A randomized, double-blind, placebo-controlled phase III study of regorafenib plus best supportive care versus placebo plus best supportive care for subjects with metastatic and/or unresectable gastrointestinal stromal tumors (GIST) whose disease has progressed despite prior treatment with at least imatinib and sunitinib

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The primary objective of this phase III study in subjects with metastatic and/or unresectable GIST who have progressed after therapy with at least imatinib and sunitinib is to compare the treatment groups in terms of Progression-Free Survival (PFS...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Soft tissue neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON36454

Source
ToetsingOnline

Brief title
BAY73-4506 Phase III GIST 3rd/4th line

Condition

- Soft tissue neoplasms malignant and unspecified

Synonym
gastrointestinal stromal tumors, GIST

Research involving
Human

Sponsors and support

Primary sponsor: Bayer
Source(s) of monetary or material Support: De sponsor (Bayer) financiert de studie

Intervention

Keyword: disease progression, dose escalation, gastrointestinal stromal tumors

Outcome measures

Primary outcome

Primary efficacy variable is:

• Progression-Free Survival (PFS), per blinded central radiology review

Secondary outcome

Secondary efficacy variables are:

• Overall Survival (OS)

• Time to Progression (TTP)

• Disease Control Rate (DCR)

• Tumor Response Rate (RR)

• Duration of Response (DOR)

Exploratory efficacy variables are:

• Health-Related Quality of Life (HRQoL)

• Pharmacokinetics of regorafenib

• Biomarker evaluation of regorafenib

Study description

Background summary

See paragraph 1 of the protocol: 'Introduction'.

Study objective

The primary objective of this phase III study in subjects with metastatic and/or unresectable GIST who have progressed after therapy with at least imatinib and sunitinib is to compare the treatment groups in terms of Progression-Free Survival (PFS), per blinded central radiology review, according to RECIST criteria (version 1.1).

The secondary objectives are to compare the regorafenib and placebo treatment groups in terms of overall survival (OS), time to progression (TTP), disease control rate (DCR), tumor response rate (RR), duration of response (DOR), and safety of regorafenib.

Additional exploratory objectives are to compare the treatment groups in terms of health related quality of life (HRQoL), to describe the pharmacokinetics of regorafenib, to explore the exposure-response relationships of regorafenib, and to conduct a biomarker evaluation of regorafenib.

Study design

This is a randomized, double-blind, placebo-controlled, multi-center, cross-over phase III study to evaluate the efficacy and safety of regorafenib in subjects with histologically proven metastatic and/or unresectable gastrointestinal stromal tumor not amenable to surgery, radiation, or a combination of different approaches with curative intent. Subjects must have shown objective disease progression or intolerance to imatinib, as well as disease progression while on sunitinib treatment.

For a complete description, please refer to paragraph 4.1 of the protocol.

Intervention

Not applicable.

Study burden and risks

An overview of the risks is also described in appendix 3 of the informed consent.

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

1. Signed informed consent obtained before any study specific procedures. Subjects must be able to understand and willing to sign a written informed consent.
2. Male or female subjects >=18 years of age.
3. Subjects with histologically confirmed metastatic and/or unresectable GIST.
4. At least imatinib and sunitinib as prior treatment regimens, with objective disease progression or intolerance to imatinib, as well as disease

progression while on sunitinib therapy. Additionally, disease progression or intolerance to other systemic therapies, as well as investigational new agents, is allowed, except prior treatment with any other vascular endothelial growth factor receptor (VEGFR) inhibitor.
5. Subjects must have at least one measurable lesion according to RECIST, version 1.1. A lesion in a previously irradiated area is eligible to be considered as measurable disease as long as there is objective evidence of progression of the lesion prior to study enrollment.
6. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1.
7. Adequate bone marrow, liver, and renal function as assessed by the following laboratory requirements conducted within 7 days of starting study treatment:
- Total bilirubin <= 1.5 x the upper limit of normal (ULN). Documented Gilbert syndrome is allowed if total bilirubin is mildly elevated (< 6 mg/dL).
- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) <=3.0 x ULN (<= 5 x ULN for subjects with liver involvement of their GIST).
- Lipase <= 1.5 x the ULN
- Serum creatinine <= 1.5 x the ULN.
- Glomerular filtration rate (GFR) >= 30 ml/min/1.73 m2 according to the Modified Diet in Renal Disease (MDRD) abbreviated formula.
- International normalized ratio (INR) <= 1.5 x ULN and partial thromboplastin time (PTT) or activated partial thromboplastin time (aPTT) <= 1.5 x ULN.
Subjects who are being treated with an anti-coagulant, such as warfarin or heparin, will be allowed to participate provided that no prior evidence of an underlying abnormality in these parameters exists. Close monitoring of at least weekly evaluations will be performed until INR and PTT are stable based on a pre-dose measurement as defined by the local standard of care.
- Platelet count >= 100000/mm3, hemoglobin (Hb) >= 9.0 g/dl, absolute neutrophil count (ANC) >= 1500/mm3. Transfusion of subjects to meet the inclusion criteria will not be allowed.
- Alkaline phosphatase limit <= 2.5 x ULN (<= 5 x ULN for subjects whose cancer involves their liver).
8. Recovery to NCI-CTCAE v4.0 Grade 0 or 1 level or recovery to baseline preceding the prior treatment from any previous drug/procedure-related toxicity (except alopecia, anemia, and hypothyroidism).

Exclusion criteria

1. Prior treatment with regorafenib. Subjects permanently withdrawn from study participation will not be allowed to re-enter the study.

2. Prior treatment with any vascular endothelial growth factor receptor (VEGFR) inhibitor except sunitinib.
3. Use of any approved tyrosine kinase inhibitors or investigational agents within 1 week or 6 half-lives of the agent, whichever is shorter, prior to receiving study drug.
4. Cancer other than GIST within 5 years prior to randomization EXCEPT for curatively treated cervical cancer in situ, non-melanoma skin cancer, and superficial bladder tumors (Ta [Non-invasive tumor], and Tis [Carcinoma in situ]).
5. Major surgical procedure, open biopsy, or significant traumatic injury within 28 days before start of study medication.
6. Pregnant or breast-feeding subjects. Women of childbearing potential not employing adequate contraception. Women of childbearing potential must have a pregnancy test performed a maximum of 7 days before start of study medication and a negative result must be documented before start of study medication.
Women of childbearing potential and men must agree to use adequate contraception (barrier method of birth control) since signing of the informed consent form until at least 3 months after the last study drug administration. The definition of adequate contraception will be based on the judgment of the treating investigator or a designated associate.
7. Congestive heart failure New York Heart Association (NYHA) >= class 2.
8. Unstable angina (angina symptoms at rest, new-onset angina, ie, within the last 3 months) or myocardial infarction (MI) within the past 6 months before start of study medication.
9. Cardiac arrhythmias requiring anti-arrhythmic therapy (beta blockers or digoxin are permitted).
10. Uncontrolled hypertension (systolic blood pressure > 140 mmHg or diastolic pressure > 90 mmHg despite optimal medical management).
11. Subjects with pheochromocytoma.
12. Arterial thrombotic or embolic events such as cerebrovascular accident (including transient ischemic attacks), or pulmonary embolism within the 6 months before start of study drug.
13. Venous thrombotic events such as deep vein thrombosis within the 3 months before start of study drug
14. Ongoing infection > grade 2 National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0.
15. Known history of human immunodeficiency virus (HIV) infection.
16. Subjects with seizure disorder requiring medication.
17. Symptomatic metastatic brain or meningeal tumors
18. History of organ allograft.
19. Subjects with evidence or history of bleeding diathesis. Any hemorrhage or bleeding event * NCI-CTCAE version 4.0 grade 3 or higher within 4 weeks prior to the start of study drug.
20. Non-healing wound, ulcer, or bone fracture.
21. Renal failure requiring hemo- or peritoneal dialysis.
22. Dehydration NCI-CTCAE version 4.0 grade >= 1.

23. Substance abuse or medical, psychological, or social conditions that may interfere with the subject*s participation in the study or evaluation of the study results.
24. Known hypersensitivity to the study drug, study drug class, or excipients in the formulation.
25. Any illness or medical conditions that are unstable or could jeopardize the safety of the subject and his/her compliance in the study.
26. Interstitial lung disease with ongoing signs and symptoms at the time of screening.
27. Subjects unable to swallow oral medications.
28. Persistent proteinuria of NCI-CTCAE version 4.0 grade 3 or higher (> 3.5 g/24 hrs, measured by urine protein:creatinine ratio on a random urine sample).
29. Any malabsorption condition.
30. Close affiliation with the investigational site, eg, a close relative of the investigator or dependent person (eg, employee of or student at the investigational site who would have access to study records and case report form [CRF] data).
31. Unresolved toxicity higher than NCI-CTCAE version 4.0 grade 1 (excluding alopecia, anemia, and hypothyroidism) attributed to any prior therapy/procedure.
32. Concomitant participation in another clinical study.
33. Left ventricular ejection fraction (LVEF) < 50% or below the LLN for the institution (whichever is higher).
34. Pleural effusion or ascites that causes respiratory compromise (>= NCICTCAE version 4.0 Grade 2 dyspnea).

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	22-03-2011
Enrollment:	9
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	Regorafenib
Generic name:	NA

Ethics review

Approved WMO Date:	29-11-2010
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	22-02-2011
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	26-04-2011
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	12-09-2011
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	20-10-2011
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

Approved WMO Date:	21-10-2011
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	19-12-2011
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	15-05-2012
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	20-08-2012
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	08-02-2013
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	16-05-2013
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	18-06-2013
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	20-08-2013
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	20-01-2015
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO	

Date:	03-02-2015
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

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	EUCTR2009-017957-37-NL
CCMO	NL34032.058.10

Study results

Date completed:	13-04-2015
Actual enrolment:	10