For screen – contains redacted information

# Avapritinib for treating inadequately controlled moderate to severe indolent systemic mastocytosis

**Technology appraisal committee D [6th May 2026]**

**Chair:** Megan John

**Lead team:** Paul Caulfield, Simon McNamara, Marco Yeung

**External assessment group:** Kleijnen Systematic Reviews

**Technical team:** George Millington, Vicky Kelly, Ross Dent

**Company:** Blueprint Medicines

# Avapritinib for treating inadequately controlled moderate to severe indolent systemic mastocytosis

- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ❑ Summary

NICE National Institute for Health and Care Excellence

# Background on indolent systemic mastocytosis

## Causes

- Mastocytosis is a condition caused by an excess number of mast cells gathering in the body's tissues
- Cause of mastocytosis is not fully known but is believed to be associated with mutation in KIT gene - KIT D816V mutation has been found in around 95% of ISM cases

## Epidemiology

- According to clinical expert opinion, 1 in 10,000 people in the UK may have indolent systemic mastocytosis.

## Diagnosis and classification

- Systemic mastocytosis can be categorised into 3 subtypes – indolent, smouldering, or advanced, depending on clinical findings according to the WHO classification system
- Classifying subtypes by symptom severity is less clear, there is no definitive method, but severity may be decided by clinician opinion and may include a symptom rating system, such as ISM-SAF

## Symptoms

- Mast cells release large amounts of histamine and other mediators, causing symptoms such as: skin rash, itchy skin, fatigue, trouble with cognition and memory, hot flushes, blood pressure changes, fainting, tachycardia, headache, vomiting, diarrhoea, organ dysfunction and anaphylaxis



Abbreviations: ISM, indolent systemic mastocytosis; SAF, symptom assessment form; WHO, world health organization

# Patient perspectives

*Patients would welcome more treatment options for ISM*

**Submissions from patient experts of The UK Mastocytosis Support Group**

- Key triggers for mast cell activation include heat/cold, stings, exercise, stress, alcohol and foods – stakeholders highlight the unpredictability of attacks and the intense impact they have on daily life
- Stakeholders report building their life to avoid their triggers, leading to loss of opportunities in their personal and professional lives
- Stakeholders note medications can cause an attack, adding stress to other medical situations
- Stakeholders highlight rashes, swelling, extreme cramps, diarrhoea, bone pain, fatigue and anaphylaxis as key debilitating symptoms, although noting symptom profile can differ significantly between people with ISM
- Stakeholders report existing treatment has been unchanged in decades and is not very effective, highlighting that they only help some with a small number of triggers
- Perspective of the ISM population towards avapritinib is positive, and a step-change – noting that some people who have taken it describe their life as 'normal' which stakeholders report is a far cry from the usual experience for people with ISM
- One stakeholder who received avapritinib described it as life-changing

"My whole body heated up and feel like it was on fire, I did sometimes get some intense itchiness… My legs, arms and chest would be covered in angry red and raised spots, and my face would be bright red and was really hot. It was an overwhelming sense of doom. "

"the drugs don't address my triggers including sensitivity to things in my environment, food stress, temperature, and exertion-induced reactions. My symptoms remain as well"

Abbreviations: ISM, indolent systemic mastocytosis

# Clinical perspectives

*Clinicians believe avapritinib is a step-change in treating ISM*

## Submissions from BAD, BSH, BSI and clinical experts

- Stakeholders highlight the debilitating symptom profile of ISM, often deeply impacting daily life
- Stakeholders note heterogeneity of symptoms, making ISM difficult to manage
- Stakeholders believe that current treatments are insufficient, one noting that they will be effective in only 40-45% of people with ISM
- Stakeholders note that existing treatment involves a large number of medications with complex dosing requirements
- Stakeholders note avapritinib is the first disease-specific drug for ISM targeting the C-KIT D816V mutation driving the clonal disease in ISM
- Stakeholders believe that the results from PIONEER show avapritinib is a clinically effective option and a step-change for treating ISM

"ISM can lead to significant systemic complications. These include debilitating effects on bone health such as osteopenia and osteoporosis, neurocognitive impairments, recurrent allergic reactions including life-threatening anaphylaxis, and a risk of progression to smouldering or advanced systemic mastocytosis. These manifestations often remain under-recognised and inadequately managed with current treatment options."

NICE

Abbreviations: BAD, British Association of Dermatologists; BSH, British Society for Haematology; BSI, British Society for Immunology; ISM, indolent systemic mastocytosis

# Equality considerations

Stakeholders highlighted a number of potential equalities issues:

- Stakeholders highlighted concern that patients face delays in diagnosis and clinicians outside of specialist centres may not be aware of new treatments available, meaning people who live farther from specialist centres may be less likely to get access to avapritinib
- Stakeholders note that avapritinib cannot be taken during pregnancy
- At scoping stage stakeholders noted that some current treatments for ISM may contain gelatine which would not be suitable for some people from certain religious backgrounds.

Are there any equality issues that can be addressed by committee?



Abbreviations: ISM, indolent systemic mastocytosis

# Avapritinib (Ayvakyt, Blueprint medicines)

| | |
|---|---|
| **Marketing authorisation (EMA)** | • **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<br>• MHRA MA submitted via IRP route |
| **Mechanism of action** | • Type 1 TKI that has demonstrated *in vitro* activity against the KIT D816V variant protein<br>• Inhibition of KIT protein halts downstream-signalling pathways that promote mast cell activation |
| **Administration** | • For ISM, the recommended dose of avapritinib is 25 mg orally once daily on an empty stomach.<br>• This is the maximum recommended dose that must not be exceeded in patients with ISM.<br>• Treatment of ISM should be continued until disease progression or unacceptable toxicity occurs. |
| **Price** | • The list price of avapritinib is £26,667.00 per pack of 30 25mg tablets (BNF, April 2026)<br>• Average cost for a course of treatment at PAS price is estimated to be [redacted] |



Abbreviations: BNF, British National Formulary; EMA, European Medicines Agency; IRP, international recognition procedure; MA, marketing authorisation; MHRA, Medicines and Healthcare products Regulatory Agency; PAS, patient access scheme; TKI, tyrosine kinase inhibitor

# Key issues

| Key issue | ICER impact |
|---|---|
| Population in NHS practice | **Unknown** |
| Generalisability of the trial | **Large** |
| Generalisability of the model | **Large** |
| Duration of treatment | **Large** |
| Progression in the model | **Large** |
| Utilities in the model | **Small** |
| Resource use in the model | **Large** |

# Avapritinib for treating inadequately controlled moderate to severe indolent systemic mastocytosis

- ❑ Background and key issues
- ✓ **Clinical effectiveness**
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ❑ Summary

NICE National Institute for Health and Care Excellence

# Key clinical trial

Clinical trial designs and outcomes

For a diagram of the study designs, see appendix

| | PIONEER - Phase 2 Randomised, double-blind, placebo controlled |
|---|---|
| **Population** | Centrally confirmed WHO diagnosis of ISM **AND** moderate to severe symptoms according to a minimum mean ISM-SAF TSS of ≥28 over a 14-day screening period |
| **Intervention** | Avapritinib + SDT (H1-blockers, H2-blockers, PPIs, leukotriene inhibitors, corticosteroids, cromolyn sodium, monoclonal antibodies. **TKIs not permitted**) |
| **Comparator** | Placebo + SDT |
| **Key outcomes** | • Mean change in TSS of the ISM-SAF from baseline to week 24<br>• ≥30% and ≥50% reduction in TSS from baseline at week 24<br>• EQ-5D utility values by disease severity category derived from PIONEER trial and PRISM study<br>• Health state distribution by TSS severity categories during initial treatment period (6 cycles) and maintenance phase<br>• TRAE incidence rates<br>• Patient distribution across mild (TSS 0-27), moderate (TSS 28-41), and severe (TSS 42-110) health states |
| **Locations** | 42 sites, majority located in Europe (n=23), with 19 located in North America |
| **Length of follow up** | 5 years |
| **Used in model?** | Yes |

Abbreviations: ISM, indolent systemic mastocytosis; PPI, proton pump inhibitor; SAF, symptom assessment form; SDT, symptom directed therapy; TRAE, treatment related adverse event; TSS, total symptom score; WHO, world health organization

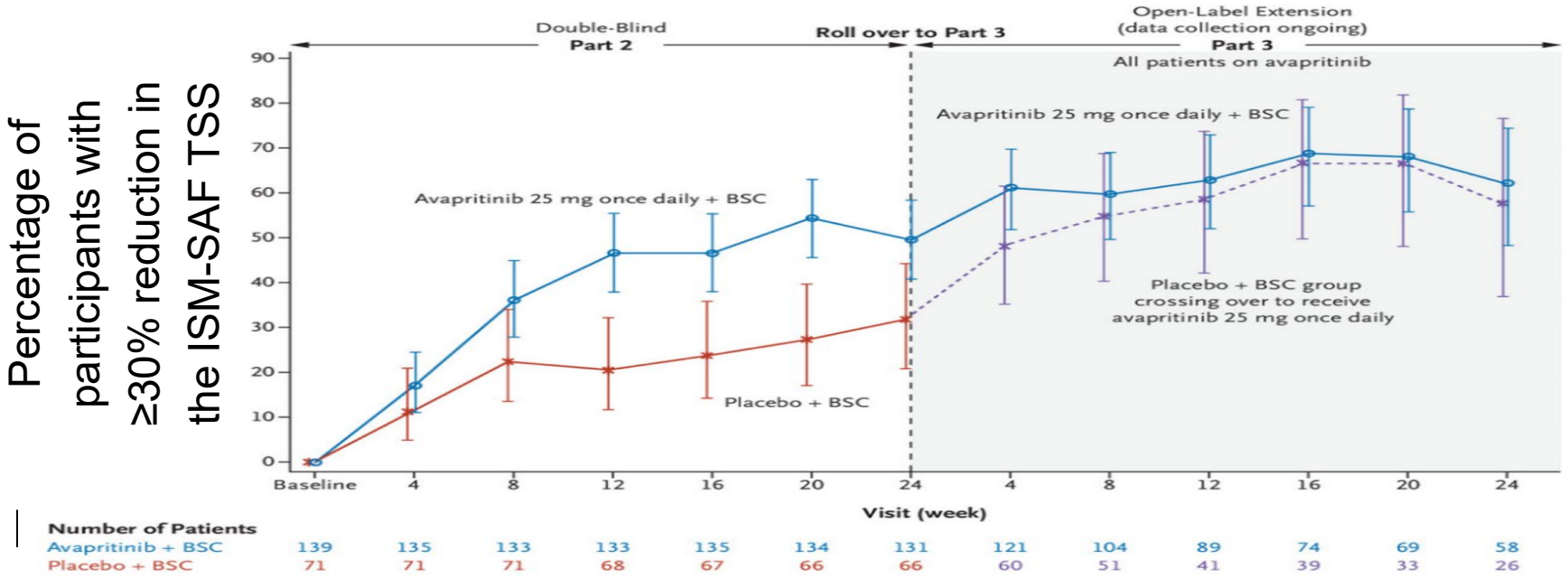
# Key clinical trial results – PIONEER

*Avapritinib shows a statistically significant improvement in TSS compared to placebo*

**Table**: Mean change in TSS (lower is better) of ISM-SAF from baseline to week 24 (PIONEER Part 2 ITT population)

| Parameter | Avapritinib 25 mg (N=141) | Placebo (N=71) |
|---|---|---|
| Baseline, Mean (SD) | 50.17 (19.15) | 52.43 (19.82) |
| Week 24, Mean (SD) | 33.48 (20.06) | 42.32 (21.03) |
| CFB, LS Mean (95% CI) | -15.58 (-18.61, -12.55) | -9.15 (-13.12, -5.18) |
| Between group difference (95% CI) | -6.43 (-10.90, -1.96; p=0.003) | |

**Figure and table:** Percentage of participants with ≥30% reduction in the ISM-SAF TSS from baseline (PIONEER ITT population)




| | Ava n/N (%) | Placebo n/N (%) |
|---|---|---|
| ≥30% reduction in TSS at week 24 (95% CI) | 64/141 (45.4%) (37.0%, 54.0%) | 21/71 (29.6%) (19.3%, 41.6%) |
| OR (95% CI) | 2.07 (1.08, 3.99) p=0.009 | |

# Key issues: Population in NHS practice

Unknown

*EAG: company's definition of moderate to severe ISM may exclude people who would receive avapritinib in NHS*

## Background

- Population in scope: Adults with inadequately controlled moderate to severe indolent systemic mastocytosis (ISM)
- Eligibility criteria in PIONEER: WHO criteria <2 B-findings and no C-findings are diagnosed with ISM **and** TSS ≥28 on the ISM-SAF over 14-day eligibility screening

## Company

- NHS clinical practice expected to follow MA - based on PIONEER - to judge eligibility confirmed by clinical experts
- MA does not specify ISM-SAF (or TSS ≥28) - not required implicitly as criteria, but will guide clinicians
- NHS clinical practice in England and Europe is aligned with the eligibility criteria of the PIONEER
- ISM-SAF TSS is an appropriate and clinically meaningful measure as symptom burden – validated by clinicians
- ITT population in PIONEER is considered highly generalisable to the UK patients eligible for avapritinib

## EAG comments

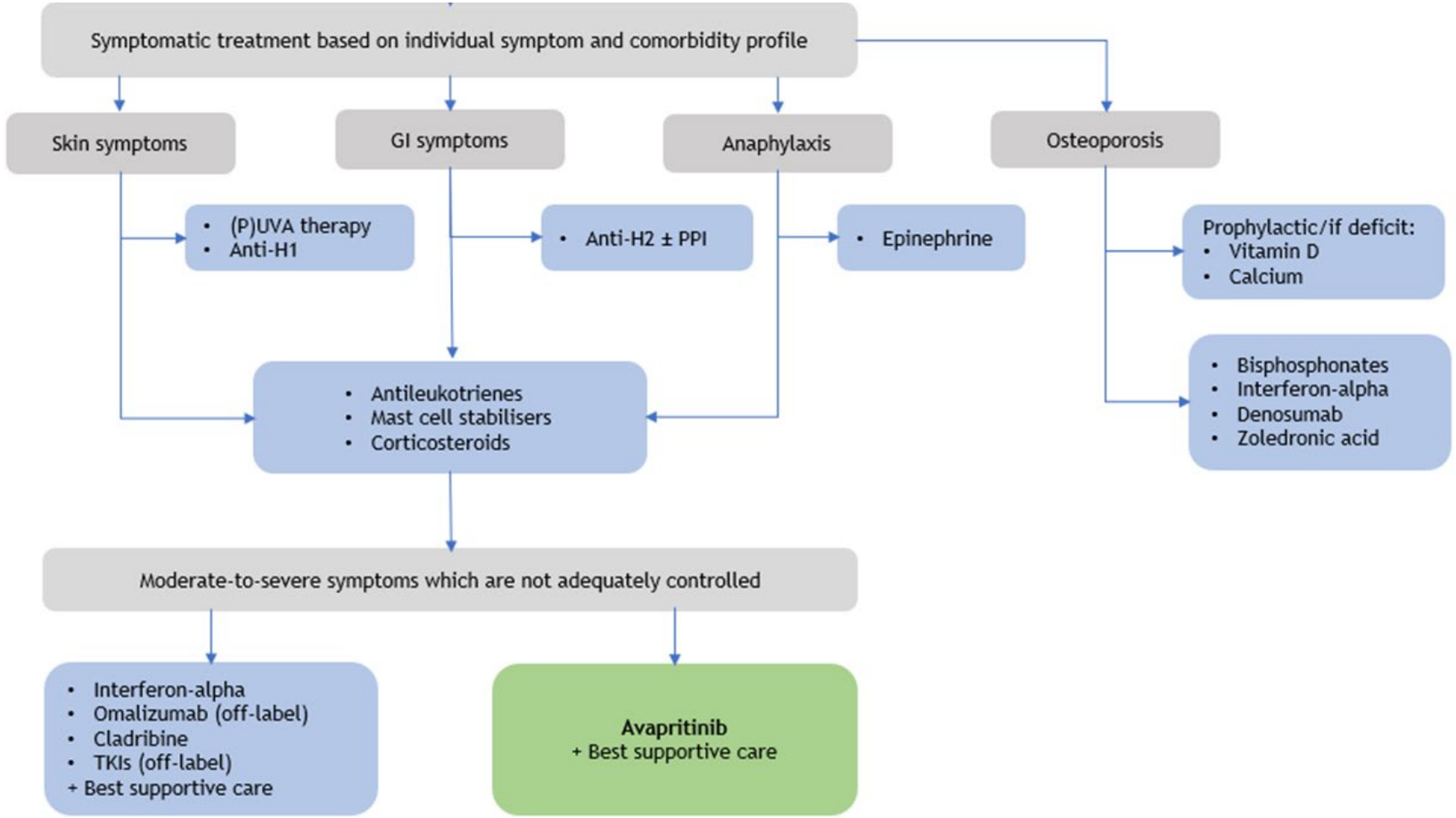
- EAG expert advised WHO criteria universally used but ISM-SAF is not used in all centres
- Expert also suggested that TSS is not used outside of research contexts
- Company clinical expert noted that people with one severe symptom – who would benefit from avapritinib - may have been excluded from trial on basis of TSS score
- People categorised as having mild disease by TSS may still be treated with avapritinib in clinical practice

Does the company's definition of moderate to severe ISM align with how it is diagnosed in NHS practice?



Abbreviations: ISM, indolent systemic mastocytosis; MA, marketing authorisation; SAF, symptom assessment form; TSS, total symptom score; WHO, world health organization

# Company treatment pathway for ISM




Does the company's treatment pathway align with NHS practice?

How would avapritinib be used in clinical practice: Is BSC the same as ECM or SDT (are the terms interchangeable)?

Are TKIs used in standard NHS practice for people with ISM?

Abbreviations: BSC, best supportive care; ECM, established clinical management; GI, gastrointestinal; ISM, indolent systemic mastocytosis; PPI, proton pump inhibitor; (P)UVA, psoralen with Ultraviolet A; SDT, symptom directed therapy; TKI, tyrosine kinase inhibitor

# Key issues: Generalisability of the trial

Large

*EAG raises potential discrepancies between PIONEER trial and NHS clinical practice*

## Background

- **Dose escalation**: 25mg to 50mg was permitted in PIONEER open label extension (not included in company base case). EMA SmPC states dose escalation beyond 25mg daily is not permitted.
- **SDT**: Around 10% of people in PIONEER received omalizumab as part of SDT
- **Treatment effects:** Not observed consistently across all ISM-SAF symptom domains

## Company

- **Dose escalation:** Dose escalators removed from analysis to ensure analysis reflects only licensed 25mg dose – comparing health state occupancy excluding escalators vs. full population show similar distributions – indicates removing escalators does not bias treatment effect estimates
- **SDT:** % patients receiving each type of SDT validated by experts

## EAG comments

- **Dose escalation:** Results of full population similar to main analysis population, but unclear what their results would have been without escalation – removing from analysis essentially censors worst responders
- **SDT:** % of patients receiving each type of SDT in PIONEER differ to clinical expert opinion.
- **Treatment effects:** Results of PIONEER by domain show treatment benefit driven by skin domain. Suggests potential heterogeneity of treatment effect across symptoms.

How does removing dose escalators impact the generalisability of the trial results?
Is there variability in treatment benefit by domain?

Large

# Key issues: Generalisability of the trial

*Table shows proportion of patients receiving type of SDT in trial vs EAG expert opinion*

| Comparator | % of patients in avapritinib + SDT arm | % of patients in placebo + SDT arm | Company expert estimation | EAG clinical expert 1 | EAG clinical expert 2 - SDT + avapritinib | EAG clinical expert 2 - SDT only |
|---|---|---|---|---|---|---|
| H1-blockers (Average) | [redacted] | [redacted] | [redacted] | 100% | 90% | 90-95% |
| H2-blocker (Cimetidine) | [redacted] | [redacted] | [redacted] | 70% | 50-60% | 50-60% |
| Omeprazole | [redacted] | [redacted] | [redacted] | 50% | 10% | 20% |
| Montelukast | [redacted] | [redacted] | [redacted] | 50% | 10-40% | 10-40% |
| Prednisolone | [redacted] | [redacted] | [redacted] | 10% | 0% (short term use only) | 0% (short term use only) |
| Cromolyn Sodium | [redacted] | [redacted] | [redacted] | 30% | 5-10% | 5-10% |
| Omalizumab | [redacted] | [redacted] | [redacted] | <5% | 0% | 5% |
| Loperamide | Not used in the PIONEER trial | Not used in the PIONEER trial | [redacted] | N/A | N/A | N/A |

Is the SDT used in PIONEER generalisable to clinical practice?

Abbreviations: SDT, symptom directed therapy

# Avapritinib for treating inadequately controlled moderate to severe indolent systemic mastocytosis

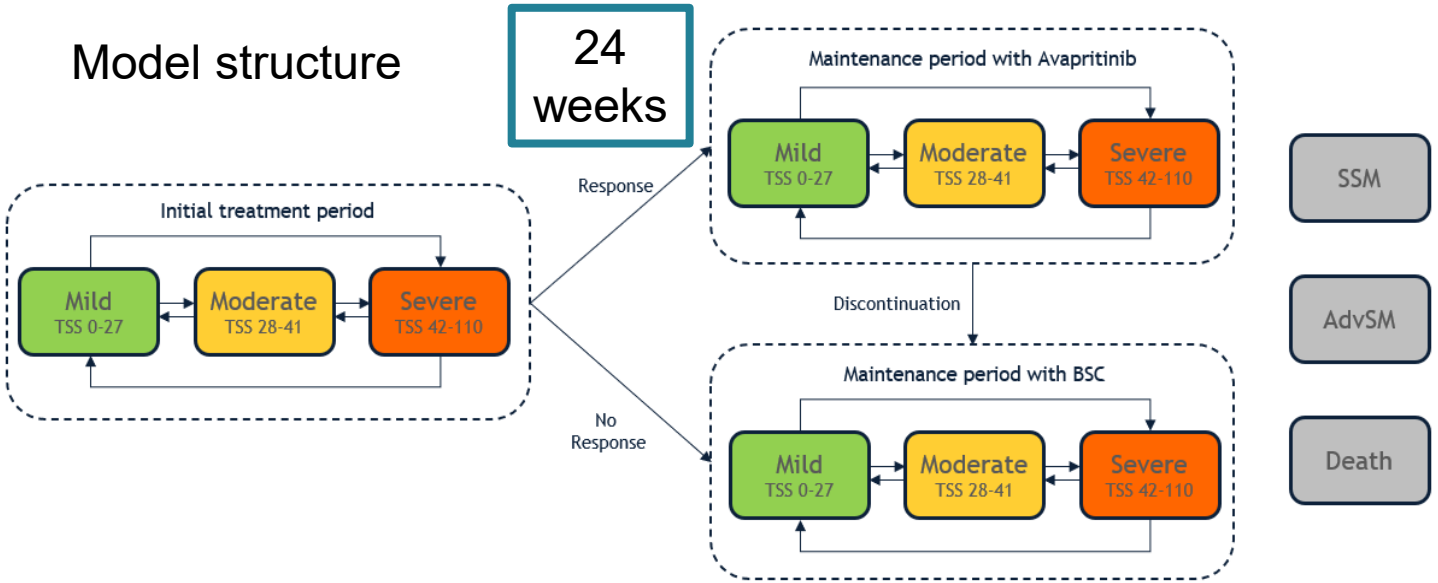
- ❑ Background and key issues
- ❑ Clinical effectiveness
- ✓ **Modelling and cost effectiveness**
- ❑ Other considerations
- ❑ Summary

NICE National Institute for Health and Care Excellence

# Company's model overview

## Company used a new disease activity model

Model structure




Company assume no mortality benefit for avapritinib in model

Technology affects **costs** by:

- Treatment acquisition (increase costs) and administration costs
- Time in less expensive health states (decrease costs)

Technology affects **QALYs** by:

- Increasing duration in the mild disease state (increase QALYs)
- Reducing duration in the severe disease state (increase QALYs)

Assumptions with greatest ICER effect:

- No stopping rule for non-responders

**EAG comments**

- EAG considers the company's symptom-based model structure, using TSS of ISM-SAF, to be appropriate
- Concerned that there is a mismatch between the disease severity classification in the company's model structure and disease severity classification in clinical practice (key issue)
- Inclusion of SSM and AdvSM health states are appropriate, however there are issues relating to progression to and from these states (key issue)

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

# Key issues: Generalisability of the model

Large

*EAG raises several concerns regarding the generalisability of the model to real-world practice*

## Background

- **Health states:** Model uses ISM-SAF TSS to determine model state and response
- **Age:** Model has a starting age of 40 (mean PIONEER baseline age = 51)
- **Dose escalation**: Base case omits dose escalation, included in scenario with no added costs for higher dose
- **TKIs:** SDT basket is modelled as including off-label TKIs – TKIs were not permitted during PIONEER

## Company

- **Health states:** Symptom-based structure consistent with both clinical management of ISM and available evidence
- **Age:** Clinical experts advised ISM would typically present earlier in life than the mean PIONEER baseline age
- **Dose escalation**: Base case excludes escalators which aligns with target population of anticipated UK MA
- **TKIs:** Off-label TKIs (e.g. midostaurin) included in base case based on observed studies indicating that TKIs are used in a small, highly selected subgroup of non-advanced SM patients – would not be reimbursed in practice

## EAG comments

- **Health states:** Unclear if ISM-SAF TSS is routinely used in the NHS **–** concerned that model may classify people as mild who would be expected to get avapritinib in NHS practice
- **Age:** EAG's clinical expert reported a mean age of 51 years in local ISM cohort → EAG use 51 starting age
- **Dose escalation**: Unclear impact on treatment effect, crossover adjustment may provide more accurate results
- **TKIs:** TKIs were not permitted during PIONEER, meaning comparative efficacy may be affected, and are not reimbursed in practice → prefer to exclude off-label TKIs from SDT basket in base case



Is the company's model generalisable to NHS practice?

Large

# Key issues: Duration of treatment

*EAG raises several concerns regarding the duration of treatment with avapritinib*

## Background

- Company base case includes a 24-week stopping rule for people who did not reach TSS response threshold (≥30% reduction in TSS), stopping due to AEs (one-off event), and a maximum treatment duration of [redacted] years based on average from parametric extrapolations deemed plausible of mean ToT from US RWE

## Company

- 24-week stopping rule based on expectation that treatment effect will be regularly assessed in practice and treatment will be stopped in the case where response is not present - 6-month timeframe considered clinically reasonable and appropriate - confirmed by clinical experts
- AE discontinuations in model based on AE discontinuations observed in PIONEER by that timepoint
- PIONEER trial data not mature enough to generate reliable extrapolations to inform the DoT benefit

## EAG comments

- Stopping rule not in line with evidence - [redacted] of people in PIONEER remained on treatment at week 24, while in the company's model it is only approximately [redacted] → EAG prefer to remove stopping rule
- Discontinuation events can only be addressed individually, mismatch in health state distribution between trial and model remains even when stopping rule disabled – unclear if this has been implemented correctly
- Unclear why AE discontinuation was applied as a one-off event – more justification required
- [redacted] years appears to be an average ToT, rather than a maximum treatment duration – likely underestimates ToT
- Maximum treatment duration may double-count discontinuation due to lack of response and AEs

NICE

Is the company's implementation of duration of treatment suitable?

# Key issues: Progression in the model

Large

*EAG note inconsistencies in the company's implementation of progression*

## Background

- **SDT:** Company assumes SDT only arm revert to baseline symptom score after the end of the trial period
- **Tunnels:** Transition to SSM and AdvSM more likely for people categorised as having severe ISM in company BC
- **Health states:** Used trial-derived heath state distributions rather than transition probabilities

## Company

- **SDT:** Clinical experts advised people receiving SDT are not expected to experience sustained change in underlying symptom severity - SDT does not alter the course of disease but provides symptom control
- **Tunnels:** Matito et al. (2013) show progression risk to more advanced SM states higher in more severe categories - increasing risk with increasing symptom severity is clinically plausible
- **Health states:** To reduce overfitting company used minimum of 10 patients per cycle to derive distributions

## EAG comments

- **SDT:** Better symptom control may impact HRQoL in the long term - not captured in the model except through their health state distribution → Prefer to have SDT arm remain in last observed health state as in avapritinib arm
- **Tunnels:** Matito et al. (2013) relates to serum tryptase levels rather than TSS health states on risk of progression
- **Tunnels:** Several errors in the company's implementation of progression - mortality benefit for avapritinib believed to be as a result of errors → Until errors corrected, prefer to disable progression to SSM and AdvSM
- **Health states:** Notes instability in health states around cycle 46 → Prefer minimum of 20 to derive health states

N

Is the company's approach to reverting symptom score to baseline in the SDT arm clinically plausible?
What is the relationship between TSS and risk of progression to SSM and AdvSM?
What should be the minimum amount of people used to derive health state distribution?

# Key issues: Utilities in the model

Small

*EAG highlight utility benefit and handling of missing data as potential issues in the company model*

## Background

- **Benefit:** A utility benefit of 0.086 is applied to avapritinib responders (≥30% reduction in TSS) who remain in the severe health state in the company's base case
- **Data:** No imputation was applied in company model for missing HRQoL data - analyses used observed data only

## Company

- **Benefit:** AB and expert opinion consistently stated a ≥30% reduction in TSS is clinically meaningful improvement
  - This may also meaningfully improve HRQoL, even if they remain in the same symptom severity category
  - Utility benefit not double-counting, symptom benefit of avapritinib would be underestimated without it
- **Data:** Did not pursue MMRM because additional assumptions required – LOCF is reasonable approximation

## EAG comments

- **Benefit:** Applying a utility benefit to responders in severe health state likely double counting - utility estimate from PIONEER for this state already included mix of responders and non-responders → removed benefit in base case
- **Data:** Unclear which patient population was used for the EQ-5D analysis, and how missing data handled (HRQoL data appears to not be MCAR) but company's observed data only approach implicitly assumes MCAR
  - Considers company's approach inadequate and recommends implementing MMRM or MI in base case

Should a utility benefit beyond health state changes be applied to avapritinib responders? How should missing utility data be handled?

NICE

Abbreviations: HRQoL, health-related quality of life; LOCF, last observation carried forward; MCAR, missing completely at random; MI, multiple imputation; Mixed Models for Repeated Measures; TSS, total symptom score

# Key issues: Resource use in the model

Large

*EAG note several unclear points related to the company's resource use figures and error in model*

## Background

- Health state costs split by responder/non-responder for mild, moderate and severe. Frequency and nature of health state unit costs sourced from Dutch advisory board asked to make a distinction between HCRU for responders and non-responders, not differentiating per health state (UK clinicians surveyed but not used)
- Responders in each health state have lower resource use costs per cycle

## Company

- Dutch advisory board resource use was chosen as the more conservative option for the base-case resource use
- Dutch and UK healthcare systems are similar enough for clinician input to be suitable for use in the model
- No clinician suggested resource use would remain the same in responders with sustained symptom improvement

## EAG comments

- Suggests UK based data should be explored for the frequency and nature of health state unit costs, noting that advisory board figures are not the most conservative in all areas (e.g. neurological domain and blood monitoring)
- When response-based stopping rule is disabled (as in EAG base case), responder cost benefit applies to full avapritinib arm – believed to be an error. EAG conducted scenario to remove responder cost benefit
- EAG corrected errors in modelling of dose-escalation – suggests model may not account for wastage (28-day cycle but 30 table packs may lead to unaccounted wastage at discontinuation

Are the company's health state costs appropriate?

Abbreviations: HCRU, healthcare resource utilisation

# Summary of company and EAG base case assumption differences

Assumptions in company and EAG base case

| Assumption | Company base case | EAG base case | ICER impact |
|---|---|---|---|
| **SSM and AdvSM tunnel states** | Included | Excluded (due to errors in model programming) | ↓ |
| **24-week stopping rule for non-responders** | Included | Excluded | ↑↑↑ |
| **Utility benefit for avapritinib responders** | Included | Excluded | ↑ |
| **Starting age in model** | 40 | 51 | ↑↑ |
| **Off-label TKIs included in SDT basket** | Included | Excluded | ↑↑ |
| **Minimum data required to calculate health state distribution** | 10 | 20 | ↑ |
| **SDT health state after trial period** | Revert to baseline | Remain in last observed health state | ↑↑↑ |

EAG also corrected an error in the conversion of the observed probabilities to the model cycle length

**EAG key scenarios**

- Include dose escalation population and costs of escalated dose with correction to the calculation (large impact)
- Remove responder benefit on resource use (large impact)



Abbreviations: AdvSM, advanced systemic mastocytosis; SDT, symptom directed therapy; SSM, smouldering systemic mastocytosis; TKI, tyrosine kinase inhibitor

# Cost-effectiveness results

All ICERs are reported in PART 2 slides

because they include confidential

PAS discounts

When the company and EAG base case ICERs are calculated using confidential prices, both are substantially **above** NICE's £25,000 to £35,000 per QALY gained range

# Avapritinib for treating inadequately controlled moderate to severe indolent systemic mastocytosis

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ✓ **Other considerations**
- ❑ Summary

NICE National Institute for Health and Care Excellence

# Uncaptured benefits, managed access, and severity

## Company

- Avapritinib is administered once daily, which may reduce treatment burden compared with the basket of SDT regimens that often involve multiple drugs or complex dosing schedules. Although this convenience could improve patient adherence and satisfaction, there is insufficient quantitative evidence to estimate its impact on utility, and KOLs did not consider it plausible to provide a reliable adjustment

## NICE technical team

- Avapritinib is provided alongside SDT. While there may be some evidence that treatment with avapritinib results in a reduction in SDT use, some SDT will likely still be required and improvements in convenience and downstream adherence are highly speculative

## Managed Access

- Company has not submitted a proposal for managed access
- Managed access team concluded there is a medium likelihood that managed access would resolve uncertainties
- For the committee to make a managed access recommendation, they would first need to request a proposal from the company and MAT would produce a full feasibility assessment based on their proposal.

## Severity

- Company: criteria for severity modifier not met

 Abbreviations: KOL, key opinion leaders; MAT, managed access team; SDT, symptom directed therapy

# Avapritinib for treating inadequately controlled moderate to severe indolent systemic mastocytosis

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ✓ **Summary**

NICE National Institute for Health and Care Excellence

# Key issues

| Key issue | ICER impact |
|---|---|
| Population in NHS practice | **Unknown** |
| Generalisability of the trial | **Large** |
| Generalisability of the model | **Large** |
| Duration of treatment | **Large** |
| Progression in the model | **Large** |
| Utilities in the model | **Small** |
| Resource use in the model | **Large** |

# Avapritinib for treating inadequately controlled moderate to severe indolent systemic mastocytosis

# Supplementary appendix

NICE National Institute for Health and Care Excellence

# WHO criteria for systemic mastocytosis category

Return to key issue

| B-findings (borderline-benign) - Indicate a high burden of MCs and expansion of the neoplastic process into multiple hematopoietic lineages, without visible impairment of organ function | C-findings (consider cytoreduction) - Are indicative of organ damage produced by MC infiltration (should be confirmed by biopsy if possible) |
|---|---|
| MC infiltration grade in the bone marrow (BM) >30% by histology and the basal serum tryptase level is >200 ng/ml | Cytopenia(s): ANC <1,000/µL or Hb<10 g/dL or PLT<100,000/µL |
| | Hepatomegaly with ascites and impaired liver function |
| Hypercellular BM with loss of fat cells, discrete signs of dysmyelopoiesis without substantial cytopenias or WHO criteria for an MDS or MPN | Palpable splenomegaly with associated hypersplenism |
| | Malabsorption with hypoalbuminemia and weight loss |
| Organomegaly: palpable hepatomegaly, palpable splenomegaly, or palpable lymphadenopathy (on CT or ultrasound: >2 cm) without impaired organ function | Skeletal lesions: large-sized osteolyses with pathologic fractures |
| | Life-threatening organ damage in other organ systems that is caused by local MC infiltration in tissues |

In SM patients in whom less than 2 B-Findings and no C-Finding are detected (category A), the diagnosis is indolent SM (ISM). When 2 or more B-Findings but no C-Findings are present, the diagnosis is smouldering SM (SSM). When 1 or more C-Findings (with or without additional B-Findings) are detected, the final diagnosis is either ASM (<20% MCs in BM smears) or MC leukaemia (MCs ≥20% on BM smears).



Abbreviations: SM, systemic mastocytosis; MCs, mast cells; WHO, World Health Organization; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm; CT, computed tomography; ANC, absolute neutrophil count; Hb, haemoglobin; PLT, platelet count.

# ISM-SAF and TSS

Return to main deck

**Table:** ISM Symptom Assessment Form (ISM-SAF) domains and scales

| Domain | Symptom | Scoring |
|---|---|---|
| GI domain (0-30) | • Abdominal pain<br>• Diarrhea (severity)<br>• Nausea | Patients are analysed as a 14-day moving average or one-time (dependent on clinic)<br>Each symptom is scored 0–10 with:<br>○ 0 = no [symptom]<br>○ 10 = worst imaginable [symptom]<br>**Individual symptom severity scores are summed to generate a TSS (0–110)**<br>Additional question asked regarding diarrhoea frequency (12th item) |
| Skin domain (0-30) | • Spots<br>• Itching<br>• Flushing | |
| Neurocognitive symptoms (0-30) | • Brain fog<br>• Headache<br>• Dizziness | |
| Other symptoms (0-20) | • Bone pain<br>• Fatigue | |

NICE

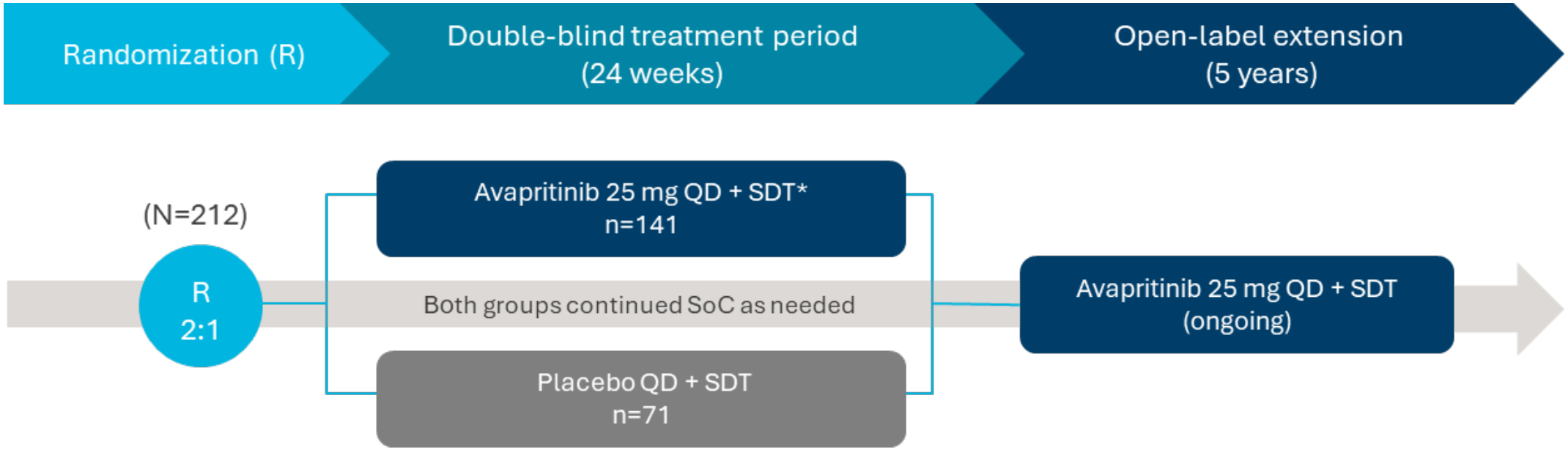
Abbreviations: ISM, indolent systemic mastocytosis; SAF, standard assessment form; TSS, total symptom score

# Key clinical trials

Clinical trial designs

Return to main deck

**Figure**: PIONEER study design




| | |
|---|---|
| Trial design | Multicentre, three-part Phase 2 study:<br>• [Part 1] Dose escalation<br>• [Part 2] Pivotal ,double-blind, placebo-controlled RCT<br>• [Part 3] Long-term open-label extension. |

Abbreviations: QD, *quaque die* (once daily); SDT, symptom directed therapy; SoC standard of care

# PIONEER trial – symptom domain results

Changes in key domains of ISM-SAF at Week 24 (PIONEER Part 2 ITT Population)

| Domain/cluster | Avapritinib 25 mg N=131 Mean (SD) change | Placebo N=66 Mean (SD) change | Difference (95% CI) | p-value |
|---|---|---|---|---|
| GI domain | -3.74 (4.87) | -3.14 (4.67) | -0.60 (-2.03, 0.83) | 0.410 |
| Skin domain | -5.87 (6.49) | -2.64 (4.11) | -3.23 (-4.73, -1.73) | < 0.0001 |
| Neurocognitive symptom cluster | -4.03 (5.22) | -2.81 (4.29) | -1.22 (-2.69, 0.25) | 0.102 |

**EAG comments**

- Treatment effects not consistent across all ISM-SAF symptom domains, with improvements primarily driven by the skin domain
- 80% of people had non-skin symptoms, however unclear what degree of overlap occurs
- May be a concern if patients become eligible for avapritinib because their symptoms are predominantly not skin-related or those of the skin not the most severe



Abbreviations: CI, confidence interval; GI, gastrointestinal; ITT, intent-to-treat; SD, standard deviation.

# Key issues: Duration of treatment (1/2)

Return to main deck

Large

*US RWE KM data with long-term extrapolations*

**Figure:** US RWE KM data and 240-month extrapolations for TTD

# Key issues: Duration of treatment (2/2)

Return to main deck

Large

*US RWE KM data with long-term extrapolations*

**Table:** US RWE KM data and 240-month extrapolations for TTD

| Distribution | Median (months) | Mean (months) | Survival 3 months | Survival 24 months | Survival 48 months | Survival 96 months |
|---|---|---|---|---|---|---|
| KM | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Exponential | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Weibull | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Gompertz | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Log Normal | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Log Logistic | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Gamma | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Gen. Gamma | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

**Company**: Given the large degree of uncertainty still present in the extrapolated parametric curves, an average DoT was taken excluding the two clinically implausible extrapolations (Gompertz and Generalised Gamma; mean DoTs of [redacted] [redacted] years respectively). This resulting in an average DoT of [redacted] years.

# Key issues: Duration of treatment

Return to main deck

Large

*PIONEER safety population KM data for time to treatment discontinuation*

**Figure:** Kaplan-Meier plot of time to treatment discontinuation in PIONEER Safety Population

Black line = overall population

**Company comments**

- KM plot illustrates the high retention rate on avapritinib, with the "Overall" curve (black line) maintaining a probability above [redacted] until approximately Month [redacted], before the final decline toward the median at [redacted] months.

# Key issues: Progression in the model

Return to main deck

Large

*EAG highlights errors in the company's implementation of progression in the model*

**EAG comments**

- Errors noted in company implementation of progression in the model:
  - probabilities of progression observed in studies with longer observation periods were incorrectly converted to the model cycle length
  - model assumes that progression in the avapritinib arm only starts in Cycle 7, while in the SDT arm it starts in Cycle 0
  - Multiple errors in programming of transitions to SSM and AdvSM states including transition between SSM to AdvSM, wrong references to people who discontinued avapritinib, use of instantaneous transition probabilities to SSM rather than cumulative probability of residing in SSM when calculating people that enter or reside in AdvSM

# Company's modelled SDT basket (TKI usage)

*Company: Off-label TKI use was included in the base case using EU data, given that this was considered reflective of clinical practice despite a lack of reimbursement in the UK*

| Comparator | Proportion of patients in avapritinib + SDT arm | Proportion of patients in SDT arm | Data source |
|---|---|---|---|
| **Midostaurin** | 0% | 9.9% | NICE TA728 - Midostaurin for treating **advanced** systemic mastocytosis |
| **Imatinib** | 0% | 3.3% | Expert opinion<br>Buonomo et al. (2022) |
| **Dasatinib** | 0% | 1.1% | Buonomo et al. (2022)<br>Verstovsek S et al. (2008) |

Return to treatment pathway

Return to key issue

Company note: UK clinicians confirmed that TKIs are rarely used in practice due to limited supporting evidence, though some use in ISM does occur

Are TKIs used in standard NHS practice for people with ISM?

NICE

Abbreviations: SDT, symptom-directed therapy; TKIs, tyrosine kinase inhibitors.

# Key issues: Resource use in the model

Return to main deck

Large

*EAG note several unclear points related to the company's resource use figures and error in model*

| Health state | Resource use cost per cycle | Reference | Justification |
|---|---|---|---|
| Mild (non-responder) | £1,510.32 | NICE TA708<br>NICE TA534<br>NICE TA753<br>PRISM study<br>NICE TA883<br>NICE TA778<br>NICE TA838<br>NICE TA814 | Dutch advisory board |
| Mild (responder) | £1,288.48 | | |
| Moderate (non-responder) | £1,800.52 | | |
| Moderate (responder) | £1,536.24 | | |
| Severe (non-responder) | £1,888.99 | | |
| Severe (responder) | £1,611.71 | | |



Abbreviations: a

Return to main deck

# Managed access

## Criteria for a managed access recommendation

**The committee can make a recommendation with managed access if:**

- the technology cannot be recommended for use because the evidence is too uncertain
- the technology has the **plausible potential** to be cost effective at the **currently agreed price**
- new evidence that could **sufficiently support the case for recommendation** is expected from ongoing or planned clinical trials, or could be collected from people having the technology in clinical practice
- data could feasibly be collected within a reasonable timeframe (up to a **maximum of 5 years**) without **undue burden**.