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Interim results of masitinib study in Alzheimer's disease: positive trend of efficacy in one of the doses tested

Final analysis will be available in Q4 2019

AB Science SA (NYSE Euronext - FR0010557264 - AB) reports the outcome from the interim analysis of study AB09004 in Alzheimer's disease.

AB09004 study design and status

Study AB09004 is an international, randomized, placebo-controlled, phase 3 study evaluating masitinib as a treatment of patients with confirmed mild to moderate Alzheimer's disease.

This study compares the efficacy and safety of masitinib when administered as an add-on therapy to cholinesterase inhibitor (donepezil, rivastigmine or galantamine) and/or memantine, to placebo as add-on to cholinesterase inhibitor and/or memantine.

Two doses of masitinib are evaluated, masitinib 4.5 mg/kg/day and a dose titration from masitinib 4.5 to 6.0 mg/kg/day, each dose having its own control arm.

The primary efficacy endpoint is the change on ADAS-Cog, which measures the effect on cognition and memory, and the secondary endpoint is change on ADCS-ADL, which assesses self-care and activities of daily living.

The study enrolled 720 patients.

Interim analysis

The interim analysis was pre-planned once 75% of the patients had reached the week 24 timepoint.

The interim analysis tests futility and conditional power ≥80% (i.e. probability of success). The protocol prospectively defines the following scenarios based on findings of the interim analysis: a) stop the study if futile; b) continue the study because test with conditional power ≥ 80% is met, with or without resampling; c) in between the two abovementioned scenarios. It is scenario (b) that would make interim analysis decisive for study continuation.

Based on the rules set by the protocol, the interim analysis has detected scenario (b) for one of the doses tested.

Study recruitment has been completed. All patients have also completed their last visit and have now exited the study. The final results will be available by Q4 2019.

Previous establishment proof of concept

As a reminder, proof of concept for the evaluation of masitinib in Alzheimer's disease was established through a 35-patient, double-blind, placebo-controlled phase 2 study. In this study, the rate of clinically relevant cognitive decline, according to the primary endpoint, ADAS-Cog response (increase > 4 points), was significantly lower with masitinib treatment compared with placebo after 12 and 24 weeks (6% versus 50%

for both; p=0.040 and p=0.046, respectively). Moreover, while the placebo treatment-arm demonstrated worsening mean ADAS-Cog, ADCS-ADL and MMSE scores, the masitinib treatment-arm reported improvements with statistical significance between treatment-arms at weeks 12 and/or 24 (respectively, p=0.016 and 0.030; p=0.035 and 0.128; and p=0.047 and 0.031). Adverse events occurred more frequently with masitinib treatment (65% versus 38% of patients); however, the majority of events were mild or moderate and transient. The phase 2 results were published in Alzheimers Res Ther. 2011 Apr 19;3(2):16. doi: 10.1186/alzrt75.

Scientific rationale

The potential therapeutic benefit of masitinib in Alzheimer's disease is linked to two possible mechanisms of action: the role of mast cells in neuroinflammation and regulation of the blood-brain-barrier (BBB) permeability; and the inhibition of the protein kinase Fyn, which is involved in amyloid-beta signaling and tau phosphorylation.

Neuroinflammation is thought to be a major contributor in the pathogenesis of Alzheimer's disease[1,2,3]. Mast cells release large amounts of proinflammatory mediators and therefore play an important role in sustaining the inflammatory network of the central nervous system. Furthermore; mast cells are found on both sides of the BBB and also have the ability to rapidly cross the BBB, thereby increasing their numbers in response to physiological stimuli. Given that the neural pool of mast cells is influenced by their ability to rapidly cross the BBB, inhibition of mast cells peripheral to the BBB could impact upon neurodegenerative disease outcome. Therefore, masitinib could be an effective drug in Alzheimer's disease because it blocks mast cells through the inhibition of the tyrosine kinases c-Kit and Lyn.

In addition to blocking mast cell activity, masitinib may exert an effect through its inhibition of the tyrosine kinase Fyn[4,5,6]. Alzheimer's disease is associated with the pathological aggregation of amyloid-beta (A-beta) plaques and tau-positive neurofibrillary tangles. Several lines of evidence implicate Fyn in the pathogenesis of Alzheimer's disease through its dual role in A-beta signaling and tau phosphorylation. Masitinib, by inhibiting Fyn, could possibly disrupt the A-beta signaling cascade and modulate the phosphorylation of tau protein, thus and preventing neurofibrillary tangles.

Targeted population

The meta-analysis of epidemiologic studies indicates that between 5 and 10 million people suffer from Alzheimer's disease in the USA and Europe. Alzheimer's disease is the most common type of dementia among western countries, corresponding to about 60% of cases. Alzheimer's disease is already the sixth leading cause of all deaths in USA and the fifth leading cause among Americans over 65 years of age.[7,8,9] Worldwide, it is thought that there are more than 15 million people affected by Alzheimer's disease.[8]

Currently, there are only five products approved for the treatment of Alzheimer's disease, four of which belong to the pharmacological class of anticholinesterases, the fifth being an NMDA inhibitor. Therefore, this remains an area of significant unmet medical need.

References

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About masitinib
Masitinib is a new 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.

About AB Science
Founded in 2001, AB Science is a pharmaceutical company specializing in the research, development and commercialization of protein kinase inhibitors (PKIs), a class of targeted proteins whose action are key in signaling pathways within cells. Our programs target only diseases with high unmet medical needs, often lethal with short term survival or rare or refractory to previous line of treatment.
AB Science has developed a proprietary portfolio of molecules and the Company's lead compound, masitinib, has already been registered for veterinary medicine and is developed in human medicine in oncology, neurological diseases, and inflammatory diseases. The company is headquartered in Paris, France, and listed on Euronext Paris (ticker: AB).

Further information is available on AB Science's website: www.ab-science.com.

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