An International, Multicenter, Open-label, Randomized, Phase 3 Study of BLU 285 vs Regorafenib in Patients with Locally Advanced Unresectable or Metastatic Gastrointestinal Stromal Tumor (GIST)

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Primary Objective:* The primary objective is to demonstrate the efficacy of avapritinib based on progression-free survival (PFS) determined by central radiological assessment per modified Response Evaluation Criteria in Solid Tumors (mRECIST),...

Ethical review	Approved WMO
Status	Completed
Health condition type	Gastrointestinal neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON48964

Source
ToetsingOnline

Brief title
BLU-285-1303

Condition

- Gastrointestinal neoplasms malignant and unspecified

Synonym
Gastrointestinal stromal tumor, sarcomas of soft tissue in the gastrointestinal tract

Research involving

Human

Sponsors and support

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

Intervention

Keyword: Avapritinib vs Regorafenib, Gastrointestinal stromal tumor

Outcome measures

Primary outcome

The primary endpoint is PFS, based on central radiological assessment per mRECIST, version 1.1, in patients with advanced GIST. Progression-free survival is defined as time from randomization to disease progression, or death due to any cause, whichever occurs first.

Secondary outcome

The key secondary endpoints are:

* Objective response rate defined as the percentage of patients whose best response is CR or PR as assessed by central radiology using mRECIST, version 1.1.

* Overall survival defined as the time from date of randomization to death due to any cause.

Study description

Background summary

Approximately 90% of patients with GIST have a tumor that is dependent on a mutation in either V-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog (KIT) (75%-80%) or the highly related protein platelet-derived growth

factor receptor alpha (PDGFR*) (10%-15%). On a molecular level, the most common sites for oncogenic mutations at the time of diagnosis are in the juxtamembrane domain (exon 11 [60%-70%]) and extracellular domain (exon 9 [5%-15%]) for KIT and in the activation loop (Exon 18) for PDGFR* where the most common activation loop mutation is D842V. The current treatment paradigm for advanced GIST involves successive use of tyrosine kinase inhibitors (TKIs) that target KIT or PDGFR*.

Avapritinib (formerly BLU-285), a highly potent and selective oral kinase inhibitor, was designed to treat imatinib-resistant GIST by targeting KIT/PDGFR* activation loop mutants. Avapritinib has potent activity on the KIT and PDGFR* activation loop mutants (exon 17/18), including the D842V mutation, with biochemical half-maximal inhibitory concentration (IC50) against all activation loop mutants of less than 2 nM. In addition, avapritinib has demonstrated considerable potency across a wide array of disease-relevant KIT mutants found in patients with GIST including those that appear as secondary mutants after imatinib treatment and those found as primary mutants in imatinib-naïve GIST.

No currently approved TKI selectively and potently inhibits activation loop mutations of KIT and PDGFR*. Thus, GISTs linked to either of these mutations represent an important medical need especially in patients who did not respond to imatinib and 1 other TKI and who have not been treated with regorafenib.

Study objective

Primary Objective:
* The primary objective is to demonstrate the efficacy of avapritinib based on progression-free survival (PFS) determined by central radiological assessment per modified Response Evaluation Criteria in Solid Tumors (mRECIST), version 1.1 in patients with advanced GIST following 2 or 3 prior TKI therapies, including imatinib, compared to patients treated with regorafenib.

The key secondary objectives are:
* To evaluate objective response rate (ORR) determined by central radiology assessment per mRECIST, version 1.1 in patients with advanced GIST treated with avapritinib compared to patients treated with regorafenib.
* To evaluate overall survival (OS) in patients with advanced GIST treated with avapritinib compared to patients treated with regorafenib.

Study design

This is an open-label, randomized, Phase 3 study in patients with locally advanced unresectable or metastatic GIST (advanced GIST) of avapritinib versus regorafenib in patients previously treated with imatinib and 1 or 2 other TKIs.

All study visits are intended to be conducted on an outpatient basis. After provision of written informed consent, patients will be evaluated for study eligibility during the screening period within 4 weeks (28 days) before study drug administration on Cycle 1 Day 1 (C1D1). During the screening period, eligibility will be confirmed; management of baseline concomitant conditions will be recorded and stabilized; and baseline symptoms will be assessed. Hematology, blood chemistry, mutation status, brain imaging (computed tomography [CT] scan or magnetic resonance imaging [MRI]), and baseline tumor assessments (CT scan or MRI) will be performed within 28 days of C1D1.

Patients will be randomly assigned, in a 1:1 ratio, to 1 of 2 treatment arms: Arm A (avapritinib) or Arm B (regorafenib) stratified by treatment regimen (third vs. fourth), geographic region (Asia vs. rest of the world), and mutation status measured in ctDNA or a tumor sample (PDGFR* D842V mutation present vs. absent). Patients randomized to Arm A will receive avapritinib 300 mg orally (PO) once daily (QD). Patients who experience disease progression on avapritinib, based on central review, will be offered the opportunity to continue taking treatment with avapritinib if there is no clinical evidence of disease progression (including worsening of laboratory values); the patient is not experiencing rapid progression of disease or a progressive tumor requiring urgent alternative medical intervention at critical anatomical sites (eg, spinal cord compression); and there has been no decline in Eastern Cooperative Oncology Group Performance Status (ECOG PS). Patients randomized to ArmA must consent to continue avapritinib treatment after disease progression.

Patients randomized to Arm B will receive regorafenib 160 mg PO QD for 3 weeks out of every 4 weeks (28 days) cycle (ie, 3 weeks on/1 week off). Patients who experience disease progression on regorafenib (Arm B), as confirmed by central radiology review, may be offered the opportunity to cross over to the avapritinib treatment arm (Arm A) after an evaluation of their disease progression and a washout period of 7 to 28 days after their last dose of regorafenib.

At least 60% of the patients enrolled should be receiving the study drug as their third treatment regimen for GIST, ie, no more than 40% of patients should be receiving the study drug as their fourth treatment regimen for GIST. In addition, patients will receive best supportive care, excluding any additional anticancer therapy such as any systemic antineoplastic therapy (including kinase inhibitors and chemotherapy), radiation therapy, or surgery.

All patients will present to the study center on C1D1 for the first dose of study drug, vital sign measurements, safety monitoring, quality-of-life (QoL) assessment, PRO assessments, electrocardiogram (ECG) assessment, and AE recording. On Cycle 2 Day 1 (C2D1) and Cycle 3 Day 1 (C3D1), patients will present to study centers for physical examination, laboratory assessments, QoL assessments, PRO assessments, and AE/concomitant medication recording. For all subsequent cycles, all patients will attend study center visits every other

cycle on Day 1 of odd cycles (ie, C5D1, C7D1 etc.) for safety monitoring including ECG, hematology, blood chemistry, QoL assessments, PRO assessments, and AE recording. At any point in time between treatment cycles patients should attend or contact the study center for AE reporting, evaluation, and medical intervention.

Tumor assessments will be performed at Baseline and then every 8 weeks (± 1 week), regardless of the scheduled treatment cycles, ie, if study treatment is interrupted or discontinued for any reason, tumor imaging should continue according to an 8-week schedule until tumor progression is confirmed by central radiology review. Computed tomography with intravenous contrast is the preferred imaging modality, unless a site of disease is better evaluated by MRI.

All patients will attend an End-of-Treatment (EOT) visit within 14 (±7) days after the last dose of study drug. A safety Follow-up visit for resolution of any ongoing AE will be made on Day 30 (±7 days) after the last dose of study drug, or at the time the patient initiates another antineoplastic therapy. Patients who discontinue study treatment before disease progression will undergo tumor assessments every 8 weeks until disease progression, death, or patient withdrawal of consent. After documentation of disease progression by central radiology review, patients are to be followed for subsequent antineoplastic therapy and survival approximately every 2 months until death, withdrawal of consent or closure of the study by the Sponsor.

Intervention

Patients will be randomly assigned, in a 1:1 ratio, to 1 of 2 treatment arms: Arm A (avapritinib) or Arm B (regorafenib) stratified by treatment regimen (third vs. fourth), geographic region (Asia vs. rest of the world), and mutation status measured in ctDNA or a tumor sample (PDGFR* D842V mutation present vs. absent).

Group A: avapritinib 300 mg orally (PO) once daily (QD), dose escalation to 400 mg PO QD is permitted
Group B: regorafenib 160 mg PO QD for 3 weeks out of every 4 weeks (28 days) cycle (ie, 3 weeks on/1 week off).

It is anticipated that patients will receive at least 1 cycle of avapritinib if randomized to Arm A and regorafenib if randomized to Arm B; no maximum treatment duration has been set. After C1, patients may continue to receive study drug until precluded by toxicity, noncompliance, pregnancy, withdrawal of consent, physician decision, progressive disease (PD), death, or closure of the study by the sponsor.

Study burden and risks

No currently approved TKI effectively inhibits exon 17 mutant KIT or D842V mutant PDGFRa. Thus, GIST dependent on either of these mutations represents an unmet medical need. Similarly, the D816V mutation in KIT, which is in exon 17, is an important driver in SM. Preclinical data suggest that avapriti nib (formerly BLU-285), a selective and potent inhibitor of exon 17 mutant KIT and D842 mutant PDGFRa, may be active in these clinical settings.
Preliminary review of efficacy data in the GIST study appears positive for both PDGFRa D842- driven GIST and treatment-resistant KIT-driven GIST.
Following review of the cumulative safety information obtained thus far in ongoing clinical trials, the benefit/risk ratio of avapritinib remains favorable for continuation of the development program.

Contacts

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Blueprint Medicines Corporation

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US
Scientific
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Sidney Street 45
Cambridge MA 02139
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Patients who are * 18 years of age.
2. Patients who have GIST, which is histologically confirmed metastatic and/or unresectable (confirmed to be unresectable by a qualified surgeon).
3. Patients who received imatinib and 1 or 2 other TKIs for the treatment of GIST, including TKIs used for adjuvant therapy. Each different TKI is counted once regardless of how often it was used, and if two different TKIs are used in combination, both TKIs are counted. Patients must have disease progression prior to enrollment. Prior use of other systemic and local therapies is not restricted.
4. Patients who have an ECOG PS of 0 to 1.
5. Patients, or legal guardian if permitted by local regulatory authorities, who provides informed consent to participate in the study.

Exclusion criteria

1. Patients who have received prior treatment with avapritinib or regorafenib.
2. Patients who have received more than 3 different TKIs for the treatment of GIST, including TKIs used for adjuvant therapy. Each different TKI is counted once regardless of how often it was used, and if two different TKIs are used in combination, both TKIs are counted.
3. Patients who are known to be both KIT and PDGRF* wild type.
4. Patients who received any systemic anticancer therapy within 1 week before the first dose of study drug. Prior radiotherapy (including stereotactic radiotherapy) to major organs within 2 weeks of the first dose of study drug, or focal radiotherapy, (including stereotactic radiotherapy), such as to bones, limbs, or other areas not involving major organs, within 3 days.
5. Patients who have clinically significant, uncontrolled, cardiovascular disease, including congestive heart failure Grades II, III or IV according to the New York Heart Association classification, myocardial infarction or unstable angina within the previous 6 months, or uncontrolled hypertension.
6. Patients who have experienced arterial thrombotic or embolic events such as cerebrovascular accident within 6 months before the first dose of study drug, or venous thrombotic events such as pulmonary embolism within the 14 days before the first dose of study drug or deep vein thrombosis within 14 days before the first dose of study drug. Patients with venous thrombotic events such as pulmonary embolism or deep vein thrombosis * 14 days before the first dose of study drug are not excluded provided they are on stabel dosis of anticoagulation, or have completed the planned coagulation regimen.
7. Patients who have experienced any hemorrhage or bleeding event NCI CTCAE version 5.0 Grade 3 or higher within 4 weeks before the first dose of study drug.

8. Patients who have a known risk of intracranial bleeding, such as a brain aneurysm that has not been removed or repaired, or history of intracranial bleeding within one year prior to randomization.
9. Patients who have a symptomatic non-healing wound, ulcer, gastrointestinal perforation, or bone fracture.
10. Patients who have poor organ function as defined by one or more laboratory parameters, as described in the protocol.
11. Patients who have received neutrophil growth factor support within 14 days of the first dose of study drug.
12. Patients who require therapy with a concomitant medication that is a strong inhibitor or strong or moderate inducer of CYP3A4.
13. Patients who have had a major surgical procedure within 14 days of the first dose of study drug. Patient has significant traumatic injury within 28 days before the first dose of study drug.
14. Patients who have a history of another primary malignancy that has been diagnosed or required therapy within 3 years before the first dose of study drug. 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. 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.
15. Patients who have a history of a seizure disorder requiring antiseizure medication.
16. Patients who have metastases to the brain.
17. Patients who are unwilling or unable to comply with scheduled visits, drug administration plan, laboratory tests, or other study procedures and study restrictions.
18. Patients who have a QT interval corrected using Fridericia's formula (QTcF) of > 450 msec
19. Women who are unwilling, if not postmenopausal or surgically sterile, to abstain from sexual intercourse or employ highly effective contraception from the time of the first dose of study drug and for at least 60 days 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 from the time of the first dose of study drug and for at least 90 days after the last dose of study drug.
20. Women who are pregnant, as documented by a serum beta human chorionic gonadotropin (*hCG) pregnancy test consistent with pregnancy, obtained within 7 days before the first dose of study drug.
21. Women who are breastfeeding.
22. Patients who have prior or ongoing clinically significant illness, medical condition, surgical history, physical finding, or laboratory abnormality that, in the Investigator's opinion, could put the patient at an unacceptable high risk for toxicities, or alter the absorption, distribution, metabolism, or excretion of the study drug; or impair the assessment of study results.

23. Patients with a known hypersensitivity to avapritinib, regorafenib, or the excipients in either study drug.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	17-04-2019
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Avapritinib
Generic name:	Avapritinib
Product type:	Medicine
Brand name:	Stivarga
Generic name:	Regorafenib
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	16-04-2018
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	24-01-2019
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	28-02-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	11-03-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	30-12-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	13-01-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	03-02-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	10-02-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	16-09-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO	

Date:	01-10-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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
EudraCT	EUCTR2017-003497-14-NL
ClinicalTrials.gov	NCT03465722
CCMO	NL65030.091.18

Study results

Date completed:	23-11-2020
Results posted:	15-04-2022

First publication
14-12-2020