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

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This study has been transitioned to CTIS with ID 2024-512585-34-00 check the CTIS register for the current data. Primary: Part 1 • To determine the RP2D of avapritinib in patients with ISM for use in Part 2 and Part 3 of the study.Part 2 • To...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Haematological disorders NEC
Study type	Interventional

Summary

ID

NL-OMON52372

Source
ToetsingOnline

Brief title
BLU-285-2203: PIONEER study

Condition

- Haematological disorders NEC

Synonym
mastcell disease

Research involving
Human

Sponsors and support

Primary sponsor: Blueprint Medicines Corporation
Source(s) of monetary or material Support: Blueprint Medicines Corporation

Intervention

Keyword: 3-part, Avapritinib (BLU-285), Indolent and smoldering SM, phase 2

Outcome measures

Primary outcome

Part 1

• The RP2D in patients with ISM.

Part 2

• Mean change in ISM-SAF TSS, from baseline to C7D1.

Part 3

• The long-term safety and efficacy of avapritinib.

Secondary outcome

Key Secondary Endpoints (Part 2 Only):

• 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 >=50% reduction in ISM-SAF TSS from baseline to C7D1.

•Proportion of patients with >=30% reduction in ISM-SAF TSS from baseline to C7D1.

• Proportion of patients with a >=50% reduction in bone marrow MCs from baseline to C7D1 or no aggregates for patients with aggregates at baseline.

Additional Secondary Endpoints:

Part 1 and Part 2

• Change in measures of MC burden from baseline to C4D1 (in Part 1) and to C7D1 (in Part 2):

o Serum tryptase.

o KIT D816V allele burden in blood.

o Bone marrow MCs.

• Change in BSC usage.

• Change in GI 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 MC-QoL, PGIS, SF-12, PGIC, and EQ-5D-5L.

• Safety and tolerability of avapritinib, as assessed by AEs, vital signs, ECGs, and laboratory tests.

• Pharmacokinetics of avapritinib.

• Correlations between avapritinib exposure and safety and efficacy endpoints.

Part 3

• Change in the following measures of MC burden:

o Serum tryptase.

o KIT D816V allele burden in blood.

o Bone marrow MCs (optional at approximately 1 year after the end of

Part 1 and Part 2 biopsy).

• Change in BSC concomitant medication usage.

• Change in "lead (most severe) symptom" and *lead (most severe) domain/symptom

cluster* score of ISM-SAF.

• Proportion of avapritinib treated patients with ISM achieving >=50% reduction

in TSS at 1 year from Part 3 Baseline (and Part 1 or Part 2 Baseline for

patients on same dose of avapritinib in both parts of the study).

• Proportion of avapritinib treated patients with ISM achieving >=30% reduction

in TSS at 1 year from Part 3 Baseline (and Part 1 or Part 2 Baseline for

patients on same dose of avapritinib in both parts of the study).

• Change in TSS, symptom cluster, domain scores, and individual symptom scores

of ISM SAF from Part 3 baseline (and from Part 1 and Part 2 baseline for

patients receiving the same dose of avapritinib in both study parts) to Part 3

C4D1, C7D1, C11D1, and C13D1.

• Changes in MC-QoL, PGIS, SF 12, PGIC, and EQ 5D-5L.

• Safety and tolerability of avapritinib, as assessed by AEs, vital signs,

ECGs, and laboratory tests.

Exploratory Endpoints:

Parts 1, 2, and 3

• Potential correlations between ISM-SAF, PGIS, other PRO and QoL measures, and individual measures of MC burden.

• Correlation of clinical features (eg, demographics, laboratory exams, concomitant medications, AEs, concomitant mutations, etc) with activity against ISM.

• Status of exploratory biomarkers (DNA, RNA, serum protein) in blood with respect to efficacy or safety related endpoints for avapritinib.

• Platelet aggregation studies at baseline and during treatment, including at the time of bleeding events.

• Change in bone density (optional, to be performed at the Investigator*s discretion).

• Change in skin MCs in patients with baseline mastocytosis in skin from baseline to C4D1 (in Part 1) and to C7D1 (in Part 2) and at C13D1 (in Part 3, optional).

• Change in percent fractional body surface area involved by mastocytosis in skin, change in lesion number, and change in pigmentation of cutaneous lesions in patients with baseline mastocytosis in skin.

• Change in percent fractional body surface area involved by mastocytosis in skin, change in lesion number, and change in pigmentation of cutaneous lesions in patients with new mastocytosis in skin at baseline of Part 3.

• Change in number of episodes of anaphylaxis, based on epinephrine use.

Study description

Background summary

Systemic mastocytosis (SM) is a rare, clonal mast cell (MC) neoplasm primarily driven by the KIT D816V mutation, and is characterized by the uncontrolled proliferation and activation of MCs, often present as aggregates in skin, bone marrow (BM), spleen, liver, gastrointestinal (GI) tract and other organs. This leads to debilitating and potentially life-threatening symptoms, including unpredictable anaphylaxis, maculopapular skin lesions, pruritis, diarrhea, cognitive impairment, fatigue, and bone pain. These symptoms have a severely negative impact on the quality of life (QoL) of patients physically, emotionally, and psychosocially. Patient*s symptoms are typically managed with significant polypharmacy with symptomatic therapies such as antihistamines, H2-blockers, proton-pump inhibitors, cromolyn, steroids, and anti-IgE antibodies. Available cytoreductive therapies, such as cladribine and midostaurin, which can reduce disease burden, have significant side effects and are used only for the small minority (5%) of patients with advanced disease, which confers reduced survival outcomes. The prevalence of SM is estimated at approximately 1 in 10,000 patients.
Ninety-five percent of SM patients are considered to have non-advanced SM (non-AdvSM), which primarily includes the World Health Organization (WHO) variant of indolent SM (ISM) as well as a small number of patients with smoldering SM (SSM). Patients with non-AdvSM suffer long term and may worsen over time with no approved treatments to reduce their burden of disease or impact their disease course. Less than 5% of patients with ISM show disease progression to severe forms of SM. SSM patients have more disease burden and organ involvement and 9% ultimately progress to AdvSM.
Five percent of SM patients have AdvSM, which includes the WHO variants of aggressive SM (ASM), SM with associated hematological neoplasm (SM-AHN) and mast cell leukemia (MCL). In addition to MC activation symptoms due to organ involvement, AdvSM patients have compromised organ function and/or aggressive pathologic features, both associated with poor overall survival. Almost 20% of patients with AdvSM eventually transform to acute myeloid leukemia. The KIT D816V mutation is the driver of disease in 95% of patients, regardless of SM subtype. Avapritinib was developed to very potently and selectively target KIT D816V, with a biochemical 50% inhibitory concentration (IC50) of 0.23 nM. Avapritinib has demonstrated potent activity against in vitro and in vivo KIT D816V models. In chronic toxicology and safety pharmacology studies in rats and dogs assessing active low doses of avapritinib, no adverse effects were observed.
In the open-label, Phase 1, BLU-285-2101 study, avapritinib at doses of 30 mg to 400 mg once daily (QD) demonstrated significant reductions in MC burden, improved baseline patient symptoms, and had a well-tolerated side-effect profile for patients with AdvSM.

Due to these preliminary results, the double-blinded placebo-controlled, Phase 2 BLU-285-2203 clinical trial was initiated to study the safety and efficacy of avapritinib in reducing symptoms and MC burden in patients with ISM with lower doses of avapritinib.
Patients were initially enrolled into Part 1 of the study, which was conducted to identify the recommended Phase 2 dose (RP2D) with the appropriate benefit-risk for patients with ISM. Due to superior tolerability and equivalent efficacy of symptom reduction by C7D1, the 25-mg QD dose was selected as the RP2D for Part 2 (see Part 1 results and Selection of Recommend Phase 2 Dose, below).
After determination of RP2D, Part 2 will open to enrollment, which is being conducted to determine the efficacy of avapritinib in reducing symptoms (compared with placebo) in conjunction with best supportive care (BSC). The primary endpoint of Part 2 is the main change in Total Symptom Score (TSS) of the ISM Symptom Assessment Form (ISM-SAF) from baseline to Cycle 7 Day 1 (C7D1). After completion of Parts 1 or 2, patients have the opportunity to receive avapritinib in an open-label extension cohort (Part 3), to further characterize the safety and efficacy of long-term treatment.

Study objective

This study has been transitioned to CTIS with ID 2024-512585-34-00 check the CTIS register for the current data.

Primary:
Part 1
• To determine the RP2D of avapritinib in patients with ISM for use in Part 2 and Part 3 of the study.

Part 2
• To determine main change in ISM-SAF TSS from baseline to C7D1, compared to placebo.

Part 3
• To assess the long-term safety and efficacy of avapritinib in ISM patients.

Key Secondary Objectives (Part 2 Only):
• To determine the proportion of avapritinib treated patients with ISM with a >=50% reduction in serum tryptase from baseline to C7D1, compared to placebo.
• To determine the proportion of avapritinib treated patients with ISM 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, compared to placebo.
• To determine the proportion of avapritinib treated patients with ISM achieving >=50% reduction in ISM-SAF TSS from baseline to C7D1, compared to placebo.
• To determine the proportion of avapritinib treated patients with ISM

achieving >=30% reduction in ISM-SAF TSS from baseline to C7D1, compared to placebo.
• To determine the proportion of avapritinib treated patients with ISM with a >=50% reduction in bone marrow MCs from baseline to C7D1, or no aggregates for patients with aggregates at baseline, compared to placebo.

Additional Secondary Objectives:
Part 1 and Part 2
• Assess change in the following measures of MC burden in each treatment cohort from baseline to C4D1 (Part 1) and C7D1 (Part 2):
o Serum tryptase.
o KIT D816V allele burden in blood.
o BM MCs.
• Assess change in BSC usage for SM symptoms.
• Assess change in GI and skin domains, neurocognitive symptom cluster (brain fog, headache and dizziness), and individual symptom scores of ISM-SAF.
• Assess change in "lead (most severe) symptom" and *lead (most severe) domain/symptom cluster* score (ie, individual symptom and domain/symptom cluster with highest mean score at baseline in each patient) of ISM-SAF.
• Assess changes in other Patient-Reported Outcomes (PROs) and QoL measures based on the 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 the 5-level EuroQol 5D (EQ-5D-5L) questionnaire.
• Assess the safety and tolerability of avapritinib, as assessed by adverse events (AEs), vital signs, electrocardiograms (ECGs), and laboratory tests.
• Assess the pharmacokinetics (PK) of avapritinib.
• Correlate avapritinib exposure with safety and efficacy endpoints.

Part 3
• Assess changes in the following measures of MC burden: o Serum tryptase.
o KIT D816V allele burden in blood.
o Bone marrow MCs (optional at approximately 1 year after the biopsy at the end of Parts 1 and 2).

• Assess change in BSC usage for SM symptoms.
• Assess change in "lead (most severe) symptom" score and *lead (most severe) domain/symptom cluster* (ie, individual symptom and domain/symptom cluster with highest mean score at baseline in each patient) of ISM-SAF.
• Assess the proportion of avapritinib treated patients with ISM achieving >=50% reduction in TSS at 1 year after initiation of avapritinib therapy.
• Assess the proportion of avapritinib treated patients with ISM achieving >=30% reduction in TSS at 1 year after initiation of avapritinib therapy.
• Assess change in TSS, symptom cluster, domain scores, and individual symptom scores of ISM-SAF from Part 3 baseline (and Part 1 or Part 2 baseline for patients on the same dose of avapritinib in both parts of the study) to C4D1, C7D1, C11D1, and C13D1.

• Assess change in other PROs and QoL measures based on the MC-QoL, PGIS, SF-12, PGIC, and EQ 5D-5L questionnaires.
• Assess the safety and tolerability of avapritinib, as assessed by AEs, vital signs, ECGs, and laboratory tests.
Exploratory Objectives:
Parts 1, 2, and 3
• Explore potential correlations between the ISM-SAF and other PRO and QoL measures and individual measures of MC burden.
• Assess correlation of clinical features (eg. demographics, laboratory tests, concomitant medications, AEs, concomitant mutations) with activity against ISM.
• Identify potential new biomarkers (DNA, RNA, serum protein) in blood for pharmacodynamic effects and safety of avapritinib.
• Assess whether avapritinib can affect platelet aggregation as a possible mechanistic contributor to bleeding events.
• Assess change in bone density by dual x-ray energy assessment (DXA)/bone densitometry scan (optional, to be performed at the Investigator*s discretion).
• Assess changes in skin lesions by photography in patients with baseline mastocytosis in skin from baseline to C4D1 (in Part 1) and C7D1 (in Part 2)
• Assess changes in skin lesions by photography in patients with new mastocytosis in skin from baseline (Part 3) to C7D1 (Part 3).
• Assess changes in MCs in skin biopsies in patients with baseline mastocytosis in skin.
• Assess change in the frequency of anaphylactic episodes based on epinephrine use.

Study design

This is a Phase 2, randomized, double-blind, placebo-controlled study comparing the efficacy and safety of avapritinib + BSC with placebo + BSC in patients with ISM whose symptoms are not adequately controlled by BSC.
In Part 1, the optimal dose of avapritinib (RP2D) will be identified in patients with ISM. In Part 2, patients with ISM will be randomly assigned to the RP2D of avapritinib identified in Part 1 + BSC, or to matching placebo + BSC. In Part 3, patients who have completed treatment in Part 1 or Part 2 of the study may participate in a long-term extension, receiving avapritinib at the RP2D + BSC.
Screening
After provision of written informed consent, patients will be evaluated for eligibility during the Screening period. In both Part 1 and Part 2, immediately after informed consent is obtained, patients will begin daily symptom reporting with the ISM-SAF questionnaire, using a hand-held device. The Investigators may, at their discretion, optimize BSC medications, which may take up to 4 weeks, but if already optimized, may proceed directly to the 14-day TSS eligibility assessment period.
Doses and schedules of BSC for SM symptom management will need to be stable for at least 14 days (which may have begun prior to signing of the informed consent form [ICF]) before the beginning of the ISM-SAF TSS eligibility period. The

patient should not be experiencing an acute flare of symptoms beyond their typical baseline symptoms. As soon as BSC is optimized, the investigator will initiate the eligibility TSS calculation over a 14-day period to determine symptom eligibility. Patients not meeting the symptom severity threshold will be deemed screen failures and will not be eligible for study participation. Patients meeting the threshold for symptom severity will continue completing the ISM-SAF daily without interruption through screening and study participation if deemed eligible.

After ISM-SAF symptom eligibility is confirmed, the screening assessment and central review period may begin, which may last up to 8 weeks. Patients meeting the threshold for symptom severity will continue completing the ISM-SAF daily without interruption into Part 3. Screening procedures will include the following: BM biopsy (an archival sample obtained within the preceding 24 weeks or a fresh sample) and skin biopsy of lesional and non-lesional skin (in patients with mastocytosis in skin) will be performed and sent to the Central Pathology Laboratory for confirmation of SM diagnosis and quantification of MCs. Patients with mastocytosis in skin may have skin photographs taken (optional, patients may choose not to undergo skin photography at any time). Additional procedures will include MRI or computed tomography scan of the brain; bone densitometry; serum tryptase, KIT D816V mutation testing; routine laboratory testing; ECG; and physical examination.

All screening procedures should be completed within a 4-week period, followed by central review and approval for enrollment, which may take up to an additional 4 weeks. Patients who fail screening due to objective criteria (ie, pathology, laboratory, other diagnostic tests) may be re-screened. Once screening procedures are completed and the patient determined to meet eligibility criteria, a 14-day baseline TSS calculation will be initiated to establish baseline TSS scores. Dosing will occur no later than 8 weeks (56 days) after the confirmation of TSS eligibility, except with written permission of the Sponsor. Patients who fail screening due to objective criteria (ie, pathology, laboratory, other diagnostic tests) may be re-screened if the objective criteria subsequently meet the eligibility criteria.

At the completion of the 14-day baseline TSS calculation, the patient will be randomly assigned to treatment and begin dosing.

Part 1

In Part 1 of the study, approximately 40 patients will be randomly assigned to 1 of 3 doses of avapritinib or to placebo. Each dose-level cohort and placebo group in Part 1 will be composed of 10 patients. The 3 dose levels of avapritinib will be tested in parallel: 25, 50, and 100 mg. Patients, study staff, and the Sponsor will be blinded to treatment assignment; however, select personnel, primarily functioning in safety reporting and conduct of the independent data monitoring committee (IDMC) will be unblinded throughout the study.

Avapritinib will be administered orally, once daily (QD) in continuous 28-day cycles. Patients will be assessed weekly for the first 4 weeks (until the RP2D is determined) for safety, laboratory monitoring, and QoL assessments. Intensive PK sampling will be performed in all patients. The ISM-SAF will be

completed daily. After completion of 12 weeks of treatment (C4D1), BM and skin biopsy will be repeated for MC quantification by the Central Pathology Laboratory and skin photographs (optional) may be taken in patients with baseline mastocytosis in skin.
The RP2D will be determined based on the efficacy, safety, and PK at each dose level. The major efficacy criterion for selection of the RP2D will be the dose of avapritinib that produces the maximum reduction in TSS, as assessed using the ISM-SAF at C4D1 compared with baseline (Day -14 to Day -1), but other measures of efficacy (eg, change in serum tryptase) and other timepoints will also be taken into consideration. Once C4D1 assessments are completed, patients will continue on assigned therapy and dose until the RP2D is determined, at which time all Part 1 patients will roll over to Part 3 where they will receive avapritinib in an open-label fashion at the RP2D.
Part 2
In Part 2 of the study, approximately 204 ISM patients will be enrolled. Patients will be randomly assigned to treatment based on a 2:1 ratio to receive avapritinib 25 mg QD + BSC (approximately 136 patients) or matching placebo + BSC (approximately 68 patients), respectively. Randomization will be stratified based on serum tryptase levels at Screening (<20 ng/mL vs >= 20 ng/mL). In addition, enrollment of patients with <20 ng/mL serum tryptase will be capped at approximately 20% (ie, approximately 40 patients) of Part 2 enrollment. Patients, study staff, and the Sponsor will be blinded to an individual patient*s treatment assignment until Part 2 is complete and all patients roll over into Part 3. Select personnel, primarily functioning in safety reporting and conduct of the IDMC will be unblinded throughout the study.
Avapritinib and placebo dosing will be administered orally, QD, in continuous 28-day cycles. Patients will be assessed every 4 weeks through C7D1 for safety, laboratory monitoring, and QoL assessments. Sparse PK sampling will be performed in all patients and a subset will receive intensive PK. For patients that opt to do so, skin photographs will be taken every 12 weeks in patients with mastocytosis in skin. The ISM-SAF will be completed daily. After completion of 6 cycles of treatment and the ISM-SAF through C7D1, BM and skin biopsy will be repeated for MC quantification by the Central Pathology Laboratory and skin photographs (optional) may be taken in patients with baseline mastocytosis in skin. Each patient completing the C7D1 assessments will roll over into the Part 3 long-term extension to receive avapritinib 25 mg QD in an open-label fashion. After all patients roll over into Part 3, all Part 2 treatment assignments will be unblinded. At this point the primary endpoint of mean change in ISM-SAF TSS from baseline to C7D1 and other efficacy endpoints will be analyzed.
Because prolonged high-dose steroids may reduce symptom scores and some objective measures of MC burden, patients who received prednisone greater than 20 mg daily or equivalent within 7 days before C7D1, or for greater than 14 consecutive days at any point from C1D1 to C7D1, will be excluded from the primary efficacy analysis.
Part 3

After all patients complete Part 1 and t

Intervention

In Part 1, patients will receive treatment for 12 weeks, then continue on assigned therapy and dose until the RP2D is determined, then roll over into Part 3. In Part 2, patients will receive treatment for at least 24 weeks, then roll over to Part 3. Patients will continue to receive treatment in Part 3 for up to 5 years, inclusive of Part 1 and Part 2.

Study burden and risks

For full details see appendix 1 in the protocol (schedule of assessments)

- participation in this study is anticipated to be maximum 5 years but the duration may be shorter or longer for any individual subject depending on individual circumstances and choices and when a subject will start with the study. This study includes a screening period of maximum 14 weeks, a treatment period part 1 (12 weeks to 12 months) OR part 2 (approx 12 weeks) and a part 3 (minimum 8 weeks).

The subjects will visit the hospital approximately 20 times during part 1 (or part 2) and part 3. A visit will take between 2 and 8 hours.
- physical examinations will be done and questions will be asked about medical history.
- ECGs will be done
- weight, height, blood pressure, temperature, heartbeat will be measured
- blood and urine sampling will be done including PK sampling.
- The investigator will also test female participants of childbearing potential for pregnancy.
• Bone marrow biopsy and aspirate will be done to confirm the SM diagnosis and document the extent of the SM
• Brain MRI or CT will be done at screening to confirm that no brain related issues are found
• Bone Densitometry Scan (DXA scan) will be done to evaluate if the bones are less dense than normal due to SM
• Skin photographs will be performed in subjects who have skin mastocytosis.After the photographs, 5-mm punch biopsies of both a skin lesion and normal skin will be performed.
• Subjects need to complete electronic questionnaires that evaluates symptoms related to SM and will complete Quality of Life questionnaires.

Possible side effects that are already known are described in the IB and patient information and in section E9

Contacts

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Blueprint Medicines Corporation

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Scientific
Blueprint Medicines Corporation

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1. Patient must be >= 18 years of age.
2. Patient must have SM, confirmed by Central Pathology Review of BM biopsy, and central review of B- and C-findings by WHO diagnostic criteria.
3. Patient must have moderate-to-severe symptoms based on minimum mean TSS over the
14-day eligibility screening period for assessment of TSS and. Minimum TSS for eligibility is >= 28.
4. Patient must have failed to achieve adequate symptom control for 1 or more baseline symptoms
, as determined by the Investigator, with at least 2 of the following symptomatic therapies: H1 blockers, H2 blockers, Proton-pump inhibitors, Leukotriene inhibitors, Cromolyn sodium, Corticosteroids, Omalizumab.
5. The patient*s symptomatic SM therapies (eg, H1 and H2 blockers) must be

stable (same dose, no new medications >= 14 days before beginning the 14-day ISM-SAF eligibility TSS assessment).
6. For patients receiving corticosteroids, the dose must be <= 20 mg/d prednisone or equivalent, and the dose must be stable for >= 14 days before beginning the 14-day ISM-SAF eligibility TSS assessment.
7. Patient must have an ECOG-PS of 0 to 2.
8. Patient must be able to give written informed consent.

Exclusion criteria

1. Patient has been diagnosed with any of the following WHO SM subclassifications:
o Cutaneous mastocytosis only (ie, without documentation of systemic involvement).
o SM-AHN.
o SSM
o ASM.
o MCL.
o MC sarcoma.
2. Patient has been diagnosed with another myeloproliferative disorder (eg, myelodysplastic syndrome, myeloproliferative neoplasm).
3. Patient has any of the following organ damage C-findings attributable to SM:
o Cytopenia.
o Hepatomegaly with ascites and impaired liver function.
o Palpable splenomegaly with hypersplenism.
o Malabsorption with hypoalbuminemia and significant weight loss.
o Skeletal lesions: large osteolytic lesions with pathologic fractures.
o Life-threatening organ damage in other organ systems that is caused by MC infiltration in tissues.
4. Patient meets any of the following laboratory criteria:
o Aspartate aminotransferase or alanine aminotransferase > 3.0 × upper limit of normal (ULN).
o Total bilirubin > 1.5 × ULN; > 3.0 × ULN if due to Gilbert's disease. (In the case of Gilbert*s disease, a direct bilirubin > 2.0 × ULN is an exclusion.)
o Albumin < 1 × LLN.
o Estimated glomerular filtration rate (eGFR; calculated using the Modification of Diet in Renal Disease equation) < 30 mL/min/1.73 m2 or creatinine > 1.5 × ULN
o Absolute neutrophil count < 1.5 × 109/L.
o Hemoglobin < 10 g/dL.
o Platelet count < 100 × 109/L.
5. Patient has received any of the following medications, therapies, or procedures in the timeframes listed:
o Any prior treatment with avapritinib.
o Any TKI, including but not limited to masitinib and midostaurin, or

investigational agentfor < 14 days or 5 half-lives of the drug (whichever is longer) before beginning the 14-day ISM-SAF eligibility TSS assessment
o Any antineoplastic drug therapy (including but not limited to cladribine and 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.
o Radiotherapy or PUVA therapy < 14 days before beginning the 14-day ISM-SAF eligibility TSS assessment.
o Any hematopoietic growth factor the preceding 14 days before beginning the 14-day ISM-SAF eligibility TSS assessment.
o Any major surgical procedure (minor surgical procedures such as central venous catheter placement, BM biopsy, and feeding tube placement are not considered major surgical procedures) < 14 days before starting the ISM-SAF for determination of eligibility.
6. Patient requires therapy with a concomitant medication that is a strong inhibitor, strong inducer, or moderate inducer of cytochrome P450 3A4 (CYP3A4) (see Appendix 9).
7. Patient has a history of a malignancy that has been diagnosed or required therapy within 3 years before the first dose of study drug. Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational agent may be included after approval by medical monitor.
8. Patient has a QT interval corrected using Fridericia's formula (QTcF) > 480 msec.
9. Patient has a history of a seizure disorder (eg, epilepsy) or requires antiseizure medication.
10. Patient has a history of a cerebrovascular accident or transient ischemic attacks within 12 months before the first dose of study drug.
11. Patient has a known risk or recent history (12 months before the first dose of study drug) of ICB (eg, brain aneurysm).
12. Patient has a primary brain malignancy or metastases to the brain.
13. Patient has clinically significant, uncontrolled cardiovascular disease, including Grade III or IV congestive heart failure greater than New York Heart Association classification II; myocardial infarction or unstable angina within the previous 6 months; clinically significant, uncontrolled arrhythmias, or uncontrolled hypertension.
14. Patient is unwilling or unable to comply with scheduled visits, drug administration plan, laboratory tests, or other study procedures, including mandatory BM and skin biopsies, and study restrictions.
15. Female patients who are unwilling, if not postmenopausal or surgically sterile, to abstain from sexual intercourse or employ highly effective contraception during the study drug administration period and for at least 6 weeks after the last dose of study drug. Men who are unwilling, if not surgically sterile, to abstain from sexual intercourse or employ highly effective contraception during the study drug administration period and for at least
6 weeks after the last dose of study drug.

16. Pregnant women, as documented by a serum beta human chorionic gonadotropin (β-hCG) pregnancy test consistent with pregnancy obtained within 7 days before the first dose of study drug. Women with β-hCG values that are within the range for pregnancy but are not pregnant (false-positives) may be enrolled with written approval of the Sponsor after pregnancy has been excluded. Women of nonchildbearing potential (postmenopausal, hysterectomy, bilateral salpingectomy, or bilateral oophorectomy) do not require a serum β-hCG pregnancy test.
17. Women who are breast feeding.
18. Patient has a prior or ongoing clinically significant illness, medical condition, surgical history, physical finding, or laboratory abnormality that, in the Investigator's opinion, could affect the safety of the patient, alter the absorption, distribution, metabolism or excretion of the study drug, or impair the assessment of study results. Patients with uncontrolled symptomatic illnesses unrelated to mastocytosis that may impact the ISM-SAF or QoL assessments (eg, Crohn*s Disease, ulcerative colitis, psoriasis, or sickle cell anemia) are excluded from the study.
19. Patient is illiterate or otherwise unable or unwilling to complete daily ISM-SAF assessments in the electronic diary (eDiary). Patient must be fluent in the language(s) available for the ISM-SAF and other QoL questionnaires.
20. Patients with known hypersensitivity to avapritinib or to any of the excipients.
21. Patient is receiving an investigational agent in another interventional study.
22. Patient is dependent on the Sponsor, Investigator or the trial site.
23. Patient is institutionalized based on an administrative or court order.
24. Patients requiring anticoagulant therapy such as warfarin, or similar agents requiring therapeutic international normalized ratio (INR) monitoring.
25. Germany only: Patients who have previously experienced reactions to local anesthesia.
26. Germany only: Patient is not eligible for an MRI due to contraindications (eg, patients with implanted defibrillators or other metallic devices not approved for MRI).

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial

Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	16-05-2019
Enrollment:	12
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	not available
Generic name:	Avapritinib

Ethics review

Approved WMO Date:	05-12-2018
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	26-02-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	28-02-2019
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	11-06-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO	

Date:	14-01-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	03-06-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	10-06-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	11-08-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	08-09-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	09-02-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	13-04-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	06-06-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	16-09-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO	

Date:	07-04-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	05-08-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	02-11-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	05-11-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	02-12-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	12-07-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	23-08-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	28-03-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	10-07-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EU-CTR	CTIS2024-512585-34-00
EudraCT	EUCTR2018-000588-99-NL
ClinicalTrials.gov	NCT03731260
CCMO	NL67517.042.18