A Phase 1/2, open-label, 2-arm study evaluating BLU-263 as monotherapy and in combination with azacitidine, in patients with KIT altered hematologic malignancies

Published: 30-11-2022
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This study has been transitioned to CTIS with ID 2023-510144-20-00 check the CTIS register for the current data. The current study is designed to evaluate the preliminary safety and efficacy of BLU-263 in patients with AdvSM, including in those with...

Ethical review	Approved WMO
Status	Pending
Health condition type	Haematopoietic neoplasms (excl leukaemias and lymphomas)
Study type	Interventional

Summary

ID

NL-OMON53678

Source
ToetsingOnline

Brief title
AZURE: Study of BLU-263 in Advanced SM

Condition

- Haematopoietic neoplasms (excl leukaemias and lymphomas)

Synonym
Advanced Systemic Mastocytosis, Mast cell disease

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Advanced Systemic Mastocytosis, Azacitidine, BLU-263, KIT D816V mutation

Outcome measures

Primary outcome

Monotherapy (Arm 1):

Part 1 (dose escalation):

Primary objective:

• To determine the RD for BLU-263 monotherapy

Primary endpoints:

• The RD will be primarily determined by the number of DLTs in the first 28

days of treatment with BLU-263 monotherapy.

Part 2 (dose escalation and expansion):

Primary objectives:

• To assess the safety and tolerability of BLU-263 monotherapy

• To assess clinical efficacy of BLU-263 given as monotherapy at the RD to

patients with AdvSM.

Primary endpoints:

• Safety profile of BLU-263, as assessed by the type, frequency, severity, timing, and relationship to study drug of any AEs or SAEs, and changes in vital signs, ECGs, and safety laboratory tests.

• Pure pathological response rate for SM in selective KIT inhibitor-naïve patients.

Combination (Arm 2):

Part 1 (dose escalation):

Primary objectives:

• To determine the RD for BLU-263 in combination with azacitidine in patients with SM-AHN.

• To assess the safety and tolerability of BLU-263 in combination with azacitidine.

Primary endpoints:

• The RD will be primarily determined by the number of DLTs (during 28 days starting from Day 15 of C1 or Day 15 of C2) with BLU-263 in combination with azacitidine.

• Safety profile of BLU-263, as assessed by the type, frequency, severity, timing, and relationship to study drug of any AEs or SAEs, and changes in vital signs, ECGs, and safety laboratory tests.

Part 2 (dose expansion):

Primary objective:

• To assess the safety and tolerability of BLU-263 in combination with azacitidine.

Primary endpoints:

• Safety profile of BLU-263, as assessed by the type, frequency, severity, timing, and relationship to study drug of any AEs or SAEs, and changes in vital signs, ECGs, and safety laboratory tests.

Secondary outcome

Monotherapy (Arm 1):

Dose escalation and expansion:

Secundary objectives:

• To assess the

ORR

• To characterize the PK profile of BLU-263 when given as monotherapy

• To determine the overall survival (OS) of patients with AdvSM treated with BLU-263

• To assess additional measures of clinical efficacy of BLU-263 given as monotherapy

Secundairy endpoints:

• Overall response rate for AdvSM, using mIWG-MRT-ECNM

• Pharmacokinetic parameters of BLU-263 including: Cmax, Tmax, AUC0-24, Vz/F, t*, CL/F, and accumulation ratio

• Overall Survival.

• Time-to-response, DOR, and PFS,

• Proportion of patients pursuing stem cell transplant.

Combination (Arm 2):

Dose escalation and expansion:

Secundary objectives:

• To assess the ORR

• To assess the PPR for SM of BLU-263 given in combination with azacitidine.

• To assess the PK of BLU-263 and azacitidine when given alone and in combination.

Secundairy endpoints:

• Overall response rate for SM, using mIWG-MRT-ECNM

• Pure pathological response for SM

• Pharmacokinetic parameters of BLU-263 and azacitidine including: Cmax, Tmax,

AUC0-24, Vz/F, t*, CL/F, and accumulation ratio

Study description

Background summary

Systemic mastocytosis is a rare, debilitating, clonal mast cell neoplasm driven by the KIT D816V mutation in ~95% of cases, which results in the abnormal activation and accumulation of mast cells.

This KIT mutation leads to the uncontrolled proliferation and activation of mast cells, which often presents as aggregates in skin, BM, spleen, liver, gastrointestinal tract, and other organs. Systemic mastocytosis 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 quality of life of patients physically, emotionally, and psychosocially. The KIT D816V mutation is considered a major therapeutic target in SM.

Similar to other hematologic diseases possessing a pathogenic driver mutation, such as chronic myeloid leukemia, SM has a spectrum of severity characterized by highly symptomatic potentially life-threatening (indolent and smoldering forms) to fulminant leukemia, all of which continue to contain the original mutation.

Systemic mastocytosis is broadly divided into advanced SM and nonadvanced SM, both of which are characterized by the uncontrolled proliferation and activation of mast cells, which often presents as aggregates in skin, BM, spleen, liver, GI tract, and other organs. Approximately 10% to 20% of patients meet the criteria for advanced SM (ASM, SM-AHN, and MCL); the remainder have nonadvanced SM.

There remains an unmet medical need in patients with AdvSM, including patients with high and very high-risk SM-AHN for a selective and targeted KIT D816V therapy that has minimal brain penetration and that can be safely combined with HMAs. BLU-263 is a potent, selective, small molecule inhibitor of exon 17 mutated KIT. It has demonstrated high in vitro potency in both the biochemical (Kd = 0.24 nM) and cellular (IC50 = 4.3 nM) settings. BLU 263 has a high degree of selectivity for KIT D816V when compared with other kinases and has limited brain penetration potential. BLU-263 is also a substrate of P-gp and ABCG2 and an inhibitor of ABCG2, all of which may further decrease brain exposure to BLU-263.

Study objective

This study has been transitioned to CTIS with ID 2023-510144-20-00 check the CTIS register for the current data.

The current study is designed to evaluate the preliminary safety and efficacy of BLU-263 in patients with AdvSM, including in those with high and very high-risk SM-AHN, in whom HMAs, and azacitidine specifically, are the standard of care. Dose Escalation will determine the RD of BLU-263 monotherapy (Arm 1) and of BLU-263 when given in combination with azacitidine (Arm 2) for the treatment of AdvSM. The study will also assess clinical efficacy by PPR and by mIWG MRT ECNM criteria (for the Combination Arm). The PK and pharmacodynamic profile of BLU-263 and of azacitidine will also be characterized when given to patients with AdvSM as monotherapy (Arm 1) as well as in combination with azacitidine (Arm 2).

Study design

This is an international Phase 1/2, open-label, 2-arm study designed to evaluate the antitumor activity, safety, tolerability, PK, and pharmacodynamics of BLU*263, an orally administered, highly potent and selective inhibitor of KIT D816V mutation, as monotherapy and in combination with azacitidine in adult patients with AdvSM.

The study will include 2 arms:

• Arm 1: evaluating BLU-263 monotherapy, daily for a 28-day cycle, in patients with AdvSM

• Arm 2: evaluating BLU-263 in combination with azacitidine (75 mg/m2/day on Days 1-7 or on Days 1-5 plus Days 8 and 9 of each 28-day treatment cycle) in patients with high risk and very high risk SM-AHN.

The study will be conducted in 2 parts, Dose Escalation and Dose Expansion. Dose Escalation will involve cohort-based dose escalation of BLU-263 monotherapy to identify the RD of BLU-263 for monotherapy Dose Expansion (Arm 1). Dose Escalation in Arm 2 will begin enrolling patients only after 1 or more dose levels of BLU-263 monotherapy have been determined to be safe by the SRC. Up to 1/3 of patients in the dose escalation cohort may have previously been treated with a selective KIT inhibitor.

Enrollment to each cohort, dose escalation, de-escalation, and dose elimination will follow Bayesian optimal interval design rules (Table 10) with a target dose-limiting toxicity (DLT) rate of 30%. Depending on the emerging safety and efficacy profile, the RD for either arm may be chosen without identifying the MTD.

Dose escalation decisions will be made by the Safety Review Committee consisting of the Sponsor Clinical Study Team and the Investigators, based on an evaluation of all relevant, available data, and not solely on DLT information.

Intervention

Study treatments:

In the Monotherapy Arm, BLU-263 is to be administered once daily for 28 days of each cycle.

In the Combination Arm, azacitidine will be administered on D1-7 or D1-5, and D8-9 of each 28-day cycle. Depending on the platelet count during the first 3 cycles, BLU-263 may be administered on D15-28 of each 28-day cycle. From C4 onwards, if the platelet count is >75 x 109/L at the end of a given cycle, BLU-263 can be administered continuously in subsequent cycles. Weekly platelet counts and associated laboratory tests must be performed during the first and second cycle of continuous BLU-263 dosing.

BLU-263 should be given by oral administration with an 8-ounce (240 mL) glass of water and with a meal that is typical for the patient. Patients should be instructed to swallow capsules whole. It is preferable that the drug is taken approximately at the same time each day. If a patient vomits during or after taking BLU-263, re-dosing is not permitted until the next scheduled dose.

Study burden and risks

Based on the results from 29 patients with ISM, the following side effects have occurred more frequently in patients who are receiving BLU-263 as compared to patients receiving placebo.

Side effects that occurred in more than one patient and more frequent than placebo:
• Headache (7 patients)
• Urinary tract infection (3 patients)
• Joint Pains (6 patients)
• Abnormal blood lab test (2 patients)
• Covid-19 infection (6 patients)
• Bone pain (2 patients)
• Liver function test abnormalities (4 patients)
• Bladder inflammation (2 patients)
• Diarrhea (5 patients)
• Eyelid swelling (2 patients)
• Leg swelling (4 patients)
• Low white blood cell count (2 patients)

• Lack of energy/fatigue (4 patients)
• Muscle pains (2 patients)
• Back pain (3 patients)
• Rash (2 patients)
• Nausea (3 patients)

Most of the reported events were mild in severity. Five patients reported side effects which were moderate in severity:
• Low white blood cell count
• Severe, potentially life-threatening allergic reaction
• Fungal infection in the throat
• High blood pressure
• Kidneys failure

Side effect you can experience from the tests during the study
You can also experience side effects from the tests during the study, such as the following:

• Blood collection: Collection of blood may cause bruising at the place where the needle goes into the skin. Fainting, and in rare cases infection, may occur.
• Blood pressure: The blood pressure cuff used to take your blood pressure may cause discomfort or bruising to the upper arm.
• ECG: The ECG involves sticking patches on the skin. The skin may become a little red or irritated if you have a response to the glue used.
• CT, MRI, and DXA scans: There is a slight risk of developing an allergic response to the substance injected as part of the scanning process. This substance is like a dye that makes certain parts of the body show up better during the scanning process. In addition, there is always a slight risk from being exposed to the low levels of x-rays used for a CT scan and a DXA scan. However, the risk from the x-rays is usually very low compared with the potential usefulness of the test.
• Biopsy (bone and and other organ): Common side effects of a biopsy are a small amount of bleeding at the time of the procedure; pain at the biopsy site, which can be treated with common pain drugs; and bruising. Rarely, an infection can occur.

Contacts

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Scientific
Blueprint Medicines Corporation

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US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

All patients:
1. Patient is >=18 years of age at the time of signing the informed consent.
2. Patient has Eastern Cooperative Oncology Group performance status of 0-2.
3. Patient, or legal guardian if permitted by local regulatory authorities, provides informed consent to participate in the study.
4. Patient must have a new BM biopsy or may use archival tissue if taken within 56 days prior to C1D1.
5. Patients receiving antineoplastic therapy within the preceding 12 weeks must have discontinued therapy due to disease progression, refractory disease, lack of efficacy, or intolerance.
6. Patient must be willing to have follow-up biopsies of BM and other affected organs to document response.
7. Patients treated with 1 prior selective KIT inhibitor (such as avapritinib or CGT9486) will be permitted on study after confirmation of KIT D816V mutation and with written approval of the study Sponsor. Patients who discontinued treatment with a prior selective KIT inhibitor due to a severe AE that was thought to be related to prior treatment will not be eligible to participate in the study.

Arm 1 (Monotherapy):
A1_1.For Arm 1, patients must have 1 of the following AdvSM diagnoses, based on

WHO diagnostic criteria. Before enrollment, the diagnosis of AdvSM must be confirmed based on central pathology laboratory assessment of BM:
a.Aggressive SM
b.Systemic mastocytosis-AHN that in the opinion of the Investigator is not considered to be a candidate for HMA monotherapy (Appendix 4). Incidental indolent, low-grade lymphoid AHNs (eg, chronic lymphocytic leukemia) not requiring treatment are eligible.
c.Mast cell leukemia, including diagnoses with an AHN component, that does not require a C-finding.
d.Upon discussion with the Sponsor, other relapsed or refractory hematologic neoplasms with evidence of aberrant KIT or PDGFR may be considered for enrollment (eg, patients with chronic myeloid neoplasms such as subvariants of MDS/MPN that harbor activating KIT exon 17 mutations but do not fulfill the diagnostic criteria of SM-AHN and patients with myeloid/lymphoid neoplasms with PDGFRa/b fusion genes and mutations conferring resistance to imatinib eg, T674I or D842V).

Arm 2 (Combination Therapy):
A2_1.For Arm 2, patients must have 1 of the following SM-AHN diagnoses, based on WHO diagnostic criteria. Diagnosis of the AHN component for SM-AHN must be confirmed based on the central pathology laboratory assessment of the BM:
a.Chronic myelomonocytic leukemia-2 (per WHO 2016)
b.High or very high-risk MDS (per IPSS-R scoring
c.Myelodysplastic syndrome/MPN accelerated diagnosis phase as defined by blast count > 10% in BM OR peripheral blood but not meeting diagnostic criteria of AML
d.Myelodysplastic syndrome with excessive blasts-2 (10-19% in BM or 5 19% in peripheral blood) (per WHO 2016)
e.Complex karyotype or >= 3 adverse risk mutations (per the IPSS-R cytogenic prognostic groups of Poor or Very Poor)
f.Upon discussion with the Sponsor and in consultation with the Response Assessment Committee where needed, hematologic neoplasms which are felt to have strong rationale to consider the combination treatment of BLU-263 and HMA may be considered for enrollment (eg, patients with chronic myeloid neoplasms, such as subvariants of MDS/MPN that harbor activating KIT exon 17 mutations but do not fulfill the diagnostic criteria of SM-AHN, and patients with myeloid/lymphoid neoplasms with PDGFRa/b fusion genes and mutations conferring resistance to imatinib, such as T674I or D842V). The RAC will retrospectively assess the eligibility of enrolled patients during the study.

Exclusion criteria

All Patients:
1. Diagnosis of a Philadelphia chromosome positive malignancy.
2. Acute myeloid leukemia.
3. If the patient is receiving corticosteroids, and the dose has not been

stable for >=7 days. This exclusion criterion is not applicable if a patient has disease that is progressing and there is a safety concern around delaying the patient's study enrollment in order to stabilize the steroid dose and it is in the patient's best interest to enroll in the study rapidly. In such cases, patients may be considered for enrollment following Sponsor Medical Monitor approval.
4. Within the 14 days prior to enrollment, patient has received any antineoplastic therapy (including midostaurin, avapritinib and other TKIs) or an investigational agent. Before obtaining the Screening BM Biopsy, at least 28 days must have elapsed since the most recent dose of Cladribine, interferon alpha, pegylated interferon and any antibody therapy (eg, brentuximab, vedotin). If the site is unsure of the appropriate wash out period for a specific drug product, they should consult the Medical Monitor.
5. Patient has received hydroxyurea within 7 days prior to the first dose of BLU-263.
6. Have any of the following laboratory abnormalities on last laboratory assessment within 14 days prior to the first dose of initiation of study drug:
a. Alanine aminotransferase and AST >3 × ULN; >5 × ULN if associated with clinically suspected liver infiltration by mastocytosis or another disease for which the patient enrolled into the study.
b. Total bilirubin >1.5 × ULN; >3 × ULN if associated with liver infiltration by the disease being treated or in the presence of Gilbert's Disease. (In the case of Gilbert's disease, a direct bilirubin >2.0 ULN would be an exclusion.)
c. Estimated (Cockcroft-Gault formula) or measured creatinine clearance <40 mL/min.
d. Absolute neutrophil count <0.5 × 109/L.
7. Patient received prior HMA therapy (e.g., azacitidine, decitabine) for the current diagnosis.
8. At the time of enrollment, patient must not be eligible for allogeneic hematopoietic stem cell transplantation, in the opinion of the Investigator. However, patients who may become eligible for transplant after cytoreduction while on study are eligible to participate.
9. Patient received prior radiotherapy within 14 days of screening BM biopsy. Prior radiotherapy given to palliate specific sites of disease (eg, bone lesion) may be allowed with written approval of the Sponsor Medical Monitor.
10. Patient received any hematopoietic growth factor (except erythropoietin) within 14 days of screening BM biopsy, or requiring growth factors to maintain adequate neutrophil or platelet levels. Those patients maintained on a chronic dose of erythropoietin, whose hemoglobin is stable, and dose of erythropoietin has not been changed in the prior 28 days are allowed on study.
11. Patient received >1 prior selective KIT inhibitor (eg, avapritinib or CGT9486).
12. Patients who discontinued treatment with a prior selective KIT inhibitor due to a severe AE that was thought to be related to prior treatment will not be eligible to participate in the study.
13. Patient requires therapy with a concomitant medication that is a strong inhibitor, strong inducer, or moderate inducer of CYP3A4.

14. Patient has had a major surgical procedure within 14 days of the first dose of study drug. Minor surgical procedures such as central venous catheter placement, bone marrow biopsy, and feeding tube placement are not considered major surgical procedures and may be performed within the 14-day window.
15. History of another primary malignancy that has been diagnosed or required therapy within 1 year prior to the first dose of study drug. The following are exempt from the 1-year limit: completely resected basal cell and squamous cell skin cancer, curatively treated localized prostate cancer, GI stromal tumor, and completely resected carcinoma in situ of any site.
16. Tryptase <20 except in patients with MCL.
17. Mean resting QTcF >480 msec, a history of prolonged QT syndrome or Torsades de pointes, or a familial history of prolonged QT syndrome.
18. Patient has a history of a seizure disorder (eg, epilepsy) or requirement for antiseizure medication.
19. Patient has a history of a cerebrovascular accident or transient ischemic attacks within 1 year prior to the first dose of study drug.
20. Patient has a known risk of intracranial bleeding, such as a brain aneurysm or history of subdural or subarachnoid bleeding.
21. A primary brain malignancy or metastases to the brain.
22. Clinically significant, uncontrolled, cardiovascular disease, including congestive heart failure Grade III or IV according to the New York Heart Association classification, myocardial infarction or unstable angina within the previous 6 months, clinically significant, uncontrolled arrhythmias, or uncontrolled hypertension.

Please refer to the study protocol for the complete list.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL
Recruitment status: Pending

Start date (anticipated):	11-05-2023
Enrollment:	6
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Azacitidine
Generic name:	Azacitidine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	BLU-263
Generic name:	BLU-263

Ethics review

Approved WMO Date:	30-11-2022
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-04-2023
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-06-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-06-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	

Date:	10-11-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	CTIS2023-510144-20-00
EudraCT	EUCTR2022-001535-87-NL
CCMO	NL82572.056.22
Other	To be determined.