Masitinib for amyotrophic lateral sclerosis – add-on therapy to riluzole

**SUMMARY**

Masitinib is intended to be used as a treatment option for patients with amyotrophic lateral sclerosis (ALS) as an add-on therapy to riluzole. Masitinib is a highly selective, orally administered, tyrosine kinase inhibitor that targets the c-Kit, Lyn and Fyn signalling pathways. By combined targeting of c-Kit, Lyn and Fyn, masitinib is particularly efficient in controlling mast cell survival, differentiation, and degranulation.

ALS, also known as Lou Gherig’s disease, is a form of Motor Neurone Disease (MND); a condition that affects parts of the nervous system that control voluntary muscle movement. ALS constitutes 65-85% of MND; the incidence rises with age and at any one time, about 3,000 people in the UK have ALS. Based on the 1,028 newly diagnosed cases per year, the average annual crude incidence rate of ALS in Europe is fairly uniform at 2.16 per 100,000 per year. Most people with ALS die from respiratory failure, usually within 3 to 5 years from the onset of symptoms, however about 10% of those with ALS survive for 10 years or more.

The only disease-modifying therapy licensed for use in MND is riluzole, other interventions aim to improve quality of life and manage the complications of the disease. Surgical intervention is also an option to enable feeding, and tracheostomy with or without ventilation support may be required to aid breathing as respiratory muscle weakness increases. Masitinib is currently in one phase III clinical trial comparing the efficacy and safety of masitinib with that of placebo in patients with ALS; results are anticipated in 2017.
TARGET GROUP

- Amyotrophic lateral sclerosis (ALS): familial or sporadic – in combination with riluzole.

TECHNOLOGY

DESCRIPTION

Masitinib (AB1010; masitinib mesilate) is a highly selective, orally administered tyrosine kinase inhibitor that targets the c-Kit, Lyn and Fyn signalling pathways. By combined targeting of these different pathways, masitinib is particularly efficient in controlling mast cell survival, differentiation and degranulation\(^1\). Mast cells are one of the key inflammatory cell types associated with chronic neuroinflammation\(^2\). Through its activity on the mast cell, masitinib may have an effect on the symptoms associated with some inflammatory and central nervous system diseases\(^a\).

Masitinib is intended for the treatment of ALS as an add-on therapy to riluzole\(^3\). It is administered orally, on a continuous basis, and dosed according to patient bodyweight. Masitinib is also in phase III trials for Alzheimer’s disease, progressive forms of multiple sclerosis, mastocytosis, severe persistent asthma, rheumatoid arthritis, Gastrointestinal Stromal Tumours (GIST), metastatic melanoma expressing a juxtamembrane mutation of c-Kit, multiple myeloma, metastatic colorectal cancer, metastatic prostate cancer and pancreatic cancer\(^a\).

INNOVATION and/or ADVANTAGES

If licenced, masitinib will provide an additional treatment option for patients with ALS, a group of patients who currently have few treatment options available.

DEVELOPER

AB Science.

AVAILABILITY, LAUNCH OR MARKETING

Masitinib is currently in phase III trials.

PATIENT GROUP

BACKGROUND

ALS, also known as Lou Gehrig’s disease, is a form of Motor Neurone Disease (MND); a condition that affects parts of the nervous system that control voluntary muscle movement. Nerve cells that control muscle cells are gradually lost causing the muscle to become weak and eventually non-functional\(^a\). ALS causes a wide range of disabilities; eventually all muscles under voluntary control are affected and individuals lose their strength and the ability to move their arms, legs and body. When muscles in the diaphragm and chest wall fail, the affected person loses the ability to breathe without ventilator support. Most people

\(^a\) Company provided information.
with ALS die from respiratory failure, usually within 3 to 5 years from the onset of symptoms. However about 10% of those with ALS survive for 10 or more years. The aetiology of ALS remains unknown, though it is hypothesised that neural degeneration is caused by excessive stimulation of glutamate receptors on neurones. There is no diagnostic test for ALS. The diagnosis requires the demonstration of clinical signs affecting both the brain and spinal cord. Diagnosis is often delayed and can take more than 16 months from the onset of initial symptoms, which are commonly non-specific and include general fatigue.

**NHS or GOVERNMENT PRIORITY AREA**

This topic is relevant to:

**CLINICAL NEED and BURDEN OF DISEASE**

ALS constitutes 65-85% of MND cases; the incidence rises with age, and at any one time about 3,000 people in the UK have ALS. Based on the 1,028 newly diagnosed cases per year, the average annual crude incidence rate of ALS in Europe is fairly uniform at 2.16 per 100,000 per year. In 2012-13 there were 2,400 admissions for MND (ICD10 G12.2) resulting in 26,239 bed days and 3,739 finished consultant episodes in England. In 2013, there were 2,170 deaths registered from MND in England and Wales.

**PATIENT PATHWAY**

**RELEVANT GUIDANCE**

**NICE Guidance**

**Other Guidance**

**CURRENT TREATMENT OPTIONS**

Riluzole is the only disease-modifying therapy licensed for use in MND. Other interventions aim to improve quality of life and manage the complications of the disease. Surgical intervention may be necessary; such interventions include percutaneous gastronomy to enable feeding as the ability to swallow decreases, and tracheostomy with or without ventilator support to aid breathing as respiratory muscle weakness increases.
### EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>EudraCT2010-024423-24; masitinib vs placebo; phase III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>AB Science.</td>
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<tr>
<td>Status</td>
<td>Ongoing.</td>
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<tr>
<td>Source of information</td>
<td>Manufacturer*</td>
</tr>
<tr>
<td>Location</td>
<td>EU (including UK), USA and other countries.</td>
</tr>
<tr>
<td>Design</td>
<td>Randomised, placebo-controlled.</td>
</tr>
<tr>
<td>Participants</td>
<td>n=381(planned). aged ≥18-80 years; ≥50kg; familial or sporadic ALS; patients diagnosed with laboratory supported, clinically probable or definite ALS according to the World Federation of Neurology Revised El Escorial criteria: disease duration from symptoms to onset no longer than 36 months at the screening visit; patient treated with a stable dose of riluzole (100mg/day) for at least 30 days prior to screening.</td>
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<tr>
<td>Schedule</td>
<td>Randomised to masitinib (dose not reported) or placebo; both oral, daily, as an add-on therapy to riluzole</td>
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<tr>
<td>Follow-up</td>
<td>48 weeks.</td>
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<tr>
<td>Primary outcome/s</td>
<td>Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS).</td>
</tr>
<tr>
<td>Secondary outcome/s</td>
<td>Combined Assessment of Function and Survival (CAFS); overall survival; survival rates; time to first tracheotomy; change of Forced Vital Capacity (FVC) from baseline to each time point; change in cystatin C level from baseline to each time point; time to first gastrectomy; absolute and relative change from baseline in Amyotrophic Lateral Sclerosis Assessment Questionnaire (ALSAQ-40) score at each time point.</td>
</tr>
<tr>
<td>Adverse effects (AEs)</td>
<td>No safety concerns reported after 1 year of treatment.</td>
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<tr>
<td>Expected reporting date</td>
<td>Initial results expected by the end of 2017.</td>
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</table>

### ESTIMATED COST and IMPACT

#### COST

The cost of masitinib is not yet known. The cost of riluzole at a dose of 100mg per day (50mg twice per day) for its current licenced indication is £320.33 for 28 days.\(^{13}\)

#### IMPACT - SPECULATIVE

**Impact on Patients and Carers**

- Reduced mortality/increased length of survival
- Reduced symptoms or disability
- Other: No impact identified

**Impact on Health and Social Care Services**

- Increased use of existing services
- Decreased use of existing services: if effective in reducing progression, symptoms or complications.
- Re-organisation of existing services
- Need for new services
- Other
- None identified
## Impact on Costs and Other Resource Use

- **Increased drug treatment costs:** additional treatment.
- **Reduced drug treatment costs**
- **Other increase in costs.**
- **Other reduction in costs:**
- **Other:**
- **None identified**

## Other Issues

- **Clinical uncertainty or other research question identified:**
- **None identified**

## INFORMATION FROM

**AB Science.**

**UK PharmaScan** ID number: AB Science did not enter information about this technology onto the **UK PharmaScan** database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR HSC has had to obtain data from other sources. **UK PharmaScan** is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use **UK PharmaScan** so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

## REFERENCES

https://www.medicinescomplete.com/mc/bnf/current/.