A 96-week, prospective, multicenter, randomised, double-blind, placebo-controlled, 2-parallel groups, Phase 3 study to compare efficacy and safety of masitinib 4.5 mg/kg/day versus placebo in the treatment of patients with primary progressive or relapse-free secondary progressive multiple sclerosis

Published: 24-03-2015
Last updated: 13-04-2024

The objective of the study is to compare the safety and efficacy of masitinib at 4.5 mg/kg/day or masitinib at 4.5 mg/kg/day with a dose escalation to 6 mg/kg/day after three month of treatment versus placebo in the treatment of patients with…

Ethical review	Not approved
Status	Will not start
Health condition type	Central nervous system infections and inflammations
Study type	Interventional

Summary

ID

NL-OMON41963

Source
ToetsingOnline

Brief title
AB07002

Condition

- Central nervous system infections and inflammations

Synonym
MS, Multiple Sclerosis

Research involving
Human

Sponsors and support

Primary sponsor: AB Science
Source(s) of monetary or material Support: AB Science

Intervention

Keyword: MS

Outcome measures

Primary outcome

Multiple Sclerosis Functional Composite (MSFC) at week 96

Secondary outcome

* MSFC at weeks 12, 24, 36, 48, 60, 72 and 84

* Timed 25-foot walk at weeks 12, 24, 36, 48, 60, 72, 84 and 96

* Nine-hole peg test, right and left hands sides (finger dexterity) at weeks

12, 24, 36, 48, 60, 72, 84 and 96

* PASAT 3 at weeks 12, 24, 36, 48, 60, 72, 84 and 96

* Walking speed at weeks 4, 8 and 12

* EDSS at weeks 12, 24, 36, 48, 60, 72, 84 and 96

* Modified Fatigue Impact Scale at weeks 12, 24, 36, 48, 60, 72, 84 and 96

* Hamilton Rating Scale for Depression at weeks 12, 24, 36, 48, 60, 72, 84 and

96

* Disability Impact Profile at weeks 12, 24, 36, 48, 60, 72, 84 and 96

* Health state Visual Analogue Scale (EQ-VAS) at weeks 12, 24, 36, 48, 60, 72,

84 and 96

* Quality of Life assessment: MSQOL-54 at weeks 12, 24, 36,48, 60, 72 and 84

* Quality of Life assessment: MSQOL-54 at week 96 for Marketing Authorization

in the European market

* Use of corticosteroids for MS

* Number of hospitalizations for relapse

* Clinical and biological safety profile: occurrence of Adverse Events,

potential changes in vital signs, ECG, chest X-ray and biological parameters.

Study description

Background summary

The presence of mast cells and increased concentration of mast cell constituent have been reported in multiple sclerosis plaques. Mast cells are clustered close to the wall of venules and capillaries.
In the nervous system, as in other tissues, activated mast cells may undergo explosive degranulation or liberate solitary granules into their microenvironement. Following activation, mast cells remains intact and viable and resynthetize their granules.
The test product works on the viability of these mast cells to inhibate the mechanism of action of the mast cells.

Study objective

The objective of the study is to compare the safety and efficacy of masitinib at 4.5 mg/kg/day or masitinib at 4.5 mg/kg/day with a dose escalation to 6 mg/kg/day after three month of treatment versus placebo in the treatment of patients with primary progressive multiple sclerosis or relapse-free secondary progressive multiple sclerosis.
Efficacy analysis will be performed after last patient 96 weeks visit.

Primary endpoint for Marketing Authorization in the European market:
- Multiple Sclerosis Functional Composite (MSFC) from week 12 to week 96

Co-primary endpoints for Marketing Authorization in the US market:
- Multiple Sclerosis Functional Composite (MSFC) at week 96

- Multiple Sclerosis Quality of Life 54 items (MSQOL-54) at 96 weeks in both MSQOL-54 composite scores for physical health and for mental health

Secondary endpoints:
-Clinical assessment at weeks 12, 24, 36, 48, 60, 72, 84 and 96:

* EDSS, Quality of Life assessment: MSQOL-54, Timed 25-foot walk, Nine-hole peg test, right and left hands sides (finger dexterity), PASAT 3, Modified Fatigue Impact Scale , Hamilton Rating Scale for Depression, Disability Impact Profile, Health state Visual Analogue Scale (EQ-VAS) at weeks 12, 24, 36, 48, 60, 72, 84 and 96

- Use of corticosteroids for MS
- Number of hospitalizations for relapse
- Clinical and biological safety profile: occurrence of Adverse Events, potential changes in vital signs, ECG, pelvic ultrasound, chest X-ray and biological parameters.

Study design

A prospective, multicenter, randomised, double-blind, placebo-controlled, 2-parallel groups, Phase 3 study

Intervention

* Group 1a: patients will receive masitinib at 4.5 mg/kg/day
* Group 1b: patients will receive masitinib at 4.5 mg/kg/day with a dose escalation to 6 mg/kg/day after three months of treatment
* Group 2a: patients will receive placebo at 4.5 mg/kg/day
* Group 2b: patients will receive placebo at 4.5 mg/kg/day with a dose escalation to 6 mg/kg/day after three months of treatment
Patients randomised in group 1b or group 2b will switch after three months of study treatment to 6 mg/kg/day. The reason to switch is led by the fact that due to increase of clearance, the masitinib plasma concentration is likely to diminish over time, so to maintain efficacy without safety issue (the same exposition to masitinib should be maintained), a switch is justified.

Study burden and risks

The patient will be regularly and medically follow up during the treatment of ninety-sic (96) weeks. The patient will have to visit the investigational site 13 times, each visit for about 2 hours.
First visit (screening visit): Before the patient can start the study, the study doctor will check if the patient meet all required criteria to participate. The patient will have a clinical examination. Different tests will be performed including routine blood and urine tests and neurologic

examination. HIV and hepatitis B & C screening tests will be performed on your blood and a screening for tuberculosis will be done using an intra-dermal reaction test or Interferon Gamma Release Assay (IGRA) test.
Additionally the patient will be asked to perform neurologic examinations to assess the progress of MS (Expanded Disability Status Scale (EDSS) and Multiple Sclerosis Functional Composite (MSFC)), or specific symptoms (Hamilton Scale for Depression) and the quality of life (Multiple Sclerosis Quality of Life MSQOL-54 Instrument, Disability & Impact Profile) * Week 0 or Baseline visit (from 1 day to 7 days after the screening visit): the study doctor will check some criteria before the patient can start the study treatment. - Following visits: 4, 8, 12, 24, 36, 48, 60, 72, 84 and 96 weeks after the baseline visit. - Final visit, 96 weeks after the baseline visit (or earlier when dropped out before the end of the trial).
At each of these visits, the study doctor will ask the patient about any other medicines that he/she has taken since the last visit, and how he/she feels. The patient will be called weekly by the site staff during the first seven weeks of treatment to check his/her physical status. Moreover, some exams will be performed. These exams can vary from a visit to another. They include: - Physical exam, including your height, weight and thyroid palpation. - Vital signs: blood pressure, heart rate and temperature will be measured. - Electrocardiogram (ECG, this is a registration of the activity of the hart) at baseline visit and at 12, 24, 36, 48 weeks and at final visit. These exams measure the activity of the heart and are painless. - Chest X-ray to check the lungs at baseline and at final visit. - Blood sampling and urinalysis for usual laboratory tests will be performed at each visit. - If the patient is a woman of child -bearing potential, a pregnancy test will be performed at screening, baseline and at final visit. In addition, blood samples will be drawn at weeks 1, 2, 3, 5, 6, 7 and 10 after the start of the treatment to check that the patient tolerates it well. - For male patients, a spermogram will be performed (optional) in order to assess the number of spermocytes, morphogenesis (biological process that turn on the organism to develop the shape) and mobility: at baseline, W4, W8, every 12 weeks and final visit. - Urinary cytology and NMP22 test will be performed at baseline visit, every 3 months and at the final visit. Urinary cytology test and NMP22 test are meant to check whether there are abnormal cells in the urines. - Neurologic examinations to assess the progress of MS (Expanded Disability Status Scale (EDSS) and Multiple Sclerosis Functional Composite (MSFC)), or specific symptoms (Hamilton Scale for Depression) and the quality of life (Multiple Sclerosis Quality of Life MSQOL-54 Instrument, Disability & Impact Profile)
Risks: SIDE EFFECTS OBSERVED IN PATIENTS TREATED WITH MASITINIB DURING STUDIES NOT RELATED TO CANCER Side effects that could appear after taking the treatment (masitinib) are presented below. However, as all treatments under development, it is possible to discover other side effects, rare and unexpected. In this case, the patient will be notified in good time of any new information which might influence their decision to maintain their participation in this study.
To date, it is not completely clear whether the side effects below are due to masitinib or to the treated disease. - Side effects reported by more than 20%

of the patients: nausea, skin toxicities and oedema (mainly eyelid and peripheral edemas). - Side effects reported between 10-20% of the patients: vomiting, skin rash, and itching - Side effects reported between 5-10% of the patients: diarrhea asthenia gastroenteritis and sinusitis.
SPECIFIC RISKS OF TREATMENT WITH MASITINIB DURING THE FIRST 2 MONTHS OF TREATMENT Severe neutropenia and severe skin toxicity.
POTENTIAL RISKS ASSOCIATED WITH MASITINIB TREATMENT Cardiac function, Reproductive organs, Renal function, Risks with pregnancy, long term risks, hepatobiliary risks, risks for the central nervous system and carcinogenetic.
RISKS RELATED TO STUDY PROCEDURES Other risks or discomforts you may experience during this study include pain, risk of bleeding and/or bruising at the blood puncture site. The risk associated with radiation exposure from having a chest X*ray is minimal. If the patient has any doubt or if the patient has side effects during the study, the patient has to contact the study doctor that will provide the patient with additional information.
A sdse reduction can be implemented for safety reasons. The dose reduction is permanent and no subsequent dose escalation will be authorized.

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. Patient suffering from either primary progressive or secondary progressive multiple sclerosis without relapse within 2 years before inclusion according to the revised McDonald*s criteria
2. Patient with EDSS score of [2.0 to 6.0] inclusive at baseline
3. Patient who had an EDSS score progression * 1 point within 2 years before inclusion
4. Patient with normal organ function defined as:
* Absolute neutrophils count (ANC) * 2 x 109/L
* Hemoglobin * 10 g/dL
* Platelets (PTL) * 100 x 109/L
* AST/ALT * 3 ULN
* Bilirubin * 1.5x ULN
* Creatinine clearance > 60 mL/min (Cockcroft and Gault formula)
* Albuminemia > 1 x LLN
* Proteinuria < 30 mg/dL (1+) on dipstick; in case of the proteinuria *1+ on the dipstick 24 hours proteinuria must be < 1.5g/24 hours
5. Male or female patient aged between 18 and 75 years old, with a weight > 50 kg and BMI between 18 and 35 kg/m².
6. Patient able to understand the patient card and to follow the patient card procedures in case of signs or symptoms of severe neutropenia or severe cutaneous toxicity, during the first 2 months of treatment.
7.Man and woman of childbearing potential (entering the study after a menstrual period, and who have a negative pregnancy test) must agree to use two methods (one for the patient and one for the partner) of medically acceptable forms of contraception during the study and for 3 months after the last treatment intake.
8. Patient able and willing to comply with study procedures as per protocol
9. Patient able to understand, sign, and date the written informed consent form at screening visit prior to any protocol-specific procedures

Exclusion criteria

1. Patient suffering from a disease other than MS that would better explain the patient*s neurological clinical signs and symptoms and/or MRI lesions
2. Patient who had a major surgery within 2 weeks of study entry
Major surgery includes all work requiring a general anesthetic. Thus all operations which involve openings into the great cavities of the body; all operations in the course of which hazards of severe hemorrhage are possible; all conditions in which the life of the patient is at

stake; all conditions which require for their relief manipulations or for the proper performance of which special anatomical knowledge and manipulative skill are essential.
3. Patient with life expectancy < 6 months
4. Patient with history of primary malignancy < 5 years except treated basal cell skin cancer or cervical carcinoma
5. 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
6. Patient with any severe and/or uncontrolled medical condition
7. Patient with a known diagnosis of human immunodeficiency virus (HIV) infection
8. Patient with known active hepatitis B, hepatitis C or tuberculosis
9. Pregnant or nursing female

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:	Will not start
Enrollment:	13

Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	masitinib
Generic name:	masitinib mesylate

Ethics review

Approved WMO Date:	24-03-2015
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Not approved Date:	26-02-2016
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	EUCTR2010-021219-17-NL
CCMO	NL51500.060.15