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

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The objective is to evaluate the efficacy and safety of two doses of masitinib (4.5 mg/kg/day and 6.0 mg/kg/day) versus matching placebo in patients diagnosed with ALS treated with Riluzole (50 mg bid).The primary objective is to demonstrate...

Ethical review	Not approved
Status	Will not start
Health condition type	Neuromuscular disorders
Study type	Interventional

Summary

ID

NL-OMON49977

Source
ToetsingOnline

Brief title
AB19001

Condition

- Neuromuscular disorders

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, Masitinib, Phase III, TKI

Outcome measures

Primary outcome

Absolute change from baseline of ALSFRS-R total score at week 48.

Secondary outcome

Progression free survival (PFS) defined as the time from randomization to

progression (decline of more than 9 points in ALSFRS-R score from baseline) or

death

* Amyotrophic Lateral Sclerosis Assessment Questionnaire 40 (ALSAQ-40) change

* Forced Vital Capacity (FVC) change

* Upper- and lower-limb muscle strength using hand-held dynamometry (HHD)

* Clinician-rated Clinical Global Impression (CGI)

* Combined Assessment of Function and Survival (CAFS)

* Overall Survival (OS)

* Event free survival (EFS) defined as the time from randomization to the first

occurrence of either death or tracheostomy

Study description

Background summary

Masitinib (AB1010) is a small molecule drug of low molecular weight, belonging to the tyrosine kinase inhibitor (TKI) family [6, 7]. Within this development, masitinib is intended for the treatment of adult patients with ALS. The exact molecular pathways causing motor neuron degeneration in ALS remain unknown, but as with other neurodegenerative diseases, it is likely to involve a complex interplay between multiple pathogenic cellular mechanisms.
Masitinib selectively inhibits specific tyrosine kinases such as colony-stimulating factor 1 receptor (CSF-1R), c-Kit, LYN, FYN, and platelet-derived growth factor receptor (PDGF-R) * and *, in the submicromolar range [7; 8]. At the cellular level, masitinib is a potent inhibitor of CSF-1R-dependent cell proliferation (IC50 90 nM), of wild-type (WT) c-Kit-dependent cell proliferation (IC50 100-300 nM), of LYN- and FYN-dependent cell proliferation (IC50 225-240 nM), and of PDGF-R-dependent cell proliferation (IC50 0.25-20 nM). Two large-scale independent studies show masitinib to have the highest selectivity from a wide range of protein kinase inhibitors, including all those approved or under clinical development at the time of publication [6; 8]. Selectivity generally indicates how safe a given targeted treatment will be, the greater the number of kinases inhibited (i.e. lower selectivity) the greater the potential for off-target effects and toxicity.
Hence, because of its potent and selective activity against CSF-1R, masitinib is able to inhibit the CSF1/CSF-1R signalling pathway thereby regulating CSF-1R-dependent cells such as microglia, the immune cells of the central nervous system that play a well know pathogenic role during ALS progression [9].
By merit of its activity against c-Kit, LYN and FYN, masitinib is also able to inhibit mast cells, an effector immune cell key in chronic inflammatory processes [10].
The development of masitinib in ALS is therefore based on the pharmacological action of masitinib in microglia and mast cells, thereby slowing microglial-related disease progression, reducing neuro-inflammation, and modulating the degenerative neuronal microenvironment in both central (CNS) and peripheral nervous systems (PNS). It is hypothesised that this multifaceted therapeutic approach produced by masitinib, appears capable of generating the beneficial treatment effects observed in humans (as evidenced by significant improvement in relevant clinical measures of disease progression from clinical assessment) and also from appropriate preclinical animal studies (as exemplified by the significantly improved survival of SOD1G93A rats in a post-paralysis therapeutic setting) [11-13].
Microglia play a fundamental pathogenic role during ALS disease progression. It is now well-established in the literature that proliferation and accumulation of microglial cells (microgliosis), which also promotes the emergence of

aberrant glial cells, is a major neuropathological feature of SOD1G93A ALS animal models [14, 15]. Microglial cells are regulated by the CSF1/CSF-1R signalling pathway. Additionally, evidence suggests that ALS is a neurodegenerative disorder in which cross-talk between mast cells, microglia and astrocytes may result in motor neuron damage [16]. Thus, while microglia and mast cells individually play important roles in sustaining the inflammatory network of the PNS and CNS, the existence of mast cell-microglia cross-talk is likely to further contribute to the exacerbation of neurodegenerative disease and to accelerate disease progression [16]. Microglia and mast cells therefore represent potential therapeutic targets in ALS for a pharmacological agent capable of simultaneously modulating their pathogenic roles.
Mast cells orchestrate inflammatory processes and contribute to the neuroinflammatory cascade by merit of the wide array of pro-inflammatory mediators they release. Indeed, mast cells represent one of the main CNS sources of cytokines and chemokines [17; 19]. In both CNS and PNS, as in other tissues, activated mast cells may undergo explosive degranulation or may steadily release granules into their microenvironment. Following activation, mast cells remain intact and viable to resynthesize their granules. Secretory granules store a wide variety of mediators, which when released into the CNS can alter the function of both neural and vascular elements. The importance of c-Kit, LYN and FYN for mast cell function and activation is well-known.

Study objective

The objective is to evaluate the efficacy and safety of two doses of masitinib (4.5 mg/kg/day and 6.0 mg/kg/day) versus matching placebo in patients diagnosed with ALS treated with Riluzole (50 mg bid).
The primary objective is to demonstrate statistically significant improvement from baseline in ALSFRS-R after 48-week treatment of two doses of masitinib versus matching placebo in patients diagnosed with ALS treated with Riluzole.
Secondary objectives are to assess the efficacy and safety of two doses of masitinib versus matching placebo in the treatment of patients diagnosed with ALS treated with Riluzole:
Clinical assessments:
* Progression-free survival (PFS): decline of more than 9-points in ALSFRS-R score from baseline or death from baseline to last patient last W48 visit
* Change in % of FVC from baseline to week 48
* Change from baseline in evaluation of upper- and lower-limb muscle strength using hand-held dynamometry (HHD) at week 48
* Combined Assessment of Function and Survival (CAFS)
* Overall Survival (OS) from baseline to last patient last W48 visit
Quality of Life assessment:
* Change from baseline in ALSAQ- 40 at week 48
Clinical Global Impression assessment:
* Change in each component of Clinician-rated CGI from baseline to week 48
Safety:
* Occurrence of Adverse Events (AE), changes on clinical examination including

vital signs (blood pressure, heart rate) and weight, Electrocardiogram (ECG) and safety laboratory results (biochemistry, haematology and urinalysis) during the study period
Pharmacodynamic/biomarker(s):
* Identification of pharmacodynamic biomarker(s) is needed to fully characterize the potential disease modifying effects of masitinib in ALS patients. The aim is to assess, before and during study treatment, cerebrospinal fluid (CSF) in up to 30 ALS patients and serum biomarkers in all randomized ALS patients known to be associated with the evolution of the disease and potentially modulated by masitinib treatment
Pharmacogenomic (in case of severe neutropenia and/or severe skin toxicity):
* Determination of the genetic polymorphisms, including HLA polymorphisms that could be associated with an increased risk of masitinib-induced severe neutropenia and severe skin toxicity
*Measurement of pharmacokinetic parameters of masitinib and Riluzole in up to 10 ALS patients per group and validate population PK model for masitinib

Study design

AB19001 is a multicenter, randomized, double-blind, placebo-controlled, phase 3 study to compare the efficacy and safety of two doses of masitinib (4.5 mg/kg/day or 6.0 mg/kg/day) in combination with Riluzole (50 mg b.i.d) versus matching placebo in combination with Riluzole (50 mg b.i.d) in the treatment of patients diagnosed with ALS.
Patients enrolled will be randomised in 3 groups :
- Group 1: 165 patients will receive a dose of masitinib (starting from 3.0 mg/kg/day during 4 weeks followed by a dose of 4.5 mg/kg/day for 4 weeks followed by a dose of 4.5 mg/kg/day of masitinib and 1.5 mg/kg/day of placebo) as add-on therapy to Riluzole at 50 mg b.i.d.
- Group 2: 165 patients will receive a dose of masitinib (starting from 3.0 mg/kg/day during 4 weeks followed by a dose of 4.5 mg/kg/day for four weeks followed by a dose of 6.0 mg/kg/day) as add-on therapy to Riluzole at 50 mg b.i.d.
- Group 3: 165 patients will receive a dose of matching placebo as add-on therapy to Riluzole at 50 mg b.i.d.

Intervention

NA

Study burden and risks

ALS is a rare progressive, fatal motor neuron disease characterised by axonal degeneration and progressive loss of the upper and lower motor neurons throughout the central nervous system. Patients with ALS experience progressive denervation and atrophy of skeletal muscles and in the majority of cases die

from respiratory failure.
To date, therapeutic options are still very limited. Riluzole is the only approved medication for modifying disease progression in ALS and apart from that treatment is mainly palliative. Although relatively well tolerated, there are hepatotoxicity concerns associated with Riluzole, and its efficacy remains insufficient. Considering the seriousness of the disease and the limited options for treatment, there is still a high unmet medical need for patients suffering from ALS.
Study AB10015 assessed a 48-week treatment with oral masitinib administered in addition to standard of care for treatment of ALS patients. The Trial enrolled a credible number of patients (n=394) and applied broad inclusion criteria in terms of disease duration (<36 months) and as well as baseline ALSFRS-R score for inclusion (no restriction).
Study AB10015 presented some methodological limitations, and the conduct and the analysis of Study AB10015 were considered by the CHMP not sufficiently robust to support registration on the basis of a single clinical study, based on interim data and safety data that were not final at the time of the final decision of the CHMP.
However, this study clearly indicated positive treatment effects on change in ALSFRS, PFS, FVC, and Quality of life is the so called normal progressors, accounting for 85% of the study population. There was no benefit on survival. There was no benefit the overall normal + fast population based on the inclusion criteria of AB10015 study.
Study AB10015 also showed significant potential benefits for patients with less advanced stage of the disease. In these patients with a baseline score of at least 1 on each of the 12 items of the ALSFRS-R score, a statistically significant treatment effect (reduction in rate of progression compared to active control group of 20.3%; p=0.0315) were considered as clinically relevant in the overall normal + fast progressor. This analysis in patients with a baseline score of at least 1 on each of the 12 ALSFRS score items accounted for 80% of the overall study population and included both Normal and Fast Progressors (>10%). This result strongly suggests of stronger treatment effect of masitinib when patients are treated at an earlier stage of the disease.
In Study AB10015, the overall safety of masitinib at 3.0 and 4.5mg/kg/in ALS patients was comparable to results observed in other indications. Most patients on masitinib sustained well documented self-limited adverse reactions which were more prevalent at the start of therapy and manageable with simple dose interruption or reduction. These included frequent gastrointestinal symptoms, peripheral fluid retention, and skin rashes typically observed with other tyrosine kinase inhibitors. Because of the nature of these reactions, and because their impact can be mitigated with dose titrations, these reactions do not represent a safety concern in a population of ALS patients.
A total of 67 patients had at least one fatal SAEs including 33 patients during the main protocol period and 34 patients during the extension period (up to the data lock point). In addition of these 67 patients who died during the planned study period, 14 patients died after the data lock point. A review of the causes of these 67 and 14 deaths revealed that most patients died of

progression of disease, cardiac and respiratory complications, and infections related to ALS. The death rates related to fatal SAEs during the main protocol period were comparable amongst study treatment groups, with a trend towards lower rates in masitinib groups compared to placebo (i.e. 7.8% in masitinib 4.5 mg/kg/days and 8.4% in masitinib 3.0 mg/kg/days versus 9.0% in placebo). During the extension period, a reverse trend was observed with higher rates in masitinib groups compared to placebo (10.9% in masitinib 4.5 mg/kg/days and 9.9% in masitinib 3.0 mg/kg/days versus 5.3% in placebo).
In the subgroup of patients matching the inclusion criteria to be applied for AB19001, a total of 15 patients had at least one fatal SAEs including 7 patients during the main protocol period and 8 patients during the extension period (up to the data lock point) . The death rates related to fatal SAEs during the main protocol period was 3.1% in masitinib 4.5 mg/kg/days and 9.1% in masitinib 3.0 mg/kg/days versus 11.1% in placebo. During the extension period, The death rates related to fatal SAEs was 12.5% in masitinib 4.5 mg/kg/days and 0.0% in masitinib 3.0 mg/kg/days versus 11.1% in placebo.
As seen in AB10015 as well as in other indications, a smaller number of patients taking masitinib may sustain more severe and potentially life-threatening reactions. Those included primarily severe skin reactions, severe neutropenia and agranulocytosis, and drug induced liver injuries. Although not frequent and fully recoverable, these reactions do represent a safety concern. With a large safety database, it has been demonstrated that the impact of those reactions on patients can be efficiently reduced with adequate risk minimization measures. These measures include exclusion of patients with pre-existing risk factors, training of study personnel, frequent monitoring assessments, reduced dosing regimens and specific dose modifications scheme adjusted to each risk. Despite the serious nature of these reactions, both their impact and frequency can be reduced with adequate measures, and therefore, those risks are considered to be acceptable for the studied indication. In particular, the number of patients experiencing any severe skin-related AEs for the overall population was reduced from 36 for the first 500 patients to 1 last 500 patients, and the number of patients experiencing any events related to severe neutropenia and related terms for the overall population was reduced from 16 for the first 500 patients to 8 last 500 patients. Based on preclinical studies, potential important risks associated with masitinib exposure have been detected, including risks of cardiac toxicity, renal toxicity and carcinogenicity. These risks have not yet been confirmed in the clinical development of masitinib. In AB10015, an apparent higher-than-expected mortality was observed in the masitinib arms compared to placebo. Thorough analyses were performed to evaluate the cause of these deaths. There was no conclusive evidence found that these deaths were associated with any cardiotoxic effect of masitinib. The most plausible cause for these deaths appeared to be ALS worsening.
A set of monitoring measures have been implemented in all studies of masitinib in order to minimize those important potential risks, which include i) Restriction of eligibility criteria, ii) Dose titration, iii) Strict dose adjustment and discontinuation rules, and iv) Implementation of a Data Safety

Monitoring Board (DSMB) for periodic benefit risk assessment.
Overall, considering the impact of ALS on the life prognosis of patients suffering from the disease, the urgent need for developing more efficacious ALS therapeutic alternatives, and based on the study results from AB10015, the potential benefit associated with masitinib outweigh the known and potential risks of masitinib in treating patients with ALS to start a confirmatory phase 3 study.

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, male or female, diagnosed with laboratory supported probable, clinically probable or definite ALS according to the World Federation of Neurology Revised El Escorial criteria

2.Patient with a familial or sporadic ALS
3.Patient aged between 18 and 75 years old inclusive at screening
4.Patient treated with a stable dose of Riluzole (100 mg/day) for at least 12 weeks prior to the baseline visit
5.Patient with an ALS disease duration from diagnosis no longer than 24 months at screening
6. Patient with an ALSFRS-R total score progression between onset of the disease and screening of
> 0.3 and <1.1 point/month
7.Patient with an ALSFRS-R total score decrease of * 1 point between screening and baseline
8.Patient with an ALSFRS-R total score of at least 26 at screening following rules below:
- at least 3 on item #3 and
- at least 2 on each of the other 11 items (i.e. item #1, #2, #4, #5a or #5b, #6, #7, #8, #9, #10, #11 and #12)
9.Patient with an ALSFRS-R total score of at least 25 at randomization following rules below:
- at least 3 on item #3 and
- at least 2 on each of the other 11 items (i.e. item #1, #2, #4, #5a or #5b, #6, #7, #8, #9, #10, #11 and #12)
10. Contraception:
- Female patient of childbearing potential (entering the study after a menstrual period and who has a negative pregnancy test), who agrees to use a highly effective method of contraception and an effective method of contraception by her male partner during the study and for 3 months and a half after the last treatment intake
- Male patient with a female partner of childbearing potential who agrees to use a highly effective method of contraception and an effective method of contraception by his female partner during the study and for 3 months and a half after the last treatment intake OR who agrees to use an effective method of contraception and a highly effective method of contraception by his female partner during the study and for 3 months and a half after the last treatment intake
Highly effective and effective methods of contraception are detailed in appendix 15.1
11.Patient able to understand, and willing to sign, and date the written informed consent form prior to any protocol-specific procedures. If verbal consent is given, a Legal Representative of the patient must sign the informed consent form
12.Patient able and willing to comply with study protocol and to come on-site as per protocol visits schedule
13.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

Exclusion criteria

1. Patient with dementia or significant neurological, psychiatric, systemic or organic disease, uncontrolled or that may interfere with the conduct of the trial or its results
2. Patient with hypersensitivity to masitinib excipients
3. Patient with an FVC < 60% predicted normal value for gender, height, and age at screening
4. Patient with a weight < 41 kg and a BMI < 21 or > 30 kg/m² at screening and at baseline
5. Pregnant, or nursing female patient
6. Patient with history (or family history) of severe skin toxicities or reactions
7. Patients treated by drugs known to be at high risk for Stevens-Johnson Syndrome or for Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome
8. Patient with history of severe bone marrow disorders such as agranulocytosis or aplasia, or with abnormal laboratory results from local laboratory assessments at screening and baseline :
- Neutropenia with ANC < 1.5x109/L
- Anemia with Hgb < LLN and red blood cell count below the LLN
- Thrombocytopenia with platelets counts < 150 x 109/L
9. Patient with history of hepatic disorders, with a known liver disease or recent alcohol abuse, or with abnormal laboratory results from local laboratory assessments defined as:
- Hepatic transaminase levels > 2 ULN at baseline, or
- Total bilirubin level > 1.5 ULN at baseline, or
- Both hepatic transaminase levels and total bilirubin level outside of the normal ranges at screening and baseline, or
- Albuminemia < 1 x LLN at screening and baseline
10. Patient with pre-existing severe renal impairment, or with abnormal laboratory results from local laboratory assessments at screening and baseline :
- 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
11. Patient with active severe infection such as herpes, tuberculosis, viral hepatitis, human immunodeficiency virus infection
12. Patient with autoimmune conditions such as systemic lupus erythematosus
13. Patient with a diagnosis of cancer or evidence of continued disease within five years before screening
14. Patient with severe cardiac conditions:
- Patient with recent history of severe cardiovascular conditions including acute myocardial infarction, unstable angina pectoris, coronary revascularization procedure, congestive heart failure of NYHA Class III or IV, stroke, including a transient ischemic attack
- Patient with cardiac conduction abnormalities at study entry including a QTc

Fredericia interval >450 milliseconds for males and >470 milliseconds for females, a second- or third-degree atrioventricular block not successfully treated with a pacemaker
- Patient presenting with edema of cardiac origin and left ventricular ejection fraction * 50%
15. Patient with risk factors for sudden unexpected death of cardiovascular origin
16. Patient who has been exposed to an investigational treatment within 3 months prior to screening
17. Patient who has been exposed to Edaravone within at least 30 days prior to screening
18. Patient treated concomitantly with drugs known to interact with cytochrome P450 (CYP450) isoenzymes (2C9, 2D6 and 3A4)

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:	11
Type:	Anticipated

Medical products/devices used

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

Brand name:	Rilutek
Generic name:	Riluzole
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	23-09-2019
Application type:	First submission
Review commission:	METC NedMec
Not approved Date:	27-08-2020
Application type:	First submission
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	EUCTR2019-001862-13-NL
CCMO	NL71135.041.19