A prospective, multicenter, randomized, open-label, active-controlled, phase III study to compare efficacy and safety of masitinib to imatinib at 400 or 600 mg in treatment of patients with gastro-intestinal stromal tumour in first line medical treatment

Published: 20-01-2011
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Safety and efficacy objectives:The objective is to compare the safety and efficacy of masitinib at 6 of 7.5 mg/kg/day to imatinib at 400 or 600 mg, in patients with gastro-intestinal stromal tumour in first line medical treatment.

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

Summary

ID

NL-OMON44826

Source
ToetsingOnline

Brief title
AB04030

Condition

- Malignant and unspecified neoplasms gastrointestinal NEC

Synonym
Gastro-Intestinal Stroma Tumor, GIST

Research involving
Human

Sponsors and support

Primary sponsor: AB Science
Source(s) of monetary or material Support: Industry;AB Science is the sponsor of this clinical trial.

Intervention

Keyword: GIST, Tyrosin-kinase-Inhibitor

Outcome measures

Primary outcome

Primary endpoint:

• Progression Free Survival (PFS)

Secondary outcome

Secondary endpoints:

• Tumour assessment:

-Overall Survival (OS)

-Time to progression (TTP)

-Objective response rate (CR + PR) at Week 12, Week 24 then every 24 weeks

Control disease rate (CR + PR + SO) at Week 12, Week 24 then every 24 weeks

Best response during study • Association between PFS, as, TTP, objective

response, control disease and the phenotype of mutations on KIT/POGF • Quality

of life assessment: Quality of Life according to the EORTC QLQ-C30

questionnaire at baseline and every 12 weeks until final visit ECOG Performance

Status at baseline and every 12 weeks until final visit • Safety profile using

the NCI CTC v4.0 classification

Study description

Background summary

1.4 Rationale for the development of masitinib in GIST
1.4.1 Comparative in vitro study of masitinib, imatinib and sunitinib activity on c-kit activating mutations identified in GIST

GIST is the most common subtype of gastrointestinal (GI) tract sarcomas, which also include leimyosarcomas, liposarcomas and other more rare histoloqical subtypes. GISTs have been reported to represent about 3% of all malignant GI tumours. These tumours are mostly due to c-Kit-activating mutations and rarely to PDGFRa-activating mutations (3%). Activating c-Kit mutations occur in 70 to 80% of cases. The majority (70%) of these mutations are in-frame-deletions and mis-sense mutations clustering in the 5'-end of the c-Kit juxtamembrane domain (JMD exon 11) which causes ligand independent activation of the receptor. One of the most representative JMD exon 11 mutations is the V5590 substitution. Mutations in the extracellular domain of c-Kit (exon 9) are present in about 10 % of GIST, in which the Ala502-Tyr503 duplication is the most frequent mutation. Functional consequences for exon 9-mutated receptors are the same than exon 11mutated
receptors. Their signaling consequences, clinical correlation and response to tyrosine kinase inhibitors are under intense investigation. Indeed, exon 11 mutants are highly sensitive to imatinib (Novartis), whereas GIST with exon 9 mutations failed to respond to this tyrosine kinase inhibitor (TKI). Because partial or lack of response or imatinib intolerance have been observed in GIST patients, it becomes important to develop new TKIs. Masitinib (AB Science) and sunitinib (Pfizer) are two of them.

Masitinib has been shown more efficient than imatinib in all the cell models tested.
1.4.2 AB1010 is able to overcome imatinib resistance in cell assay
Cell lines sensitive to tyrosine kinase inhibitors can be rendered resistant in vitro by exposing the cells to low concentrations of inhibitor, followed by exposure to progressively increased concentrations. Resistance to imatinib mesylate has been induced in cell lines that were initially sensitive to 1 µM. Resistance to AB1010 has been induced in cell lines that were initially sensitive to 0.2 µM. These observations suggest that it is critical to use high initial concentrations (above IC50) of kinase inhibitor to avoid the induction of resistance.
1.5 Overall conclusions
The toxicity profile of masitinib is acceptable and similar to imatinib.
Efficacy of masitinib shows a superiority trend over imatinib on PFS and overall survival. These results are encouraging and support the initiation of a comparative phase III study -to compare the efficacy and safety of AB1010 over

imatinib and in particular, test the non-inferiority/superiority efficacy (superior PFS at month 24) and similar safety of masitinib over imatinib.

Study objective

Safety and efficacy objectives:
The objective is to compare the safety and efficacy of masitinib at 6 of 7.5 mg/kg/day to imatinib at 400 or 600 mg, in patients with gastro-intestinal stromal tumour in first line medical treatment.

Study design

This is a prospective, multicenter, randomized, open-label, active-controlled, non-inferiority, phase III study to compare efficacy and safety of masitinib to imatinib at 400 or 600 mg in treatment of patients with gastro-intestinal stromal tumour in first line medical treatment.

Intervention

NA

Study burden and risks

not applicable.

Contacts

Public
AB Science

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FR
Scientific
AB Science

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FR

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Histologically proven, metastatic or locally advanced non resectable, or recurrent post surgery GIST
2. Naïve patient or patient previously treated with imatinib as neoadjuvant/adjuvant who relapsed after
imatinib discontinuation
3. Measurable tumour lesions with longest diameter >= 20 mm using conventional techniques or >= 10 mm with
spiral CT scan according RECIST criteria
4. C-Kit (CD117) positive tumours detected by immuno-histochemically or PDGFR positive if c-kit negative
5. ECOG < 1
6. Patient with adequate organ function:

Exclusion criteria

1. Patient previously treated by tyrosine kinase inhibitors except imatinib in case of inclusion criteria 2
2. Patient treated for a cancer other than GIST within 5 years before enrolment, with the exception of basal cell carcinoma or cervical cancer in situ
3. Patient with active central nervous system (CNS) metastasis or with history of CNS metastasis
4. Patient presenting with cardiac disorders defined by at least one of the following conditions:· Patient with recent cardiac history (within 6 months) of:
- Acute coronary syndrome
- Acute heart failure (class III or IV of the NYHA classification)
- Significant ventricular arrhythmia (persistent ventricular tachycardia, ventricular fibrillation, resuscitated sudden death)· Patient with cardiac failure class III or IV of the NYHA classification· Patient with severe conduction disorders which are not prevented by permanent pacing (atrio-ventricular block 2 and 3, sino-atrial block)· Syncope without known aetiology within 3 months· Uncontrolled severe hypertension, according to the judgment of the investigator, or symptomatic hypertension

5. Patient with history of poor compliance or history of drug/alcohol abuse, or excessive alcohol beverage consumption that would interfere with the ability to comply with the study protocol, or current or past psychiatric disease that might interfere with the ability to comply with the study protocol or give informed consent
6. Patient with any condition that the physician judges could be detrimental to subjects participating in this study, including any clinically important deviations from normal clinical laboratory values or concurrent medical events
Previous treatment
7. Treatment with any investigational agent within 4 weeks prior baseline
8. Treatment by imatinib as neoadjuvant/adjuvant therapy within 4 weeks prior baseline

Study design

Design

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	23-02-2012
Enrollment:	20
Type:	Actual

Medical products/devices used

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

Generic name:	Imatinib

Ethics review

Approved WMO Date:	20-01-2011
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-11-2011
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-12-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-12-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-02-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-02-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-12-2014
Application type:	Amendment

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-11-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-07-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-03-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-03-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-09-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-06-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-06-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	

Date:	30-10-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-11-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2008-000973-40-NL
ClinicalTrials.gov	NCT00812240
CCMO	NL34450.078.10

Study results

Date completed: 28-05-2019

Summary results
Trial ended prematurely