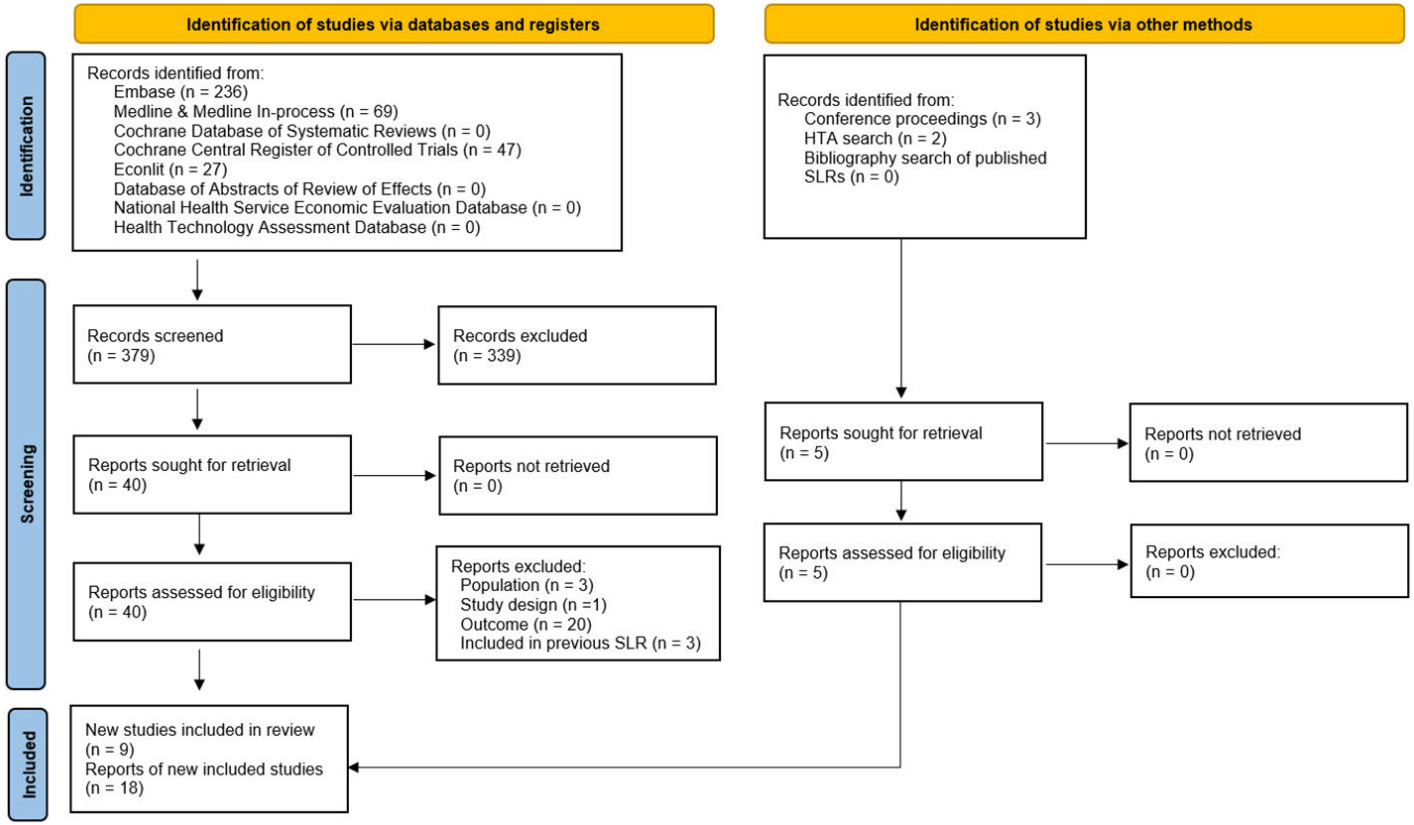

Figure 21 Study selection flow diagram for economic studies (Second update SLR: March 2025)

Abbreviations: Embase, Excerpta Medica database; HTA, health technology assessment; SLR, systematic literature review.

Table 75 List of studies included in the economic systematic literature review, global SLR

First author, year	Title	Publication type	Outcomes reported
November 2022			
Broesby-Olsen, 2018	Omalizumab prevents anaphylaxis and improves symptoms in systemic mastocytosis: Efficacy and safety observations	Journal article	HRQoL
Lortholary, 2017	Masitinib for treatment of severely symptomatic indolent systemic mastocytosis: a randomised, placebo-controlled, phase 3 study	Journal article	HRQoL
Mesa, 2022	Perceptions of patient disease burden and management approaches in systemic mastocytosis: Results of the TouchStone Healthcare Provider Survey	Journal article	Cost and resource use
Padilla, 2021	Psychometric evaluation of the Indolent Systemic Mastocytosis Symptom Assessment Form (ISM-SAF) in a phase 2 clinical study	Journal article	HRQoL
Petrilla, 2022	Comorbidity and Disability in Medicare Beneficiaries Newly Diagnosed with Non-Advanced Systemic Mastocytosis (Non-AdvSM)	Conference abstract	Cost and resource use
Sullivan, 2021	Healthcare Resource Utilization and Costs of Medicare Fee for Service Beneficiaries Newly Diagnosed with Moderate to Severe Non-Advanced Systemic Mastocytosis	Conference abstract	Cost and resource use
Van Anrooij 2016	Patient-reported disease-specific quality-of-life and symptom severity in systemic mastocytosis	Journal article	HRQoL

First update: November 2023			
Siebenhaar, 2023	Safety and efficacy of lirentelimab in patients with refractory indolent systemic mastocytosis: a first-in-human clinical trial	Journal article	HRQoL
Gotlib, 2023	Avapritinib versus Placebo in Indolent Systemic Mastocytosis	Journal article	HRQoL
Bose, 2023	Initial Results from Summit: An Ongoing, 3-Part, Multi-Center, Randomized, Double-Blind, Placebo-Controlled Phase 2 Clinical Study of Bezuclastinib in Adult Patients with Nonadvanced Systemic Mastocytosis (NonAdvSM)	Conference abstract	HRQoL
Second update: March 2025			
Veitch et al., 2023	A Snapshot Audit of Symptom Burden in Patients with Indolent Systemic Mastocytosis Utilising the ISM-SAF© within a UK Centre of Excellence: Guy's and St Thomas' NHS Foundation	Conference abstract	HRQoL
Tashi et al., 2023	Elenestinib, an investigational, next generation KIT D816V inhibitor, reduces mast cell burden, improves symptoms, and has a favorable safety profile in patients with indolent systemic mastocytosis: analysis of the harbor trial	Conference abstract	HRQoL
Akin et al., 2024	Favorable Efficacy and Safety Profile of Avapritinib Is Maintained in the Context of Omalizumab Treatment	Conference abstract	HRQoL
Pyatilova et al., 2025	Avapritinib improves disease control and quality of life in patients with indolent systemic mastocytosis: First results of the real-world evidence study AVATAR	Conference abstract	HRQoL

Komarow et al., 2025	A Phase 2 Randomized Double-Blinded Placebo-Controlled Study to Evaluate the Safety and Efficacy of Subcutaneous Sarilumab in Improving the Quality of Life in Participants with Indolent Systemic Mastocytosis	Conference abstract	HRQoL
Mounie et al., 2025	Lifetime Disability-Adjusted Life-Year Assessment of Indolent Systemic Mastocytosis	Journal article	HRQoL
Rein et al., 2024	Updated Efficacy and Safety Results of Patients Receiving Selected 100mg Bezuclastinib Dose and Participating in the Open-Label Extension of Summit: A Randomized, Double-Blind, Placebo Controlled Phase 2 Clinical Trial of Bezuclastinib in Adult Patients with Nonadvanced Systemic Mastocytosis	Conference abstract	HRQoL
Zeiger et al., 2025	Patient-Reported Burden of Indolent Systemic Mastocytosis in a Managed Care Organization	Journal article	HRQoL
Gianeetti et al., 2024	Avapritinib Decreased Symptom Burden in Patients With Indolent Systemic Mastocytosis in the Registrational Double-Blind, Placebo-Controlled PIONEER Study	Conference abstract	HRQoL

Abbreviations: HRQoL, health-related quality of life; SLR, systematic literature review.

I.1.4 Excluded fulltext references

Table 76 List of studies excluded from the economic systematic literature review following full-text review, global SLR

First author, year	Title	Journal	Exclusion reason
November 2022			

N/A	N/A	N/A	N/A
First update: November 2023			
Schmidt, 2022	Health-related quality of life and health literacy in patients with systemic mastocytosis and mast cell activation syndrome	Orphanet Journal of Rare Diseases	Population
Shields, 2023	Psychometric evaluation of the Indolent Systemic Mastocytosis Symptom Assessment Form (ISM-SAF©) and determination of a threshold score for moderate symptoms	Orphanet Journal of Rare Diseases	Outcomes
Second update: March 2025			
No authors listed, 2024	A 24-week with possible extension, prospective, multicenter, randomized, double blind, placebo-controlled, 2-parallel group with a randomization 1: 1, phase III study to compare efficacy and safety of oral masitinib to placebo in treatment of patients with Smouldering or Indolent Severe Systemic mastocytosis with handicap, unresponsive to optimal symptomatic treatment.	N/A	Exclude on outcomes
Lübke, 2024	A clinical, morphological and molecular study of 70 patients with gastrointestinal involvement in systemic mastocytosis. Scientific reports.	Sci Rep	Exclude on outcomes
No authors listed, 2023	A study of the safety and effectiveness of lirentelimab as a treatment for people with indolent systemic mastocytosis.	Br J Dermatol	Exclude on outcomes
Livideanu, 2023	Calculation of Disability-adjusted Life Years (DALY) in Patients with Indolent Systemic Mastocytosis (ISM).	Journal of Allergy and Clinical Immunology	Exclude on outcomes

Bugaut, 2024	Cladribine improves cutaneous manifestations, Dermatology Life Quality Index, and Mastocytosis Quality of Life of patients with mastocytosis.	Journal of the American Academy of Dermatology	Exclude on study design
Schmidt, 2023	Correction: Health-related quality of life and health literacy in patients with systemic mastocytosis and mast cell activation syndrome.	Orphanet Journal of Rare Diseases	Exclude on population
Mullen, 2024	Cost-effectiveness of point of care smoking cessation interventions in oncology clinics.	British Journal of Cancer	Exclude on population
Kaakati, 2025	Demographics, types of patient-reported allergic diseases, and anaphylaxis in mastocytosis: a single-center US experience.	The Journal of Allergy and Clinical Immunology: In Practice	Exclude on outcomes
Moraly, 2024	Efficacy and safety of mammalian target of rapamycin inhibitors in systemic mastocytosis: A nationwide French pilot study	American Journal of Hematology	Exclude on outcomes
Maurer, 2024	Exploring the spectrum of indolent systemic mastocytosis: analysis of high-risk disease features in the PIONEER study.	Journal of Allergy and Clinical Immunology	Exclude on outcomes
Romantowski, 2025	IL-4, TSLP and IL-31 Cytokine Profiles as Related to Psychometric Measures in Patients with Mastocytosis. International.	Journal of Molecular Sciences	Exclude on outcomes
Barete, 2023	Is lirentelimab the ‘magic bullet’to fight pathological mast-cell activation in systemic mastocytosis?	British Journal of Dermatology	Exclude on outcomes

Bose, 2024	MPN-332 Initial Results From Summit: An Ongoing, 3-Part, Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase 2 Clinical Study of Bezuclastinib in Adult Patients With Non-Advanced Systemic Mastocytosis (NonAdvSM).	Clinical Lymphoma Myeloma and Leukemia	Exclude on outcomes
Mesa, 2023	PCR136 The Burden of Systemic Mastocytosis in Select European Countries: Evidence from the Prism Patient Survey.	Value in Health	Exclude on outcomes
Triggiani, 2023	PCR81 Diagnosis and Treatment Patterns in European Patients with Systemic Mastocytosis.	Value in Health	Exclude on outcomes
Siebenhaar, 2024	Physician and patient perspectives on relevant and burdensome symptoms of non-advanced systemic mastocytosis.	J Allergy Clin Immunol	Exclude on outcomes
Shields, 2023	Psychometric evaluation of the Indolent Systemic Mastocytosis Symptom Assessment Form (ISM-SAF©) and determination of a threshold score for moderate symptoms.	Orphanet J Rare Dis	Exclude on outcomes
Siebenhaar, 2022	Qualitative Research to Understand the Patient Experience in Non-Advanced Systemic Mastocytosis.	Journal of Allergy and Clinical Immunology	Exclude on outcomes
McComish, 2023	Randomized controlled trial of omalizumab in treatment-resistant systemic and cutaneous mastocytosis (ROAM)	The Journal of Allergy and Clinical Immunology	Exclude on outcomes
Koch, 2024	Sport as tool for symptom reduction in patients with systemic mastocytosis – is it feasible? Results of a multicenter survey of the East German Study Group for Hematology and Oncology (OSHO #97)	Oncol Res Treat	Exclude on population
Rueff, 2024	The burden of indolent systemic mastocytosis in Europe: Results from the PRISM patient survey.	Allergologie	Exclude on outcomes

Hartmann, 2024	The burden of systemic mastocytosis in Europe: results from the PRISM patient survey.	Oncol Res Treat	Exclude on outcomes
Nicoloro-SantaBarbara, 2024	The five dimensions of the indolent systemic mastocytosis patient experience - uncovering the "real-world" experience of patients with indolent systemic mastocytosis.	J Allergy Clin Immunol	Exclude on outcomes
Tanasi, 2024	Underlying systemic mastocytosis in patients with unexplained osteoporosis: score proposal.	Bone	Exclude on outcomes
Gotlib, 2023	Avapritinib versus placebo in indolent systemic mastocytosis.	NEJM evidence	Included in previous SLR update
Bose, 2023	Initial results from Summit: an Ongoing, 3-Part, Multi-center, Randomized, Double-Blind, placebo-controlled phase 2 clinical study of Bezuclastinib in Adult patients with Nonadvanced systemic mastocytosis (NonAdvSM).	Blood	Included in previous SLR update
Siebenhaar, 2023	Safety and efficacy of lirentelimab in patients with refractory indolent systemic mastocytosis: a first-in-human clinical trial.	British Journal of Dermatology	Included in previous SLR update

Abbreviations: N/A, not applicable; SLR, systematic literature review.

I.1.5 Local adaptation

To support this submission for avapritinib for the treatment of non-AdvSM in Denmark, the global SLR was adapted by excluding all studies not relevant to a Danish setting. The objective of the global SLR was to identify all available economic evidence for avapritinib in patients with non-AdvSM to communicate the value of avapritinib in non-AdvSM to stakeholders, specifically to HTA agencies globally, and to identify potential economic and utility inputs for the cost-effectiveness model comparing avapritinib with existing treatments. None of the identified sources from the global SLR were deemed eligible for inclusion in the local adaptation. The local adaptation is illustrated in Figure 22.

Targeted literature review – HRQoL studies

In addition to the SLR, a targeted literature review (TLR) was conducted to identify and collect relevant inputs for the HSUV model. The TLR was conducted pragmatically, focusing only on disutility values. Ten sources were identified and used in the HRQoL model (Table 77)

Table 77 List of studies included to identify HRQoL studies, TLR

Source name/database	Location/source	Search strategy	Date of search
Blueprint Medicines Corporation. [Data on file] (2023) (48)	Supplementary health-related quality of life data from the PATHFINDER study: NCT03580655	Hand search	04.07.2025
Sullivan PW, Slejko JF, Sculpher MJ, Ghushchyan V. (2011) (49)	Catalogue of EQ-5D scores for the United Kingdom	Hand search	04.07.2025
Araújo A, Parente B, Sotto-Mayor R, Teixeira E, Almodôvar T, Barata F, Queiroga H, Pereira C, Pereira H, Negreiro F, Silva C. (2008) (50)	An economic analysis of erlotinib, docetaxel, pemetrexed and best supportive care as second or third line treatment of non-small cell lung cancer.	Hand search	04.07.2025
NICE. TA250 (51)	Technology appraisal guidance: Eribulin for the treatment of locally advanced or metastatic breast cancer TA250: www.nice.org.uk	Hand search	04.07.2025
Lloyd A, Nafees B, Narewska J, Dewilde S, Watkins J. (2006) (52)	Health state utilities for metastatic breast cancer	Hand search	04.07.2025
NICE. TA124	Technology appraisal guidance: Pemetrexed for the treatment of non-small-cell lung cancer TA124: www.nice.org.uk	Hand search	04.07.2025

NICE GID-TA10024 (54)	Technology appraisal guidance: Neuroendocrine tumours (metastatic, unresectable, progressive) - everolimus and sunitinib GID-TA10024: www.nice.org.uk	Hand search	04.07.2025
NICE. CG173 (55).	Technology appraisal guidance: Neuropathic pain – pharmacological management: appendix F: www.nice.org.uk		
Farkouh (2012)	N/A	Hand search	04.07.2025
Shaker (2019)	N/A	Hand search	04.07.2025

Abbreviations: EQ-5D, EuroQoL five-dimension; HRQoL, health-related quality of life; TLR, targeted literature review.

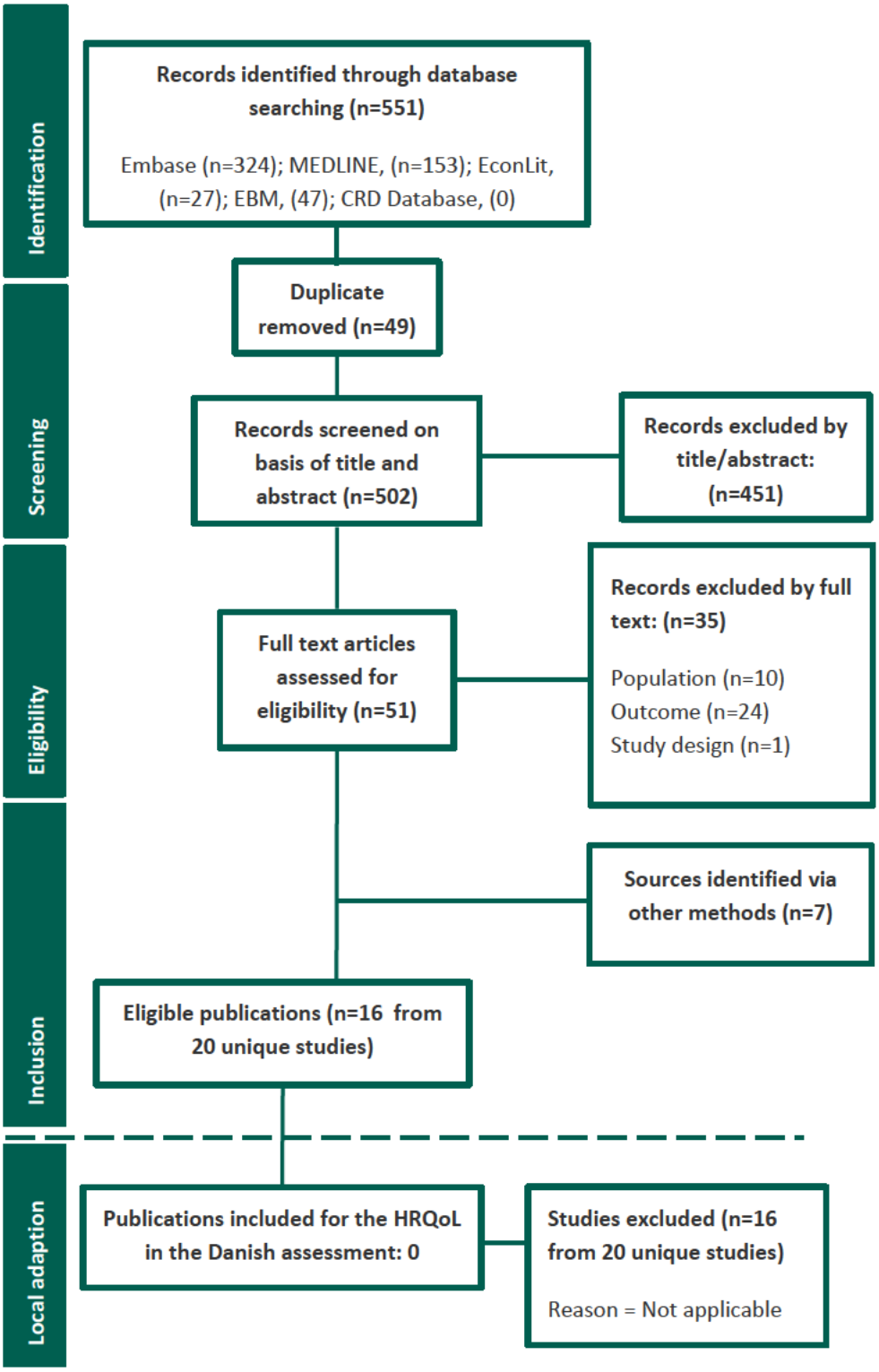

Figure 22 PRISMA diagram including local adaptation (HRQoL)

Abbreviations: EconLit, American Economic Association's electronic database; Embase, Excerpta Medica database; HRQoL, health-related quality of life.

I.1.6 Quality assessment and generalizability of estimates

No quality assessment was conducted for the resource use and costs and utilities/HRQoL studies.

I.1.7 Unpublished data

N/A

Appendix J. Literature searches for input to the health economic model

J.1 External literature for input to the health economic model

An economic SLR was conducted in 2022 and updated in 2023 to identify all available economic evidence for avapritinib in patients with non-AdvSM to communicate the value of avapritinib in non-AdvSM to stakeholders, specifically to HTA agencies globally, and to identify potential economic and utility inputs for the cost-effectiveness model comparing avapritinib with existing treatments. To avoid repetition, the full economic SLR (covering both HRQoL and inputs for the health economic model across the original (2022) and first updated (2023) SLRs) is provided in Appendix I. As previously stated, the economic SLR was further updated in 2025 and split into two components: one focusing on HRQoL and the other on HCRU. The HRQoL findings from the 2025 update is also reported in Appendix I, while this section specifically presents the results of the 2025 HCRU update.

Objective

The primary aim of the 2025 SLR was to identify cost and healthcare resource utilisation studies for patients with non-AdvSM.

J.1.1 Information sources

The same sources used for the HRQoL SLR update in 2025 (listed in in Appendix I), were also used for the HCRU SLR update. This includes both electronic databases and grey literature sources, as detailed in Table 55, Table 56 and Table 57. All searches were conducted on the same day, 31 March 2025.

J.1.2 Search strategies

The search strategy for the March 2025 update is provided bellow. The search strategy for grey literature is done the same way as in Appendix I, Table 72.

Table 78 HCRU search strategy [Embase] (March 31, 2025)

No.	Query	Results
#1	exp systemic mastocytosis/	3,904
#2	exp mast cell leukemia/	1,870
#3	exp indolent systemic mastocytosis/	470

#4	("systemic mastocytosis" or "indolent systemic mastocytosis" or "indolent mastocytosis").ti,ab.	3,828
#5	(systemic mastocytosis or NonAdvSM or ISM or SSM).ti,ab.	9,721
#6	1 or 2 or 3 or 4 or 5	11,904
#7	exp economics/	251,813
#8	exp economic aspect/	2,877,808
#9	exp socioeconomics/	1,658,235
#10	exp pharmacoeconomics/	251,700
#11	exp health economics/	1,120,548
#12	(Economic* or pharmacoeconomic* or price* or pricing).ti,ab.	577,429
#13	exp "hospital cost"/	48,899
#14	exp "health care cost"/	366,098
#15	exp "cost control"/	80,225
#16	exp financial management/	584,728
#17	exp health care financing/	14,253
#18	exp budget/	35,965
#19	(Low adj1 cost).ti,ab.	110,180
#20	exp "drug cost"/	90,743
#21	(Cost adj1 variable).ti,ab.	495
#22	exp "cost of illness"/	22,193
#23	exp "cost"/	433,347
#24	((Healthcare or health*care) adj1 cost*).ti,ab.	34,016
#25	(Fiscal or funding or financial or finance).ti,ab.	358,515
#26	exp fee/	46,297
#27	exp "cost minimization analysis"/	4,241
#28	(Cost adj1 estimate*).ti,ab.	9,738

#29	exp health savings account/	64
#30	(High adj1 cost).ti,ab.	32,594
#31	(Unit adj1 cost*).ti,ab.	6,071
#32	(Economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti.	326,100
#33	economic model*.ab.	6,629
#34	exp economic model/	4,821
#35	(budget* or Productivit*).ti,ab.	158,375
#36	("Health care" and cost*).ti,ab.	102,226
#37	"Length of stay".ti,ab.	168,496
#38	(Health and resource).ti,ab.	98,167
#39	(Resource adj2 utili*ation).ti,ab.	32,274
#40	(Hospitali*ation adj2 (rate or frequency)).ti,ab.	12,117
#41	exp productivity/	54,326
#42	(Resource adj3 use*).ti,ab.	30,037
#43	(Visit adj3 (inpatient or outpatient or emergency or physician*)).ti,ab.	19,037
#44	(Lost and work* and day*).ti,ab.	6,368
#45	7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44	3,771,791
#46	6 and 45	814
#47	limit 46 to yr="2023 -Current"	189

Abbreviations: HCRU, healthcare resource utilisation.

Table 79 HCRU search strategy [Medline] (March 31, 2025)

No.	Query	Results
#1	exp Mastocytosis, Systemic/	1,419
#2	exp Leukemia, Mast-Cell/	255

#3	indolent systemic mastocytosis.mp.	224
#4	("systemic mastocytosis" or "indolent systemic mastocytosis" or "indolent mastocytosis").ti,ab.	2,243
#5	(systemic mastocytosis or NonAdvSM or ISM or SSM).ti,ab.	6,598
#6	1 or 2 or 3 or 4 or 5	6,969
#7	exp Economics/	752,832
#8	economic aspect.mp.	258
#9	socioeconomics.mp.	1,140
#10	pharmacoeconomics.mp. or exp Economics, Pharmaceutical/	4,536
#11	health economics.mp.	8,665
#12	(Economic* or pharmacoeconomic* or price* or pricing).ti,ab.	469,821
#13	exp Hospital Costs/	12,311
#14	exp Health Care Costs/	74,795
#15	exp "Cost Control"/	34,474
#16	exp Financial Management/	91,460
#17	exp Healthcare Financing/	1,380
#18	exp Budgets/	14,330
#19	(Low adj1 cost).ti,ab.	102,228
#20	exp Drug Costs/	17,992
#21	(Cost adj1 variable).ti,ab.	334
#22	exp "Cost of Illness"/	36,764
#23	exp "Costs and Cost Analysis"/	277,500
#24	((Healthcare or health*care) adj1 cost*).ti,ab.	19,802
#25	(Fiscal or funding or financial or finance).ti,ab.	231,931
#26	exp "Fees and Charges"/	31,644
#27	cost minimization analysis.mp.	733

#28	(Cost adj1 estimate*).ti,ab.	6,131
#29	exp Medical Savings Accounts/	551
#30	(High adj1 cost).ti,ab.	24,638
#31	(Unit adj1 cost*).ti,ab.	3,449
#32	(Economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti.	253,476
#33	economic model*.ab.	4,125
#34	exp Models, Economic/	16,796
#35	(budget* or Productivit*).ti,ab.	133,856
#36	("Health care" and cost*).ti,ab.	73,027
#37	"Length of stay".ti,ab.	89,646
#38	(Health and resource).ti,ab.	73,027
#39	(Resource adj2 utili*ation).ti,ab.	18,107
#40	(Hospitali*ation adj2 (rate or frequency)).ti,ab.	7,227
#41	productivity.mp. or exp Efficiency/	126,469
#42	(Resource adj3 use*).ti,ab.	21,348
#43	(Visit adj3 (inpatient or outpatient or emergency or physician*)).ti,ab.	10,682
#44	(Lost and work* and day*).ti,ab.	3,435
#45	7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44	1,710,812
#46	6 and 45	316
#47	limit 46 to yr="2023 -Current"	92

Abbreviations: HCRU, healthcare resource utilisation.

Table 80 HCRU search strategy [CDSR] (March 31, 2025)

No.	Query	Results

#1	("systemic mastocytosis" or "mast cell leukemia" or "indolent systemic mastocytosis" or NonAdvSM or ISM or SSM).mp. [mp=title, short title, abstract, full text, keywords, caption text]	11
#2	limit 1 to last 3 years	0

Abbreviations: CDSR, Cochrane Database of Systematic Reviews; HCRU, healthcare resource utilisation.

Table 81 HCRU search strategy [CENTRAL] (March 31, 2025)

No.	Query	Results
#1	exp Mastocytosis, Systemic/	18
#2	exp Leukemia, Mast-Cell/	2
#3	indolent systemic mastocytosis.mp.	56
#4	("systemic mastocytosis" or "indolent systemic mastocytosis" or "indolent mastocytosis").ti,ab.	99
#5	(systemic mastocytosis or NonAdvSM or ISM or SSM).ti,ab.	319
#6	1 or 2 or 3 or 4 or 5	323
#7	limit 6 to yr="2023 -Current"	47

Abbreviations: HCRU, healthcare resource utilisation.

Table 82 HCRU search strategy [Econlit] (March 31, 2025)

No.	Query	Results
#1	("systemic mastocytosis" or "mast cell leukemia" or "indolent systemic mastocytosis" or NonAdvSM or ISM or SSM).mp. [mp=heading words, abstract, title, country as subject]	317
#2	limit 1 to yr="2023 -Current"	27

Abbreviations: EconLit, American Economic Association's electronic database; HCRU, healthcare resource utilisation.

Table 83 HCRU search strategy [NHS EED] (March 31, 2025)

No.	Query	Results
#1	(systemic mastocytosis) OR (mast cell leukemia) OR (NonAdvSM OR ISM OR SSM) IN DARE, NHSEED, HTA FROM 2023 TO 2025	0

Abbreviations: HCRU, healthcare resource utilisation; NHSEED, National Health Service Economic Evaluation Database.

Note: Inception to 1st Quarter 2016 (Database no longer updated after this point)

J.1.2.1 Eligibility criteria

Potentially relevant publications were reviewed and assessed to collate a final set of studies that formed the main body of the cost and healthcare resource evidence. To determine the final set of studies eligible for review, explicit inclusion and/or exclusion criteria were applied to the literature search results. The inclusion and exclusion criteria are specified in Table 84 and were applied to the literature search results to identify the final set of studies that formed the main body of the cost and healthcare resource evidence.

Table 84 Inclusion/exclusion criteria for HCRU SLR (2025)

Criteria	Inclusion Criteria	Exclusion Criteria

Population	• Adult (age ≥18 years) patients with non-advanced systemic mastocytosis (non-AdvSM)[a] which includes:
	  ○ Indolent systemic mastocytosis (ISM)
	• Smoldering systemic mastocytosis (SSM)
		• Any other population, including, but not limited to:
		  ○ Advanced systemic mastocytosis (AdvSM)
		  ○ Aggressive systemic mastocytosis (ASM)
		  ○ Mast cell leukemia (MCL)
		  ○ SM with an associated hematologic neoplasm (SM-AHN)
		• Patients with diseases other than non-AdvSM
		• Paediatric population
		• Healthy volunteers

Intervention	• No restrictions	• None
Comparators	• No restrictions	• None
Outcomes	• Cost and resource use data such as direct costs, indirect costs, total costs, length of hospitalisation/ hospital stay, physician visits, etc	• Studies not reporting cost and resource use data
Study design	• Observational/clinical studies reporting cost and resource use data • Economic evaluations reporting cost and resource use data • Systematic reviews[b]	• Letters, comments, and editorials • Case series or case reports or case studies • Studies reporting clinical data only
Language	• No limits	• None
Countries	• No limits	• None
Time limit	• Studies published 2023 onwards	• Studies published before 2023

Abbreviations: HCRU, healthcare resource utilisation; ISM, indolent systemic mastocytosis; non-advSM non-advanced systemic mastocytosis; SLR, systematic literature review; SSM, smoldering systemic mastocytosis.

Notes: [a] Studies assessing mixed population of SM were included at the abstract/ title screening stage. At the full text screening stage, studies were only included if data is reported separately for non-AdvSM types: ISM and SSM.

[b] Bibliographies of systematic review articles were screened to ensure that all relevant studies are identified in the SLR.

J.1.3 Systematic selection of studies

Systematic database searches for the second update SLR were conducted on March 31, 2025, and the results were limited to studies published after January 1, 2023. Of the 355 publications initially identified and screened from multiple databases, 346 were excluded, leaving nine publications for further evaluation of eligibility. Of these, seven publications were excluded during second screening. Four relevant publications were identified from grey literature search. Therefore, a total of six publications were included in the review. The original SLR identified three cost and HCRU studies, while the first update SLR identified none. Figure 23 Study selection flow diagram for HCRU studies (March 2025)Figure 23 presents a PRISMA flow diagram illustrating the study selection process for the second update SLR.

Table 85 presents a summary of all the included publications (including the tree HCRU publications from the original SLR in 2022). A list of publications excluded during full-text screening from the 2025 update, with exclusion reasons are reported in Table 86.

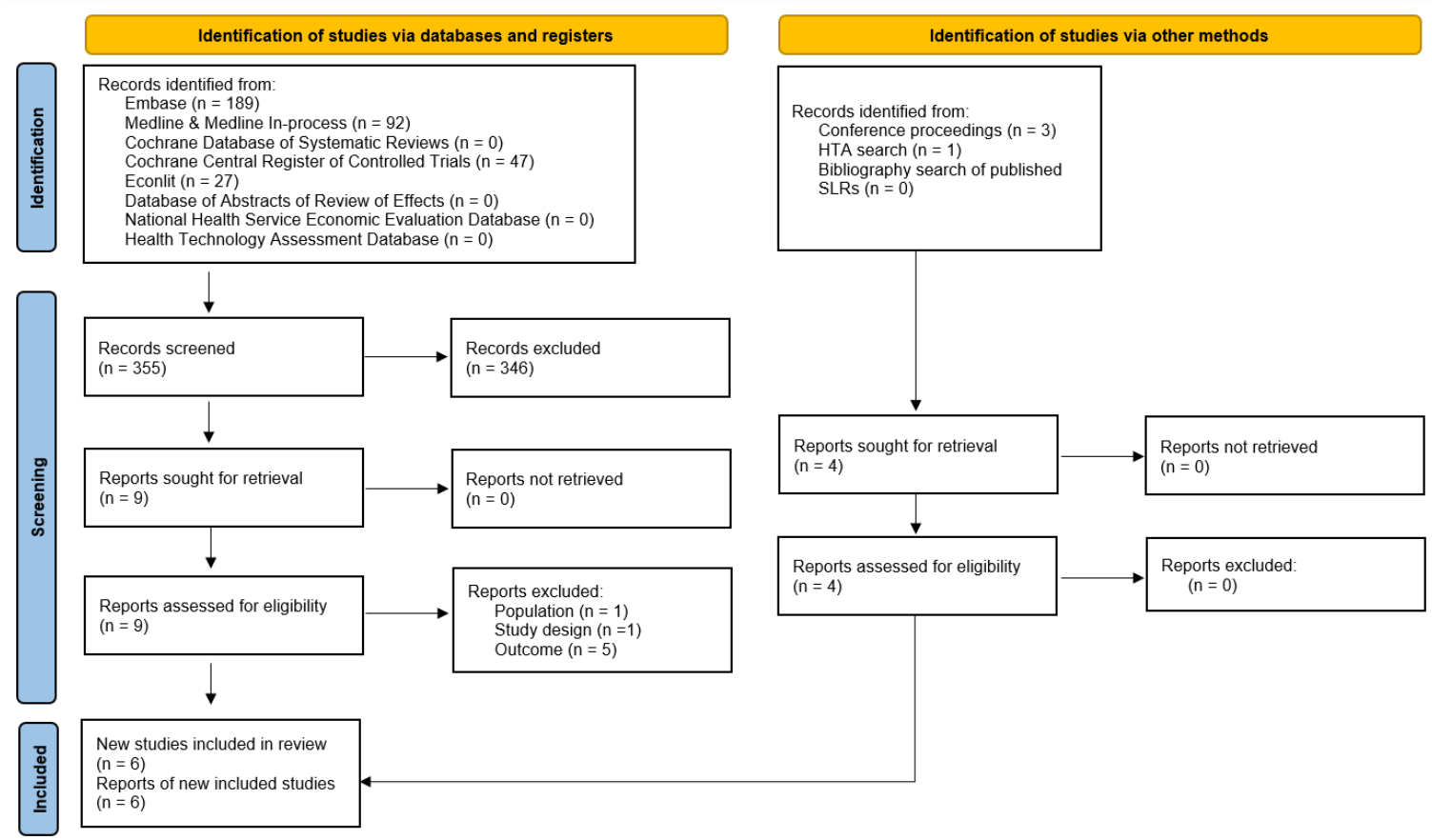

Figure 23 Study selection flow diagram for HCRU studies (March 2025)

Abbreviations: Embase, Excerpta Medica database; HTA, health technology assessment; SLR, systematic literature review.

Table 85 List of studies included in the HCRU SLR

First author, year	Title	Publication type	Outcomes reported
November 2022			
Mesa, 2022	Perceptions of patient disease burden and management approaches in systemic mastocytosis: Results of the TouchStone Healthcare Provider Survey	Journal article	Cost and resource use
Petrilla, 2022	Comorbidity and Disability in Medicare Beneficiaries Newly Diagnosed with Non-Advanced Systemic Mastocytosis (Non-AdvSM)	Conference abstract	Cost and resource use
Sullivan, 2021	Healthcare Resource Utilization and Costs of Medicare Fee for Service Beneficiaries Newly Diagnosed with Moderate to Severe Non-Advanced Systemic Mastocytosis	Conference abstract	Cost and resource use
Second update: March 2025			
Zeiger et al 2025	Patient Reported Burden of Indolent Systemic Mastocytosis in a Managed Care Organization	Journal article	Cost and resource use
Ruëff et al 2024	The burden of indolent systemic mastocytosis in Europe: Results from the PRISM patient survey	Conference abstract	Cost and resource use
Mukherjee et al 2023	Decreased survival among patients with indolent systemic mastocytosis: a population-level retrospective cohort analysis using healthcare claims dataset	Conference abstract	Cost and resource use
Pongdee et al 2025	Assessing Real-world Natural History of Indolent Systemic Mastocytosis: Retrospective Matched Cohort Study from Mayo Clinic Electronic Health Records	Conference abstract	Cost and resource use

Chen et al 2025	Patient Reported Burden of Indolent Systemic Mastocytosis in White vs. Non-White Patients	Conference abstract	Cost and resource use
Gemeinsamer Bundesausschuss, 2024	Avapritinib (new therapeutic indication: indolent systemic mastocytosis (ISM))	HTA document	Cost and resource use

Abbreviations: HCRU, healthcare resource utilisation; HRQoL, health-related quality of life; HTA, health technology assessment; ISM, indolent systemic mastocytosis; SLR, systematic litertaure review.

J.1.4 Excluded full text references

Table 86 List of studies excluded from the HCRU SLR following full-text review (Second update - March 2025)

First author, year	Title	Journal	Exclusion reason
Livideanu, 2023	Calculation of Disability-adjusted Life Years (DALY) in Patients with Indolent Systemic Mastocytosis (ISM).	Journal of Allergy and Clinical Immunology	Exclude on outcomes
Roskoski, 2024	Cost in the United States of FDA-approved small molecule protein kinase inhibitors used in the treatment of neoplastic and non-neoplastic diseases.	Pharmacological Research	Exclude on study design
Lam, 2023	Cost of drug wastage from dose modification and discontinuation of oral anticancer drugs.	JAMA oncology	Exclude on population
Kevin, 2024	MASTering systemic mastocytosis: Lessons learned from a large patient cohort.	Journal of Allergy and Clinical Immunology	Exclude on outcomes
Mesa, 2023	PCR136 The Burden of Systemic Mastocytosis in Select European Countries: Evidence from the Prism Patient Survey.	Value in Health	Exclude on outcomes

Tse, 2024	Systemic Mastocytosis: Shedding Light on A Rare and Complicated Disease.	Journal of Allergy and Clinical Immunology	Exclude on outcomes
Hartmann, 2024	The Burden of Systemic Mastocytosis in Europe: Results from the PRISM Patient Survey.	Oncology Research and Treatment	Exclude on outcomes

Abbreviations: FDA, food and drug administration; HCRU, healthcare resource utilisation; ISM, indolent systemic mastocytosis; SLR, systematic litertaure review.

J.1.5 Local adaptation

To support this submission for avapritinib for the treatment of non-AdvSM in Denmark, the global SLR was adapted by excluding all studies not relevant to a Danish setting. None of the identified sources from the global SLR were deemed eligible for inclusion in the local adaptation. The local adaptation is illustrated in Figure 22.

Targeted literature review – Health economic model

In addition to the SLR, a TLR was conducted to identify and collect relevant HCRU inputs. fifteen sources were identified and used in the health economic model (Table 87).

Table 87 List of studies included to identify HCRU studies, TLR

Source name/database	Location/source	Search strategy	Date of search
Gotlib J, Castells M, Elberink HO, et al. (2023) (46)	Avapritinib versus Placebo in Indolent Systemic Mastocytosis	Hand search	04.07.2025
Blueprint Medicines Corporation, (2022) (47)	Clinical Study Report - A 3 part, randomized, double blind, placebo controlled phase 2 study to evaluate safety and efficacy of avapritinib (BLU-285), a selective kit mutation-targeted tyrosine kinase inhibitor, in indolent and smoldering systemic mastocytosis with symptoms inadequately controlled with standard therapy. Internal report: unpublished.	Hand search	04.07.2025
ClinicalTrials.gov. (NCT03731260). (44)	(PIONEER) Study to Evaluate Efficacy and Safety of Avapritinib (BLU-285), A Selective KIT Mutation-targeted Tyrosine Kinase Inhibitor, Versus Placebo in Patients With Indolent Systemic Mastocytosis	Hand search	04.07.2025
Blueprint Medicines Corporation (2023) (58)	PRISM Partial Results	Hand search	04.07.2025
Blueprint Medicines Corporation (59)	PRISM [data on file]	Hand search	04.07.2025
Matito (2013) (11)	Serum tryptase monitoring in indolent systemic mastocytosis: association with disease features and patient outcome	Hand search	04.07.2025
Trizuljak (2020) (14)	Clinical features and survival of patients with indolent systemic mastocytosis defined by the updated WHO classification	Hand search	04.07.2025

Escribano (2009) (60)	Prognosis in adult indolent systemic mastocytosis: a long-term study of the Spanish Network on Mastocytosis in a series of 145 patients. J Allergy Clin Immunol. 2009;124(3):514-521. doi:10.1016/j.jaci.2009.05.003	Hand search	04.07.2025
NICE TA708 (61)	Technology appraisal guidance: Budesonide orodispersible tablet for inducing remission of eosinophilic oesophagitis TA708: www.nice.org.uk	Hand search	04.07.2025
NICE TA534 (62)	Technology appraisal guidance: Dupilumab for treating moderate to severe atopic dermatitis TA534: www.nice.org.uk	Hand search	04.07.2025
NICE TA753 (63)	Technology appraisal guidance: Cenobamate for treating focal onset seizures in epilepsy TA753: www.nice.org.uk	Hand search	04.07.2025
NICE TA883 (64)	Technology appraisal guidance: Tafasitamab with lenalidomide for treating relapsed or refractory diffuse large B-cell lymphoma TA883: www.nice.org.uk	Hand search	04.07.2025
NICE TA838 (65)	Technology appraisal guidance: Slow-release potassium bicarbonate–potassium citrate for treating distal renal tubular acidosis TA838: www.nice.org.uk	Hand search	04.07.2025
NICE TA814 (66)	Technology appraisal guidance: Abrocitinib, tralokinumab or upadacitinib for treating moderate to severe atopic dermatitis TA814: www.nice.org.uk	Hand search	04.07.2025
Tefferi et al. (2019) (67)	Smoldering mastocytosis: Survival comparisons with indolent and aggressive mastocytosis	Hand search	04.07.2025

Abbreviations: HCRU, healthcare resource utilisation; TLR, targeted literature review.

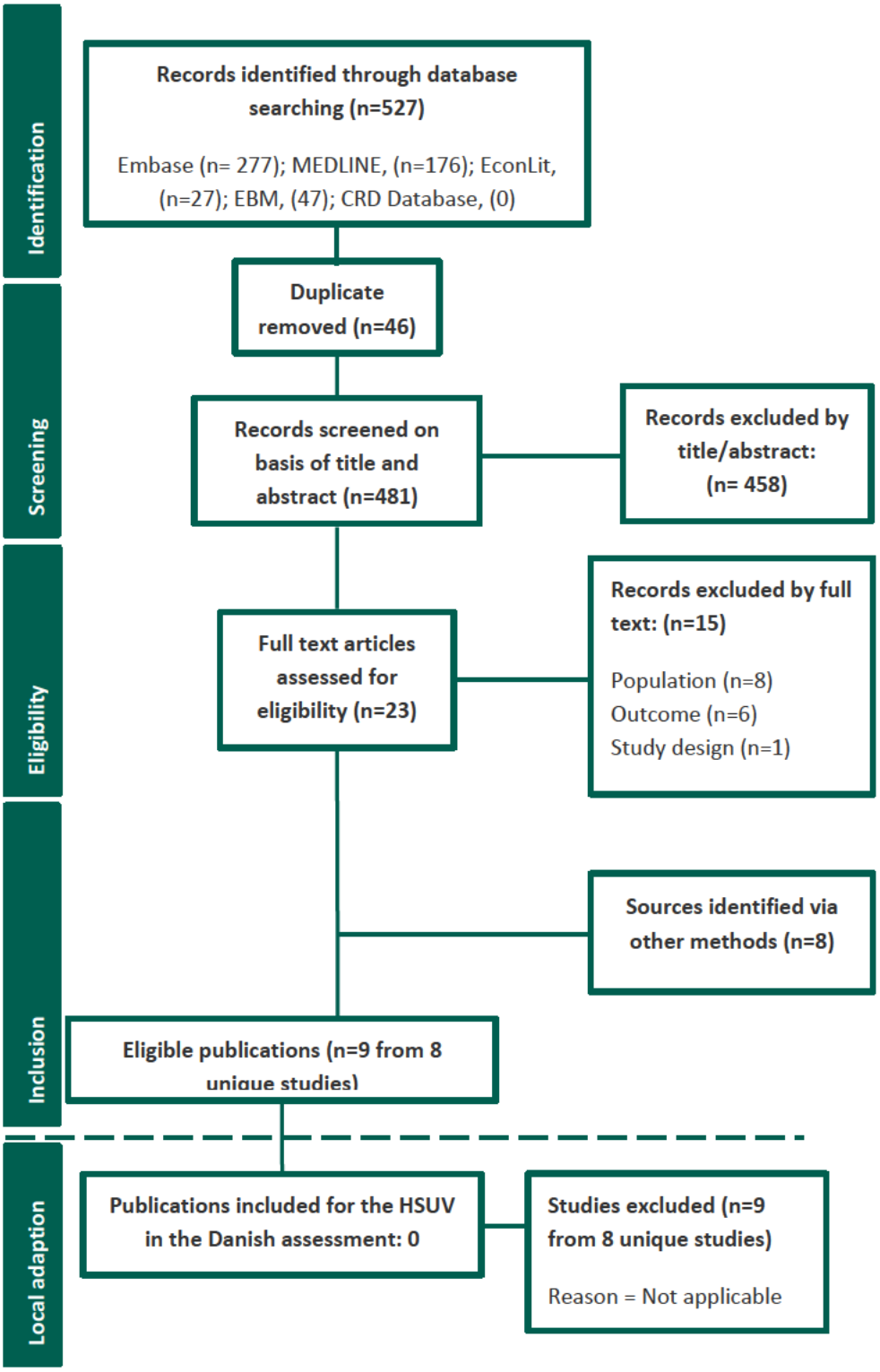

Figure 24 PRISMA diagram including local adaptation (HCRU)

Abbreviations: EconLit, American Economic Association's electronic database; Embase, Excerpta Medica database; HCRU, healthcare resource utilisation.

J.1.6 Quality assessment and generalizability of estimates

No quality assessment was performed for included cost and healthcare resource utilisation studies.

J.1.7 Unpublished data

N/A

Appendix K. Resource use frequencies applied in the health economic model

Table 88 presents the average percentage of patients experiencing any symptoms, which are used in the calculation of the health state-specific resource use frequencies applied in the health economic model (Table 89).

Table 88 Proportion of patients experiencing any symptom by disease and TSS health state

Average percentage experiencing any symptoms, non-responders			Average percentage experiencing any symptoms, responders		
Mild	Moderate	Severe	Mild	Moderate	Severe
0.77	0.92	0.96	0.39	0.46	0.48

Table 89 Resource use frequency per TSS health state and responder status by cycle length

Resource	Unadjusted resource use frequency per cycle	Adjusted resource use frequency per cycle, non-responders			Adjusted resource use frequency per cycle, responders		
		Mild	Moderate	Severe	Mild	Moderate	Severe
Gastrointestinal domain: outpatient consultation	0.33	0.26	0.31	0.32	0.13	0.15	0.16
Skin domain: Dermatology outpatient consultation	0.47	0.36	0.43	0.45	0.18	0.21	0.23

Resource	Unadjusted resource use frequency per cycle	Adjusted resource use frequency per cycle, non-responders			Adjusted resource use frequency per cycle, responders		
		Mild	Moderate	Severe	Mild	Moderate	Severe
Skin domain: Dermatologist nurse visit	0.04	0.03	0.04	0.04	0.02	0.02	0.02
Neurologic domain: outpatient consultation	0.86	0.66	0.79	0.83	0.33	0.40	0.41
Accident & Emergency visit	0.01	0.01	0.01	0.01	0.00	0.00	0.00
Hospitalization	0.01	0.01	0.01	0.01	0.00	0.00	0.00
Daycase admission	0.02	0.01	0.01	0.02	0.01	0.01	0.01
Anaphylaxis without complications	0.16	0.12	0.14	0.15	0.06	0.07	0.08
Anaphylaxis with complications	0.16	0.12	0.14	0.15	0.06	0.07	0.08
EpiPen use	0.08	0.06	0.07	0.07	0.03	0.04	0.04
Bone marrow biopsy	0.38	0.29	0.35	0.37	0.15	0.17	0.18
ECG	0.15	0.12	0.14	0.15	0.06	0.07	0.07
Haematology visit	0.31	0.24	0.28	0.30	0.12	0.14	0.15
Biochemistry test: renal - Urin test	0.31	0.24	0.28	0.30	0.12	0.14	0.15
Coagulation test	0.40	0.31	0.37	0.39	0.15	0.18	0.19
Serum chemistry tests	0.40	0.31	0.37	0.39	0.15	0.18	0.19
Photography	0.00	0.00	0.00	0.00	0.00	0.00	0.00

Resource	Unadjusted resource use frequency per cycle	Adjusted resource use frequency per cycle, non-responders			Adjusted resource use frequency per cycle, responders		
		Mild	Moderate	Severe	Mild	Moderate	Severe
CT scan	0.15	0.12	0.14	0.15	0.06	0.07	0.07
Chest X-ray	0.08	0.06	0.07	0.07	0.03	0.04	0.04
Ultrasound scan	0.08	0.06	0.07	0.07	0.03	0.04	0.04
MRI scan	0.15	0.12	0.14	0.15	0.06	0.07	0.07
Full blood count	0.31	0.24	0.28	0.30	0.12	0.14	0.15
Bone densitometry	0.04	0.03	0.04	0.04	0.01	0.02	0.02

Abbreviations: CT, computed tomography; ECG, electrocardiography; TSS, total symptom score.

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