A dose-finding phase Ib multicenter study of imatinib in combination with the oral phosphatidyl-inositol 3-kinase (PI3K) inhibitor BYL719 in patients with gastrointestinal stromal tumor (GIST) who failed prior therapy with imatinib and sunitinib

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Primary:- To determine the MTD and/or a recommended phase II dose (RP2D) of BYL719 when administered orally in combination with imatinib 400 mg q.d.Secondary:- Assess the safety and tolerability profile of imatinib and BYL719 administered in...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Malignant and unspecified neoplasms gastrointestinal NEC
Study type	Interventional

Summary

ID

NL-OMON40177

Source
ToetsingOnline

Brief title
Imatinib combined with BYL719 in patients with GIST

Condition

- Malignant and unspecified neoplasms gastrointestinal NEC

Synonym
Gastrointestinal Stromal Tumor; GIST

Research involving
Human

Sponsors and support

Primary sponsor: Novartis Pharma B.V.
Source(s) of monetary or material Support: Farmaceutische industrie

Intervention

Keyword: BYL719, GIST tumor, imatinib, PI3-K

Outcome measures

Primary outcome

Maximum Tolerated Dose and/or the Recommended Phase 2 Dose

Secondary outcome

Adverse effects, PK, disease progression

Study description

Background summary

More than 50% of patients with advanced GIST tumors has disease progression after first line 1st treatment with imatinib. Sunitinib is available as 2nd line treatment. However sunitinib has limitations due to adverse effects, such as hypothyroidism and heart failure. In case imatinib and sunitinib have failed, there is no accepted standard treatment available. Therefore BYL719 may fulfill this medical need.
BYL719 is a small orally bioavailable class I *-selective PI3K inhibitor belonging to the 2-aminothiazole class.
See also page 23 of the protocol: Study rationale and purpose.

Study objective

Primary:
- To determine the MTD and/or a recommended phase II dose (RP2D) of BYL719 when administered orally in combination with imatinib 400 mg q.d.
Secondary:
- Assess the safety and tolerability profile of imatinib and BYL719 administered in combination.

- Evaluate the effect of BYL719 on steady-state PK of imatinib and the effect of imiatinib on steady-state PK of BYL719
- Characterize the steady state and population PK profiles of imatinib and BYL719 when administered in combination.
- Perform a preliminary assessment of the clinical activity of imatinib and BYL719 combination treatment in patients with advanced GIST.

Study design

This open-label, phase Ib, dose-finding study in which safety and tolerability of escalating doses of BYL719 in combination with imatinib administered at a dose of 400mg q.d. in patients with metastatic and/or unresectable GIST, who have failed prior therapy with imatinib and sunitinib, will be investigated.
The study will comprise 2 parts: a dose escalation part to establish the MTD and/or RP2D and
a dose expansion part at the MTD or RP2D . The expected overall number of recruited patients is in the range of 45 to 55, of which 8 in NL.

Intervention

Treatment with imatinib plus BYL719

Study burden and risks

Risk: adverse effects of (combination of) imatinib and BYL719. Tumor biopsy
Burden: Screening visit. Mono-therapy visit. Cycle 1: 4 visits. Cycle 2 and above: 2 visits/cycle
Every visit: fasting for blood tests.
Physical examination
CT/MRI scan thorax/abdomen/pelvis (however same frequency as during regular care).
ECG, MUGA scan or echocardiography
Blood draws every visit (3-4 mL per occasion)
Long hospital stays for PK measurements (0-8 en 24h post dose)
Pregnancy tests (if relevant)
Tumor biopsy: dose escalation patients at screening only if no archival tumor is available. Dose expansion patients at screening and at end of study (irrespective of availability of archival tumor tissue)

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. Male or female patients * 18 years of age
2. WHO performance status of 0-2
3. Histologically confirmed diagnosis of GIST that is unresectable or metastatic
4. Available tissue specimen:
* Dose-escalation part: patients archival tumor tissue. Fresh if archival is unavailable.
* Dose-expansion part: patients archival tumor tissue plus fresh pre-treatment biopsy
5. Failed prior therapy with imatinib followed by sunitinib for the treatment of unresectable or metastatic GIST. Note the following specific criteria for the two parts of the trial:
- Dose escalation part: patients who failed prior therapy with imatinib and then have failed therapy with sunitinib. Treatment failure may be due to either disease progression on therapy (both imatinib aand sunitinib) or intolerance to therapy (sunitinib). Dose escalation part patients may have had additional lines of therapy than imatinib and sunitinib.
- Dose expansion part: patients must have documented disease progression on both imatinib and sunitinib. In addition, patients may have had up to 3 lines of prior therapy. Patients must have been treated with imatinib and must have been treated with sunitinib and then may have received one other line of therapy.
6. Radiological (CT/MRI) confirmation of disease progression (RECIST criteria) during prior therapy with imatinib and sunitinib will be required for patients entering the Dose Expansion

part
7. At least one measurable lesion, as defined by RECIST version 1.1, will be required for patients entering the Dose-expansion part.

Exclusion criteria

1. Previous treatment with PI3K inhibitors
2. Patient has active uncontrolled or symptomatic central nervous system (CNS) metastases
3. Patient with diabetes mellitus requiring insulin treatment and/or with clinical signs
4. Patient who has not recovered to grade 1 adverse events of imatinib and/or sunitinib
5. Patient has active cardiac disease or dysfunction, see protocol page 36
6. History of significant bleeding disorder unrelated to cancer
7. Patients who have not recovered from prior surgery
8. Patients who have received wide field radiotherapy within 4 weeks or limited field radiation for palliation within 2 weeks
9. Patient is currently receiving chronic treatment with steroids, immunosuppressive agent, strong/moderate CYP3A4 inhibitors/inducers, warfarin, phenytoin, QT-prolongators or Torsade de Pointes inducers (see protocol for details and washout).
10. Pregnancy, lactation
11. Females of child-bearing potential and males not using safe contraception.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	29-04-2013
Enrollment:	8
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Glivec
Generic name:	imatinib
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	05-02-2013
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	09-04-2013
Application type:	First submission
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:	05-06-2013
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	08-11-2013
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	11-11-2013
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	14-04-2014
Application type:	Amendment

Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	22-04-2014
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	20-06-2014
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	26-06-2014
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	30-10-2014
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	18-12-2014
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	02-04-2015
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	03-04-2015
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	16-04-2015
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	19-11-2015
Application type:	Amendment

Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	09-12-2015
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	20-12-2016
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	EUCTR2012-003273-25-NL
ClinicalTrials.gov	NCT01735968
CCMO	NL43135.058.13