



PRESS RELEASE

NEW DATA REVEAL THE DELETERIOUS ROLE OF ACTIVATED MAST CELLS ON MOTOR NEURONS IN AMYOTROPHIC LATERAL SCLEROSIS (ALS) AND THE PROTECTIVE EFFECT OBSERVED UPON TREATMENT WITH MASITINIB

RESULTS PUBLISHED IN THE PEER-REVIEWED JOURNAL *ACTA NEUROPATHOLOGICA COMMUNICATION*, FURTHER SUPPORT MASITINIB'S POTENTIAL BENEFIT IN ALS

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AB Science SA (Euronext - FR0010557264 - AB) today announced the publication of a pathogenic mechanism triggered by mast cells in the amyotrophic lateral sclerosis (ALS) spinal cord that can be targeted by masitinib. These findings add to the growing body of evidence linking mast cells with a pathogenic role in neurodegenerative conditions by describing, for the first time, disease-specific mast cell characteristics (phenotype) and their precise localization in postmortem ALS patients' spinal cords, as well as the mechanism of mast cells to induce motor neuron damage and/or vascular dysfunction in ALS.

The publication, led by researchers from the Institut Pasteur de Montevideo, the University of Alabama at Birmingham (UAB), the Oregon State University (OSU) and the IMAGINE Institute of Paris, is entitled, "*The pathogenic role of c-Kit+ mast cells in the spinal motor neuron-vascular niche in ALS*" [1].

This article and its accompanying online supplemental material are freely accessible online from the peer-reviewed scientific journal *Acta Neuropathologica Communications* website:

<https://actaneurocomms.biomedcentral.com/articles/10.1186/s40478-021-01241-3>.

"In this research, we have shown for the first time that mast cell number and trafficking into the spinal cord of an ALS animal model were downregulated by masitinib, with subsequent neuroprotective effects in ALS. Overall, these data further reinforce the rationale for masitinib's potential neuroprotective effect in ALS patients", said Emiliano Trías, senior author of the paper.

"These new data further corroborate the biological plausibility for using masitinib in ALS and support previous clinical findings that masitinib may provide a greater benefit if administered at an early stage of the disease course", said Professor Luis Barbeito, Head of the Neurodegeneration Laboratory (Institut Pasteur in Montevideo, Uruguay).

It has previously been shown that upon activation, mast cells undergo degranulation with the ability to increase vascular permeability, orchestrate neuroinflammation and modulate the neuroimmune response. However, the prevalence, pathological significance, and pharmacology of mast cells in the central nervous system of ALS patients remain largely unknown. Kovac and colleagues showed that mast cells and their c-Kit+ precursors infiltrate into the degenerating spinal cord of both ALS patients and an animal model of ALS. This phenomenon is accompanied by marked blood spinal cord barrier pathology, characterized by frequent morphological abnormalities, allowing the leakage (extravasation) of cells from blood, including c-Kit+ mast cell precursors. Because masitinib potently inhibits the SCF/c-Kit pathway in mast cells, the administration of masitinib (50 mg/kg/d) in post-paralysis SOD1^{G93A} mice for 10 days significantly reduced the number of mast cells in the lumbar motor neuron-vascular niche, with respect to control mice.

Masitinib-treated animals also showed a 30-40% reduction in microvascular abnormalities relative to control mice and a 50% reduction in the number of c-Kit+ mast cell precursors infiltrating the spinal cord parenchyma.

Together, these findings provide the first description of disease-associated mast cell phenotypes in the ALS spinal cord and reveal novel potential interactions between mast cells and the cellular components of the motor neuron-vascular niche.

These results are consistent with a masitinib protective effect via c-Kit inhibition, preventing the trafficking of mast cell precursors and mast cell local differentiation in the motor neuron-vascular niche.

These new pharmacology data add to the growing body of literature [2–6] that support recently published clinical findings showing that masitinib may provide a survival benefit if administered at an early stage of the disease course [7–8].

As a reminder, the survival analysis followed all patients originally randomized in study AB10015 for an average duration of 75 months from the date of diagnosis. In ALS patients with mild or moderate disease severity at baseline, it was seen that treatment with 4.5 mg/kg/day masitinib (n=50) as an add-on to standard riluzole prolonged survival by 25 months relative to those treated with riluzole alone (n=63) (median OS of 69 versus 44 months, respectively, P=0.037) with a 44% reduced risk of death. People with mild or moderate ALS comprised patients that had not suffered a complete loss or severe impairment of ALSFRS-R related functionality at the time of masitinib treatment initiation (i.e., patients with a score of at least 2 on each ALSFRS-R individual component). This population corresponds closely to the patient cohort enrolled in confirmatory phase 3 study, AB19001.

About Acta Neuropathologica Communications

Acta Neuropathologica Communications, the sister journal to *Acta Neuropathologica*, has an impact factor of 6.5, articles on mechanisms of neurological disease based on experimental or human tissues using molecular, cellular and morphological techniques.

References

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About amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is a fatal motor neuron disorder that is characterized by progressive loss of the upper and lower motor neurons at the spinal or bulbar level. The disease belongs to a group of disorders known as motor neuron diseases, which are characterized by the gradual degeneration and death of motor neurons. In ALS, both the upper motor neurons and the lower motor neurons degenerate or die, and stop sending messages to muscles.

The prevalence of ALS in western countries is fairly uniform at 6 per 100,000 persons, corresponding to around 30,000 cases in Europe and 20,000 in the USA.

The first drug treatment for ALS, riluzole (Rilutek), was approved in 1995. In Europe, there has been no new treatment approved since riluzole.

About masitinib

Masitinib is a 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, inflammatory diseases and viral 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.

Forward-looking Statements - AB Science

This press release contains forward-looking statements. These statements are not historical facts. These statements include projections and estimates as well as the assumptions on which they are based, statements based on projects, objectives, intentions and expectations regarding financial results, events, operations, future services, product development and their potential or future performance.

These forward-looking statements can often be identified by the words "expect", "anticipate", "believe", "intend", "estimate" or "plan" as well as other similar terms. While AB Science believes these forward-looking statements are reasonable, investors are cautioned that these forward-looking statements are subject to numerous risks and uncertainties that are difficult to predict and generally beyond the control of AB Science and which may imply that results and actual events significantly differ from those expressed, induced or anticipated in the forward-looking information and statements. These risks and uncertainties include the uncertainties related to product development of the Company which may not be successful or to the marketing authorizations granted by competent authorities or, more generally, any factors that may affect marketing capacity of the products developed by AB Science, as well as those developed or identified in the public documents published by AB Science. AB Science disclaims any obligation or

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