INTERNATIONAL ALLIANCE OF ALS/MND ASSOCIATIONS

AB Science - Masitinib
August 2022

Background

Masitinib is an oral tyrosine kinase inhibitor that can inhibit macrophage and mast cell proliferation, while also stimulating their apoptosis, thereby reducing neuroinflammatory response. In preclinical SOD1 rat models of ALS/MND, treatment with masitinib seven days after the onset of paralysis resulted in slowed disease progression, decreased microglosis and extended survival by 40%.

A phase 2/3 clinical trial published in 2019 assessed the potential efficacy of mastinib in ALS/MND. The study was a double-blind, placebo-controlled trial that measured two doses of masitinib, 3.0 mg/kg/day and 4.5 mg/kg/day over 48 weeks using the ALSFRS-R. A primary efficacy population of participants declared as normal progressors (<1.1 pts/month decline on ALSFRS-R) at the 4.5 mg/kg/day dose were declared to experience significant benefit vs. placebo, with a statistically significant 27% slowing of functional decline. A survival analysis from the same trial, published in 2021, demonstrated a significant survival benefit of 25 months versus placebo in a subgroup receiving 4.5 mg/kg/day, having a baseline ALSFRS-R progression rate <1.1pts/month and a score of 2 or more at baseline for each ALSFRS-R component.

The preliminary data from this study underpinned the decision to proceed with a phase 3 clinical trial. This is currently recruiting at more than 40 sites in 13 countries, with a goal of 495 participants across three arms; placebo, 4.5 mg/kg/day and 6.0 mg/kg/day. The trial will measure ALSFRS-R over 48 weeks as the primary outcome, with a quality of life measure, progression free survival, SVC, HHD and a combined assessment of function and survival (CAFS) as secondary outcomes. Based on the data obtained from the previous trial, eligibility will require a certain rate of progression and particular total and subscores on each of the items of the ALSFRS-R at screening.

It should also be noted that while masitinib demonstrated reasonable safety and tolerability in the phase 2/3 trial, there is a history of severe adverse events across several trials testing masitinib in various conditions including ischemic heart disease, autoimmune-like hepatitis and Stevens-Johnson Syndrome. There was a higher proportion of severe adverse events in the treatment arms of the trial and one third of the individuals on the 4.5 mg/kg/day dose had adverse events requiring dose reduction. In June 2021, a voluntary hold on worldwide clinical studies of masitinib was announced to investigate the potential risk of ischemic heart disease, which has since been lifted. This information should not discount evaluation of a potential effect in ALS/MND, but are important for treating physicians to be aware of.

Recently, AB Science announced that Health Canada has started review of a New Drug Submission for masitinib in the treatment of ALS/MND under the Notice of Compliance with Conditions (NOC/C) policy. If approved, the academic and clinical community need to consider whether the existing data from the phase 2/3 study is sufficient to warrant treatment of people with ALS/MND until the phase 3 trial readout occurs. The results of the first study, while intriguing, represent strong preliminary data to inform the ongoing phase 3 trial, but have a number of aspects that make it difficult to determine if the reported effects are due to chance. It should be noted that data from non-pivotal phase 2 or 2/3 studies are expected to provide the required information for designing the optimal phase 3 efficacy trials and questions around the reliability of results at this stage are not unique to this situation.

Summary

Given the available evidence, it is the opinion of the SAC that masitinib is an intriguing compound with preliminary results suggestive of a potential effect on ALS/MND progression and survival, but that the clinical and academic community has reservations as to whether the existing data is sufficient to warrant confidence in these effects. The ongoing phase 3 clinical trial is necessary to determine if there is any effect of masitinib in ALS/MND. Should regulatory bodies like Health Canada provide conditional approval of masitinib based on the existing data, further communication will be developed, but until then, there is as-yet no reason to recommend use of masitinib for the treatment of people living with ALS/MND.