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Independent Publication from experts highlights the potential of masitinib in Alzheimer's disease

AB Science SA (NYSE Euronext - FR0010557264 - AB), a pharmaceutical company specializing in the research, development and commercialization of protein kinase inhibitors (PKIs), today announces the publication of a wide-ranging independent review article entitled 'Masitinib for the treatment of mild to moderate Alzheimer's disease' in the peer-reviewed journal Expert Review of Neurotherapeutics.

Authored by leading researchers in the fields of Alzheimer's research, including Prof. Antoni Camins (Faculty of Pharmacy, University of Barcelona), this article reviews the role of neuroinflammation and the specific contribution of mast cells to Alzheimer's disease (AD) pathophysiology. In particular, the potential therapeutic role of masitinib in AD is presented with commentary on its dual actions as an inhibitor of mast cell–glia axis and a Fyn kinase activity in the context of AD pathology.

An extract from the 'Expert commentary' section of this article reads as "*With the involvement of multiple signaling cascades, it is quite possible that a single drug could target more than one pathway. Such is the case of masitinib, a TKI which is capable of both c-kit and Fyn inhibition. Masitinib, in combination with other disease-modifying compounds, could be instrumental in improving dendritic integrity in memory circuits. Dual actions of masitinib may lead to improvements in synaptic plasticity in patients with mild to moderate forms of* AD."

This publication is accessible online from the peer-reviewed journal Expert Review of Neurotherapeutics and can be cited as: Folch J, et al. Masitinib for the treatment of mild to moderate Alzheimer's disease. Expert Rev Neurother. 2015 May 11:1-10. (doi:10.1586/14737175.2015.1045419). The publication can be accessed through the pubmed link : http://www.ncbi.nlm.nih.gov/pubmed/25961655.

Expert Review of Neurotherapeutics provides expert reviews on the use of drugs and medicines in clinical neurology and neuropsychiatry. The Expert Reviews Series is exceptional as the expert authors expand beyond their article's conclusion and offer their opinion about future progression in that area.

Alain Moussy, CEO and co-founder of AB Science, said: *"This publication is a positive news because it was initiated by independent experts and confirms the scientific rationale and potential for masitinib in Alzheimer's disease. It follows the recent positive milestone of futility analysis that was successfully passed for the on-going phase 3 study of masitinib in this indication. The next step will be the interim analysis of the study, which is expected end of 2016".*

Phase 3 status of masitinib in Alzheimer Disease

The on-going phase 3 is a double-blind, randomized, placebo-controlled study (AB09004) designed to assess the safety and efficacy of masitinib in patients with confirmed mild to moderate Alzheimer's disease. The treatment period is 24 weeks. In this study, masitinib is given as add-on therapy to cholinesterase inhibitor (donepezil, rivastigmine or galantamine) and/or memantine). The main measures are the change in two commonly used clinical assessments: the effect on ADCS-ADL, which measures self-care and activities of daily living assessed, and the effect on ADAS-Cog, which the effect on cognition and memory.

The current phase 3 study AB09004 in Alzheimer's disease has been assessed as non futile by the Independent Data Monitoring Committee (IDMC). A futility analysis tests the inability of a clinical study to

achieve its efficacy objective. Hence, a conclusion that a study is not futile suggests that a clinical study can achieve its stated efficacy objective and is worth pursuing. The IDMC recommendation was performed after about one third of the patients were enrolled into the study and had reached the 24 week treatment duration of the study.

The study previously passed all reviews of safety data by the Independent Data Safety and Monitoring Committee, indicating that there was no major or unexpected safety concern with masitinib in this patient population.

Previous clinical proof of concept

As a reminder, proof of concept for the evaluation of masitinib in Alzheimer's disease was established by a phase 2 study. This was a double-blind, placebo-controlled study to evaluate masitinib in patients suffering from mild to moderate Alzheimer's disease after a 24-week treatment period. A total of 35 patients were included. 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 showed 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 have been published in Alzheimers Res Ther. 2011 Apr 19;3(2):16. doi: 10.1186/alzrt75.

Scientific rationale

The therapeutic benefit of masitinib in Alzheimer's disease is expected to be exerted through 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 Aβ signaling and Tau phosphorylation.

Neuroinflammation is thought to be a major contributor in the pathogenesis of Alzheimer's disease[1,2,3]. 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. These cells release large amounts of proinflammatory mediators and therefore play an important role in sustaining the inflammatory network of the central nervous system. Mast cell–microglia cross talk is also thought to contribute to the exacerbation of acute symptoms of chronic neurodegenerative disease and accelerate disease progression. Masitinib's effectively inhibits the survival, migration and activity of mast cells through inhibition of essential growth and activation signaling pathways. 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.

Additionally, perivascular localized mast cells secrete numerous vasoactive molecules that regulate BBB permeability, which may be of therapeutic significance because a defective BBB is a common finding in Alzheimer's disease. Therapies such as masitinib with potential to maintain or reinforce the integrity of the BBB could thus be beneficial in Alzheimer's disease.

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

Targeted population

Estimations in the prevalence of Alzheimer's disease varies. Yet Alzheimer's disease remains a major health problem with between 5 and 10 million people affected 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 cause among Americans aged more than 65 years.[6,7,8]. Worldwide it is thought that there are more than 15 million people affected by Alzheimer's disease.[8]

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Status of masitinib clinical development in human medicine

Masitinib is currently developed in 13 phase III indications; 7 in oncology, 3 in inflammatory diseases, and 3 in neurodegenerative diseases. Additionally, a large phase II clinical program is ongoing, mainly in oncology. In case of positive results, phase III studies will be initiated following these phase II studies. Overall, clinical development has been initiated in more than 30 countries, without any licensing agreement. Therefore, AB Science has retained full ownership of masitinib.

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 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 in cancers, inflammatory diseases, and central nervous system diseases, both in humans and animal health.

AB Science has developed a proprietary portfolio of molecules and the Company's lead compound, masitinib, has already been registered for veterinary medicine in Europe and in the USA. The company is currently pursuing thirteen phase 3 studies in human medicine in first-line and second-line GIST, metastatic melanoma expressing JM mutation of c-Kit, multiple myeloma, metastatic colorectal cancer, metastatic prostate cancer, pancreatic cancer, mastocytosis, severe persistent asthma, rheumatoid arthritis, Alzheimer's disease, progressive forms of multiple sclerosis, and Amyotrophic Lateral Sclerosis. The company is headquartered in Paris, France, and listed on Euronext Paris (ticker: AB).

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

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