DNA Finance

Your analyst: Claire Bendao
claire.bendao@dnafinance.fr
+33 6 43 57 83 95

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AB Science (EURONEXT: AB)

Executive Summary

On May 29, 2024, AB Science announced that the Committee for Medicinal Products for Human Use (CHMP) had adopted a trend towards a negative opinion on the application for conditional marketing authorization of masitinib for Amyotrophic Lateral Sclerosis (ALS). This decision was aligned with our analysis from last March: *"The recent negative feedback from Health Canada certainly increases the risk of an aligned response from the European Medicines Agency (EMA)."* This stance results from four major clinical objections raised by the EMA regarding the Phase II/III trial.

However, the EMA's decision applies solely to the conditional approval of masitinib, considering Phase II/III results. Generally, obtaining health authorities' approval based only on a single trial is extremely complex as the agency typically requires a second Phase III study to confirm the initial clinical efficacy advanced results. Therefore, AB Science is currently conducting a confirmatory Phase III trial in ALS to validate the Phase II/III results. The design of this confirmatory Phase III trial seems to meet the EMA's expectations raised by the clinical objections. Thus, if the results of this study are positive, we believe masitinib is approvable for ALS by health agencies.

Taking a broader perspective and situating AB Science's product within the current landscape of advanced developments in ALS, masitinib appears to be well-positioned. Indeed, since the beginning of 2024, the landscape of advanced clinical developments for ALS has been completely disrupted due to the successive study failures of biotechnology companies in which much hope had been placed: Ferrer Internacional (Spain), Denali Therapeutics (US) as well as its strategic partner Sanofi (FR), and Amylyx Pharmaceuticals (US). Despite the diverse attempts to develop drugs in this therapeutic area driven by pharmaceutical companies, only generic riluzole, and edaravone (Mitsubishi Tanabe), approved only in the US and Canada, are currently marketed for the broad ALS population. However, their limited efficacy leaves ALS patients with no highly effective treatment, and these three recent failures have significantly reduced the number of studies currently in advanced development phases.

While these failures have been dramatic for ALS patients, they have nonetheless shed light on the expectations and requirements of the health agencies, offering biotechnological companies developing ALS treatments a clearer framework to align with these expectations and maximize the chances of approval.

In this evolving landscape, where competition has diminished, and in light of the recommendations recently established by health agencies, AB Science, currently conducting a confirmatory Phase III study to reproduce the previously demonstrated Phase II/III efficacy of masitinib, emerges as a well-positioned player.

Our analysis focuses on the credibility of this ongoing Phase III study regarding the expectations of health agencies and its positioning within the current landscape of advanced developments in the field of ALS.

In this context, this note will first explain the reasons for the recent negative feedback from the EMA and analyze how the ongoing Phase III trial addresses the clinical objections raised by the EMA. Secondly, it will offer an overview of the treatment options approved or in development to address ALS patients. Then, it will delve into the recent events that have impacted the landscape of advanced clinical developments and highlight what these successive failures have revealed regarding the expectations of health authorities. Finally, it will assess how AB Science's clinical development in ALS aligns with these expectations, thereby strengthening the company's position as a key player in the ALS development field.

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Recent negative feedback from the EMA on masitinib Phase II/III for ALS

AB Science develops masitinib, a tyrosine kinase inhibitor, which has demonstrated through several publications to target the innate immune system in the microenvironment of the neurons through mast cells and microglia. The company is advancing this product across various neurological indications, including ALS.

ALS is a devastating rare neurological disease affecting the nerve cells responsible for controlling muscle movement and breathing. Over time, these neurons gradually degenerate and die, resulting in muscle weakness, stiffness, paralysis, and ultimately, death. As the disease progresses, individuals gradually lose their ability to move, speak, eat, and breathe independently. Globally, the annual incidence rate is currently estimated at 1 in 50,000, and the prevalence rate averages 1 in 20,000 per year, amounting to a total of 250,000 patients. With an anticipated life expectancy of 27-41 months from time of symptom onset, developing a new effective treatment strategy is essential.

In 2017, AB Science completed its Phase II/III study followed by a post-hoc analysis published in 2021. Based on these results, AB Science decided to pursue early market access from both the EMA and Health Canada with only one Phase III trial. While this decision was certainly worth considering, as it attempted a development shortcut that was unlikely but not impossible, it diverged from the conventional pathway. Even though AB Science's dossier presented significant strengths, obtaining approval based solely on one advanced trial remains extremely complex in ALS.

On May 29, 2024, AB Science announced that the CHMP had leaned towards a negative opinion on the application for conditional marketing authorization of masitinib in ALS. During a webinar hosted by the management the following day, it was disclosed that the CHMP raised four major clinical objections, which were pivotal in their decision :

- Issues regarding Good Clinical Practices (GCP),
- Exclusion of fast-progressing patients ("Fast Progressors") from the primary analysis study population,
- Handling of data regarding treatment discontinuation, and
- The fact that the proposed population for the label —patients with less severe symptoms at baseline—was identified post-hoc

The crucial focus now is to analyze the confirmatory Phase III in light of this EMA feedback. As it is designed in a way that addresses the previous clinical objections raised by the EMA, we anticipate that if the results replicate those observed in Phase II/III among the selected population—patients with less severe symptoms at baseline—masitinib is poised for approval in the ALS indication.

TABLE 1
Phase III design in light of EMA's 4 major clinical objections

EMA's major clinical objections on the Phase II/III	Phase III in light of these major clinical objections
GCP deviations to the protocol	GCP inspection of Phase III conducted by ANSM in 2019 authorizing Phase III continuation
Exclusion of fast-progressing patients for the primary outcome	Population selected at the beginning of the study and validated by FDA and EMA
Handling of data regarding treatment discontinuation (missing data)	Statistical treatment of missing data validated by FDA and EMA prior to study start
Post-hoc identification of a subgroup for the label	Phase III conducted in the population identified in Phase II/III as the most promising

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Current Landscape in the ALS field

Riluzole (Rilutek; Sanofi), approved in 1995, marked the initial step in ALS treatment, albeit with modest efficacy, prolonging symptom progression and survival by only three months. Decades of research ensued until the FDA granted approval for a new therapy, Edaravone (Radicava; Mitsubishi Tanabe), in May 2017. In pivotal Phase III trials, intravenous edaravone demonstrated a significant slowing of physical function decline, with a +2.5-point difference (p = 0.0013) compared to placebo, as measured by the ALS Functional Rating Scale-Revised (ALSFRS-R), which ranges from 0 to 48, with higher scores reflecting better functional status. Based on these results, the US, Canada, and Japan approved the drug; however, the EMA did not pursue approval due to insufficient efficacy evidence.

The modest life extension offered by approved drugs emphasizes the urgent need for improved treatments. Given the disease's complexity and the multitude of potential mechanisms to address it, there is an opportunity to enhance treatment effectiveness by combining existing therapies with new ones.

Thus, numerous biotechnology companies are currently working on developing potential treatments for ALS aimed at slowing or halting its progression.

TABLE 2

Current Overview of Advanced ALS Trials in the broad population of ALS patients

Sources:

Current State and Future Directions in the Therapy of ALS – *Cells*, 2023 June

Evaluating emerging drugs in phase II & III for the treatment of amyotrphic lateral sclerosis – *Taylor & Francis*

Therapeutic Agent	Company	Pathway	Study Cohort	Clinical Phase	Study Duration
Masitinib	AB Science	Neuroinflammation	495	Phase IIIb	48 weeks
MSC-NTF cells	BrainStorm Cell Therapeutics	Stem cells	200	Phase IIIb	24 weeks
Memantine	University of Edinburgh	Excitotoxicity	800	Phase II/III	72 weeks
Trazodone	University of Edinburgh	Oxidative stress	800	Phase III	72 weeks
Deferiprone	Lille University Hospital	Oxidative stress	372	Phase II/III	48 weeks
Triumeq	Macquarie University	Neuroinflammation	390	Phase III	96 weeks
MN-166/Ibudilast	MediciNova	Neuroinflammation	230	Phase II/III	48 weeks
DNL343	Denali	Oxidative stress	240	Phase II/III	24 weeks
ABBV-CLS-7262	AbbVie/Calico	Oxidative stress	300	Phase II/III	24 weeks

Among the companies that are most advanced in their clinical development, AB Science stands out as it is the only company which has published positive Phase IIb/III results on the ALSFRS-R score at week 48.

AB Science's masitinib reached its primary endpoint in a Phase IIb/III study, demonstrating statistically a +3.3-point difference (p = 0.014) in the ALSFRS-R score at week 48 compared to placebo for patients classified as "Normal Progressors", defined as the primary analysis population, representing 84% of the total Phase IIb/III ALS participants.

Following the recommendations of health agencies, AB Science conducted a long-term survival analysis on participants, with an average follow-up of 75 months from diagnosis, showing a trend of increased survival of +6 months (p = 0.076). In addition, because the Phase IIb/III study had broad inclusion criteria in terms of disease severity, with no restriction on the ALSFRS-R score at baseline, AB Science conducted a post-hoc subgroup analysis according to baseline.

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This analysis was of interest because there was a greater proportion (20%) of very severe patients (i.e. score of 0 on any ALSFRS-R item) in the masitinib arm as compared with the control arm (8%). As highlighted by the management, this subgroup analysis revealed a strong and consistent treatment effect when excluding this very severe patients, with a survival benefit of +12 months (p = 0.0192). Such a consistent and substantial increase represents excellent very promising results compared to other drugs on the market.

TABLE 3

Masitinib effect on the subgroup 'prior to any complete loss of function' in Normal Progressors

*CIR = Imputation of missing data based on Copy Increments in Reference methodology

Differential treatment effect (Masitinib 4.5 vs placebo)		**Subgroup 'Prior to any complete loss of function'** (Normal Progressors)
ΔALSFRS-R (CIR*)	Diff. of mean	3.13
	p-value	0.0308
Combined Assessment of Function and Survival (CAFS)	Relative benefit	20.2%
	P-value	0.0290
Quality of Life (ALSAQ-40) (CIR*)	Diff. of mean	-6.22
	p-value	0.044
Forced Vital Capacity (FVC) (CIR*)	Diff. of mean	7.59
	p-value	0.0384
Median PFS	Gain	+ 9 months
	Median [95% CI]	25 [17; NE] vs 16 [11; 19]
	p-value log rank	0.0057
Median OS (Long-term) (censoring of placebo at time of switch to masitinib)	Gain	+ 12 months
	Median [95% CI]	53 [36; NE] vs 41 [30; 54]
	p-value log rank	0.0192

Thus, to replicate the promising efficacy observed in the Phase IIb/III and long-term analysis, AB Science initiated a confirmatory Phase III trial for masitinib in ALS in 2021. The primary endpoint, ΔALSFRS-R at week 48, focuses on a large cohort of "Normal Progressor" patients in early disease stages, very close to the sub-population of interest determined in the post-hoc Phase IIb/III study.

The University of Lille's Phase II/III trial with deferiprone, and AbbVie and Calico's Phase II/III trial with ABBV-CLS-7262 are also advanced in the landscape, with results expected within the year. However, contrary to AB Science, none of these studies have demonstrated an effect of their compound at week 48. Unless exceptional results arise from their Phase II/III trials, they will likely need to conduct a second confirmatory Phase III study to validate, if successful, their findings.

Additionally, even though its first Phase III study failed to meet its primary endpoint, the biotechnology company BrainStorm Cell Therapeutics announced in April 2024 that the FDA has provided written agreement under a special protocol assessment (SPA) for the design of its confirmatory Phase III trial, based on ad-hoc results and evaluation of biomarkers, enabling the company to initiate its second Phase III in 2024. The fact that the first Phase III study did not meet its primary endpoint, along with the study's duration being limited to week 24 with only 200 patients from a subpopulation of the initial study, presents elements that reduce the chances of success for the study.

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A series of failures in advanced clinical trials for ALS in Q1 2024

At the beginning of 2024, both Sanofi and Denali Therapeutics' receptor-interacting protein kinase 1 inhibitor, as well as Ferrer Internacional's free radical scavenger, have failed to achieve their ALSFR-S primary endpoints in Phase II and III studies, respectively. More recently, on March 8, 2024, Amylyx Pharmaceuticals announced the failure of their neuroprotective agent, Relyvrio, to achieve primary efficacy endpoints in the global Phase III PHEONIX trial. Consequently, the drug was withdrawn from the US and Canadian markets, where it had respectively received full approval (US) and Conditional Approval (Canada), based on the Phase II CENTAUR results, and had been marketed since Q4 2022.

These three failures on efficacy criteria reflect the complexity of developing an effective treatment for this aggressive disease with complex pathophysiology, leaving a sparse landscape of advanced biotechnology companies in this indication.

Insights from failures: Enhancing the understanding of health authority expectations in ALS studies

Two successive Phase III trials on a large cohort of patients

One key and complex element of ALS studies is the high 'discontinuation rate', which refers to missing data due to patients stopping treatment, mainly because of disease progression. On average, when looking at ALS studies, this proportion corresponds to approximately 30-35% of patients. Concerning this subject, the EMA recommends applying a penalty to these patients - then considered as placebo ("jump-to-reference" method), which complicates the statistical analysis of the results.

Thus, in order for studies to provide statistically solid and robust results, recent decisions from health agencies have shown that although guidelines may allow for a single trial to demonstrate a drug's effectiveness in certain urgent cases, they typically require compelling evidence from a second pivotal clinical trial, involving large study cohorts (several hundreds of participants) to consider a drug for approval.

Consistency of efficacy endpoints

Regarding primary efficacy endpoints, regulatory agencies' recommendations for ALS trials notably include measuring the change in the ALSFRS-R scale from baseline, with a "jump-to-reference" for patients who discontinued, as well as a trend in survival data. Additionally, evaluations of Amylyx Pharmaceuticals' Phase III trials has shown that agencies require the study to meet its secondary endpoints, which serve as valuable indicators of disease progression (muscle strength, respiratory function, and health-related quality of life). Finally, health authorities also require consistency in results, which can be reflected notably in a dose-response effect.

Study duration

In terms of duration, the recommendation by both agencies to assess an endpoint at 48 weeks, rather than 24 weeks, has proven to be crucial. Indeed, the recent Phase III failure of Amylyx Pharmaceuticals indicated that data at week 24 (from the initial study with positive results) did not predict the outcome at week 48 (from the subsequent confirmatory study where results were negative).

Similarly, edaravone was approved in the US and Canada based on a 24 weeks study, numerous trials were launched in European centers to obtain conclusive results and marketing authorization from the EMA, but they failed one after another. Among these studies, Ferrer Internacional recently conducted a Phase III study (ADORE) to investigate the efficacy and safety of an oral edaravone in ALS patients over 48 weeks. However, in January 2024, Ferrer Internacional announced that its Phase III study failed to meet its primary efficacy endpoint in the change of ALSFRS-R and key secondary endpoints, leaving the European market without access to edaravone for the foreseeable future.

This failure adds to several post-approval study failures on edaravone that did not meet their primary endpoints in demonstrating the product's efficacy, including two studies by Mitsubishi Tanabe and one by Witzel et al. We can therefore assume that from now on, both agencies will require results at 48 weeks before evaluating a potential approval.

AB Science's positioning considering recent agency feedback and the current competitive landscape

The recent feedbacks from agencies has led to a clearer understanding of their expectations regarding clinical design and results required in ALS trials. This understanding is crucial and beneficial for biotechnology companies to maximize their chances of demonstrating efficacy and advancing towards market authorization.

Based on this feedback, AB Science's confirmatory Phase III study intended to validate the results achieved with masitinib in Phase IIb/III appears to have a robust design. If it delivers good and significant results, it will be well-positioned to meet the expectations of regulatory agencies.

A second Phase III to confirm results from the Phase IIb/III

Health authorities do not usually grant market authorization based on Phase II or Phase II/III results unless the therapeutic agent's mechanism of action and clinical data from initial trials are exceptionally robust. Furthermore, the recent failures of Ferrer Internacional and Amylyx Pharmaceuticals have highlighted the need for a pivotal study to either confirm or refute the results of the initial study.

Thus, the negative response from the EMA regarding the ongoing conditional approval application, based solely on previous results, is not indicative of the outcome of the confirmatory Phase III, and so the decision of the health authorities when evaluating the forthcoming confirmatory Phase III data.

AB Science's confirmatory study design leveraging encouraging past results and aligned with agency recommendations to maximize success

AB Science's confirmatory Phase III, currently under recruitment, aims to demonstrate the effect of masitinib at 4.5 mg/kg/day, combined with riluzole, on change in ALSFRS-R score at week 48, in a specific cohort of ALS "Normal Progressor" patients with baseline functional score ≥ 2 on each ALSFRS-R items. This design aligns with the patient subgroup that demonstrated the greatest survival benefit with masitinib in the long-term survival analysis. From a mechanistic perspective, this conclusion is relevant because masitinib does not regenerate neurons; it is a disease modifier that can slow down disease progression. Moreover, there is clinical consistency in the results, notably the fact that masitinib exhibits a dose-response efficacy between 3 mg/kg/day and 4.5 mg/kg/day on the primary endpoint.

Furthermore, AB Science's study design meets the expectations of health agencies. Firstly, the confirmatory study size, involving approximately 500 patients split into two arms receiving masitinib at different doses and one arm receiving a placebo, ensures statistical robustness. Additionally, the selection of primary (ALSFRS-R score) and secondary (Progression-free Survival, Quality of Life, Forced Vital Capacity, muscle strength, Combined Assessment of Function and Survival) endpoints measured at 48 weeks conforms to agency recommendations.

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Conclusion

In light of recent regulatory decisions regarding masitinib's conditional approval in ALS and considering the recent failures of other advanced developments in the field, we believe that AB Science's ongoing confirmatory Phase III study is a necessary step for the company towards masitinib approval.

In a competitive landscape that has evolved significantly in recent months, AB Science now stands out as the company with the most advanced clinical trial in ALS. The company is particularly well-positioned as it is currently the only one to have demonstrated positive results at week 48 on the ALSFRS-R score, timepoint required by health agencies.

Furthermore, the confirmatory Phase III appears to be well-designed to validate the previous results and aligns with the expectations raised by the health agencies, facilitating market access for the drug upon positive results. As a consequence, the progression of this Phase III is now the most important key value driver of the company.

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