PRESS RELEASE

AB SCIENCE ANNOUNCES THAT HEALTH CANADA HAS ISSUED A NOTICE OF DEFICIENCY-WITHDRAWAL (NOD/w) FOR MASITINIB IN AMYOTROPHIC LATERAL SCLEROSIS

AB SCIENCE INTENDS TO SUBMIT A REQUEST FOR RECONSIDERATION

Paris, 26 February, 2024, 6.15pm CET

AB Science SA (Euronext - FR0010557264 - AB) today announces that Health Canada has issued a Notice of Deficiency-Withdrawal (NOD/w) regarding its New Drug Submission (NDS) for masitinib in the treatment of amyotrophic lateral sclerosis (ALS).

Health Canada stated that a Request for Reconsideration can be filed within 30 days of receiving the NOD/w.

AB Science intends to submit a Request for Reconsideration. The reconsideration process will re-examine, with new assessors, the decision based on information that was included in the original submission. During this process, the applicant may be given an opportunity to be heard for the first time by a panel of experts. The reconsideration process could take up to 6 months.

The key major clinical concerns considered unresolved at the end of the procedure and the rationale for reconsideration are as follows:

1) Multiple amendments have been made that create uncertainty of the reliability of the study data

A request for reconsideration could be filed on the basis of the following points:

The Agency recognized that:

- Changing the status of a study from phase 2 to phase 3 may not be uncommon, especially in rare or terminal diseases.
- Multiple amendments may be an inevitable situation in some studies, including for strategic reasons, and that the number of amendments (3) made for study AB10015 are in line with the average number of amendments (3.3 per protocol) highlighted in a recent Tufts Center for the Study of Drug Development report [1].
- Amendments of study AB10015 were not data-driven.
- Study AB10015 had broad inclusion criteria with a heterogenous population, and the Agency did not dispute the need to limit heterogeneity.
- Post-onset decline of 1.1 point per month may be a relevant prognostic factor and therefore the distinction between Normal and Fast progressors may be less arbitrary than initially considered.

However, the Agency considered that amendments have been made late and were not sufficiently justified. Counterarguments to this could include:

- The distinction between Normal and Fast progressors was made in an entirely blinded and sufficiently prospective manner, in terms of timing (2.5 years prior to unblinding) and in terms of data accrual (12% of the enrolled patients who could have reached the study's primary analysis timepoint, meaning 88% of the data remained to be acquired and only 8 Fast progressor patients, across 3 treatment arms, could have reached the study's primary analysis timepoint).
- Excluding Fast progressor patients from the primary analysis was adequately justified for the reasons of limiting missing data, as recommended by relevant guidelines. An expectation of there being a high discontinuation rate for Fast progressor patients at the study's primary analysis timepoint of 48 weeks was confirmed with a discontinuation rate of over 50% versus 25% for Normal progressor patients.

This amendment was also adequately implemented, being a decision from the study's principal coordinator and steering committee that was validated by all agencies, including Health Canada, in a context of a pivotal study.

2) Missing data have been treated in the planned primary and sensitivity analyses with LOCF (last observation carried forward) imputation method, potentially creating a bias in favor of treatment

A request for reconsideration could be filed on the basis of the following points:

The Agency recognized that the concern about the non-linearity of the distribution of the ALSFRS-R data set used for the test of the primary analysis (ANCOVA test) was resolved by the positive pre-specified rerandomization test, which does not make assumptions about the normality of the data distribution.

However, the Agency considered that the LOCF method used for imputation of missing data could potentially bias results in favor of masitinib. Counterarguments to this could include:

- Various sensitivity analyses, not based on LOCF method and requested by agencies, were performed using different recognized methodologies for imputing missing data, including multiple imputation (p=0.020), the most conservative jump-to reference (JTR) analysis (p=0.039), and copy of increment (CIR) analysis (p=0.0477), all pointing toward the superiority of masitinib.
- The predefined Progression Free Survival (PFS) endpoint, which is not affected by LOCF methodology, was significantly increased by 4 months.
- The non-parametric Combined Assessment of Function and Survival (CAFS) endpoint, incorrectly assumed by the Agency to be based on LOCF methodology, whereas it is not, approached the conventionally statistically significant outcome of 5% (p=0.0776), even though the study was not powered for this secondary endpoint.
- AB Science provided a methodologically justified new claim "patients with ALS prior to any loss of function", where CAFS and Overall Survival (OS) are significantly improved.

3) New proposed claim, a subgroup called "patients with ALS prior to loss of function" which shows a significant gain in OS and CAFS is considered post hoc

A request for reconsideration could be filed on the basis of the following points:

AB Science proposed a reduced claim "patients with ALS prior to any loss of function", this reduced claim being justified by the strict application of EMA guidance (EMA/CHMP/539146/2013) on the investigation of subgroups in confirmatory clinical trials.

While the Agency recognized that this claim may be logical and in line with ALS guidelines recommending selecting ALS patients as early as possible, they also considered that this EMA guidance was only applicable for pre-specified subgroups. A counterargument to this opinion, in favor of it being applicable to AB10015, is that this EMA guidance states that "*it might be of interest to identify a subgroup that has not been pre-specified as part of the confirmatory testing strategy, where efficacy and risk-benefit would be convincing*".

In this claim, the treatment effect is exceptionally strong, with a significant CAFS (p= 0.0290) and significant long-term median OS benefit of +10 months (p=0.0395), and +22 months (p=0.0192) when placebo-treated patients who switched to masitinib during the extension period are censored at the time of the switch.

The Agency also considered that OS could have been biased by confounding factors. A counterargument to this could be that OS is the gold standard endpoint in ALS and is unbiased regardless of post study treatments because no drug has demonstrated OS benefit (except riluzole which was available to all patients) and because all patients had the same possibility to benefit from tracheostomy or permanent or non-permanent ventilation.

Based on the supporting arguments and counterarguments outlined above, AB Science intends to submit a Request for Reconsideration. Other points of concern identified by the agency will also be responded to.

Reference

[1] Getz K. , Smith Z. , Botto E. , Murphy E. , & Dauchy A.. New benchmarks on protocol amendment practices, trends and their impact on clinical trial performance. 2023. https://doi.org/10.21203/rs.3.rs-3168679/v1

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 undertaking to update the forward-looking information and statements, subject to the applicable regulations, in particular articles 223-1 et seq. of the AMF General Regulations.

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