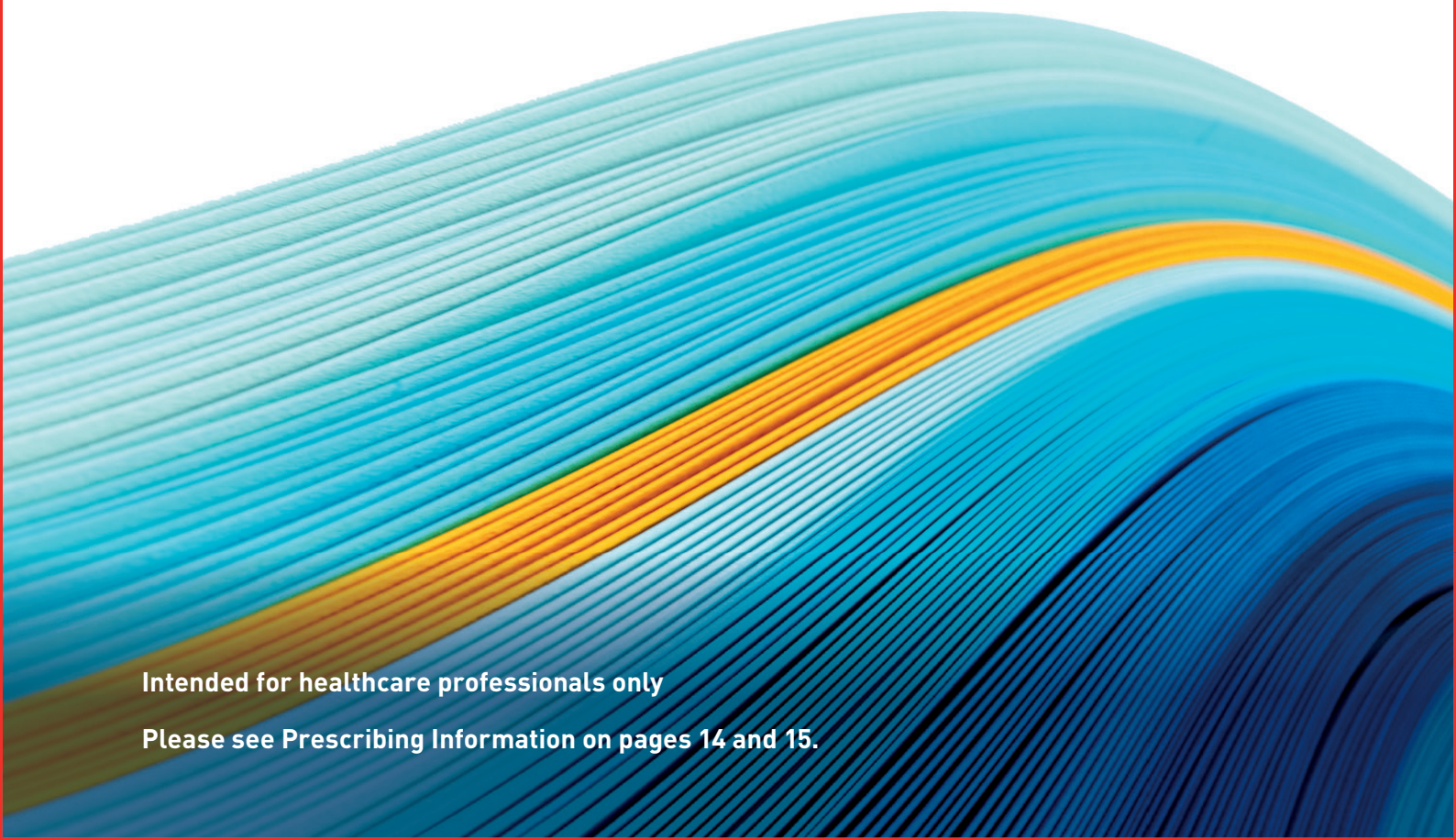
AYVAKYT®
(avapritinib)

AYVAKYT® (avapritinib) is indicated for the treatment of adult patients with indolent systemic mastocytosis (ISM) with moderate to severe symptoms inadequately controlled on symptomatic treatment.

NOW APPROVED

The First and Only Targeted Therapy for Adults With Indolent Systemic Mastocytosis (ISM)[1,2]



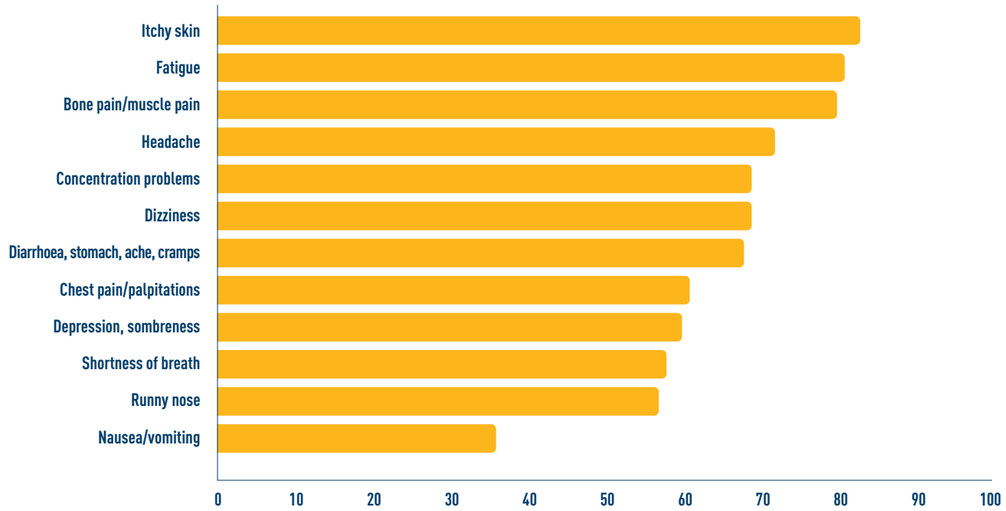
Intended for healthcare professionals only

Please see Prescribing Information on pages 14 and 15.

Patients with ISM experience high symptom burden and impaired daily functioning despite best supportive care[2,3]

ISM is a mast cell disease that is unpredictable in nature and can cause a range of symptoms across multiple organ systems[2–4]

SYMPTOMS OF INDOLENT SYSTEMIC MASTOCYTOSIS (N=164)[5]



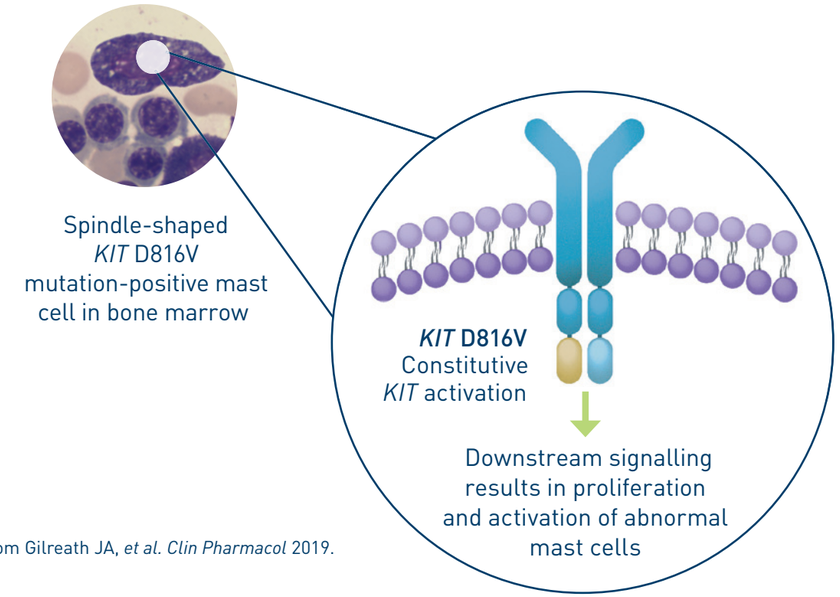
- Many patients with ISM report severe symptom burden despite taking several medications for managing their symptoms[3]

Patients with ISM report professional, psychosocial and psychological consequences of living with their unpredictable disease[6]

ISM is driven by the *KIT* D816V mutation in ~95% of cases[7,8]

Historically, there have been no approved treatments that selectively target the underlying driver of disease in ISM[2]

The *KIT* D816V mutation constitutively activates downstream signalling pathways regulating cellular functions, including proliferation and survival of abnormal mast cells.[9]



Adapted from Gilreath JA, *et al. Clin Pharmacol* 2019.

- SM can cause a range of symptoms across multiple organ systems,[2] and over the course of a year 30% of patients seek emergency care[6]

Patients are often left with temporary relief for persistent symptoms[2]

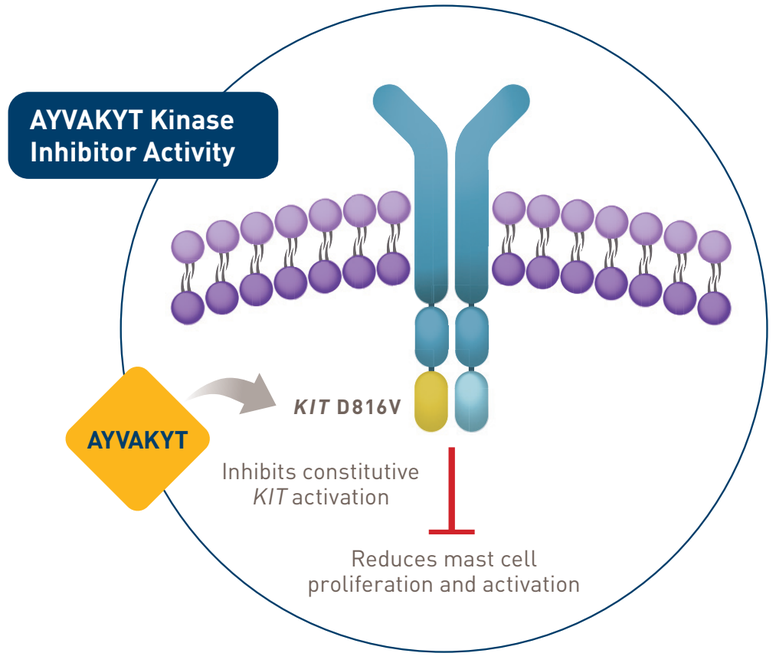
KIT=KIT proto-oncogene, receptor tyrosine kinase; SM=systemic mastocytosis.

AYVAKYT® (avapritinib)

AYVAKYT is the first and only approved precision medicine for ISM, inhibiting *KIT* D816V, the underlying driver of disease[1,2]

AYVAKYT potently and selectively inhibits *KIT* D816V[1]

AYVAKYT demonstrated greater inhibitory potency for *KIT* D816V vs wild type *KIT* in cellular assays.[1]

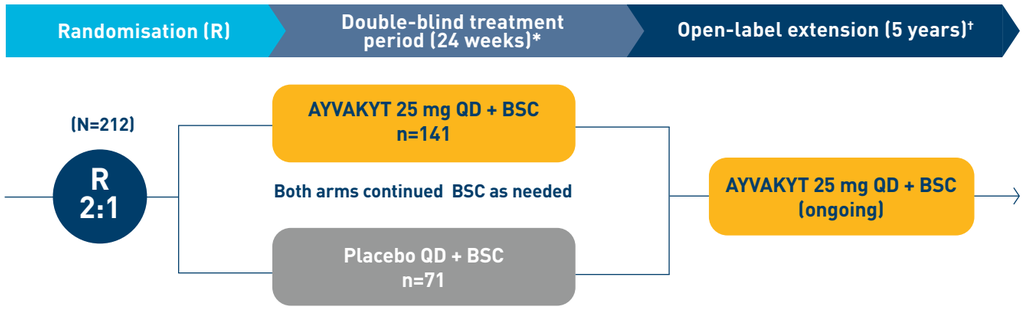


KIT=KIT proto-oncogene, receptor tyrosine kinase.

AYVAKYT was evaluated in the largest ever trial of patients with ISM, PIONEER[1,2]

PIONEER was a phase 2, multipart, randomised, placebo-controlled, double-blind trial evaluating the safety and efficacy of AYVAKYT 25 mg vs placebo—both with concomitant best supportive care (BSC) over 24 weeks—**in patients with ISM with moderate to severe symptoms not adequately controlled by BSC alone.**[1,2]

STUDY DESIGN[1,2]



*OLE: ongoing open-label extension study is evaluating the long-term safety and efficacy of AYVAKYT 25 mg for up to 5 years.
†All eligible patients either continued AYVAKYT 25 mg daily or switched from placebo to AYVAKYT 25 mg daily.

- Key eligibility criteria: ≥18 years of age; ISM confirmed by central pathology review; uncontrolled moderate to severe ISM, defined as ISM-SAF TSS ≥28[1,2]
- **Primary endpoint:** Mean change in ISM-SAF TSS from baseline to Week 24[1,2]
  - **Select key secondary endpoints:** ≥50% reduction in serum tryptase levels; ≥50% reduction in *KIT* D816V VAF; ≥50% reduction in bone marrow mast cells[1,2]
  - **Additional select secondary endpoints:** Mean change in ISM-SAF individual symptom scores[2]

BSC=best supportive care; ISM-SAF=Indolent Systemic Mastocytosis-Symptom Assessment Form; OLE=open-label extension; QD=once daily; TSS=total symptom score; VAF=variant allele fraction.

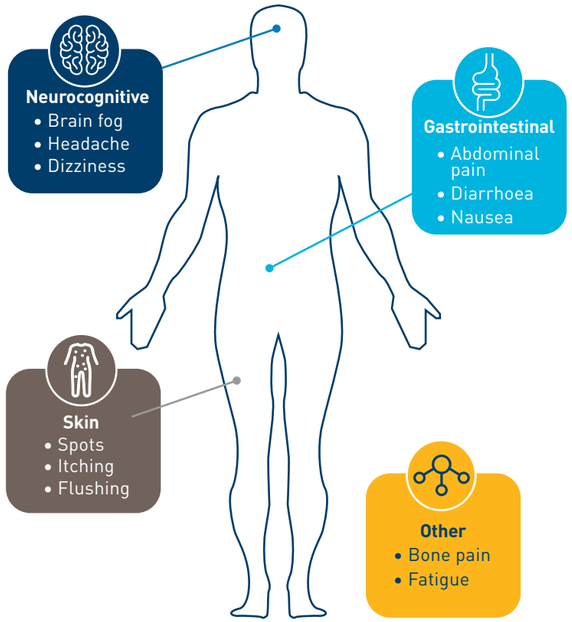
Please see Prescribing Information on pages 14 and 15.

AYVAKYT® (avapritinib)

The Indolent Systemic Mastocytosis–Symptom Assessment Form (ISM–SAF) is a validated symptom assessment tool[10]

The ISM-SAF was developed to measure the severity of 11 ISM-related symptoms and was designed with input from regulatory authorities, patients and therapeutic area experts[10]

Individual symptom scores are evaluated, and the 11 symptom severity scores are combined to calculate the TSS (0–110).[10]



Scoring

Individual symptoms scored 0–10 daily

0=no symptom, 10=worst imaginable symptom

A biweekly average ISM–SAF TSS was used to evaluate efficacy endpoints in PIONEER[2]

ISM-SAF=Indolent Systemic Mastocytosis-Symptom Assessment Form; TSS=total symptom score.

Please see Prescribing Information on pages 14 and 15.

Patient characteristics in PIONEER were balanced between both arms[2]

Patients in PIONEER were required to have failed to achieve adequate symptom control for one or more ISM symptoms with at least two symptomatic treatments.[1,2]

SELECT BASELINE PATIENT CHARACTERISTICS (N=212)[2]

Patient characteristics	AYVAKYT + BSC (n=141)	Placebo + BSC (n=71)
Median age (range)	50 years (18–77)	54 years (26–79)
Sex	71% female, 29% male	76% female, 24% male
Mean ISM-SAF TSS (SD)	50.2 (19.1)	52.4 (19.8)
Median number of BSC treatments (range)	3 (0–11)	4 (1–8)
Median serum tryptase, ng/mL (range)	38.4 (3.6–256.0)	43.7 (5.7–501.6)
KIT D816V positivity	84%	89%
Mast cell aggregates present	75%	80%

- BSC medications allowed in the PIONEER study included anti-immunoglobulin E antibody (omalizumab), corticosteroids, cromolyn sodium, H1 antihistamines, H2 antihistamines, leukotriene inhibitors and proton pump inhibitors[1,2]
- Other baseline characteristics were similar between treatment groups[2]

BSC=best supportive care; ISM-SAF=Indolent Systemic Mastocytosis-Symptom Assessment Form; *KIT*=KIT proto-oncogene, receptor tyrosine kinase; SD=standard deviation; TSS=total symptom score.

Please see Prescribing Information on pages 14 and 15.

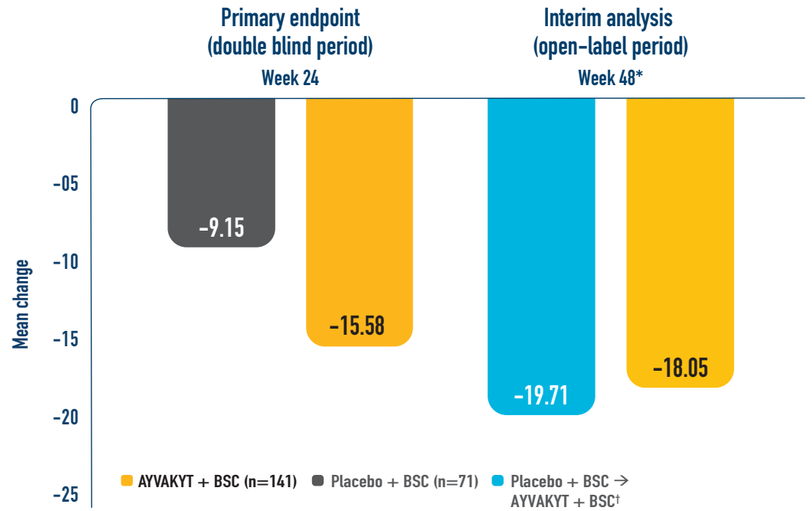
AYVAKYT® (avapritinib)

AYVAKYT added to BSC showed significant improvement in patients' overall symptom burden vs placebo[1,2]

PRIMARY ENDPOINT[1]

Week 24	AYVAKYT + BSC n=141[1]	Placebo + BSC n=71[1]	*P*-value
Mean change in ISM-SAF TSS (95% CI)[1]	**-15.58** (-18.61, -12.55)	**-9.15** (-13.12, -5.18)	**0.003**

MEAN CHANGE IN ISM-SAF TSS AT WEEK 24 AND 48[1]



* For AYVAKYT-treated patients who rolled over into the open-label long-term study, PIONEER Part 3.
† Placebo patients were allowed to move into an open-label ongoing AYVAKYT crossover arm, with TSS data available from Week 24 onwards.

AYVAKYT demonstrated a deepening reduction in mean TSS sustained over time. Patients in the AYVAKYT+BSC arm continued to report improvement on mean TSS for at least 48 weeks[1]

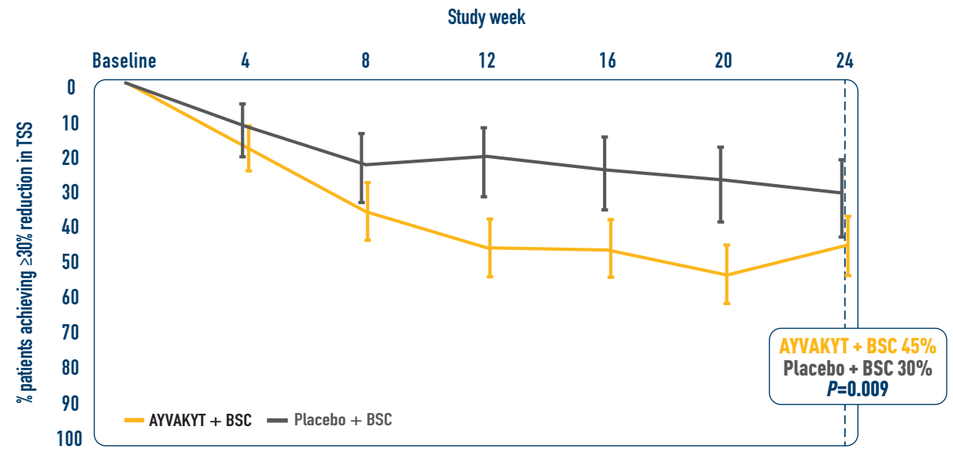
Patients in the AYVAKYT + BSC arm demonstrated statistically significant reductions in TSS vs placebo + BSC through Week 24[1]

BSC=best supportive care; CI=confidence interval; ISM-SAF=Indolent Systemic Mastocytosis-Symptom Assessment Form; TSS=total symptom score.

AYVAKYT demonstrated statistically significant improvements using ≥30% TSS threshold[1]

KEY SECONDARY ENDPOINT[1]

PROPORTION OF PATIENTS ACHIEVING ≥30% REDUCTION IN ISM-SAF TSS THROUGH 24 WEEKS[1,2]



Number of patients							
AYVAKYT + BSC	139	135	133	133	135	134	131
Placebo + BSC	71	71	71	68	67	66	66

A 30% reduction in TSS was selected as a valid and conservative threshold for clinically important improvement in symptoms[10]

Patients in the AYVAKYT + BSC arm demonstrated clinically meaningful reductions in TSS vs placebo + BSC at Week 24, as judged using a conservative threshold for %TSS reduction[1,10]

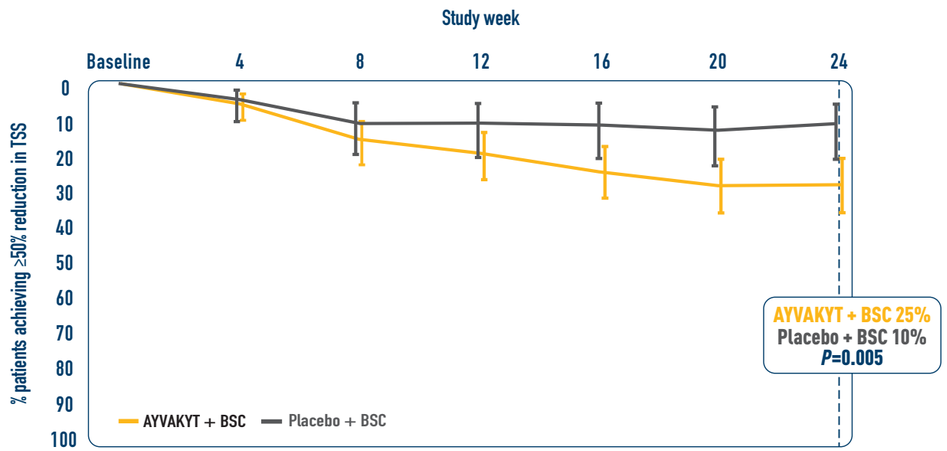
BSC=best supportive care; ISM-SAF=Indolent Systemic Mastocytosis-Symptom Assessment Form; TSS=total symptom score.

AYVAKYT® (avapritinib)

AYVAKYT demonstrated statistically significant improvements using ≥50% TSS threshold[1]

KEY SECONDARY ENDPOINT[1]

PROPORTION OF PATIENTS ACHIEVING ≥50% REDUCTION IN ISM-SAF TSS THROUGH 24 WEEKS[1,2]



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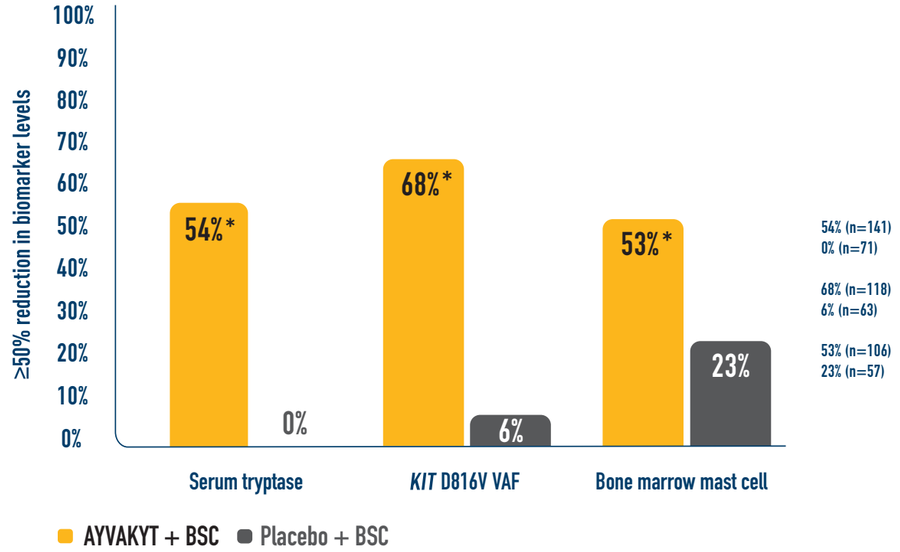
BSC=best supportive care; ISM-SAF=Indolent Systemic Mastocytosis-Symptom Assessment Form; TSS=total symptom score.

AYVAKYT demonstrated significant reductions in objective measures of mast cell burden through 24 weeks[1]

KEY SECONDARY ENDPOINTS[1]

More than half of patients treated with AYVAKYT + BSC experienced ≥50% reductions in serum tryptase, *KIT* D816V VAF and bone marrow mast cell levels[1]

PROPORTION OF PATIENTS ACHIEVING ≥50% REDUCTION IN BIOMARKER LEVELS AT 24 WEEKS[1]



* *P*<0.0001 vs placebo + BSC.

ITT analysis: For patients with high-dose steroid use within 7 days before Week 24, or greater than 14 consecutive days at any point from baseline to Week 24, the Week 24 score was set to missing.

BSC=best supportive care; ITT=intention to treat; *KIT*=KIT proto-oncogene, receptor tyrosine kinase; VAF=variant allele fraction.

AYVAKYT® (avapritinib)

No serious adverse reactions or fatal adverse reactions occurred in 141 patients receiving AYVAKYT plus BSC[1]

The most common AEs reported in the AYVAKYT plus BSC treatment arm were flushing and oedema of which almost all were Grade 1 or 2[1*]

ADVERSE REACTIONS REPORTED IN CLINICAL STUDIES OF AYVAKYT IN PATIENTS WITH ISM[1]

Adverse reactions*	AYVAKYT + BSC All grades, n=141 (%)	AYVAKYT + BSC Grades ≥3, n=141 (%)
Insomnia	5.7	-
Flushing	9.2	1.4
Photosensitivity reaction	2.8	-
Peripheral oedema†	12.1	-
Face oedema	7.1	-
Blood alkaline phosphatase increased	6.4	0.7

* Per National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. Adverse reactions reported in Part 2 of the PIONEER study in ≥5% of patients.
† Including oedema peripheral and peripheral swelling.
- No adverse reactions reported.

- Discontinuation due to adverse reactions occurred in <1% of patients receiving AYVAKYT, and no serious adverse reactions or fatal adverse reactions occurred[1]
- 94% of peripheral oedema reactions and 90% of face oedema reactions reported were Grade 1—none were Grade ≥3 or led to treatment discontinuation[1]

BSC=best supportive care.

AYVAKYT is recommended as one daily tablet in ISM[1]

AYVAKYT should be taken:[1]

- As one 25 mg tablet orally
- Once daily
- On an empty stomach, at least 1 hour before or at least 2 hours after a meal

A modified starting dose of AYVAKYT is recommended for patients with severe hepatic impairment: 25 mg orally once every other day. Patients requiring dose reduction below 25 mg once every other day must discontinue treatment.[1]

Concomitant use of AYVAKYT with strong or moderate CYP3A inhibitors must be avoided.[1]

 Please see Prescribing Information on pages 14 and 15.

AYVAKYT® (avapritinib)

[EU Prescribing Information/Safety Information]

INDICATION

AYVAKYT® (avapritinib) is indicated for the treatment of adult patients with indolent systemic mastocytosis (ISM) with moderate to severe symptoms inadequately controlled on symptomatic treatment.

IMPORTANT SAFETY INFORMATION

Contraindications—Hypersensitivity to the active substance or to any of the excipients.

Haemorrhage—AYVAKYT at higher doses has been associated with an increased incidence of haemorrhagic adverse reactions, including serious and severe adverse reactions, like gastrointestinal haemorrhage and intracranial haemorrhage.

Intracranial haemorrhage—Serious intracranial haemorrhage (ICH) may occur with AYVAKYT treatment. No events of ICH occurred in the 141 patients with ISM receiving 25 mg of AYVAKYT during the 24-week duration of Part 2 of the PIONEER study. Permanently discontinue AYVAKYT if ICH of any grade occurs.

Cognitive effects—Cognitive effects, such as memory impairment, cognitive disorder, confusional state, and encephalopathy, can occur in patients receiving AYVAKYT. In patients with ISM, cognitive effects can be one of the disease symptoms. Patients with ISM must notify their healthcare professional if they experience new or worsening cognitive symptoms.

Fluid retention—In patients with ISM, localised (peripheral, facial) oedemas have been reported with a frequency category of at least common.

QT interval prolongation—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.).

CYP3A4 inhibitors and inducers—Co-administration with strong or moderate CYP3A inhibitors must be avoided because it may increase the plasma concentration of AYVAKYT. Co-administration with strong or moderate CYP3A inducers should be avoided because it may decrease the plasma concentrations of AYVAKYT.

Photosensitivity—Exposure to direct sunlight must be avoided or minimised due to the risk of photosensitivity associated with AYVAKYT. Patients must be instructed to use measures such as protective clothing and sunscreen with high sun protection factor (SPF).

Sodium—This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially “sodium-free”.

Fertility, pregnancy and lactation—AYVAKYT can cause foetal harm when administered to a pregnant woman. Advise pregnant woman of the potential risk to the foetus. The pregnancy status of women of reproductive potential must be verified prior to initiating AYVAKYT treatment.

Women of childbearing potential must use effective contraception during treatment and for 6 weeks after the last dose of AYVAKYT. Males with female partners of childbearing potential must use effective contraception during treatment and for 2 weeks after the last dose of AYVAKYT.

Breastfeeding must be discontinued during treatment with AYVAKYT and for 2 weeks following the final dose.

Adverse reactions—Common adverse reactions (≥5% of ISM patients taking AYVAKYT) were peripheral oedema, flushing, face oedema, increased blood alkaline phosphatase, insomnia.

Please see the accompanying full Prescribing Information for AYVAKYT.

AYVAKYT® (avapritinib)

AYVAKYT is the first and only targeted therapy approved for ISM[1,2]

Patients with ISM can experience high symptom burden across multiple organ systems[2–4]

AYVAKYT potently and selectively inhibits ***KIT*** **D816V[1], the underlying driver of ISM[1,2]**

One 25 mg AYVAKYT tablet daily is well tolerated with a clinical safety profile comparable to BSC[1,2*]

AYVAKYT demonstrated statistically significant improvements for all primary and key secondary efficacy endpoints vs placebo in PIONEER[1*]

The **most common AEs reported in the AYVAKYT treatment arm were flushing and oedema** of which almost all were Grade 1 or 2[1†]

* In a phase 2, randomised, placebo-controlled, double-blind clinical trial.

† Per National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. Adverse reactions reported in Part 2 of the PIONEER study in ≥5% of patients.

BSC=best supportive care.

Please see Important Safety Information on pages 14 and 15, and the accompanying full Prescribing Information for AYVAKYT.

KIT=KIT proto-oncogene, receptor tyrosine kinase.

References: 1. AYVAKYT® (avapritinib). Summary of Product Characteristics. Available at: https://www.ema.europa.eu/en/documents/product-information/ayvakyt-epar-product-information_en.pdf. Last accessed April 2024. **2.** Gotlib J, *et al. NEJM Evid.* 2023;2(6). **3.** Mesa RA, *et al. Cancer*. 2022;128(20):3700–3708. **4.** Jennings SV, *et al. Immunol Allergy Clin North Am.* 2018;38(3):505–525. **5.** van Anrooj B, *et al. Allergy.* 2016;71(11):1585–1593. **6.** Mesa RA, *et al. Cancer*. 2022;128(20):3691–3699. **7.** Muñoz-González JI, *et al. Blood*. 2019;134(5):456–468. **8.** Ungerstedt J, *et al. Cancers.* 2022;14(16):3942. **9.** Gilreath JA, *et al. Clin Pharmacol.* 2019:11:77-92. **10.** Padilla B, *et al. Orphanet J Rare Dis.* 2021;16:434.

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AYVAKYT® (avapritinib)