A Randomized, Double-Blind, Placebo-Controlled Phase 2/3 Study of BLU-263 in Indolent Systemic Mastocytosis

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This study has been transitioned to CTIS with ID 2024-516728-32-00 check the CTIS register for the current data. To determine RD of elenestinibTo assess if treatment with elenestinib improves outcomes compared to placebo + BSC, as assessed using the...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON56049

Source
ToetsingOnline

Brief title
HARBOR: Study of BLU-263 for ISM

Condition

- Other condition

Synonym
Mast cell disease - systemic mastocytosis

Health condition

myeloproliferatieve aandoening

Research involving
Human

Sponsors and support

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

Intervention

Keyword: BLU-263, KIT D816V mutation, Monoclonal mast cell activation syndrome, Systemic Mastocytosis

Outcome measures

Primary outcome

Part 1:

Primary objective:

- To determine RD of elenestinib

Primary endpoint:

- Safety and tolerability as determined by treatment-emergent adverse events

(hereafter referred to as AEs), serious treatment emergent adverse events

(hereafter referred to as SAEs), and changes in safety laboratory parameters,

vital signs, and ECG evaluations.

- PK and PD data.

- The mean change in ISM-SAF TSS from Baseline at Week 13

Part 2:

Primary objective:

- To assess if treatment with elenestinib improves outcomes compared to placebo

+ BSC, as assessed using the ISM-SAF

Primary endpoint:

- Proportion of patients with moderate to severe ISM who achieve at least a 30% reduction in ISM-SAF TSS from Baseline at Week 25

Part 3:

Primary objective:

- To assess the long-term safety and tolerability of treatment with elenestinib
- To assess the long-term efficacy of treatment with elenestinib

Primary endpoint:

- Safety and tolerability determined by AEs, SAEs, and changes in safety laboratory parameters, vital signs, and ECG evaluations
- The mean change in ISM-SAF TSS from elenestinib Baseline (The last available observation prior to the first dose of elenestinib)

Secondary outcome

Part 1:

Secondary objective:

- To assess the change in measures of mast cell burden from treatment with elenestinib+BSC or placebo+BSC
- To assess the change in ISM-SAF individual symptom scores from treatment with elenestinib+BSC or placebo+BSC
- To assess the time to achieve a 30% reduction in ISM-SAF TSS, ISM-SAF, GSS, ISM-SAF,SSS, and ISM-SAF Neurocognitive Symptom Cluster Score

Secondary endpoint:

- The mean change in the following measures from Baseline at Week 13:

Serum tryptase

KIT D816V allele fraction in blood

BM mast cells

- The mean change in ISM-SAF individual symptom scores from Baseline at 12 weeks of treatment (Week 13)

- The time to achieve a 30% reduction in ISM-SAF TSS, ISM-SAF GSS, ISM-SAF SSS, and ISM-SAF Neurocognitive Symptom Cluster Score from randomization among patients who achieve such a reduction on or before 12 weeks of treatment (Week 13)

Part 2:

Secondary objective:

- To assess if treatment with elenestinib+BSC improves outcomes compared to placebo+BSC, as assessed using:

- serum tryptase

- PB KIT D816V allele fraction

- mean change in ISM-SAF TSS from Baseline

- BM mast cells

Secondary endpoint:

- The proportion of patients who achieve at least a 50% reduction in serum

tryptase from Baseline to after 24 weeks of treatment (Week 25), among patients with Baseline ISM-SAF TSS >= 28 and Baseline tryptase >= 20 ng/mL

- The proportion of patients who achieve at least a 50% reduction in PB KIT D816V allele fraction, or a reduction to undetectable levels, from Baseline at to after 24 weeks of treatment (Week 25), among patients with Baseline ISM-SAF >= 28 and detectable mutation at Baseline

- The mean change in ISM-SAF from Baseline to after 24 weeks of treatment (Week 25), among patients with Baseline ISM-SAF >= 28

- The proportion of patients who achieve at least a 50% reduction in BM mast cells, or a reduction to no aggregates, from Baseline to to after 24 weeks of treatment (Week 25), among patients with ISM-SAF TSS >= 28 and aggregates at Baseline

Part 3:

Secondary objective:

- To assess the change in

measures of mast cell burden

BSC usage for SM symptoms

ISM-SAF Individual Symptom Scores and ISM-SAF Lead Symptom Score (LSS)

in other PROs and QoL measures

- To assess the time to achieve a 30% reduction in ISM-SAF TSS, ISM-SAF GSS, ISM-SAF SSS, and ISM-SAF Neurocognitive Symptom Cluster Score

Secondary endpoint:

- The mean change in the following measures from elenestinib Baseline:

Serum tryptase

KIT D816V allele burden in blood

- The change in the number of concomitant medications identified as BSC from Baseline

- The mean change in ISM-SAF Individual Symptom Scores from Baseline

- The mean change in ISM-SAF LSS from Baseline

- The time to achieve a 30% reduction in ISM-SAF TSS, ISM-SAF GSS, ISM-SAF SSS and ISM-SAF Neurocognitive Symptom Cluster Score from the first dose of elenestinib among patients who achieve such a reduction on or before 1 year of elenestinib therapy

- The mean change in the following measures from Baseline to after 24 weeks of treatment (Week 25):

MC-QoL score

PGIS score

SF-12 score

EQ-5D-5L score

Study description

Background summary

SM is a rare, clonal mast cell neoplasm driven by the KIT D816V mutation in up to ~95% of cases. This mutation leads to the uncontrolled proliferation and activation of mast cells, often present as aggregates in skin, BM, spleen, liver, GI tract, and other organs. SM can be associated with 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 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, corticosteroids, and anti-IgE antibodies.

The prevalence of SM is estimated at approximately 1 in 10,000 people. Ninety-five percent of patients with SM are considered to have non-AdvSM, which includes the WHO variant of ISM as well as a small number of patients with 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. Approximately 5% of patients with ISM show disease progression to severe forms of SM associated with poor overall survival. Avapritinib, a selective KITD816V inhibitor, was approved for use in adult patients with ISM in the US in May 2023 and in the EU for patients with moderate to severe symptoms who are inadequately managed by current symptomatic treatment in November 2023. However, further therapies targeted at improving both the underlying disease driver and disease-related symptoms are lacking. SSM is defined by the presence of at least 2 B-findings, resulting from high mast cell burden, and no Cfindings (organ dysfunction). B-findings include pronounced mast cell burden (>30% in BM biopsy, high KIT D816V VAF, high serum tryptase), signs of myeloproliferation or myelodysplasia without clear evidence of an AHN, and organomegaly. SSM diagnosis also includes no signs of aggressive disease or an AHN. The clinical course in SSM is often characterized by slow progression and patients may remain stable for years or may progress into a more advanced variant (ASM, MCL or SM with an AHN). Patients with SSM progress to AdvSM or transform to leukemia in approximately 9% of cases and have a worse survival compared to ISM patients.

mMCAS is a rare clonal mast cell disease defined by the presence of the KIT D816V mutation. Like SM, mMCAS is classified as a primary mast cell disorder, with an inherent genetic defect in the mast cells or their progenitors. With mMCAS, Baseline tryptase levels are often normal but can increase during symptomatic episodes. Clinical presentation includes episodic symptoms of mast cell degranulation, such as flushing, lightheadedness, abdominal cramping, nausea, and diarrhea. Severe episodes of syncope and anaphylaxis have been associated with mMCAS. Monoclonal mast cell activation syndrome does not fit the WHO criteria for SM; however, 1 or 2 minor criteria may be present (eg, c-KIT mutation or CD25 expression on BM analysis). Some of these patients can be found to have systemic mastocytosis on future biopsies. Spontaneous resolution of mMCAS or systemic mastocytosis has not been described to date. Similar to the patients with ISM, mMCAS patients have limited treatment options that often times offer minimal control of their disease and related symptoms. There are no approved therapies for mMCAS patients that reduce burden of disease or alter the disease course. Many mMCAS patients continue to have

substantial burden of disease despite significant polypharmacy with symptomatic therapies that are primarily directed at mitigating the release or effects of mast cell mediators.

Elenestinib (BLU-263) is a potent, selective, small molecule inhibitor of the KIT exon 17 mutant enzyme, KIT D816V. Its potency is demonstrated in vitro in both the biochemical (dissociation constant, Kd = 0.24 nM) and cellular (half-maximal inhibitory concentration, [IC50] = 4.3 nM) settings. Elenestinib has a high degree of selectivity for KIT D816V when compared against other kinases, transmembrane or soluble receptors, ion channels, transporters, and other enzymes. The calculated Kp,uu (AUC 0-inf, brain dialysate/unbound AUC 0-inf, plasma) was 0.06, suggesting limited brain penetration potential for elenestinib.

This study is designed to determine the RD and assess the safety and efficacy of elenestinib in patients with ISM, SSM, or mMCAS whose symptoms are not adequately controlled by BSC. There are 5 parts to the study and 2 open-label PK groups:

• Part 1 of the study contains 3 dose groups and a placebo group to determine the RD of elenestinib
for patients with ISM.
• Part 2 of the study will assess if elenestinib treatment in addition to the BSC improves outcomes
in patients with ISM compared to placebo + BSC.
• Part 3 of the study is an open-label extension to further characterize long-term safety and efficacy
of elenestinib.
• Part S will explore elenestinib treatment + BSC in patients with SSM in an open-label design.
• Part M will explore elenestinib treatment + BSC in patients with mMCAS in an open-label
design.

A PK group of up to 20 patients may be enrolled prior to and/or in parallel to Part 1. An additional PK group of approximately 60 patients may also be enrolled prior to Part 2. Both PK groups are to better characterize PK, safety, and efficacy of elenestinib in patients with ISM. Patients in each PK group may have a wider range of TSSs than the randomized portions of the study or have selected comorbidities or co-medications with potential to impact elenestinib PK.

Study objective

This study has been transitioned to CTIS with ID 2024-516728-32-00 check the CTIS register for the current data.

To determine RD of elenestinib
To assess if treatment with elenestinib improves outcomes compared to placebo + BSC, as assessed using the ISM-SAF
To assess the long-term safety and tolerability of treatment with elenestinib
To assess the long-term efficacy of treatment with elenestinib

Study design

This is a randomized, double-blind, placebo-controlled, Phase 2/3 study comparing the efficacy and safety of elenestinib + BSC with placebo + BSC in patients with ISM, SSM, or mMCAS whose symptoms are not adequately controlled by BSC. In Part 1, the RD of elenestinib will be identified in patients with ISM who have an ISM-SAF TSS >= 28. In Part 2, patients with ISM, regardless of ISMSAF TSS, will be randomly assigned to the RD of elenestinib identified in Part 1 + BSC or to matching placebo + BSC. In Part 3, patients who have completed Part 1 or Part 2 of the study will participate in a long-term extension, receiving open-label elenestinib at the RD + BSC. In Part S, patients with SSM will receive 100 mg of open-label elenestinib + BSC. In Part M, patients with mMCAS will receive the RD of open-label elenestinib + BSC.

Screening (All Parts)
After provision of written informed consent, patients will be evaluated for eligibility during the Screening period.

In Part 1 and PK groups, after consent is provided, the ISM-SAF should be completed daily to determine the 14-day average eligibility TSS. No other Screening assessments can be performed during the 14-day Eligibility TSS period. The patient will continue to complete the ISM-SAF throughout the Screening period. Once the Eligibility TSS is determined; other Screening assessments may begin. Baseline TSS should be calculated prior to C1D1. Patients in Part 2 will complete the ISM-SAF daily through Screening to determine a Baseline score, but inclusion in the study is not dependent upon a particular TSS. No other Screening assessments can be performed during the 14-day Eligibility and Baseline TSS period. Note: C1D1 must be delayed until a valid 14-day average Baseline TSS has been obtained for Part 1 and Part 2.

In Part S and Part M, after informed consent is provided, patients will begin completing the ISM-SAF, the MC-QoL, and all other Screening procedures simultaneously. Screening should last no longer than 8 weeks (56 days), except with written permission of the Sponsor. Randomization in Part 1 and Part 2 will occur after patients are deemed eligible to participate following Screening. Please refer to Section 8.10.1 for more details on the Screening Period.

Part 1
In Part 1 of the study, approximately 40 evaluable patients with ISM with TSS >= 28 will be equally randomized (1:1:1:1 ratio) to 1 of 3 doses of

elenestinib+BSC or to placebo. Randomization will be stratified based on centrally measured serum tryptase levels at screening (< 20 ng/mL versus >= 20 ng/mL) with approximately 7 patients with serum tryptase levels >= 20 ng/ml in each group. The 3 dose levels (25 mg, 50 mg, or 100 mg) of elenestinib+BSC and placebo will be tested in parallel. Patients, study staff, and the Sponsor will be blinded to treatment assignment; however, select personnel, primarily functioning in safety reporting, clinical pharmacology, and conduct of the IDMC will be unblinded throughout the study. Elenestinib will be administered orally, once daily (QD) continuously. Patients will be assessed weekly for the first 4 weeks for safety, laboratory monitoring, and QoL assessments. Pharmacokinetic sampling will be performed in all patients. The pharmacokinetics data may be unblinded after the completion of intensive PK collections (C1D1 and C1D15) of all patients. The ISM-SAF will be completed daily. After completion of 12 weeks of treatment, BM and skin biopsy will be repeated for mast cell quantification by the Central Pathology Laboratory and skin photographs (optional) may be taken in patients with baseline mastocytosis in skin. The RD will be determined based on the efficacy, safety, and PK data at each dose level from Part 1 and the PK groups. The major efficacy criterion for selection of the RD will be the dose of elenestinib that produces the maximum reduction in TSS, as assessed using the ISM-SAF at 12 weeks of treatment (Week 13) compared with Baseline. Other measures of efficacy (eg, change in serum tryptase)
will also be taken into consideration. Once assessments after 12 weeks of treatment (Week 13) are completed, and the interim placebo crossover dose is determined, all patients will be unblinded and continue treatment in Part 1 until RD is determined. Patients randomized to elenestinib will remain in Part 1 on their current dose; dose modifications are permitted (criteria for dose modification are outlined in Section 7.3.1). Patients receiving placebo in Part 1 will receive elenestinib at the interim placebo cross-over dose. This interim placebo cross-over dose may be different than the RD for Parts 2, Part 3, and Part M. Once RD is determined, all patients will roll over into Part 3 at the RD. Please refer to Section 4.3.1 for details on the interim placebo cross-over dose.

Part 2
In Part 2, of the study, approximately 303 patients with ISM will be enrolled (at least 204 evaluable patients with TSS >= 28 and up to 99 patients with TSS < 28). Once the targeted sample size in Part 2 for patients with TSS >= 28 has been met, enrollment of patients with TSS < 28 may stop even if the number of patients in the TSS < 28 group is less than 99. Patients will be randomly assigned to treatment at a 2:1 ratio to receive the RD of elenestinib + BSC or matching placebo + BSC, respectively. Randomization will be stratified based on TSS score (< 28 and > 28) and on centrally measured serum tryptase levels at Screening (< 20 ng/mL versus >= 20 ng/mL). In addition, enrollment of patients with < 20 ng/mL serum tryptase will be capped at approximately 20% for patients with TSS >= 28 and approximately 20% for patients with TSS <28. Elenestinib and

placebo dosing will be administered orally, QD, continuously. Patients will be assessed through 24 weeks of treatment (Week 25) for safety, laboratory monitoring, and QoL assessments. Sparse PK sampling will be performed in all patients. For patients with mastocytosis in skin who opt to do so, skin photographs will be taken every 12 weeks. The ISM-SAF should be completed daily. After completion of 24 weeks of treatment, the ISM-SAF, BM, and skin biopsy will be repeated for mast cell quantification by the Central Pathology Laboratory and skin photographs (optional) may be taken in patients with baseline mastocytosis in skin. Each patient completing the assessment after 24 weeks of treatment (Week 25) will roll over into the Part 3 long-term extension to receive the RD of elenestinib QD in an open-label fashion. The Week 25 assessments will be the Baseline for Part 3. After all patients in Part 2 roll over into Part 3, all Part 2 treatment assignments will be unblinded. At this point the primary endpoint of proportion of patients with a >=30% reduction in TSS from Baseline to after 25 weeks of treatment (Week 25) and other efficacy endpoints will be analyzed.

Part 3
After all Part 1 patients have completed Part 1 and the RD has been determined or as each patient in Part 2 completes their study assessments after 24 weeks of treatment (Week 25), patients will roll over to Part 3. All patients will receive open-label treatment with the RD of elenestinib.
In Part 3, Part 1 patients who received elenestinib will have study visits every 4 weeks until Week 25, then every 8 weeks until Week 49. After Week 49, patients will have study visits every 12 weeks for a total treatment duration of up to approximately 4 years, inclusive of Part 1. Part 1 patients who received placebo may have weekly visits until Week 5 in Part 3 at the discretion of the Investigator.
In Part 3, patients rolling over from Part 2 will have weekly visits until Week 5 and will then follow the same schedule as Part 1 patients according to the SoA in Table 4.
Additional ad hoc study visits may occur based on the Investigator*s clinical judgement.
The ISM-SAF will be completed daily for patients in Part 1 and Part 2, and Q

Intervention

In Part 1 of the study, approximately 40 patients with ISM with TSS >= 28 will be equally randomized (1:1:1:1 ratio) to 1 of 3 doses of elenestinib +BSC or to placebo +BSC.

In Part 2, of the study, approximately 303 patients with ISM will be enrolled (approximately 204 patients with TSS >= 28 and up to 99 patients with TSS < 28). Patients will be randomly assigned to treatment based on a 2:1 ratio to receive the RD of elenestinib + BSC or matching placebo + BSC, respectively.

After all Part 1 patients have completed Part 1 and the RD has been determined

or as each patient in Part 2 completes their study assessments after 24 weeks of treatment (Week 25), patients will roll over to Part 3. All patients are eligible to receive open-label treatment with the RD of elenestinib .

In Part 3, patients who received elenestinib in Parts 1 or 2 will have study visits every 4 weeks until after 24 weeks of treatment (Week 25), then every 8 weeks until Week 49. After Week 49, patients will have study visits every 12 weeks for a total treatment duration of up to approximately 4 years, inclusive of Part 1 or Part 2 as applicable.
Patients assigned to placebo during Part 1 or Part 2 who are starting elenestinib for the first time in Part 3 may have weekly visits until Week 5 at the discretion of the Investigator and will then follow the same schedule in Part 3 that patients who received elenestinib in Part 1 or Part 2 will follow as per SoA (Table 4)

In Part S of the study (exploratory), approximately 20 patients with SSM will receive open-label elenestinib at a dose of 100 mg QD + BSC. Formulation and administration will be the same as described above for Part 2 but will not include a placebo arm. An alternative lower dose may be selected by the Investigator after consultation with the Sponsor. Assessments will be collected as described in the SoA (Table 5). BM biopsies will be required for PPR assessment by the Central Pathology Laboratory. Patients will continue to be treated up to approximately 4 years.

In Part M of the study (exploratory), approximately 20 patients with mMCAS will receive open-label elenestinib QD + BSC. Dose, formulation, and administration will be the same as described above for Part 2 but will not include a placebo arm.

Two PK groups may be enrolled to better evaluate the PK, safety, and efficacy of elenestinib. SM patients may have GI issues and/or take concomitant medications that may impact absorption of elenestinib requiring more specific guidance to optimize dosing. Optional PK group(s) is/are therefore included. An optional PK group of up to 20 patients may be enrolled prior to and/or in parallel to Part 1. An additional PK group of up to 20 patients may also be enrolled prior to Part 2.

Both PK groups will receive elenestinib in an open label fashion. Patients enrolled in optional PK group prior to and/or parallel to Part 1 will receive elenestinib 50 mg QD. For patients enrolled in optional PK group prior to Part 2, elenestinib will be administered orally, QD at the RD and will not exceed doses previously determined to be safe.

Study burden and risks

POSSIBLE DISCOMFORTS AND RISKS OF BLU-263
During the study, you may have discomforts and possible risks from BLU-263 and

from the study procedures. BLU-263 has been studied in healthy volunteers and SM patients; however, safety information is considered limited and your experience may be different. The clinical study with BLU-263 in patients with Indolent Systemic Mastocytosis (ISM) is still ongoing. Some side effects are unknown, and there is always the possibility that unknown risks may occur. Additionally, discomforts and risks may vary from person to person. Everyone taking part in the study will be watched carefully for side effects; however, doctors do not know all the discomforts and risks that may happen. There is always the possibility that unknown risks may occur. These may be mild or severe, and in some cases may be long-lasting, or may never go away. There may even be a risk of death. If any discomforts or risks occur, you must tell your study doctor.
Your doctor may give you medications to help lessen some of the discomforts and risks. Depending on your side effect to BLU-263 occurs, your doctor may interrupt or reduce the study drug dose or stop the study drug.

Possible Side Effects Observed in Patients with ISM

Based on results from 115 patients, who were dosed at 25 mg, 50 mg, 75 mg and 100 mg, most of the patients were treated up to 35 weeks, the following side effects have been reported in patients who are receiving BLU-263:

Very common side effects (in at least in 10% of the patients)
• Diarrhoea
• Headache
• Nausea
• Oedema (swelling of lower legs and hands, swollen eyelid)
• Joint pains
• Abdominal Pain
• Lack of energy/ fatigue
• Respiratory infections
• Dizziness
• Flushing
• Muscle pain
Common side effects (between 5% and 10% of the patients)
• Back pain
• Itchy skin
• Changes in laboratory tests, which may indicate injury to the liver or muscle (e.g.: Blood alkaline phosphate increased)
• Weight increased
• Increased blood pressure
• Vomiting
• Abdominal swelling
• Constipation
• Rash
• Bone pain
• Cough

• Trouble sleeping
• Urinary tract infection
• Hair loss
• Redness of skin
• Inflammation of the stomach and intestines
• General feeling of discomfort, illness or lack of well-being

Most of the reported events were mild or moderately severe.

Possible Side Effects Based on Animal Studies
What happens in animals does not always predict what will happen to people who take the same drug. Based on studies of high doses in animals, other possible effects in humans of BLU-263 are:
• Low number of red blood cells and white blood cells.
• Loss of cells in organs that support your body*s immune response (e.g., bone marrow, lymph nodes, spleen etc.).
• Effects on male reproductive system including shrinkage of testes and prostate gland.
• Effects on female reproductive system including increased mucus production in the vagina, bleeding in the ovaries and uterus, and ovarian cysts.
• Bleeding in the brain, and pituitary gland (a gland important in controlling growth and development and regulating other glands).
• Increase in the size of the heart.
• Clustering of a type of white blood cells in the lungs.
• Abnormal levels of liver enzymes in blood
• A risk of abnormal development of the embryo and fetus if BLU-263 is administered to a pregnant woman.

RISK TO THE UNBORN CHILD

Female patients: We do not know if the study drug BLU-263 will affect mother*s milk or an unborn child. Therefore, breast-feeding and pregnant women are not allowed to take part in the study. Due to unknown risks and potential harm to the unborn child/ infant, you should not become pregnant or nurse a baby while on this study. You must have a negative pregnancy test prior to enrolling in the study.
Unless you cannot have children because of surgery or other medical reasons (you had an effective tubal ligation, or had the ovaries or the uterus removed; or you are post-menopausal), you must use a highly effective method of birth control from the time of signing the informed consent form, and throughout the entire study drug treatment period, and for 30 days following the last dose of study drug. Highly effective methods of birth control with low user dependence include:
• Hormonal birth control pills/oral contraceptives, injectable contraceptives, contraceptive patches, or contraceptive implants (female patients using this

method must also agree to use a back-up barrier method, preferably a male condom)
• Intrauterine devices (IUD)
• Intrauterine hormone-releasing system (IUS) (female patients using this method must also agree to use a back-up barrier method, preferably a male condom).
• Bilateral tubal occlusion
• Male partner vasectomy or other method of surgical sterilization provided that the partner is your only sexual partner and a doctor has confirmed that the sterilization was successful.
• Abstinence of heterosexual intercourse if it is the preferred and usual lifestyle
The following methods of contraception are not considered highly effective and are not acceptable:
• Oral hormonal contraceptives that do not inhibit ovulation (progesterone-only pills, often called *mini pills*)
• Barrier methods including condoms, cervical caps, or diaphragm with or without spermicide
You must use birth control methods as directed above, unless you completely avoid having heterosexual intercourse.

Male patients: While BLU-263 does not have direct effects on sperm, you should not get your partner pregnant during the study drug period due to potential abnormal development of the embryo and fetus. Even if you are surgically sterilized (i.e. have had a vasectomy) you must agree to use an appropriate method of barrier contraception (latex condom with a spermicidal agent) from the time of signing the informed consent form, and throughout the entire study drug treatment period, and for 90 days following the last dose of study drug. Or, you should completely avoid having heterosexual intercourse. Male patients must agree to not donate sperm from the first dosing until at least 90 days after the last dosing.
All patients (male or female): If you or your partner becomes pregnant during this study, you must tell the study doctor immediately. The doctor will advise you of the possible risks to your unborn child and discuss options for managing the pregnancy with you. For female patients who become pregnant while on this study, the study drug will be stopped immediately, and the pregnancy will be followed until conclusion.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

All Patients
• Patient must be >= 16 years of age at the time of signing the informed consent/assent. (In France, Sweden, Germany, and Spain, only patients who are >= 18 years of age are allowed).
• Patient must have an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 to 2.

With ISM in Part 1 and Part 2
• Patient must have moderate-to-severe symptoms based on minimum mean total symptom score (TSS) of the ISM Symptom Assessment Form (ISM-SAF) over the 14-day eligibility screening period.

With ISM in Part 1, Part 2 and PK groups
• Patient has confirmed diagnosis of ISM, confirmed by Central Pathology Review of BM biopsy and central review of B- and C-findings by WHO diagnostic criteria. Archival biopsy may be used if completed within the past 12 months.
• 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 administered: H1 blockers, H2 blockers,

proton-pump inhibitors, leukotriene inhibitors, cromolyn sodium, corticosteroids, or omalizumab.
• Patients must have BSC for ISM symptom management stabilized for at least 14 days prior to starting screening procedures.
• For patients receiving corticosteroids, the dose must be <= 20 mg/d prednisone or equivalent, and the dose must be stable for >= 14 days.

With mMCAS in Part M

• Patients must have mMCAS, confirmed by Central Pathology Review of BM biopsy. An archival biopsy may be used if completed within the past 12 months.
• Patients must have tryptase < 20 ng/mL.
• Patients must have KIT D816V in peripheral blood (PB) or BM and/or CD25+ Mast cells in BM.
• Patients must have symptoms consistent with mast cell activation (despite BSC) in at least two organ systems characterized by cutaneous flushing, tachycardia, syncope, hypotension, diarrhea, nausea, vomiting and gastro-intestinal cramping) and serum blood tryptase (sBT) levels above 8 ng/mL OR Severe (Ring and Messmer grading >= II, recurrent anaphylaxis, including but not limited to hymenoptera venom, drug or food, regardless of sBT levels.

With ISM in PK Groups
• See inclusion criteria for All patients and Part 1/Part 2
• Accrual may be limited to patients who have specific disease manifestations (ie, GI involvement) or are taking acid-reducing agents to better explore the impact of these features on PK.

With SSM in Part S:
• Patient has confirmed diagnosis of SSM, confirmed by Central Pathology Review of BM biopsy and central review of B- and C-findings by WHO 2022 diagnostic criteria . No archival BM biopsies will be accepted without approval from the Sponsor.

For the full list of inclusion criteria we would like to refer you to page 66-67 of the protocol.

Exclusion criteria

• Patient has been diagnosed with any of the following WHO systemic mastocytosis (SM) sub-classifications: cutaneous mastocytosis only, smoldering SM, SM with associated Hematologic neoplasm, aggressive SM, mast cell leukemia, or mast cell sarcoma.
• Patient has been diagnosed with another myeloproliferative disorder.
• Patient has organ damage C-findings attributable to SM.
• Patient has clinically significant, uncontrolled, cardiovascular disease

• Patient has a QT interval corrected using Fridericia's formula (QTcF) > 480 msec.
• Patient has previously received treatment with any targeted KIT inhibitors.
• Patient has a history of a primary malignancy that has been diagnosed or required therapy within 3 years. The following prior malignancies are not exclusionary: completely resected basal cell and squamous cell skin cancer, curatively treated localized prostate cancer, and completely resected carcinoma in situ of any site.
• Time since any cytoreductive therapy including mastinib and midostaurin should be at least 5 half-lives or 14 days (whichever is longer), and for cladribine, interferon alpha, pegylated interferon, or antibody therapy < 28 days or 5 half-lives of the drug (whichever is longer), before beginning the screening period.
• Patient has received radiotherapy or psoralen and ultraviolet A (PUVA) therapy < 14 days before beginning the screening period.
- pregnant or not willing to use highly effective contraception methods
• Patient has known active SARS-CoV-2infection (Germany Only).
• Patients not eligible for an MRI due to contraindications (eg, patients with implanted defibrillators or other metallic devices not approved for MRI [Germany only]).

For an overview of all exclusion criteria we would like to refer you to page 67-70 of the protocol.

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):	25-07-2022

Enrollment:	10
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	Elenestinib
Generic name:	Elenestinib
Product type:	Medicine
Brand name:	Elenestinib-B
Generic name:	Elenestinib-B

Ethics review

Approved WMO Date:	23-07-2021
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	28-04-2022
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	24-05-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	13-07-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	16-08-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO	

Date:	27-10-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	14-08-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	21-09-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	24-11-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	29-11-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	10-05-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	12-09-2024
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	CTIS2024-516728-32-00
EudraCT	EUCTR2020-005173-28-NL
ClinicalTrials.gov	NCT04910685
CCMO	NL78017.042.21