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AB SCIENCE ANNOUNCES FILING OF MARKETING AUTHORIZATION APPLICATION FOR ALSITEK IN THE TREATMENT OF AMYOTROPHIC LATERAL SCLEROSIS (ALS) AND ITS VALIDATION BY THE EUROPEAN MEDICINES AGENCY (EMA)

AB Science announced that it has filed an application for conditional Marketing Authorization to the European Medicines Agency (EMA) for Alsitek (masitinib) in the treatment of amyotrophic lateral sclerosis (ALS). This application has now been validated by EMA and review by the Committee for Medicinal Products for Human Use (CHMP) has begun. The CHMP has a target of 210 active evaluation days to review the application.

The application is based on results from the phase 2/3 AB10015 study and its long-term survival follow-up. Study AB10015 was a randomized, double-blind, placebo-controlled trial over a 48-week treatment period, conducted with 394 ALS patients and evaluating Alsitek in combination with riluzole versus riluzole alone. Detailed results from study AB10015 and its long-term survival analysis have been published in the journals *Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration* and *Therapeutic Advances in Neurological Disorders*.

This decision to file followed a pre-submission meeting held with the CHMP Rapporteur during which new data generated with Alsitek in ALS were presented, in particular, a clinical benefit in terms of a 25-month increase in median overall survival for patients with moderate ALS, which is a cohort that closely resembles newly diagnosed patients. During the pre-submission meeting, AB Science also presented how issues listed in the previous CHMP assessment for Alsitek on ALS (EMA/406203/2018) were resolved, in particular:

- The mode of action of Alsitek in ALS, which has been well-demonstrated and published in peer-reviewed publications.
- A remonitoring of all efficacy and safety data and a complete reassessment of the Alsitek safety database.
- Additional analyses for the primary efficacy endpoint, imputing all missing data for early discontinuation, and a conservative analysis imputing missing data with a penalty for patients who discontinued Alsitek for lack of efficacy or toxicity. These analyses were positive, and all showed a treatment effect in favor of Alsitek and convergent with the primary analysis.
- Long-term follow-up survival data showing a significant benefit in favor of Alsitek in moderate ALS patients (between group difference in median OS of +25 months, hazard ratio 0.56 (95%CI [0.32;0.96])).

Alain Moussy, CEO and co-founder of AB Science said: *"ALS is a devastating disease and there is a tremendous need for new treatments that can improve the life of the patients to be available as soon as possible. AB Science is committed to deliver a new disease modifying treatment to the ALS community, a drug that can change the perspective of the patients in the long run. AB Science will continue to work closely with all agencies in the world to deliver masitinib to patients in an optimal regulatory pathway".*

About study AB10015

Study AB10015 was a randomized, placebo-controlled phase 2/3 clinical trial. The aim of this study was to assess the efficacy and safety of Alsitek at two different doses (4.5 or 3.0 mg/kg/day) when given as an add-on therapy to riluzole during 48 weeks, as compared with placebo given as an add-on therapy to riluzole, in patients with ALS. This study used a prospectively stratified design based on Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised (ALSFRS-R) progression rate calculated from disease-onset to baseline (ΔFS). A cut-off at 1.1 points/month distinguished between 'Normal Progressor' (ΔFS<1.1) and 'Fast Progressor' (ΔFS≥1.1) patients. The primary efficacy endpoint was the change in ALSFRS-R from baseline to week 48 between treatment groups (Alsitek versus placebo) in the 'Normal Progressor' population.

The prespecified primary efficacy analysis on patients receiving Alsitek 4.5 mg/kg/day with a ΔFS of less than 1.1 points/month ('Normal Progressors') showed a significant benefit over placebo with a between-group difference in ΔALSFRS-R of 3.4 points (9.2 vs. 12.6); p=0.016. This corresponds to a 27% slowing in the rate of functional decline. Sensitivity analyses based on multiple imputation, imputing all data at week 48 for all patients with early discontinuation, and multiple imputation with jump-to-reference, treating early discontinuation in the Alsitek group as if receiving placebo from the time of discontinuation, remained significant (ΔALSFRS-R of 3.4 points; p=0.020 and ΔALSFRS-R of 2.8 points; p=0.039, respectively).

A sensitivity analysis was performed in patients with moderate ALS (baseline ALSFRS-R score ≥2 on each individual component of the ALSFRS-R and ΔFS<1.1), which corresponds to selection of ALS patients early in the course of their disease and is also consistent with newly diagnosed patients. In this cohort, there was a significant 44% reduced risk of death (between group difference in median OS of +25 months, log rank p=0.0478; hazard ratio 0.56 (95%CI [0.32;0.96], Cox p=0.036) with long-term survival follow-up. The benefit was already apparent at the end the study's blinded treatment period, with a significant 65% reduced risk of death (hazard ratio 0.35 (95%CI [0.13;0.95], Cox p=0.039)).

About masitinib

Masitinib is an orally administered tyrosine kinase inhibitor that targets mast cells and macrophages, important cells for immunity, through inhibiting a limited number of kinases. Based on its unique mechanism of action, masitinib can be developed in a large number of conditions in oncology, in inflammatory diseases, and in certain diseases of the central nervous system. In oncology due to its immunotherapy effect, masitinib can have an effect on survival, alone or in combination with chemotherapy. Through its activity on mast cells and microglia and consequently the inhibition of the activation of the inflammatory process, masitinib can have an effect on the symptoms associated with some inflammatory and central nervous system diseases and the degeneration of these diseases.

Source: **AB Science**