A prospective, multicenter, randomised, double-blind, placebo-controlled, parallel groups, phase 2/3 study to compare the efficacy and safety of masitinib versus placebo in the treatment of patients suffering from Amyotrophic Lateral Sclerosis (ALS)

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The purpose of this study is to compare the efficacy and the safety of an experimental drug, masitinib,in combination with riluzole to placebo in combination with riluzole administered during 48 weeks to patients suffering from ALS.You will be…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Cranial nerve disorders (excl neoplasms)
Study type	Interventional

Summary

ID

NL-OMON44970

Source
ToetsingOnline

Brief title
AB10015

Condition

- Cranial nerve disorders (excl neoplasms)

Synonym
ALS, Amyotrophic Lateral Sclerosis

Research involving
Human

Sponsors and support

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

Intervention

Keyword: ALS, TKI

Outcome measures

Primary outcome

Change from baseline to week 48 in Amyotrophic Lateral Sclerosis functional

rating scale (ALSFRS)-Revised

Secondary outcome

-Combined Assessment of Function and Survival (CAFS)

-Survival defined as the time from randomisation to the date of documented

death or first tracheotomy

-Time to first tracheotomy defined as the time from randomisation to the

time of the first tracheotomy

-Change of Forced V ital Capacity (FVC) from baseline to each t ime point

(week 4, 8, 12, 24, 36, 48)

-Number of failure defined as a 9-point drop in ALSFRS-R or death from

baseline

-Change from baseline to each time point (week 4, 8, 12, 24 and

36) in Amyotrophic Lateral Sclerosis

functional rating scale (ALSFRS)-Revised

- Survival rate defined as the rate of patients alive without tracheotomy

at each time point (week 12, 24,

36 and 48)

- Change in cystatin C level from baseline to each time point

- Absolute and relative change in ALSAQ- 40 at each time point

- Safety: occurrence of Adverse Events (AE), changes on clinical

examination including vital signs and

weight, ECG and laboratory exams (biochemistry, hematology and urinalysis)

Study description

Background summary

Motor neurons are nerve cells located in the brain, brainstem, and spinal cord that serve as controlling units and vital communication links between the nervous system and the voluntary muscles of the body. Messages from motor neurons in the brain (called upper motor neurons) are transmitted to motor neurons in the spinal cord (called lower motor neurons) and from them to particular muscles.

In ALS, both the upper motor neurons and the lower motor neurons degenerate or die, ceasing to send messages to muscles. Although the exact pathophysiological mechanisms underlying neurodegeneration in ALS remain uncertain, a common pathological hallmark is the presence of ubiquitin-immunoreactive cytoplasmic inclusions in degenerating neurons, followed by a strong inflammatory reaction.

Emerging evidence suggests that neuro-inflammation may be a pathological characteristic of ALS and could therefore represent a potential therapeutic target for a pharmacological agent to help treat this severe disease.

Recent studies have shown inflammatory markers in affected neural tissues of ALS patients and suggest that inflammation in ALS spinal cord and cortex is based on innate immune responses by macrophages and mast cells and adaptive immune responses by T cells.

Mast cell seems to play a central role in the inflammatory process in ALS. Several researches highlight key mechanism of action of mast cells. Mast cells infiltrate spinal cord of ALS patients. Elevated TNF alpha levels, which is expressed through mast cells, have been reported in ALS patients and have been

shown to induce motorneuron death

Study objective

The purpose of this study is to compare the efficacy and the safety of an experimental drug, masitinib,
in combination with riluzole to placebo in combination with riluzole administered during 48 weeks to
patients suffering from ALS.
You will be proposed to participate in optional ancillaries studies:
- Pharmacogenomic sub-study- Specific risks associated with masitinib
If during treatment (whatever treatment you are receiving) you
present severe side effects
(decrease of white blood cells or severe skin toxicity) an additional blood sampling of 4 ml will be
performed and sent to Institut Paoli Calmettes in Marseille, France, under responsibility of Professor
Dubreuil. A genetic analysis will be conducted in order to better
understand why the patient is presenting those side effects.

- Pharmacokinetic sub-study
The aim of this test is to measure the concentration of riluzole
in your blood before and after
riluzole intake when masitinib is used as add-on therapy.

Study design

This is a multicenter, randomised, double-blind, placebo-controlled, parallel groups, phase 2/3 study to compare the efficacy and safety of masitinib at 4.5 or 3 mg/kg/day in combination with riluzole as add-on therapy versus placebo in combination with riluzole as add-on therapy in the treatment of patients suffering from Amyotrophic Laterale Sclerosis (ALS) for 48 weeks.

Patients enrolled will be randomised in 3 groups:
* Group 1: 127 patients will receive masitinib at 4.5 mg/kg/day + riluzole
* Group 2: 127 patients will receive masitinib at 3 mg/kg/day + riluzole
* Group 3: 127 patients will receive placebo + riluzole

Randomisation will be performed with a minimization algorithm on (Stratification):
- ALS patients population (*Normal progressors*(progression before randomization<1.1) VS *Faster progressors* (progression before randomization>=1.1))
- Progression of ALSFRS-R score (point/month) from date of first symptom to baseline (ALSFRS-R score at date of first symptom supposed to be 48) , Balanced between treatment groups in each of ALS patients population *Normal

progressors* and *Faster progressors*
- Site of onset (Bulbar vs Others)
- ALSFRS-R score at baseline
- Age at baseline
- Region (North America and West Europe versus Est Europe versus Other Countries)

At Week 48 patient visit, patients will be proposed to enter a double-blind extension phase if benefit is assessed as positive by investigator as compared to expected deterioration and if tolerability is acceptable.

Study treatment will be discontinued in case of:
- Informed consent withdrawal
- Adverse or undercurrent event considered intolerable by the patient or incompatible with continuation
of the study according to the investigator
-Protocol violation (e.g., noncompliance with treatment administration, prohibited treatment needed)

Intervention

NA

Study burden and risks

The patient will be regularly and medically follow up during the treatment of 48 weeks. He/she will have to visit the research location for 8 visits.

- First visit (screening visit): Before the patient can start the study, the study doctor will check that you 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.

Additionally you will be asked to answer a Specific Quality of Life Questionnaire for ALS

- Baseline visit (from 1 day to 7 days after the screening visit): the study doctor will check some criteria before you can start the study treatment.

- Following visits: 4, 8, 12, 24, 36, 48 weeks after the baseline visit.

- Final visit, 48 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 you about any other medicines that you have taken since the last visit, and how you feel. the patient will be called weekly by the site staff during the first two months 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 and weight.

- 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.

- A Forced Vital Capacity that is an evaluation of the vital capacity (VC) measured when the patient is exhaling with maximal speed and effort during the course of an examination called a spirometry and that is painless. The FVC will be assessed at baseline and at week 4, 8, 12, 24, 36 and 48 and at the final visit (If this is not week48).

- Blood sampling (about 2 to 4 teaspoonfuls depending on the visit, 10-20ml) 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 (about 1 teaspoonful, 5ml) samples will be drawn at weeks 1, 2, 3, 5, 6, 7 and 10 and every 4 weeks 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 and then every 12 weeks.

- Neurologic examinations to assess the progress of your ALS using the ALSFRS-R (Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised) and a Specific Quality of Life Questionnaire for ALS.

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 sinusitis abdominal pain and face edema

SPECIFIC RISKS OF TREATMENT WITH MASITINIB DURING THE FIRST 2 MONTHS OF TREATMENT

Severe neutropenia
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 nerveous system

RISKS RELATED TO RILUZOLE

Like all medicines, riluzole can cause side effects as described in the prescribing information for riluzole.
The study doctor will inform the patient about these potential side effects. If the patient experience any of these, tell your doctor immediately.

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.

Contacts

Public
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FR
Scientific
AB Science

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Parijs 75008
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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. Female or male patient aged between 18 and 75 years of age, with a weight > 50 kg and BMI between 18 and 35 kg/m².
2. Familial or sporadic ALS
3. Patient diagnosed with laboratory supported, clinically probable or definite ALS according to the World Federation of Neurology Revised El Escorial criteria (Brooks, 1994)
4. Disease duration from symptoms onset no longer than 36 months at

the screening visit
5. Patient treated with a stable dose of riluzole (100 mg/day) for at least 30 days prior to screening
6. Patient with a FVC (Forced Vital Capacity) equal to or more than 60% predicted normal value for gender, height, and age at the screening visit
7. Patient with life expectancy >= 6 months
8. Patient with adequate organ function at screening and baseline:
• Absolute Neutrophils Count (ANC) >= 2 x 109/L
• Hemoglobin >= 10 g/dL
• Platelets (PTL) >= 100 x 109/L
• AST/ALT <= 3 ULN
• Bilirubin <= 1.5 ULN
• Albuminemia > 1 x LLN
• Creatinine clearance > 60 mL/min (Cockcroft and Gault formula)
• 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
9. Female patient of childbearing potential (entering the study after a menstrual period and who have a negative pregnancy test), who agrees to use two highly effective 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. Acceptable forms of contraception are explained in the protocol (v4.0 dd16-Mar-2015) on page 5.
10. Male patients must use medically acceptable methods of contraception if your female partner is pregnant, from the time of the first administration of the study drug until three months following administration of the last dose of study drug. Acceptable methods are explained in the protocol on page 5.
Male patients must use two highly effective 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. Acceptable methods are explained in the protocol on page 5.
11. Female patient of childbearing potential must have a negative pregnancy test at screening and baseline
12. Patient able and willing to comply with study procedures as per protocol
13. Patient able to understand, and willing to sign, and date the written informed consent form at screening visit prior to any protocol-specific procedures
14. Patient able to understand, and willing to follow the safety procedures mentioned on the patient card in case of signs or symptoms of severe neutropenia or severe cutaneous toxicity, during the first two months of treatment

Exclusion criteria

1. Patient with history of hematologic, hepatic, respiratory disorder that is clinically significant for his/her participation in the study
2. Patient who underwent tracheotomy and /or gastrostomy

3. Patient with a diagnosis of cancer or evidence of continued disease within five years before starting study treatment
4. Patient with significant sensory abnormalities, dementia, other neurologic diseases, uncompensated medical illness and psychiatric illness
5. Patient who have participated in a clinical trial within 3 months prior to screening
6. Pregnant, or nursing female patient
7. Patient with a known diagnosis of human immunodeficiency virus (HIV) infection
8. Patient with known hepatitis B, hepatitis C or tuberculosis
9. Patient with any severe and/or uncontrolled medical condition
10. Patient having 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
11. 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;12. Patient treated with any investigational agent within 3 months prior
to screening

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):	02-11-2015
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	masitinib
Product type:	Medicine
Brand name:	Rilutek
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	02-09-2015
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	21-09-2015
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	19-07-2016
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	02-02-2017
Application type:	Amendment
Review commission:	METC NedMec

Approved WMO Date:	20-03-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	25-08-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	04-09-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	09-05-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	07-06-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	08-10-2018
Application type:	Amendment
Review commission:	METC NedMec

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	EUCTR2010-024423-24-NL
CCMO	NL50742.041.14

Study results

Date completed: 31-10-2018

Actual enrolment: 10

Summary results
Trial is onging in other countries