Jean Pierre LOZA
Financial Analyst / *Equity Analyst*
jean-pierre.loza@inextenso-finance.fr
Plus 33 1.41.09.44.80

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AB Science

Targeted therapies: for the central nervous system, inflammatory diseases and oncology

AB Science offers an attractive investment opportunity with a diversified clinical development program addressing unmet medical needs, whether they are very prevalent pathologies (Multiple Sclerosis, Alzheimer's disease) or orphan pathologies (Amyotrophic Lateral Sclerosis, Indolent Systemic Mastocytosis, Refractory Acute Myelogenous Leukemia), and adapted to the partnership strategy recently implemented by the company.

Two scientifically powerful platforms...

AB Science is developing two scientifically supported platforms with innovative and unique mechanisms of action. Derived from the first, masitinib specifically addresses pathologies of the Central Nervous System, as well as pathologies involving mast cells, an innate immune cell, involved in multiple pathophysiological phenomena. A new microtubule-destabilizing agent, AB8939, is derived from the second platform. This innovative molecule has multiple potential advantages over its predecessors, including insensitivity to degradation by myeloperoxidase and a strong synergistic effect with the standard treatment, azacitidine.

... including masitinib which is perfectly positioned...

In amyotrophic lateral sclerosis (ALS), the approach proposed with masitinib significantly improves the current standard of care. Masitinib, by inhibiting the tyrosine kinases KIT and CSF1R, acts via the activation of mast cells and microglia both in the CNS and in the peripheral nervous system with the clinical effect observed an increase in the lifespan of ALS patients, especially in patients in the early stage of the disease, while improving their functional abilities. By targeting mast cell and microglia-mediated neuroinflammation, masitinib reduces physical decline and transition to disability in progressive forms of multiple sclerosis (MS). The action of masitinib in Alzheimer's disease (AD) is mainly in the reduction of cognitive decline observed in patients. In addition, the action of masitinib on mast cells has also been proven, particularly in indolent systemic mastocytosis (SIM) as well as potentially in mast cell activation syndrome (MAS) and sickle cell anemia (SCD).

...with proven clinical results...

AB Science's clinical portfolio is now very advanced and is expected to deliver a number of results from confirmatory phase III clinical studies, particularly in ALS and MSI. Earlier clinical outcomes are also expected with masitinib in SAM and SCD, as well as with AB8939 in refractory acute myeloid leukemia. Masitinib is currently being evaluated by the Canadian and European regulatory authorities in the context of a conditional marketing authorization application for ALS, which represents a strong potential for acceleration in the short term in the event of a favorable outcome, without jeopardizing the prospect of eventual registration based on the ongoing confirmatory study, in the event of an unfavourable outcome.

Good "timing" to invest: Strong buy

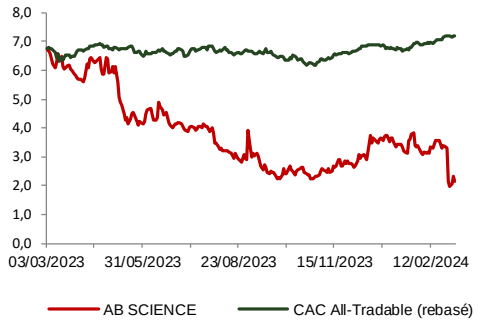
We initiate coverage of the company with a strong buy opinion and a price target of €3.79.

Recommendation	**1. Strong Buy**
Closing Price on 04 March 2024	**€ 2.130**
Target price	**€ 3.79 (+77.8%)**

Market data	
Reuters / Bloomberg ticker	AB-FR.PA / AB:FP
Market capitalisation (€m)	108.8
Enterprise value (€m)	95.9
Free Float (€m)	32.88 (30.2 %)
Number of shares	51 071 072
Daily volume	€ 578 851
Capital turnover rate (1 year)	77.16%
High (52 weeks)	€ 6.75
Low (52 weeks)	€ 1.96

Performances

Absolute perf.	1 month	6 months	12 months
	-32.8%	-29.8%	-68.4%



Current shareholding structure

Other Investors : 63,6% ; AMY SAS : 23,1% ; Alain Moussy : 13,3%

Agenda

Q2 2024: EMA decision
30 4 2024: Annual results 2023

Key figures

	2022	2023E	2024E	2025E	2026E
Sales (€m)	0.95	0.93	0.99	1.1	1.19
Change (%)	NS	NS	NS	*NS*	*NS*
EBITDA (€m)*	-18.89	-19.1	-17.89	-18.78	-19.41
EBIT (€m)*	-19.26	-19.19	-17.98	-18.69	-19.32
Ebit margin (%)	NS	NS	NS	NS	NS
Net profit gp sh. (€m)	-19.59	-19.45	-18.27	-19.01	-19.67
Net margin (%)	NS	NS	NS	NS	NS
EPS	-0.42	-0.38	-0.36	-0.37	-0.39

Ratios

	2022	2023E	2024E	2025E	2026E
EV / Sales	185.47	58.62	163.73	166.13	171.02
EV / EBITDA*	-17.61	-5.8	-8.2	-8.12	-9.42
EV / EBIT*	-17.15	-5.66	-8.04	-8.08	-9.37
P / E	-16.8	-6.59	-6.58	-5.1	-5.59
Gearing (%)	NS	NS	NS	NS	NS
Net debt / EBITDA*	2,44	2,42	3,34	2,30	2,54
ROCE (%)	-142%	-61%	-248%	38%	33%

* : EBITDA & EBIT under IFRS, ie taking into account R&D activation

Company Overview

Founded in 2001, AB Science is a clinical-stage company that designs and develops its own therapeutic molecules and specializes in chemically synthesized molecules, particularly tyrosine kinase inhibitors, a class of drugs that modify signaling pathways within cells.

AB Science has initiated a series of clinical trials in different indications with masitinib, a molecule that selectively inhibits KIT, CSF1R tyrosine kinases and thus modulates the activity of mast cells and macrophages, cells on the front line of innate immunity, involved in many neurodegenerative and inflammatory phenomena.

In neurodegenerative pathologies such as amyotrophic lateral sclerosis (ALS), progressive forms of multiple sclerosis (MS) and Alzheimer's disease (AD), it is the anti-neuroinflammation and neuroprotection counterpart of masitinib that is mobilized. The involvement of mast cells opens up another field of indications for masitinib, such as indolent systemic mastocytosis (MSI), mast cell activation syndrome (MAS), but also sickle cell anemia (SCD). Developments are underway with masitinib in Covid and metastasized prostate cancer eligible for docetaxel.

AB Science is already at a very advanced stage, as masitinib is in confirmatory phase III, the last stage before registration, in 4 indications, ALS, progressive forms of MS, AD, and MSI. In addition, the company has approached two regulatory authorities (EMA, Health Canada), for a conditional registration of masitinib in ALS based on an initial Phase IIB study that was positive.

AB Science is also developing a new platform in hemato-oncology based on microtubule destabilizing molecules (MDMs). AB8939, currently in phase I, the first compound from this platform, combines several advantages for its development in AML, namely an ability to overcome the mechanisms of "multidrug resistance", an ability not to be deactivated by myeloperoxidase, and finally a strong synergistic effect with the reference treatment, azacitidine.

SWOT

Forces

- Recognized know-how with innovative products;
- Stable management and scientific team involved in the capital;
- Two innovative proprietary platforms at different stages of maturity;
- Statistically demonstrated efficacy in multiple indications for MND and inflammatory diseases;

Weaknesses

- Limitation of self-financing capacity;

Opportunities

- Structurally important growth markets;
- Actual Medical Needs in MND and Inflammation;
- Masitinib in the conditional registration phase (Canada, EMA);
- Barriers to entry for innovative treatments in the sector;

Threats

- Need for additional funds for further development;
- Development of the two main assets could progress less quickly than expected.
- Very active competition in MND as well as in oncology or chronic inflammation;
- Refund policy and binding regulatory aspects;

Valuation Method

We have used several methods to promote AB Science. First, by evaluating the most clinically advanced projects (phases III initiated), then by making a sum of the parts. Next, we used a DCF and stock market comparables.

Project-Based Risk-Adjusted NPV (rNPV)

Our valuation by the rNPV model is based for the base scenario on 2 very advanced indications: SLA, MSI and to a lesser extent on the LMA and SMD stands at €5 per share.

Sum of the Parts (SOP)

The sum-of-parts method makes it possible to take into account the specificities of each project with its own criteria. This method shows a fair value of the share of €4.79 per share

Portfolio-wide DCF

The discounted operating free cash flow, with a weighted average cost of resources of 14.8%, values the stock at €4.64 per share.

Stock market comparables

After having composed a sample, admittedly not exhaustive, nevertheless significant, of a dozen companies active in neurology and neuro-oncology. The stock market multiples approach, using only EV/turnover ratios, results in a valuation of €1.13 per share.

Course Objective

Based on these methods, a price target of €3.79 and a strong buy recommendation emerge from these methods. However, several scenarios lead us to sensitivity analysis.

Synthesis and Opinion

It is a real opportunity to position ourselves today on AB Science, first and foremost because the company has a diversified and mature clinical development program, supported by convincing clinical results recognized by numerous peer-reviewed publications, and which is at the last stage of development before an application for regulatory registration: confirmatory Phase III.

A first confirmatory phase III study is underway in ALS with the objective of confirming the slowing of the progression of the disease. Another phase III study is currently underway in indolent mastocytosis. In addition, the FDA has authorized the company to perform two confirmatory Phase III trials with masitinib, one in progressive Multiple Sclerosis and the other in Alzheimer's disease, validating the relevance of the Phase IIB results obtained in these indications.

Thus, the company's newsflow should be sustained over the next 12 months with the continuation of these trials. In addition, the partnership strategy recently initiated by the company offers a short-term valuation perspective.

In addition, two applications for conditional registration in ALS are currently under review by the EMA and Health Canada (reconsideration request pending), and if one is granted, the company would then be in a "blue sky" situation. On the other hand, we consider that a refusal would not constitute either a failure of the program (because the rule remains to register on the basis of two phase III studies), nor a questioning of the relevance of the use of masitinib in ALS, which could be validated by the ongoing confirmatory phase III.

This is why we are initiating coverage of AB Science with a Strong Buy Opinion and a price target of €3.79 per share, i.e. a significant upside potential of +77.8%.

1 Investment Thesis

AB Science: Two molecules with varying degrees of advancement from two distinct platforms...

AB Science is a biopharmaceutical company that designs and develops molecules in several major public health indications and currently has two platforms in clinical development. From the first platform, masitinib is an inhibitor of tyrosine kinases, intracellular enzymes essential in the mechanisms of information transfer between the outside and inside of cells. This oral molecule was designed and developed to target certain cells of the innate immune system: mast cells and macrophages/microglia. These cells were initially confined as simple effectors of the allergic reaction, but scientific advances have shown their involvement in many other pathological mechanisms, in particular neurodegenerative diseases, but also inflammatory diseases and certain cancers. AB Science's other platform is organized around microtubule destabilizing agents. It currently addresses hematological cancers for which resistance to anti-tubulin agents has been demonstrated. A first molecule has been identified and synthesized, AB8939. In addition to a very high activity *in vitro* and *in vivo*, particularly in mouse PDX models of cytarabine resistance, this new chemical molecule has three characteristics that are very relevant for development in acute myeloid leukemia (AML), particularly for refractory or relapsed patients. It is not transported by PgP/BRCP efflux pumps and therefore evades the main mechanisms of multidrug resistance, from which naturally occurring tubulin inhibitors (*taxanes* and *vinca-alkaloids*) suffer. It is not deactivated by myeloperoxidase, as are *vinca-alkaloids*, an enzyme present in myeloid cells, and finally it has a strong synergistic effect with azacitidine, the reference treatment for AML.

... in three major types of indications...

AB Science focuses on neurodegenerative diseases (MNDs) such as amyotrophic lateral sclerosis (ALS), progressive forms of multiple sclerosis (MS), Alzheimer's disease (AD), for which there is a significant unmet medical need. For ALS, which is an orphan disease, there is no treatment that can at least stop the progression of the disease, if not reverse it. The same is true for progressive forms of MS or AD. The neuroprotective action proposed by masitinib, which is exerted both on the central nervous system via its action on microglia and mast cells and on the peripheral nervous system, via its action on mast cells, is very innovative. There is now a strong scientific consensus that drugs targeting these immune cells are at the forefront of research into the pathophysiological mechanisms of neurodegenerative diseases, and that drugs targeting these targets will have strong therapeutic potential.
Similarly, masitinib has clear applications in specific mast cell pathologies such as Indolent Systemic Mastocytosis (MSI), Mast Cell Activation Syndrome (MAS), a group of disabling pathologies characterized by mechanisms of uncontrolled mast cell activation in a variety of tissues and organs. Within these pathologies, the supply of masitinib, which targets the essential element of the pathophysiology of these conditions, appears to be quite safe. Mast cells could also play an important role in severe forms of sickle cell anemia and masitinib could thus play a beneficial role in the treatment of vaso-occlusive crises associated with this disease, and the clinical development of masitinib in phase 1/2 in partnership with the AP-HP in sickle cell anemia is one of the winning projects funded under the sixth call for projects "university hospital research in health" of the Investment Program of the future. In addition to these priority developments, masitinib is also in clinical development in metastatic prostate cancer, with a phase III study that has been carried out, and in Covid with two phase II studies expected in 2024.

With AB Science's second platform, it addresses oncology and more specifically certain hematological cancers such as Acute Myelogenous Leukemia (AML), Myelogenous Syndromes (MDS), as well as other indications such as sarcomas. In these indications, AB Science's pipeline is still in the preclinical and Phase I clinical phase, with a first product AB8939. Initial data show that these molecules that destabilize the tubulin have a particularly interesting therapeutic profile, both in terms of mode of action and targeting. Myelogenous leukemias mainly affect elderly individuals (> 60 years of age) and their prevalence is increasing in view of the general increase in life expectancy. In addition, AB Science is developing a second product with a new formulation for sarcomas (solid tumors for which the medical needs are also very high).

... in important markets with unmet medical needs...

According to Allied Market Research, the global market for ALS treatments was estimated to be over $662.3 million in 2022 and is expected to grow by 4.6% over the period 2022-2032. In 2032, the value of the contract is expected to be $1,039 million. Although considered a rare disease, ALS affects 450,000 people worldwide, including 30,000 people in the United States alone, and therefore has significant market potential. The increasing prevalence of ALS as well as the development of new therapeutic approaches are among the key elements driving the growth of this market. The FDA recently registered several molecules to treat ALS including *edaravone* (Radicava™) in 2017, *sodium phenylbutyrate combined with taurursodiol*, Relyvrio™ in 2022, and *tofersen* (Qalsody™) in 2023. In addition, the demand for therapeutic alternatives that modify the course of the pathology is growing. Despite a low average patient life expectancy of between 2 and 5 years, the costs of ALS in the U.S. are close to $6 billion. While the standard of care remains riluzole, a molecule registered in 1995, the care provided to patients in advanced stages ranges from $145,000 for Radicava™ to $185,000 for Qalsody™, which only treats a familial form (SOD1 mutation) of the disease.

The market for the treatment of indolent systemic mastocytosis is also booming. It was expected to reach $437.4 million in 2023 and post an average annual growth of 6.2%, until 2033. This growth takes into account the better understanding of the pathophysiology of this disease, in particular with the involvement of the tyrosine kinase KIT of mast cells and its mutations, and the emergence of new therapeutic alternatives recorded. Indeed, *avapritinib*

(Ayvakit™), a selective inhibitor of the mutated KIT tyrosine kinase D816V, initially registered in advanced gastrointestinal tumors (GIST) in 2020, has had its approval extended to aggressive mastocytosis, then to indolent systemic mastocytosis with an annual cost that we estimate at $198,000. Nevertheless, there is still a medical need for this rare disease since the standard treatments for MSI consist of relieving symptoms by reducing mast cell activation and therefore the release of "intramast cell" mediators.

Multiple sclerosis (MS) is one of the leading causes of neurological disability in young adults. This explains the significant size of the global Multiple Sclerosis (MS) market was estimated at $25.2 billion in 2023 and is expected to grow with an annual average of 4.76% during the forecast period 2023-2030 to reach $34.9 billion in 2030. This autoimmune disease is very heterogeneous. There are three main subtypes: relapsing forms of MS (RRMS), primary progressive MS (PPMS) and secondarily progressive MS with two subforms: secondarily progressive active (a-MS) and secondarily progressive inactive (nPS-MS). Although significant progress has been made in the relapsing-remitting form of multiple sclerosis, with more than a dozen products registered, there is still a very significant unmet medical need in the treatment of primary progressive multiple sclerosis (PPMS) and non-active secondary progressive multiple sclerosis (PSMS), as there is no effective treatment for nPS-MS and there is only one registered in the PPMS. MS affects nearly 2.3 million people worldwide and it is estimated that about 50% of MS patients will have MS-PP (10%) and/or MS-PSn (40%) during the course of their disease. There is therefore an urgent need to treat this important population. Thus, the primary progressive multiple sclerosis treatment market is expected to grow at an annual growth rate of 14.7% for the period 2022-2031, driving it from $828.4 million in 2022 to more than $3.2 billion (2031). In March 2017, Roche's *ocrelizumab* (Ocrevus™) received marketing authorization from the FDA for relapsing MS as well as primary progressive forms. This anti-CD20 antibody, which has an annual cost of $75,000, is estimated to have generated nearly $3.5 billion in sales globally in the first half of 2023.

The Alzheimer's disease market was estimated at $2.2 billion in 2020 and is expected to grow at a CAGR of 20% during the forecast period (2021-2035), reaching $13.7 billion. This acceleration is due to the ageing of the world's population, but also to the introduction of a new therapeutic class, anti-Ab antibodies, which is transforming the management of the disease while reducing therapeutic wandering. Several molecules in this class have been registered very recently in 2021 and 2023 in prodromal or very mild forms of the disease. These treatments, by influencing the course of the pathophysiology, modify the course of the disease, in particular by reducing the cognitive decline observed in these patients. However, these new molecules, although they have profoundly transformed the clinical and regulatory vision, are not active and effective in patients with mild to moderate dementias, who remain without a therapeutic solution. It is estimated that there are currently more than 6 million Americans of all ages living with Alzheimer's disease in the U.S. alone, and that number is expected to rise to about 13 million by 2050, with equally explosive health care costs associated with the disease, estimated at around $305 billion (2020).

... on which AB Science represents a real opportunity.

We believe that AB Science represents a real investment opportunity. First of all, because fundamentally the science on which the two platforms are based is robust and internationally recognized (numerous scientific publications) and arouses the interest of Key Opinion Leaders (KOLs). Secondly, masitinib offers a real interesting and differentiating therapeutic alternative for neurodegenerative pathologies such as ALS, MS or AD. In ALS, masitinib is one of the most advanced drug candidates in non-familial forms, following the recent failures of the RIPK1 inhibitor developed by Sanofi and a new oral formulation of edaravone developed by Ferrer, and pending the results of the confirmatory phase III study of Relyvrio. In progressive forms of MS, masitinib is also favourably positioned as a tyrosine kinase inhibitor, following uncertainties about BTK inhibitors in MS, *evrobrutinib* having failed in phase III in relapsing forms of multiple sclerosis, and *tolebrutinib* and *fenebrutinib* being put into *clinical hold* by the FDA due to liver risks. Finally, masitinib is known to be the most advanced drug candidate in mild and moderate AD (MMSE score [14-25]), while recently registered anti-Ab antibodies (*lecanemab* and *donanemab* were registered in presymptomatic and mild forms (MMSE scores [22–30] and MMSE [20–28], respectively).

2 Introduction

Listed on compartment B of Euronext Paris since 2010, AB Science is a biopharmaceutical company that develops innovative small chemical molecules resulting from its own research and acting on the innate immune system. Since its creation, AB Science has been committed to providing therapeutic solutions to meet certain unmet medical needs. The company currently has two drug candidates in the clinical phase, including masitinib in late-stage clinical development (confirmatory phase III).

AB Science, with masitinib, a tyrosine kinase inhibitor, aims to address neurodegenerative pathologies and those involving mast cells. This class of drugs has so far mainly been used successfully against cancers[1], but a growing number are registered or developed in non-oncology indications, including *sirolimus*, *tofacitinib* or *fedratinib* in indications such as kidney transplantation, rheumatoid arthritis or myelofibrosis or Bruton's tyrosine (BTK) inhibitors developed in neurology.

[1] Roskoski, R. Jr. et al., Properties of FDA-approved small molecule protein kinase inhibitors: A 2020 update. *Pharmacological Research, 152,104609*

AB Science is developing masitinib in three neurodegenerative indications, amyotrophic lateral sclerosis, progressive forms of multiple sclerosis, and Alzheimer's disease. In these diseases, the deleterious involvement of mast cells and microglia cells has been proven, and the approach of specifically inhibiting certain tyrosine kinases (c-KIT, LYN, FYN and CSF1R) that modulate the activity of these cells, seems particularly relevant. Based on this strong scientific and biological rationale, AB Science has been able to obtain the first evidence of the safety and efficacy of this approach in phase IIb/III clinical studies, which have been the subject of peer-reviewed publications. In all three indications, masitinib is now in confirmatory Phase III stages, the final steps before registration. Masitinib is also the subject of clinical development in pathologies characterized by mast cell involvement, namely indolent systemic mastocytosis (confirmatory phase III), mast cell activation syndrome (phase II) and sickle cell anemia (phase I/II). In addition, masitinib is also in clinical development in metastatic prostate cancer, with a phase III study that has been carried out, and in Covid, with two phase II studies expected in 2024.

AB Science is developing another drug candidate, AB8939, derived from a second "Microtubule Destabilizer Agents (MDA)" platform. AB8939 has three properties that have been tested mainly *in vitro* and *in vivo* and make it a very serious candidate for development in acute myeloid leukemia (AML), particularly for refractory or relapsed patients. It is not transported by PgP/BRCP efflux pumps and therefore evades the main mechanisms of "multidrug resistance", it is not deactivated by myeloperoxidase, an enzyme present in myeloid cells, and finally it has a strong synergistic effect with azacitidine, the reference treatment for AML.

With these two platforms, AB Science targets highly prevalent indications (Alzheimer's disease, progressive forms of multiple sclerosis) and rare indications (amyotrophic lateral sclerosis, indolent systemic mastocytosis, mast cell activation syndrome, severe forms of sickle cell anemia, refractory acute myeloid leukemia), all of which represent proven and unmet medical needs.

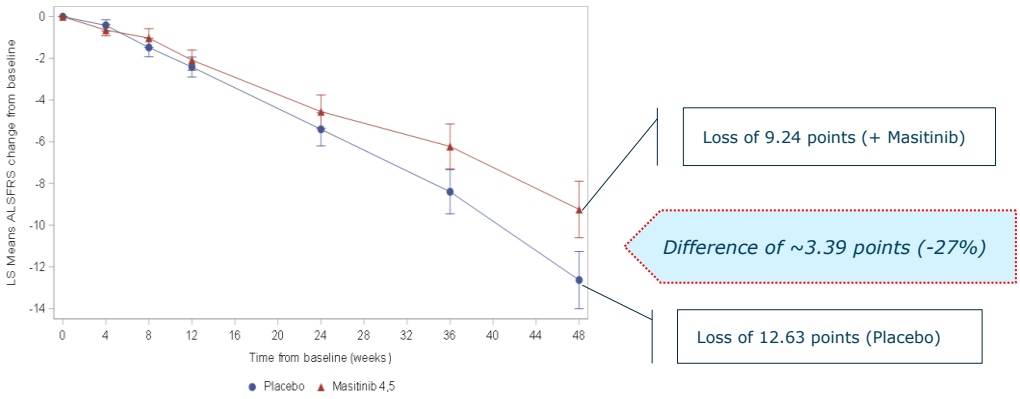
In addition, masitinib is currently being evaluated by Canadian and European regulatory authorities in the context of an application for conditional marketing authorization in ALS, which represents a strong potential for acceleration in the short term in the event of a favorable outcome, without calling into question the prospect of eventual registration based on the ongoing confirmatory study in the event of an adverse outcome.

3 Clinical validity: Proven clinical results…

AB Science's clinical pipeline is currently developing along three main axes: neurodegenerative diseases, inflammation and cancer. First, masitinib is used for three neurodegenerative diseases with significant unmet medical needs, namely Amyotrophic Lateral Sclerosis (ALS), progressive forms of Multiple Sclerosis (MS) and Alzheimer's disease (AD). The rationale for applying the mechanism of action of masitinib in these pathologies is part of a strategy to prevent neurodegeneration.

3.1 Phase IIb/III of Masitinib in ALS: Improved Overall Survival

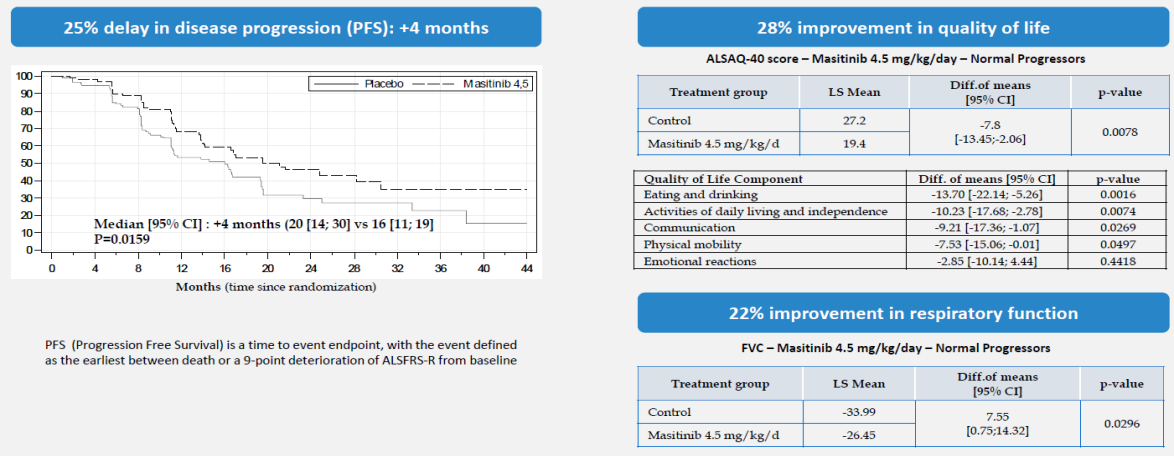
This double-blind, placebo-controlled, Phase IIb/III (AB10015, NCT02588677) study enrolled 390 patients treated for 48 weeks with the objective of comparing the efficacy and safety of masitinib in combination with riluzole compared to standard of care riluzole alone, in patients with ALS. After 1:1:1 randomization, two arms received two different dosages of masitinib (4.5 mg/kg/day and 3.0 mg/kg/day) in combination with riluzole while the third arm received placebo + riluzole. The primary endpoint of the study was the change in ALSFRS-Revised (Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised) score at 48 weeks. The ALSFRS-R score assesses the evolution of 12 physical functions of a person over time, based on a score of 4 to 0 on each of the functions. The first analysis was preplanned in patients with so-called "normal" progression (rate of deterioration of the functional score less than 1.1 points per month), representing approximately 85% of the patients in the study. To be eligible, patients had to have ALS for less than 36 months, a respiratory function score (CVF) ≥60%. There was no restriction on the minimum ALSFRS-R score at baseline. The results of this study were published in 2020 by Mora et al. in the journal Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, and in 2021 for long-term survival data by Mora et al. in the journal Therapeutic Advances in Neurological Disorders.



Source : Mora JS, et al. Masitinib as an add-on therapy to riluzole in patients with amyotrophic lateral sclerosis: a randomized clinical trial. Amyotroph Lateral Scler Frontotemporal Degener. 2020; 21(1-2):5-14.

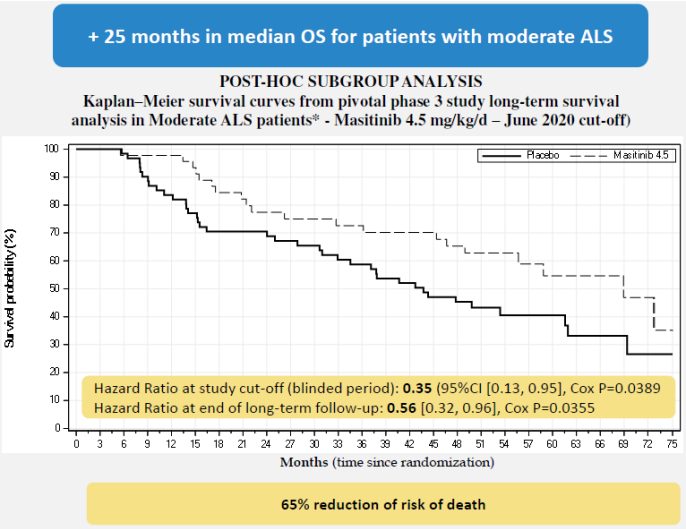
The first analysis of the study showed that masitinib at 4.5 mg/kg/day (+ riluzole) induced a slowing (-27%) of functional deterioration as measured by the ALSFRS-R score in patients with "normal" progression. This slowdown is statistically significant ($p<0.014$) and clinically relevant since, according to the literature, a reduction greater than or equal to 20% in the ALSFRS-R score reflects an overall improvement in the functional criteria of patients with ALS. In addition, studies show that the ALSFRS-R score can be used to estimate the lifespan[2][3] of ALS patients.
The secondary endpoint of this Phase IIb/III study was progression-free survival, defined as deterioration of ALSFRS-R score greater than 9 points or death. Masitinib induces a statistically significant improvement ($p=0.0159$) of the order of 25% (+4 months) in progression-free survival in the population of the main analysis (see left side of the figure below).

[2] Cedarbaum, J.M. et al. The ALSFRS-R: a revised ALS functional rating scale that incorporates assessments of respiratory function. BDNF ALS Study Group (phase III). *J. Neurol Sci.* 1999; 169:13-21.
[3] Kaufmann, P. et al. Excellent inter-rater, intra-rater, and telephone-administered reliability of the ALSFRS-R in a multicenter clinical trial, *Amyotrophic Lateral Sclerosis*, 2007; 8: 42-46.



Source : Mora JS, et al. Masitinib as an add-on therapy to riluzole in patients with amyotrophic lateral sclerosis: a randomized clinical trial. Amyotroph Lateral Scler Frontotemporal Degener. 2020; 21(1-2):5-14.

In addition, the quality of life measured by the ALSAQ-40 score (40 items - Amyotrophic Lateral Sclerosis Assessment Questionnaire) and the respiratory function measured by the FVC (Forced Vital Capacity) are assessed by 28% and 22% respectively (see right side of the figure above). The ALSAQ-40 scale is a specific ALS score, which evaluates patients' quality of life through a questionnaire covering about forty items. It should be noted, however, that ALS does not induce any cognitive impairment during the course of the disease. Another important finding from this phase IIb/III study is that masitinib's efficacy increases with decreasing severity of the condition.



Source : Mora JS, Bradley WG, Chaverri D, et al. Long-term survival analysis of masitinib in amyotrophic lateral sclerosis. Ther Adv Neurol Disord. 2021;14:17562864211030365.

Thus, as can be seen in the figure above, the analysis of long-term survival (75 months) in the "post-hoc" subgroup of moderate patients (ALSFRS-R score ≥2 on each item) shows that masitinib provides an additional 25 months to median overall survival and a 65% reduction in the risk of death. These data compare positively with a number of results in the literature.

3.2 Phase IIb/III of Masitinib in MS: Slowing Progression

AB Science is leading a development plan for masitinib in progressive forms of multiple sclerosis (MS), initiated by an exploratory proof-of-concept (AB04011 phase IIa; NCT01450488). Since masitinib acts at the level of innate immune cells (macrophages/microglia, mast cells), it influences the course of the disease.

3.2.1 Proof of concept and definition of beneficiaries

A first attempt (AB04011; NCT01450488) double-blind, placebo-controlled study was conducted with 35 patients with primary progressive MS (PPMS), or secondary progressive MS without relapse (PSMS). The phase IIa study showed that masitinib had a statistically significant effect at 12 months on impairments observed in patients by improving MSFC scores (+103% from baseline) compared to placebo (-60%). The MSFC, or Multiple Sclerosis Functional Composite, is an MS-specific scale that measures mobility, hand and arm ability, and cognitive function. Although response was measured across patients, when the trial patient population was segmented into PPMS and

PSMS, there was a better response from these two subpopulations after 12 months (see figure below). The results were published by Vermersch et al. in the journal BMC Neurology

		Placebo	Masitinib		
		All (n=6)	All (n=24)	PPMS (n=9)	SPMS (n=15)
Relative change in MSFC score*	Mean ± SD	-60% ± 190	103% ± 189	134% ± 268	84% ± 130
Relative change in T25FW	Mean ± SD	26% ± 55	5% ± 26	13% ± 17	-1% ± 29
Relative change in 9-HPT	Mean ± SD	0% ± 13	-7% ± 9	-5% ± 7	-8% ± 10
Relative change in PASAT-3"	Mean ± SD	24% ± 30	41% ± 111	19% ± 66	55% ± 131
Absolute change in EDSS score	Mean ± SD	0.3 ± 1.0	0.0 ± 0.5	0.1 ± 0.4	0.0 ± 0.5

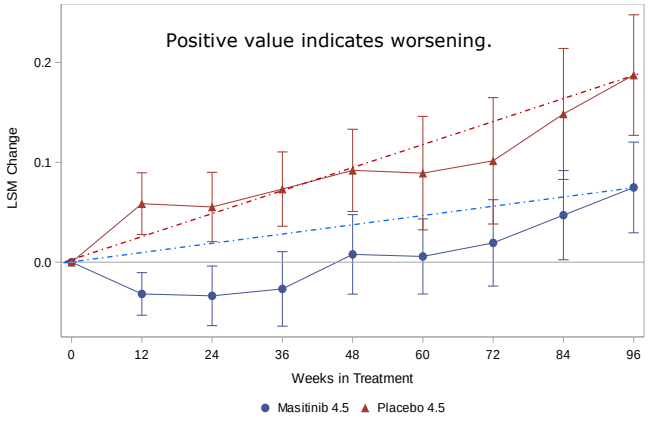
Source : Vermersch P, et al. Masitinib treatment in patients with progressive multiple sclerosis: a randomized pilot study. BMC Neurol. 2012;12:36.

In view of the improvement in the MSFC score, the company has decided to perform a phase IIb/III in patients with primary progressive multiple sclerosis (PPMS) or non-active secondary progressive multiple sclerosis (non-active PSMS).

3.2.2 Encouraging results on the evolution of disability

This double-blind, placebo-controlled, Phase IIb/III (AB07002, NCT01433497) study enrolled 611 patients treated for 96 weeks with the objective of comparing the efficacy and safety of masitinib for the treatment of MS patients versus placebo. After 2:1 randomization, two arms received two different dosages of masitinib (4.5 mg/kg/day and 6.0 mg/kg/day) while the third arm received placebo. The primary endpoint of the study was absolute change in the Expanded Disability Status Scale (EDSS) score. The EDSS is a scale used internationally to assess the various motor, sensory, urinary, intestinal, visual and cognitive symptoms related to MS, markers of the evolution of 7 major neurological functions, including: walking perimeter (pyramidal function), balance and coordination (cerebellar function), skin sensitivity (sensory function). To be eligible, patients had to have relapsed-free primary progressive MS (P-MS) or non-relapsed secondary progressive MS (PS-MS) for ≥2 years, be between 18 and 75 years of age, with an EDSS score between 2.0 and 6.0, regardless of time since disease onset. The findings were published in 2022 by Vermersch et al. in the journal Neurology Neuroimmunology & Neuroinflammation.

Statistical analysis of the results of this study showed that the primary endpoint was met. Masitinib induced a statistically significant reduction in disability progression in a highly representative sample of a difficult-to-treat population, with a median EDSS of 5.5 and nearly 50% of whom had an EDSS of 6. In this population, masitinib 4.5 mg/kg/day significantly improved EDSS scores -0.097 points (CI: 97%, [-0.192 to -0.002]; p=0.0256), and this benefit was observed in all patients, for both the PPMS and the PNMS forms (-0.128 and -0.104, respectively).



Treatment	N	Means (all changes from baseline in EDSS at 8 time points)	Means Difference
PPMS			
Masitinib 4.5 mg/kg/day	79	0.029	**-0.128**
Placebo	45	0.158	
nSPMS			
Masitinib 4.5 mg/kg/day	120	-0.052	**-0.104**
Placebo	56	0.051	

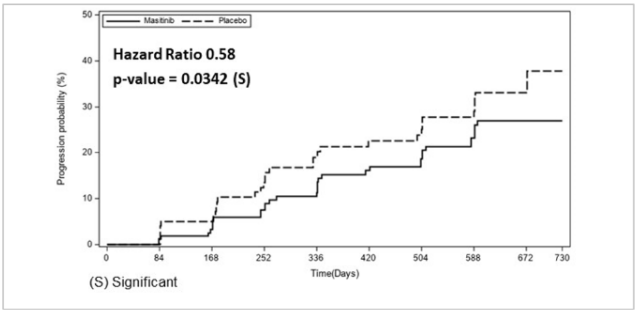
Positive value of Means indicates worsening. Negative value of Means Difference favors masitinib

Source : Vermersch P, et al. Efficacy and Safety of Masitinib in Progressive Forms of Multiple Sclerosis: A Randomized, Phase 3, Clinical Trial. Neurol Neuroimmunol Neuroinflamm. 2022; 9(3):e1148

In addition, masitinib has an effect on reducing the risk of progression of patients' disability, as can be seen in the Kaplan-Meier curves below. The number of patients with a first progression of EDSS was 34/199 for masitinib dosed at 4.5mg/kg/day, i.e. 17.1% compared to almost double at 30.7% for placebo, i.e. 31 patients/101. This corresponds to a 42% reduction in the risk of first progression with masitinib.

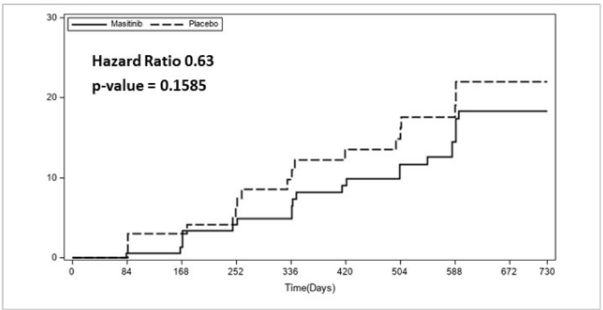
Significant 42% risk reduction of time to disability progression

Prespecified Analysis on EDSS
Kaplan Meier plot of Analysis of time to First EDSS progression



37% risk reduction of time to confirmed disability progression

Prespecified Analysis on EDSS
Kaplan Meier plot of Analysis of time to Confirmed (3 months) EDSS progression



Source : Vermersch P, et al. Efficacy and Safety of Masitinib in Progressive Forms of Multiple Sclerosis: A Randomized, Phase 3, Clinical Trial. Neurol Neuroimmunol Neuroinflamm. 2022; 9(3):e1148.

Similarly, the progression of confirmed EDSS at three months (12 weeks) was observed in 22 patients/199 who received masitinib, or 11.1%, while it affected 18/101 patients in the placebo arm, or 17.8%. This corresponds to a 37% reduction in the risk of confirmed first progression with masitinib at 4.5 mg/kg/day. In addition, masitinib also significantly reduced (p = 0.013) the risk of progression to an EDSS score ≥7.0 (confirmed at 12 weeks), with no patients (0%) progressing at this point over 96 weeks in the masitinib group compared to 4 patients (4%) in the placebo group. No significant treatment effect on EDSS was observed for high-dose masitinib (6.0 mg/kg/day). In addition, the safety of masitinib in MS remains in line with the known safety profile.

The results of the proof-of-concept phase IIa as well as those of the phase IIb/III showed that masitinib had a therapeutic benefit for patients with either PPMS or PSMS. Indeed, the improvement observed with masitinib, even if the study was not sized to detect a statistically significant effect, compares favorably with other molecules in progressive forms: 37% reduction in the EDSS test (confirmed at 3 months) for masitinib (PPMS and non-active PSMS) compared to 24% with *ocrelizumab* (PPMS-MS only) and 21% for *siponimod* (effect due to active PSMS).

Drug	Study Size (patients)	Type of Progressive MS	Hazard Ratio	Reduction in confirmed (3 months) disability progression
Masitinib 4.5 mg/kg/day	300	PPMS and nSPMS	0.63	37% (NS)
Ocrelizumab	732	PPMS	0.76	24% (S)
Siponimod	1,651	SPMS (active & non-active)	0.79 (effect driven by active)	21% (S)

S: Statistically Significant. NS : Not Statistically Significant

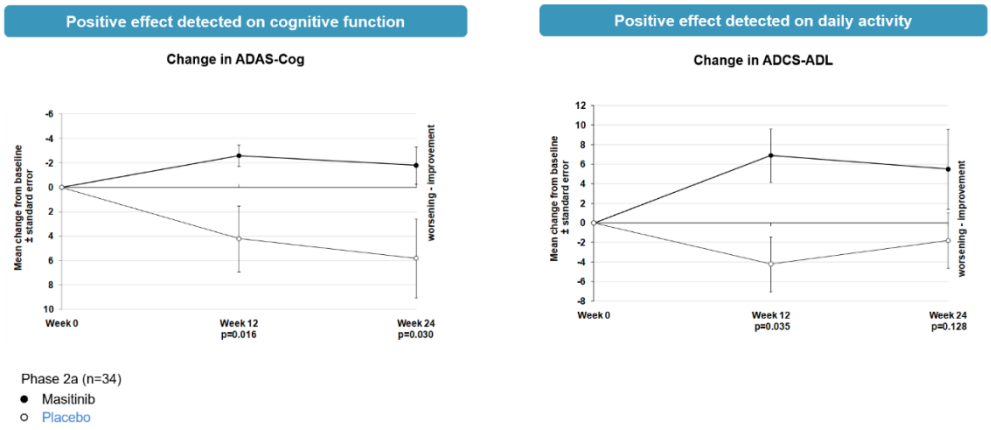
Source: adapted from discussions with AB Science

3.3 Phase IIb/III of masitinib in AD: strengthening positioning

Masitinib is developed in Alzheimer's disease, in patients in the mild to moderate stage of the disease, i.e. in patients who already have symptoms of cognitive and functional losses.

3.3.1 Phase IIa: the proof of concept...

A first phase IIa trial (AB04024; NCT00976118) double-blind, placebo-controlled study with a parallel group of 34 patients showed that masitinib had a positive effect on cognitive function as measured by ADAS-Cog variations as well as daily activities as measured on the ADAS-ADL scale.



Source : Piette F, et al. Masitinib as an adjunct therapy for mild-to-moderate Alzheimer's disease: a randomized, placebo-controlled phase 2 trial. Alzheimer's Res Ther. 2011; 3(2):16.

After randomization, Cohort A (26 patients) received two doses of masitinib (3 and 6 mg/kg/day) in combination with a cholinesterase inhibitor and memantine, while Cohort B also received a cholinesterase inhibitor, memantine and placebo. Efficacy endpoints were ADAS-Cog scores, which measure cognitive function, and ADAS-ADL scores, which measure functional capacity. The results of this exploratory study showed that the clinically relevant rate of cognitive decline according to the ADAS-Cog response (increase >4 points) after 12 and 24 weeks was significantly lower with masitinib than with placebo (6% vs. 50% for both time points; p=0.040 and p=0.046, respectively). In addition, while the placebo group experienced worsening of mean ADAS-Cog, ADAS-ADL, and MMSE scores, the masitinib group showed improvements, with statistical significance between treatment groups at week 12 and/or week 24 (P=0.016 and 0.030, respectively; P = 0.035 and 0.128; and P = 0.047 and 0.031). This exploratory phase IIa resulted in a publication by Piette et al. and justified the initiation of a phase IIb/III.

3.3.2 .. and confirmation of effects on cognition

This Phase IIb/III (AB09004; NCT01872598) double-blind, placebo-controlled, enrolled 718 patients treated for 24 weeks, with the objective of comparing the efficacy and safety of masitinib added to the standard therapy in Alzheimer's disease (memantine + anticholinesterase) versus placebo in combination with memantine + anticholinesterase, in patients with mild AD. The study was divided into two sub-studies: one to test with 1:1 randomization, masitinib 4.5 mg/kg/day + standard of care on 182 patients versus placebo + standard of care (176 patients) and the other sub-study with masitinib 6.0 mg/kg/day + standard of care on 186 patients again versus placebo + standard of care (92 patients). To be eligible, patients had to have AD with an MMSE score between 12 and 25 and be over 50 years of age. The results were published in 2023 by Dubois et al. in the journal Alzheimer's Research & Therapy.

Source : Dubois B, et al. Masitinib for mild-to-moderate Alzheimer's disease: results from a randomized, placebo-controlled, phase 3, clinical trial. Alzheimer's Res Ther. 2023 Apr. 22; 15(1):85.

Change in ADAS-Cog - ANCOVA Analysis (Full Analysis Set) - M4.5 vs Placebo

Treatment	n	LS Mean (95% CI)	LS Mean Difference (97.51% CI)	p-value
Masitinib 4.5 mg/kg/day + memantine and anticholinesterase	182	**-1.46** (-2.46, -0.45)	**-2.15** (-3.48, -0.81)	**0.0003**
Placebo + memantine and anticholinesterase	176	**0.69** (-0.36, 1.75)		

Change in ADCS-Adl - ANCOVA Analysis (Full Analysis Set) - M4.5 vs Placebo

Treatment	n	LS Mean (95% CI)	LS Mean Difference (97.51% CI)	p-value
Masitinib 4.5 mg/kg/day + memantine and anticholinesterase	182	**1.01** (-0.48, 2.50)	**1.82** (-0.15, 3.79)	**0.0381**
Placebo + memantine and anticholinesterase	176	**-0.81** (-2.36, 0.74)		

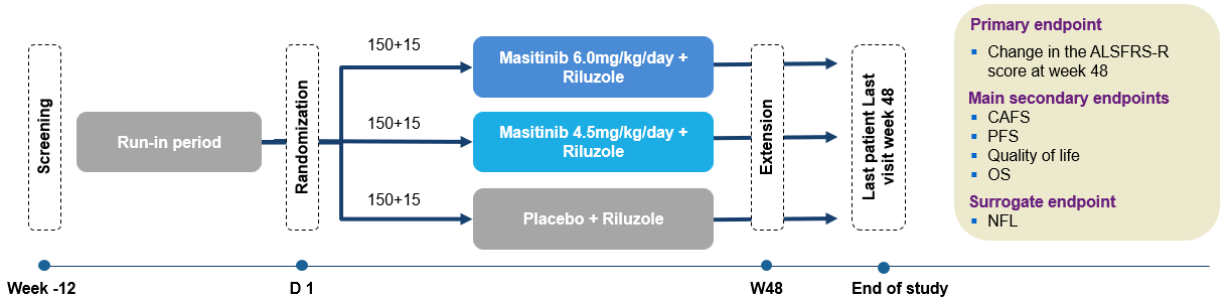
Statistical analysis of the data showed that masitinib 4.5 mg/kg/day (memantine + anticholinesterase) provides a statistically significant benefit in reducing disease-related cognitive impairment and improving the ability to perform daily activities. For the primary endpoint (ADAS-Cog), the difference between masitinib and placebo after 24 weeks was -2.15 (97.5% CI [-3.48, -0.81]); p<0.001) (masitinib -1.46 vs. placebo +0.69) and this benefit was maintained after 48 weeks of treatment. The difference between masitinib and placebo for the daily activities endpoint after 24 weeks was 1.82, reflecting an overall functional improvement (masitinib: 1.01 vs. placebo: -0.81). In the second sub-study, with a masitinib dose of 6.0 mg/kg/day, no treatment effect was observed on ADAS-Cog or ADCS-ADL. The safety of use is in line with that observed in previous trials (ALS, MS) and compatible with chronic pathologies.

4 ... that prepare for the demonstration of clinical utility and regulatory

At the end of all these phases IIb/III in the various neurodegenerative indications (ALS, progressive forms of MS and AD), AB Science is now in a particularly favorable position to confirm the relevance of the use of masitinib in confirmatory trials.

4.1 Phase 3 SLA Confirmation (AB19001; NCT03127267)

The results of the Phase IIb/III AB10015 study showed that the neuroprotective action of masitinib in the central nervous system and peripheral nervous system had a favorable effect on the course of the disease and warranted the initiation of a confirmatory Phase III masitinib in ALS. This trial with an optimized design, which has already begun, is in the recruitment phase with patients at an earlier stage of the disease. Indeed, as the conclusions of previous studies stated, masitinib is expected to have increased efficacy for these patients at a less advanced stage of the disease than those included in the AB10015 study.



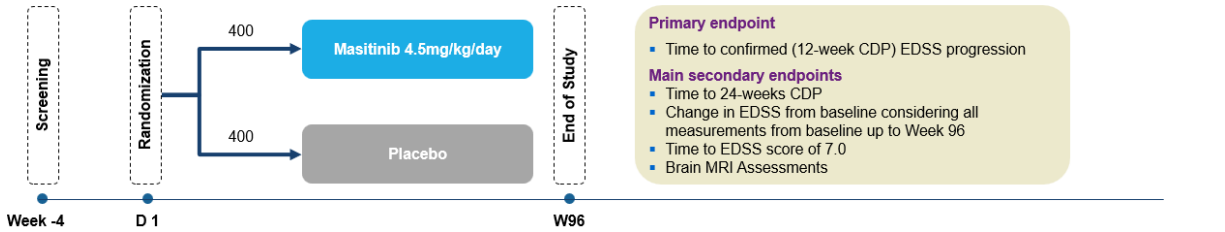
Source: IEF adapted from discussions with the company

The Phase III (AB19001; NCT03127267) is a double-blind, placebo-controlled, 3-arm (1:1:1) study (see diagram above) comparing the efficacy and safety of two doses of masitinib (4.5 and 6 mg/kg/day) in combination with riluzole with placebo in combination with riluzole in 495 ALS patients. The primary endpoint of the study is the comparison of ALSFRS-R score after 48 weeks of treatment. The inclusion criteria are deliberately restrictive: relatively recent ALS diagnosis (<24 months) and moderate stage (baseline functional score ≥ 2 for each ALSFRS-R item). A 12-week pre-screening period aims to confirm the rate of disease progression, in order to exclude patients with slow progression (less than one point of decline during this period) or rapid progression (more than 4 points of decline during this period). It should be noted that the study includes 45 rapidly progressing patients among the 495 patients on an exploratory basis. As can be seen, the inclusion criteria are relatively restrictive in order to improve the statistical power of the result, constraints that can slow down the recruitment and inclusion of patients. In addition, the availability of new molecules may also have an influence on patient recruitment.

The design of this study is quite close in patient inclusion criteria to the design of the edaravone registration study (NCT00330681). Because ALS is a heterogeneous disease, the goal of such designs is to include patients who are less likely to discontinue before the end of the study, reducing the standard deviation and reducing the number of patients to detect a statistically significant effect. It should be noted that despite these deliberately limited criteria, edaravone has obtained a broad indication in the treatment of all patients with ALS.

4.2 Confirmatory Phase III in MS (MAXIMS, NCT05441488)

The results of the Phase IIb/III (AB07002) study showed that targeting the innate immune system via mast cells and microglia was a relevant strategy for the treatment of progressive forms of MS. As a result, AB Science has received approval to conduct a confirmatory Phase III study.



Source: adapted from discussions with the company

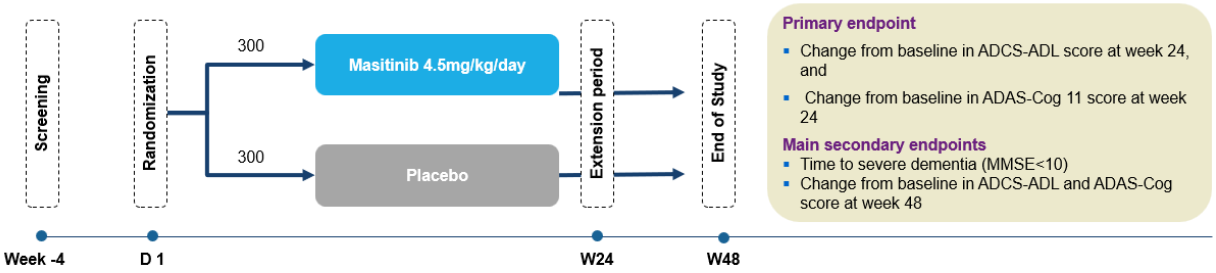
The Phase III (AB20009; NCT05441488) is a double-blind, placebo-controlled, 2-arm study (1:1 randomization) comparing the efficacy and safety of masitinib at 4.5 mg/kg/day with placebo in 800 patients with primary progressive multiple sclerosis (PPMS) or non-active secondary progressive MS (nMS). The primary endpoint of the study is the comparison of time to confirmed progression (at 12 weeks) of EDSS score progression. This progression is defined as a one-point worsening when the EDSS score is <5.5 at baseline or 0.5 if the baseline EDSS is > 5.5 (measured between randomization and week 96). The inclusion criteria of the study are classic for this indication,

with the onset of symptoms less than five years before inclusion, with no relapse diagnosed at least two years before inclusion, with an EDSS score of 3 to 6. In addition, patients will need to have an absence of T1 brain lesions measured by MRI (Magnetic Resonance Imaging). It should also be considered that there are few therapeutic alternatives for patients with PPMS or PSMS, given the uncertainties surrounding BTK inhibitors in MS (see Section 9.3).

4.3 Confirmatory Phase 3 in AD (AB21004, NCT05564169)

The results of the Phase IIb/III (AB09004) study led regulatory agencies to authorize a confirmatory Phase III clinical study. The objective of this study is to confirm the therapeutic benefits of masitinib in the time it takes to worsen cognitive and physical deficits in patients with mild to moderate Alzheimer's disease.

Source: adapted from discussions with the company



The Phase III (AB21004; NCT05564169) a double-blind, placebo-controlled, 2-arm parallel study (1:1 randomization) comparing the efficacy and safety of masitinib 4.5 mg/kg/day (in combination with a cholinesterase inhibitor and/or memantine) in 600 patients with mild to moderate AD. The primary endpoint of the study is the comparison of the change in ADAS-Cog scores and ADCS-ADL after 24 weeks of treatment. The inclusion criteria are as follows: AD defined according to the IWG (International Working Group) and confirmed by a biomarker (Amyloid PET scan positive or equivalent), with ADCS-ADL < 73 and MMSE score between 14 and 25. AB Science positions masitinib on a distinct therapeutic strategy from recently registered anti-Ab drugs for AD that have been registered for patients with AEFI or MMSE >21 (mild to very mild impairment).

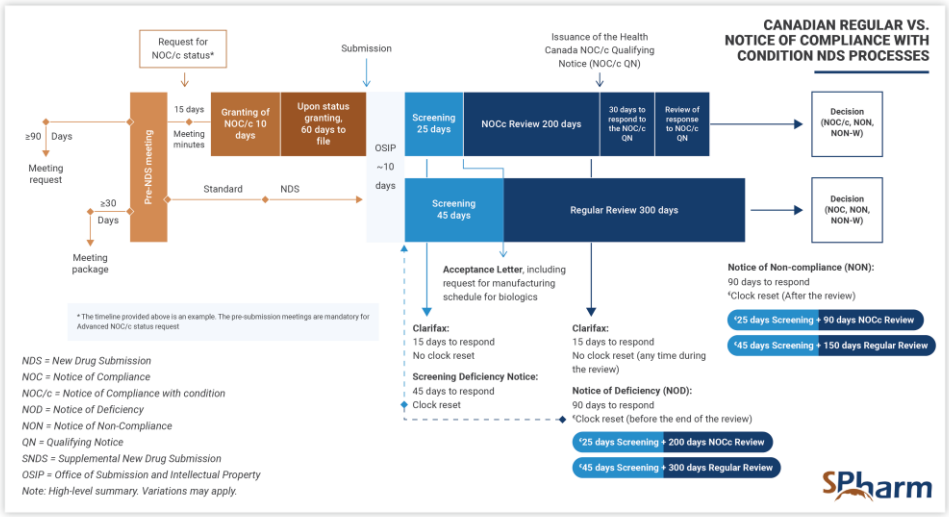
4.4 Can we count on conditional registration before confirmatory Phase III?

In February 2022, Health Canada, Canada's drug regulatory agency, authorized AB Science to submit an application for conditional marketing authorization for masitinib for the treatment of ALS under the status of NOC/c (Notice Of Compliance with conditions). A few months later, a similar conditional registration application was filed with the EMA to grant review authorization for a conditional registration of masitinib in ALS. These somewhat unusual procedures are only possible for drugs with promising clinical data and significant unmet medical needs.

In May 2022, Health Canada issued a positive opinion for the review of the dossier based on efficacy data from the AB10015 trial, long-term survival data (mean follow-up of 75 months post-diagnosis) and safety data. The Canadian agency is expected to issue its decision in the first half of 2024. AB Science has also submitted a conditional marketing application to the EMA based on the results of the AB10015 study. The European agency has asked AB Science to respond in writing to the outstanding questions at D195 instead of addressing these questions during the Oral Examination. Based on this new information, the CHMP is not expected to give its opinion until Q2 2024.

4.4.1 The Canadian NOC/c Process

The "Notice Of Compliance with conditions (NOC/c)" offers the opportunity for a company to bring a new drug to market during the clinical development process, and therefore more quickly. An authorization under the NOC/c policy contains terms and conditions that the sponsor must comply with after the drug has been authorized. A quid pro quo is the completion of the clinical development program agreed upon with Health Canada, often a confirmatory Phase III. It is a possible procedure and proposed only for severe, severely debilitating conditions and when there is promising evidence of clinical efficacy based on available data. In addition, there must be no therapy available in Canada.



Source : S Pharm

4.4.2 Health Canada's response and that of AB Science

On February 27, Health Canada issued its Notice of Non-Compliance-Withdrawal (NON-R) for masitinib in amyotrophic lateral sclerosis. Among the reasons for the decision are the following main clinical objections. First, modifications (amendments) were made to the study protocol, but they were too late in relation to the conduct of the trial and would have been insufficiently justified, leading to uncertainty about the reliability of the data. Secondly, some statistical methods used to address the missing data (patients who left the study) could have biased the results in favour of masitinib. However, AB Science used several other sensitivity analyses (multiple imputation, JTR and CIR) not based on the LOCF method, which demonstrate the superiority of masitinib. Finally, the proposed new patient population, a subgroup of "ALS patients before any loss of function" that shows a significant gain in overall survival is considered by the agency to be "post hoc". The proposal of this sub-group would be for the Canadian agency to conduct a statistical analysis specified after the conclusion of the study and the collection of data.

AB Science has indicated that it intends to submit a request for reconsideration that allows for assessment by new assessors, responding to Health Canada's objections. AB Science has 30 days to submit its request for review, with the review procedure taking up to 6 months. Regarding the changes made to the trial protocol, AB Science points out that the number of these "amendments" (3) is in line with the Canadian agency's process guidelines, which stipulate that the average number should be 3.3 per study. In its request for reconsideration, the company is expected to again draw the regulator's attention to the different methods of sensitivity analysis used on the clinical trial data, and to the fact that the choice of the patient subpopulation "ALS patients before loss of function", based on the EMA's guideline (EMA/CHMP/569146/2013) which relates to the investigation of subgroups of patients in confirmatory clinical studies. On the basis of this data, AB Science has 30 days to submit its request for review, with the review procedure taking up to 6 months.

4.4.3 Conditional MA according to the EMA

Conditional marketing authorization is possible for medicinal products registered by centralized procedure. This type of MA depends on Article 14.7 of Regulation (EC) No. 726/2004 (33) and is described in Regulation (EC) No. 507/2006 which is specific to it. It concerns:

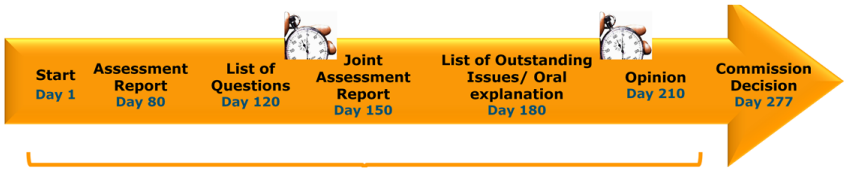
- medicines for the treatment, prevention or medical diagnosis of serious disabling diseases or life-threatening diseases.
- medicines intended for use in emergency situations in response to public health threats and requiring rapid market access.
- drugs designated as orphan drugs.

The conditional MA granted by the EMA is valid for only one year instead of the usual five . In addition, it is only granted if the following requirements are met:

- the benefit/risk ratio is favorable,
- the medicine meets unmet medical needs, i.e. there is no effective method of diagnosis, treatment or prevention of the disease.
- The public health benefits outweigh the risk of uncertainty due to incomplete evaluation of the medicine.

The provisional nature may be renewed if an interim report is provided by the applicant. The conditional MA is granted for a period of one year and can be renewed each year. When the specific obligations (completion of a clinical study and demonstration of a favorable benefit/risk ratio, provision of additional clinical data, etc.) have been met, the CHMP may at any time adopt an opinion in favor of granting a "normal" MA.

Source : https://www.ema.europa.eu/en/documents/presentation/presentation-centralised-procedure-european-medicines-agency_en.pdf



On 26 January, the EMA's Committee for Medicinal Products for Human Use (CHMP) proposed to AB Science to respond in writing to the outstanding questions at D195 of the procedure instead of addressing these questions during the Oral Explanation. A change of attitude and this unusual proposal at this stage of the procedure are difficult to explain but will allow the company to respond more fully and fully than in an oral presentation. It also gives the CHMP more time to review and assess the responses.

However, while we believe that the decisions of Health Canada and the EMA are important in terms of validating the clinical strategy of masitinib in ALS, and also commercially, since they would allow the molecule to be sold quickly, with a positive impact on the stock market, we remain convinced that the issue is fundamentally in the results of the confirmatory phase III in ALS. This is most certainly where the real upside lies. The results of the confirmatory phase III started in the SLA will be mandatorily requested by the regulatory agencies (cf. the conditional application process), whether or not there is a positive response to the conditional registration application. Moreover, a refusal of conditional registration would not call into question the ability to carry out the ongoing confirmatory Phase III. As a result, AB Science has been ahead of regulatory agencies' requests. If the results of this confirmatory phase III study are positive, AB Science will therefore be entitled to file a "normal" MA application supported by a body of clinical data.

5 Masitinib: A demonstration on the verge of success in MNDs?

Neurodegenerative diseases (Alzheimer's, Parkinson's, epilepsy, schizophrenia, multiple sclerosis) have in common the characteristic of attacking the central nervous system (CNS): the brain and spinal cord. These pathologies induce nerve degeneration by weakening and/or destroying neurons. Preventing this neurodegeneration is one of the most important unmet medical needs. Despite the sometimes very different symptoms, there are many similarities between these neurodegenerative diseases. First, the loss of neuronal cells is involved in premature mortality (years of life lost due to disease), disability (years of healthy life lost due to disability) and associated cognitive impairment. Secondly, the communication networks established by synapses between neurons and other brain cells (astrocytes, microglia, oligodendrocytes) are particularly exposed to their environment, with multiple pathological mechanisms that can alter them: external aggressions (pathogens, trauma), epigenetic or genetic mechanisms, modification of cellular integrity.

In addition, since neurons and other cells are difficult to replace, any dysfunction or abnormality (inflammation, cerebral homeostasis disruption, etc.) will have significant consequences. Epigenetic modifications (reversible changes in genes) or genetic mutations (irreversible changes) are sometimes the cause of neurodegenerative pathologies (cf. ALS and frontotemporal degeneration with the mutation of the C9orf72 gene). Cellular integrity can be affected by inflammation, oxidative stress or the appearance and aggregation of toxic proteins (Alzheimer's disease, Parkinson's disease, Huntington's disease). These three pathologies are characterized by a degeneration of neurons that inevitably leads to death. Similarly, chronic inflammation of the brain plays an important role in the onset of multiple sclerosis and certain depressive states and even depression.

5.1 Astrocytes, microglia, and mast cells...

Scientific and technological advances resulting from the visualization of vascular or inflammatory phenomena by imaging[4] have made it possible to advance the diagnosis of neurodegenerative diseases. Today, neuroinflammation (inflammation of the CNS) is recognized as being associated with neurodegenerative diseases. Initially, studies focused on the morphological changes of astrocytes and microglia, but today the track of mast cells residing in the brain and CNS is now the subject of particular attention. Indeed, mast cells, cells of innate immunity, are among the "first cells to react" when exposed to a stimulus (allergens, antigens, bacteria, trauma, etc.)[5]Tags: Their action

[4] Boulouis G, *et al*. MRI for in vivo diagnosis of cerebral amyloid angiopathy: Tailoring artifacts to image hemorrhagic biomarkers. *Rev Neurol*, 2017 ; 173(9): 554-561.
[5] Hendriksen, E., et al. Mast cells in neuroinflammation and brain disorders. *Neurosci. Biobehav. Rev.* 2017; 79: 119–133.

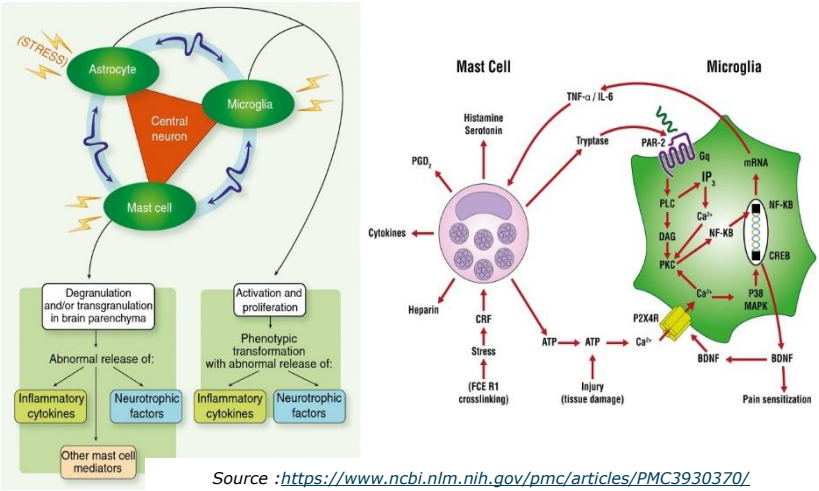
at the CNS level is part of a three-partner relationship: microglia-astrocytes-mast cells. This is because these three cell types act in a very intertwined way.

- Microglia, which make up about 10% of CNS cells, are the immune cell in the CNS, responsible for monitoring and eliminating microbes or other external elements[6]. The primary function of microglia is to maintain brain homeostasis, removing cellular debris (synaptic material) while regulating cell death and neurogenesis. Microglia are also responsible for the presentation of antigens to T cells. In addition, microglia, in response to variations in their environment, release cytokines and chemokines. In addition, microglia are directly involved in the renewal of myelin in the adult brain by phagocytosing myelin[7].

- Astrocytes, which make up the largest population of glial cells (30% CNS cells), are responsible for regulating neuronal synapses. By releasing gliotransmitters (glutamate, ATP, GABA, D-Serine), astrocytes influence the activity of the neural network. They help maintain the integrity of the blood-brain barrier[8] , thus fulfilling neuroprotective functions. In response to changes in the external environment, astrocytes undergo profound morphological transformations, which lead to two different subpopulations of astrocytes: A1 and A2 astrocytes. A2 maintains cervical homeostasis, while A1 helps decrease neuronal survival, growth, and synaptogenesis[9]. A recent review[10] confirmed that reactive astrocytes were involved in neurodegenerative disorders.

- Mast cells, cells of innate immunity, play a rather special role. Since their maturation is dependent on the tissue microenvironment[11], their function goes far beyond the simple mediation of allergic reactions. They participate in the rapid immune response with macrophages. Their involvement in pathophysiological processes such as inflammation, fibrosis and tumor development [12]is well established. Mast cells are found in the vicinity of peripheral nerves in tissues throughout the body[13]. In addition, it is known that the number and location of mast cells in the brain can change depending on external factors such as infection, trauma or stress. The tissue environment therefore exerts an influence not only on the maturation of mast cells, but also on their ability to activate. When activated, they also exert profound effects on their microenvironment and neighboring cells (astrocytes, microglia, neurons).

Today, this microglia-astrocytes-mast cell association is very well described, particularly for its involvement in neuroinflammation, neurogenesis and neurodegeneration. Mast cells also affect the disruption/permeability of the blood-brain barrier allowing the entry of toxins and immune cells exacerbating an inflammatory microenvironment.



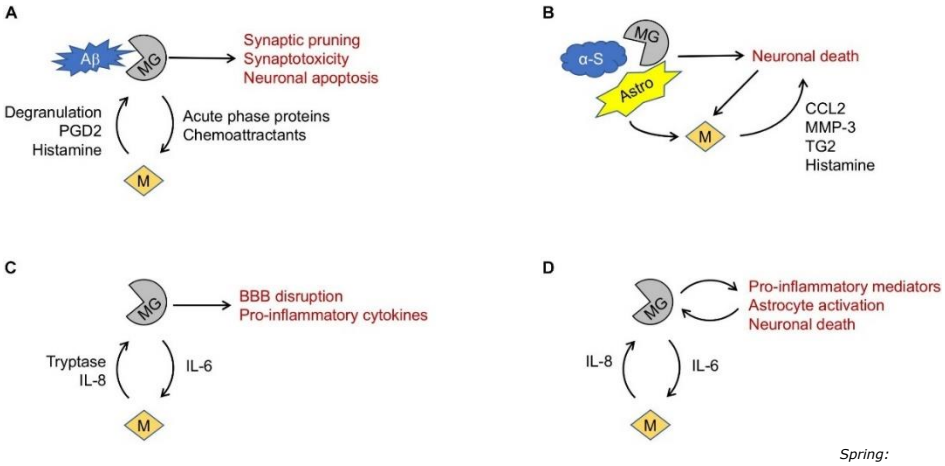
Source :https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3930370/

5.2 … and masitinib: relationships in MNDs

Masitinib selectively inhibits tyrosine kinases present in mast cells and macrophages, which derive from pluripotent hematopoietic progenitors that express the different markers such as c-KIT (or CD117), the immunoglobulin (Ig) E (Fc□RI) receptor in the Fc region. Masitinib is thought to act on activated cells of the neuroimmune system by targeting both the peripheral adaptive immune system and the innate CNS immune system[14].

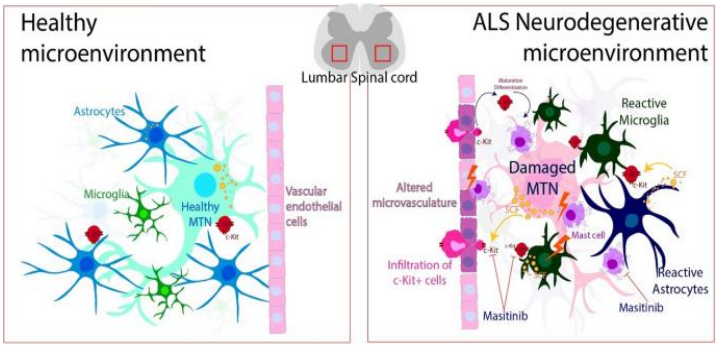
[6] Rock, R.B. et al. Role of Microglia in Central Nervous System Infections. *Clin. Microbiol. Rev*. 2004; 17: 942–964.
[7] Safaiyan, S. et al. White Matter Aging Drives Microglial Diversity. *Neuron* 2021 ; 109: 1100–1117.e10.
[8] Alvarez, J.I.; Katayama, T.; Prat, A. Glial Influence on the Blood Brain Barrier. *Glia* 2013 ; 61: 1939–1958.
[9] Liddelow, S.A et al. Neurotoxic Reactive Astrocytes Are Induced by Activated Microglia. *Nature* 2017; 541:481–487.
[10] Lawrence, J.M. et al. Roles of Neuropathology-Associated Reactive Astrocytes: A Systematic Review. *Acta Neuropathol. Commun*. 2023 ; 11: 42.
[11] Gupta, K., and Harvima, I. T. Mast cell-neural interactions contribute to pain and itch. *Immunol. Rev*. 2018; 282: 168–187.
[12] Galli SJ, Tsai M. Mast cells: versatile regulators of inflammation, tissue remodeling, host defense and homeostasis. *J Dermatol. Sci*. 2008; 49: 7-19
[13] *Ibid.*
[14] B. Sever, H. *et al.* Comprehensive research on past and future therapeutic strategies devoted to treatment of amyotrophic lateral sclerosis. *Int. J. Mol. Sci.*, 2022; **23** (5): 2400.

Several mechanisms explain the involvement of mast cells in the main neurodegenerative diseases. Thus, in Alzheimer's disease (scheme A), phagocytosis of amyloid β (Aβ) fragments by microglia can trigger the release of mediators causing mast cell degranulation. Mast cell products may in turn promote microglia-mediated neurotoxicity. In B, in Parkinson's disease, misfolded a-synuclein (a-S) can trigger the death of dopaminergic neurons via microglia. Astrocytes, microglia, and dying neurons can all promote mast cell recruitment and the release of mediators that exacerbate neuronal death.



Spring:

In amyotrophic lateral sclerosis (Scheme C), TNF-α and IL-6 produced by microglia can promote mast cell recruitment, activation and degranulation. The release of mediators such as tryptase and IL-8 can reciprocally activate microglia, exacerbating the breakdown of the blood-brain barrier (BBB) and the release of pro-inflammatory cytokines. Similarly, we can see in Figure D that in Huntington's disease, an upstream interaction between microglia and mast cells can promote a pro-inflammatory and neurotoxic environment and thus make mast cells reactive to the cause of IL-6 production.



Source : The pathogenic role of c-Kit+ mast cells in the spinal motor neuron-vascular niche in ALS

By targeting mast cells, masitinib acts on both the peripheral adaptive immune system and the innate CNS immune system. By regulating mast cell kinases, masitinib shifts the neuroimmune system from a neurotoxic state to a neuroprotective state, resulting in a remodeling of the neuronal microenvironment that reduces neuronal damage. A remodeling of the neural microenvironment in the case of the SLA described in the figure above.

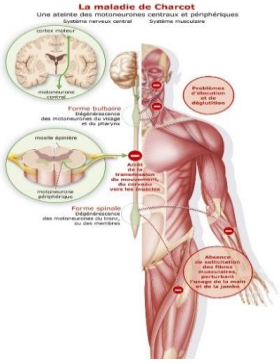
5.3 Reminders about neurodegenerative diseases

As mentioned, these pathologies share a certain number of common characteristics, such as the fact that they are pathologies that primarily affect the neuron and its environment, their progressiveness and their inevitability, as well as they are currently conditions for which there is no curative therapeutic solution.

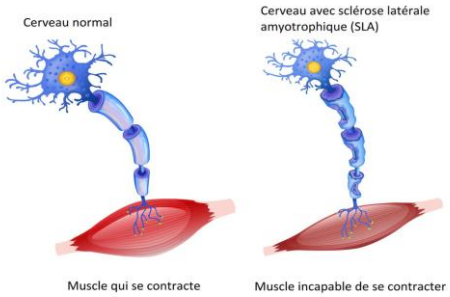
5.3.1 Amyotrophic lateral sclerosis (ALS)

Amyotrophic lateral sclerosis (ALS) is a serious and debilitating neurodegenerative disease in which the upper and lower motor neurons (motor neurons) degenerate. Also known across the Atlantic as Lou Gehrig's disease or in France as Charcot's disease, it is one of the most common motor neuron disorders. It leads to death within 3 to 5 years of diagnosis.

The clinical picture results in a progressive and inevitable paralysis of the muscles of voluntary motor skills. It is by no means a question of muscular damage, but of neuronal damage. These neurons are the nerve cells connected to skeletal muscles (muscles that are voluntarily mobilized) and their deterioration leads to an inability to contract and mobilize them during conscious actions (figure below right).



Source: ALS or Charcot's Disease |



Source: Charcot's disease: first symptoms, life expectancy (journaldesfemmes.fr)

Both types of motor neurons are affected: the "central" ones located in the brain and the "peripheral" ones located in the brainstem and spinal cord. Peripheral motor neurons act as a relay between central motor neurons and muscles. The progression of ALS patients is progressive paralysis involving muscle weakness and stiffness, slurred speech and nasal disorders, difficulty chewing or swallowing, spasticity, and then loss of the ability to walk. Death often occurs due to respiratory failure.

ALS segmentation has been achieved in several ways. Firstly, by its etiology, which is 90% sporadic, i.e. the pathology affects individuals with no family or particular genetic risk, except for the appearance of random mutations affecting a gene that is strongly involved.

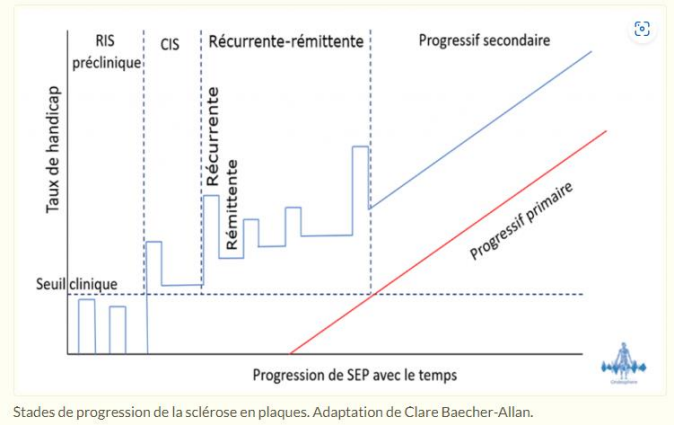
The remaining 10% of cases are familial in origin. In particular, there is a mutation in the SOD1 gene. However, several other genes have been identified such as C9ORF72 whose mutation has been observed in more than 40% of familial forms or TARDBP, FUS/TLS. Then, localization is also an element of segmentation since in 30% of cases it begins at the level of the brainstem (bulbar forms) and in 70% of cases, its origin is peripheral (spinal forms).

Its multifactorial origin makes it very difficult to establish its pathophysiology. Several mechanisms have been proposed to explain the initiation and maintenance of neuronal degeneration such as protein folding defects leading to mitochondrial dysfunction, defects in the maturation of messenger RNAs (cf. TDP-43 mutation), hyperexcitability of motor neurons or a chronic inflammatory state supported by astrocytes, microglia and macrophage cells. Its annual incidence is relatively low since in France there are around 2.7 new cases per 100,000 people, or nearly 2500 new cases per year. The population of people living with ALS (prevalence) is around 6,000 cases with almost 28,000 people affected in Europe. There are nearly 1,200 deaths per year.

5.3.2 Multiple Sclerosis (MS)

Multiple Sclerosis (MS) is the second most common age-related neurodegenerative disease after Alzheimer's disease (AD). MS is an autoimmune disease, which occurs when the immune system turns against its own cells and attacks the central nervous system (brain and spinal cord). CNS immunity is provided by a physical barrier, the BBB, and glia cells, while B and T cells are segregated outside the CNS by the BBB[15]. The first component to be attacked is myelin, a biological membrane that surrounds axons. It serves as an insulator and protection for nerve fibers, while also intervening in accelerating the propagation of nerve impulses. Any degradation has potentially devastating effects. Demyelination lesions create plaques where nerve conduction fails, and they are coupled with neuroinflammation and axonal degeneration[16]. The progression of MS is traditionally marked by 4 stages (see figure below), starting at the subclinical stage when the patient does not feel anything abnormal. The pathology can also be discovered accidentally by imaging (MRI). It is described as Radiologically isolated Syndrome (RIS).

[15] J. Kipnis, Immune system : The « seventh sense », *J. Exp. Med.*, 2018; 215 (2): 397-398.
[16] Baecher-Allan, C. et al. Multiple Sclerosis : Mechanisms and Immunotherapy. *Neuron.* 2018; 97: 742-768.



Stades de progression de la sclérose en plaques. Adaptation de Clare Baecher-Allan.

- The first symptoms exceed the thresholds for the detection of disability, and the patient is at the stage of CIS (Isolated Clinical Syndrome).
- Next, the relapsing-remitting clinical stage (RRMS) which is characterized by episodes of neurological dysfunction (flare-ups) interspersed with periods of recovery (remission). With 85% of cases, it is the most common form of MS.
- Then, when the neurological dysfunction worsens gradually and steadily, it is the secondarily progressive clinical stage (MS-SP) in 50% of cases.
- There is also an initially progressive or primary progressive form (PPMS), characterized by a slow and continuous worsening of symptoms, without flare-ups. This is only 10 to 15% of cases.

The degradation of myelin in nerve fibers leads to two processes:

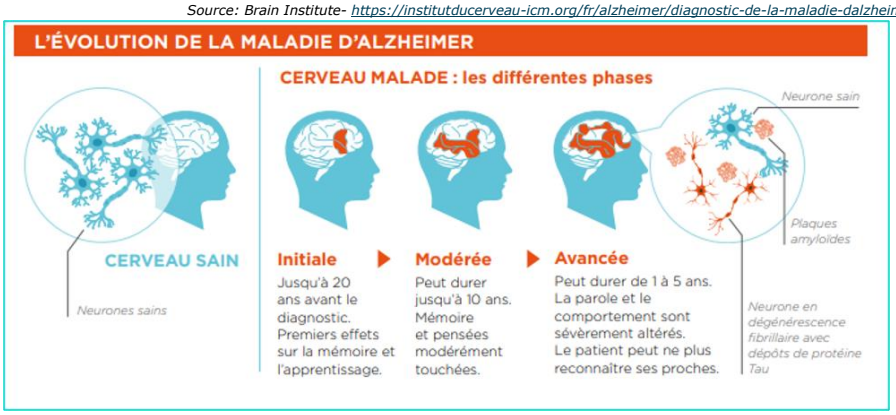
- At the appearance of localized foci of inflammation that recruit a number of inflammatory actors such as mast cells and other pro-inflammatory compounds as well as cells in charge of cervical immunity such as microglia, astrocytes, and oligodendrocytes.
- A The transmission of nerve impulses is deteriorated by the state of degradation of nerve cells and fibers as a result of demyelination. Various disorders and disabilities appear as a result of these lesions.

Thus, in the pathophysiology of MS, we find the same three actors (microglia, reactive astrocytes and activated mast cells). The interaction of these three components will have the effect of amplifying the mechanisms of inflammation initiated at the level of myelin. It is estimated that there are currently 120,000 people with MS in France. In addition, its incidence is estimated at 3,000 new cases each year, mainly among young adults. Indeed, MS is often diagnosed between the ages of 25 and 35 with a preponderance of women (3/4). It is the leading cause of non-traumatic disability in young adults.

5.3.3 Alzheimer's Disease (AD)

Alzheimer's disease (AD) is the most common cause of dementia, accounting for between 60% and 80% of dementia cases. It results from a slow degeneration of neurons. It begins at the level of a brain structure essential for memory, the hippocampus. This degradation will then spread to the entire brain. This disease develops over many years, in slow and progressive stages before symptoms appear.

Source: Brain Institute- https://institutducerveau-icm.org/fr/alzheimer/diagnostic-de-la-maladie-dalzheimer/



Indeed, the major problem with AD is the difficulty in diagnosing it. It is certainly possible to combine the clinical examination to assess the patient's cognitive functions and behavior with more objective elements such as an MRI (visualization of the loss of volume of the hippocampus), a PET scan (monitoring of the carbohydrate metabolism of the brain: energy level) or a CSF puncture (Cerebrospinal fluid: variation of the two main proteins of AD: amyloid protein and tau protein). The two main pathophysiological features characteristic of AD are amyloid-β plaques (Aβ)

and neurofibrillary tangles (NFEs). The degree of dementia correlates with the distribution of these NFEs that invade the brain. In addition, brain tissue from AD patients shows the presence of microglia and activated astrocytes around the Aβ plaques, as well as high levels of cytokines, indicating that inflammation is a contributing factor to the development of the disease.

It is now recognized that AD develops in 4 stages:

- Stage 1: mild cognitive impairment with mild memory impairment that does not affect daily life (MMSE>27).
- Stage 2: mild dementia (initial) – difficulty for the patient to perform daily tasks without external help (more severe symptoms, mild disability, spread of the disease) (26<MMSE>21).
- Stage 3: moderate dementia – the disease has spread and affects multiple cognitive functions with increasing memory loss; Daily assistance for daily life (11<MMSE>20).
- Stage 4: severe dementia (advanced) – severely reduced short- and long-term memory, as well as other cognitive functions, total loss of patient autonomy (10<MMSE).

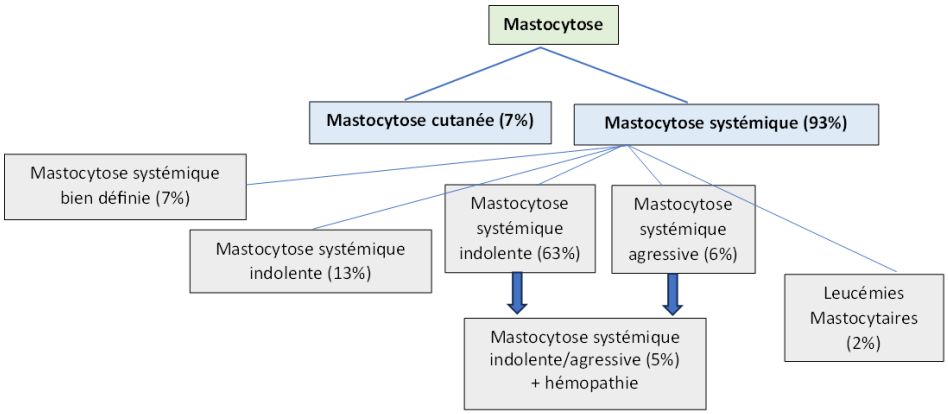
The latest estimates indicate 1,300,000 people with AD in France, a frequency of 2 to 4% of the French population. It mainly affects people over 65 years of age, although early forms occur before the age of 65, which in 10% of cases are hereditary. Over the age of 80, it affects 15% of the general population. All predictions estimate that the prevalence will increase significantly with the aging of the population, i.e. 2.2 million cases in 2050. In addition, its incidence is estimated at 225,000 new cases each year. It is the first cause of entry into institutions in France. It is estimated that there were 58 million people with AD worldwide in 2019, including 5.8 million Americans.

6 Other indications for Masitinib

In addition to macrophages (microglia in the nervous system) found in neurodegenerative pathologies, masitinib also acts on mast cells by modulating their activation and degranulation via the inhibition of three tyrosine kinases (KIT, LYN, and FYN). It is therefore particularly suitable for mast cell-associated pathologies (mastocytosis, mast cell activation syndrome) or in other conditions in which mast cells play a central role (sickle cell anemia). The activation of mast cells leads to degranulation and thus the release of multiple chemical mediators, which make the diagnosis and treatment of mast cell diseases particularly difficult.

6.1 Mast cell diseases

Pathologies affecting mast cells are mainly mastocytosis, which is a set of pathologies characterized by abnormal clonal activation and/or proliferation of mast cells with accumulation in the skin and/or bone marrow and other organs[17]. In 2016, both the International Consensus Classification (ICC) and the WHO proposed a revision of the mastocytosis classification system by subdividing it into a cutaneous form (often pediatric that regresses at puberty) and a systemic form. Systemic mastocytosis, which mainly affects adults, can be further subdivided into indolent, incubating or smoldering, aggressive or mast cell leukemias (mast cell leukemias).[18]



Source: Adapted from Sanchez-Munoz et al. Modern Pathology, 2011; (24) :1157-68.

With masitinib, AB Science targets indolent systemic mastocytosis, which is a mild form of the disease, but which presents skin damage and a spectrum of symptoms consistent with the diffuse localization of mast cells.

[17] Valent P et al. Diagnostic criteria and classification of mastocytosis: A consensus proposal. *Leuk Res.* 2001; (25):603-25.
[18] Pardanani A et al. Advanced systemic mastocytosis – Revised classification, new drugs and how we treat. *Br J Haematol*. 2024; (204): 402-414.

6.1.1 Indolent systemic mastocytosis (ISM)

Indolent systemic mastocytosis is therefore a benign and chronic form of systemic mastocytosis (MS). It is characterized like MS by an abnormal accumulation of neoplastic mast cells in the bone marrow and in other organs including the skin. A rare disease, it is also associated with "chronic" mast cell activation. The symptoms are numerous and disabling, such as fatigue, nausea, vomiting, abdominal pain, diarrhea, anaphylaxis, hypotension, diffuse musculoskeletal pain, osteopenia and osteoporosis[19]. In addition, there is an abnormal degranulation of mast cells, which releases chemical mediators that can affect the central nervous system, leading to psychiatric symptoms such as depression, anxiety and cognitive impairment[20].

The activating mutation (D816V) in the gene encoding the stem cell factor receptor c-KIT causes uncontrolled proliferation and activation of mast cells. However, the disease can also manifest in the absence of this activating mutation. However, there is no cure for MSI, and more generally for mastocytosis. Faced with the heterogeneity of mastocytosis and symptoms, individualization of treatment seems to be a prerequisite. The ultimate therapeutic objective is to improve patients' quality of life in two ways: the reduction of all symptoms and the control of mast cell proliferation. Symptomatology reduction consists of the avoidance of any triggers for mast cell degranulation. This is achieved by certain lifestyle measures such as the elimination of certain foods, medications, hymenopteran bites, sports activities that are too intense, temperatures that are too extreme, which can trigger mast cell activation. The associated pharmacological treatment is based on H1 and/or H2 antihistamines.

Controlling mast cell proliferation requires molecules capable of interacting with mast cell activation, such as *ketotifen* from the antiallergy class, *cromolyn*, a mast cell stabilizer, and *omalizumab* (Xolair™), the first anti-IgE monoclonal antibody for the treatment of asthma and chronic urticaria. However, a new class of molecules has emerged with tyrosine kinase inhibitors, which act on mast cell proliferation and survival. *Midostaurin* (Novartis' Rydapt™), which inhibits a large number of tyrosine kinases including FLT3 and KIT kinases, was initially registered for the treatment of certain mutated FLT3 leukemias (AML), as well as proliferative mast cell pathologies (aggressive, indolent systemic mastocytosis, and mast cell leukemias). In 2020, the FDA registered *avapritinib* (BluePrint Medicine's Ayvakit™) for the treatment of GIST. Then in 2021, the FDA extended its approval to the treatment of advanced systemic mastocytosis, including MSI. However, several warnings have been issued, in particular about an increased incidence of hemorrhagic adverse events (gastrointestinal, intracranial in patients with GIST or mastocytosis). Precautions for use also suggest QT prolongation and cognitive impairment.

The number of patients with systemic mastocytosis is particularly difficult to estimate because the diagnostic tools are relatively new. In addition, the multiplicity of symptoms does not facilitate the diagnosis. However, the latest estimates[21] point to about 32,000 people with systemic mastocytosis in the U.S., 95% of whom could be categorized as non-advanced. MSI is the most common type of mastocytosis of non-advanced mastocytosis (82% of reported cases). It is estimated that the prevalence in Europe for MS would be of the same order, since according to Orphanet, it is between 1 case per 10,400 individuals and 1 case per 7,700 people, i.e. between 42,696 and 57,667 affected people.

6.1.2 Mast cell activation syndrome (MAS)

Mast cell activation syndrome (MAS) shares with mastocytosis an increased and inappropriate activation of mast cells with excessive release of chemical mediators but is distinguished by an almost total absence of clonal proliferation or infiltration of organs by mast cells[22]. This massive release of chemical mediators causes anaphylaxis symptoms and/or allergic symptoms such as hives, swelling, hypotension, difficulty breathing, and severe diarrhea. SAMA has often been associated with postural orthostatic tachycardia syndrome (PAS) and Ehlers-Danlos syndrome, although the nature of this relationship is unclear. The manifestations of mast cell activation syndrome are often similar to those of systemic mastocytosis. Affecting several organs or locations, there are cardiovascular, dermatological, gastrointestinal, neurological and respiratory symptoms. The objectives of the treatment are twofold: firstly, to refine the diagnosis and to relieve the patient.

Indeed, the lack of response to treatments may suggest that SAMA is not in question. Primary treatment may consist of a lifestyle change, avoiding triggers such as mastocytosis, allergy or anaphylactic shock. Then, the common pharmacological treatments are:

- Mast cell stabilizers such as *cromolyn.*
- H1 antihistamines such as *cetirizine* or *ketotifen*.
- H2 antihistamines such as *fexofenadine* or *famotidine*.
- Anti-leukotrienes such as *montelukast*, *zafirlukast* or *zileuton*.
- *Omalizumab* (anti-IgE) reduces mast cell reactivity and activation.
- In acute episodes, *epinephrine* is recommended, as it is for the treatment of anaphylaxis.

[19] Sokol H et al. Gastrointestinal manifestations in mastocytosis: a study of 83 patients. *J Allergy Clin Immunol* 2013; 132(4):866–73.e1–3.
[20] Moura DS, et al. Neuropsychological features of adult mastocytosis. *Immunol Allergy Clin North Am* (2014) 34(2):407–22. 1
[21] Cohen SS et al. Epidemiology of systemic mastocytosis in Denmark. *Br J Hematol.* 2014; 166 (4) : 521-28.
[22] Weiler, CR et al. AAAAI Mast Cell Disorders Committee Work Group Report: Mast cell activation syndrome (MCAS) diagnosis and management. *J Allergy Clin Immunol.* 2019; 144 (4):883–896.

The epidemiology of this disease, which is relatively new since the first publications date back to 2010, therefore remains difficult to estimate[23]. For many scientific authors, it is most likely underdiagnosed. Some studies postulate a prevalence of up to 17% of the population[24].

6.1.3 Mast cells and cytokine storm: an application to Covid 19

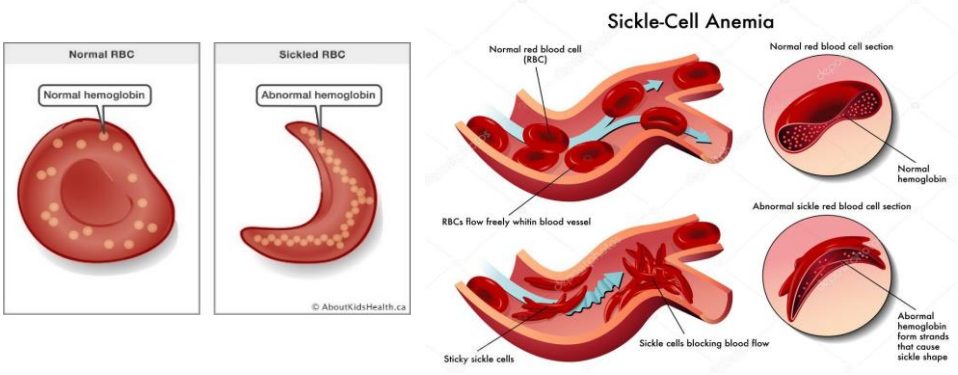
During the coronavirus pandemic, several scientific studies highlighted the involvement of mast cells in the exaggerated production of cytokines and other inflammatory mediators. Indeed, infection with the SARS-Cov-2 virus would induce a syndrome of activation or hyperactivation of mast cells with the consequence of a massive degranulation of chemical mediators leading to a "cytokine storm". This phenomenon is indeed a strong activation of mast cells and not mastocytosis, since there is, a priori, no mast cell proliferation.

Several authors also point to the possibility of activation of macrophages, another component of the innate immune system[25]. The chemical mediators released in an excessive and inappropriate manner are histamine, heparin, cytokines (IL-6, IL-1, IL-8,), prostaglandins, TNF-a, proteases, leukotrienes, etc., which act on the lungs. Masitinib through its tyrosine kinase inhibitory action (KIT, FYN, LYN and CSF1R) acts on the main TKs of mast cell activation and on the receptor of factor 1 for stimulating macrophage colonies. Based on this rationale, AB Science has initiated a first phase II (NCT04622865) clinical study of 200 patients to evaluate the anti-inflammatory activity of masitinib in adults hospitalized without age limitation (18 to 80 years and beyond) with moderate to severe COVID-19 disease. This double-blind, placebo-controlled, randomized 1:1 trial compares a single dose of masitinib (6 mg/kg/day) in combination with IsoQuercetin + supportive™ care to a dose of placebo + supportive care. The primary endpoint is clinical status at 15 days based on a 7-point ordinal scale: 1) no hospitalization, no limitations in activities; 2) no hospitalization, limitations in activities; 3) hospitalization, not requiring oxygen; 4) hospitalization, requiring oxygen; 5) hospitalization, without invasive ventilation or high oxygen flow device; 6) hospitalization, with invasive ventilation or high oxygen flow device; 7) Death. A first read-out of this trial is expected in the first half of 2024.
A second phase II study (NCT05047783) was initiated to evaluate the antiviral effect of masitinib + current optimal therapies on inpatients or outpatients (score 4 and 5 on the WHO scale) with mild to moderate Covid-19. This study, of 78 patients in a double-blind, placebo-controlled, dose-escalation setting, whose primary endpoint is masitinib-induced reduction in SARS-Cov-2 viral load. A scientific paper published in Science[26] in 2021 had shown that masitinib blocked the replication activity of the virus by binding to the 3Cl protease of SARS-Cov-2. In addition, the authors show that the anti-inflammatory effect of masitinib would improve lung function in a feline model of asthma. First results are expected in Q2 2024.

6.2 Sickle cell anemia or sickle cell anemia

Sickle cell anemia is an abnormality of hemoglobin (Hb), the main component of red blood cells (RBCs). Hemoglobin carries oxygen from the lungs to the tissues, which is the physiological impact of any change in this essential "constant" for the body. This protein composed of 2 subunits of a-globin and 2 subunits of b-globin, is present during sickle cell anemia.
A single, one-time mutation of B-globin. The change in the conformation of b-globin leads to the appearance of a new hemoglobin, hemoglobin S (Hb-S). After releasing oxygen, HbS clumps together into large fibers that travel through the red blood cell, giving it its characteristic sickle shape.

These deformations of the RBC make them more fragile (hemolysis more frequent) and paradoxically more rigid, and also more adherent. By sticking together, RBCs slow down blood flow within the vessels, leading to blockages and hindrances to oxygen supply. In addition, the lifespan of sickle cell RBCs is greatly reduced since it is 10 to 20 days while that of non-affected RBCs is 120 days.



[23] Akin C. et al. Mast Cell Activation Syndrome: Proposed Diagnostic Criteria. *J. Allergy Clin. Immunol.* 2010, *126*, 1099–1104.
[24] Afrin LB et al. Diagnosis of mast cell activation syndrome: A global consensus -2. Diagnosis. 2021; 8(2): 137-152.
[25] McGonagle D et al. The Role of Cytokines including Interleukin-6 in COVID-19 induced Pneumonia and Macrophage Activation Syndrome-Like Disease. *Autoimmun Rev.* 2020; 19 (6): 102537
[26] Drayman N et al. Masitinib is a broad coronavirus 3CL inhibitor that blocks replication of SARS-Cov-2. Science. 2021; (373):931-36.

The sickle conformation of sickle cell RBCs also induces accelerated elimination by the spleen (acute splenic sequestration), which can damage the spleen and increase the risk of infections. In addition, patients with sickle cell disease suffer from debilitating episodes of painful vaso-occlusive crises (blockage of blood microvessels). The sickle cell crisis is an acute painful crisis, considered the most devastating complication of sickle cell anemia, it is the result of the occlusion of blood vessels, which cause excruciating musculoskeletal and visceral pain, an increased risk of heart attack and stroke. It can ultimately lead to progressive damage to various organs [27] (acute chest syndrome) and early mortality.

The severe pain experienced requires medical attention (analgesics) and an increase in hospitalizations, with 30-day and 14-day rehospitalization rates of 33.4% and 22.1% in the United States, respectively[28]. Despite considerable progress in the treatment and prevention of sickle cell complications, which has led to longer life expectancies, life expectancy is still 20 to 25 years lower than in the population without sickle cell disease.

Significant medical needs remain for the treatment of patients with sickle cell disease, as the current standard of care (regular transfusions sometimes combined with hydroxyurea) is merely symptomalogical. Allogeneic hematopoietic stem cell transplants have become a standard treatment, as they are the only truly curative treatment in the long term. However, this technique is only used in 10% of cases, as it is associated with significant potential toxicity as well as strong immunological constraints (HLA compliance between donor and recipient). However, over the last two years, there has been an acceleration in the proposal of gene therapies with the aim of definitively curing these pathologies. First, with the FDA registration of Bluebird Bio's *betibeglogene autotemcel* Zynteglo™ (LentiGlobin) in thalassemia-b and *exagamglogen's autotemcel* Casgevy™ from Vertex and CRISPR Therapeutics, the first CRISPR-based therapy, which has been registered for the treatment of sickle cell disease.

Several recent scientific papers have described the existence of clinical and biological signs of mast cell activation in mouse models and in patients with sickle cell disease. This activation, which is often objectified by an increase in plasma histamine and substance P, is thought to promote, when observed, neurogenic inflammation [29]. The involvement of mast cells in the worsening of the pathophysiological mechanisms of sickle cell anemia justifies the use of masitinib, an inhibitor of KIT, LYN and FYN, three tyrosine kinases involved in the activation of mast cells and basophils. On the basis of this rationale, the SIKMAST project that AB Science had submitted in the call for projects "University Hospital Research in Health (RHU)" of the Investment for the Future Program (PIA) operated by the ANR (National Research Agency) was selected and should receive funding of 9.2 million euros. The funds will be used to:

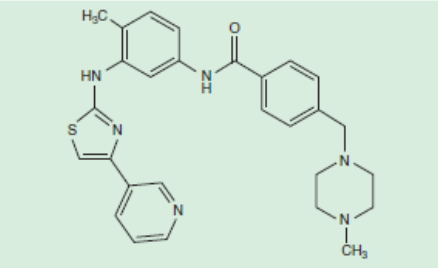
- *"on the one hand, to identify and validate biomarkers from a database of 1500 patients (including 700 already identified) highlighting the role of mast cells and basophils in the orchestration of acute and chronic complications of sickle cell disease,*
- *and secondly, to demonstrate in a phase 2 clinical trial the efficacy of masitinib in the treatment of acute and chronic complications of sickle cell disease in patients identified from biomarkers. »*

The Assistance Publique-Hôpitaux de Paris (AP-HP) will be the sponsor of these phase II studies, while AB Science will supply masitinib and will be involved in the monitoring of masitinib pharmacovigilance data. According to the consortium agreement, AB Science has full latitude to carry out as it sees fit, the possible phase III which will succeed phase II in the event of success, on the condition that AB Science pays the APHP royalties when masitinib is marketed in sickle cell anemia. In addition, AB Science has strengthened its intellectual property with the filing of a new patent which, if granted, will extend the international protection of masitinib in the treatment of sickle cell anemia until 2040. This pathology represents a major challenge for global public health, since the mutation is now found in the population of many countries and the incidence of this disease is increasing significantly, since it is estimated that 300,000 children are born each year with sickle cell disease and that by 2050 there will be 400,000 births. It affects 100,000 children and adults in the USA and 26,000 people in France

7 Masitinib: Tyrosine Kinases and Targeted Therapies

AB Science is developing a first platform of tyrosine kinase inhibitors (TKIs), from which the company's first active ingredient, masitinib, is derived. This potent and selective oral inhibitor primarily targets receptor-associated tyrosine kinases for stem cell growth factor SCF/c-KIT, CSF-1 (CSF1R), platelet-derived growth factor (PDGF-R) as well as the SRC-kinases LYN and FYN. [30] SCF and c-KIT act on several physiological mechanisms such as erythropoiesis, lymphopoiesis, megakaryopoiesis, gametogenesis, melanogenesis, with SCF also being an important growth factor and activator of mast cells and eosinophils[31].

[27] Ware RE, de Montalembert M, Tshilolo L, Abboud MR. Sickle Cell Disease. *Lancet.* 2017; 390 (10091):311-323.
[28] Brousseau DC, et al. Acute care utilization and rehospitalizations for sickle cell disease. *JAMA*. 2010;303(13):1288–94.
[29] Allali S et al. Increased plasma histamine levels in patients with sickle cell disease. The Journal of Internal Medicine. 2018 ; 39(2):A56-A57
[30] Trias E, et al. Post-paralysis tyrosine kinase inhibition with masitinib abrogates neuroinflammation and slows disease progression in inherited amyotrophic lateral sclerosis. *J Neuroinflammation*. 2016; 13(1):177.
[31] Broudy VC. Stem cell factor and hematopoiesis. Blood 1997; 90:1345–64.



Molecular Targets	IC50 (nM)	Kd (nM)
Tyrosine Kinase Receptors		
CSF1R	90 ± 35	7.6
KIT	20 ± 2	8.1
KINASES from the SRC family		
FYN	240 ± 130	140
LYN	225 ± 40	61

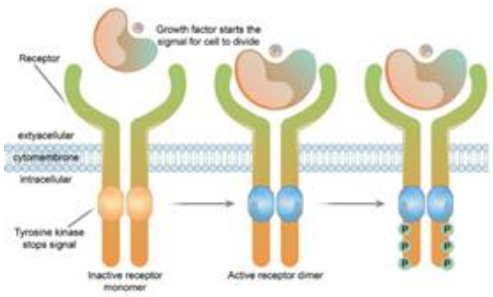
Source : AB Science, IEF

In addition, this receptor was a potential therapeutic target for the treatment of inflammatory pathologies, due to its involvement in the "up-regulation" of inflammatory conditions[32]. In addition, certain mutations in c-KIT, have been implicated in a variety of neoplasms, including gastrointestinal stromal tumors (GIST), mastocytosis, acute leukemias, melanomas, and other cancers[33].

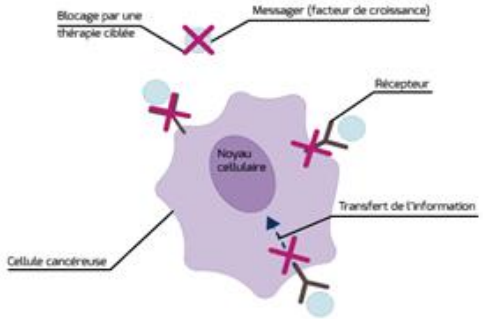
The specificity of action of masitinib in KIT, CSF1R, PDGFR and LYN/FYN has been demonstrated:

- by the analysis of its binding profile (Kinomescan) to 442 wild-type or mutant kinases, which identified 12 kinases to which masitinib binds significantly in vitro.
- these binding measurements were supplemented by inhibition measurements of these kinases by measuring the IC50 value, which corresponds to the inhibitor concentration required to observe half of the maximum inhibition. IC50 data confirmed that masitinib inhibits only a limited number of them, namely KIT (20 nM), CSF1R (90 nM), PDGFRA/B (50/110 nM) and the kinases FYN, LYN and LCK (200-300 nM).

These selectivity data, independently replicated and confirmed by Anastassiadis et al.[34] and Davis et al.[35] show that AB Science's masitinib is a highly selective inhibitor of tyrosine kinases present in mast cells and macrophages, in particular its primary target KIT and CSF1R. Indeed, these cells derive from pluripotent hematopoietic progenitors that express on their surface the markers c-Kit (or CD117), CD34, CD13 and the immunoglobulin (Ig) E (Fc□RI) receptor Fc region. Moreover, it is now registered in veterinary medicine for the treatment of certain canine tumors[3637]. Tyrosine kinases play an essential role in the cellular machinery. Indeed, they are responsible for the transit of information or a compound between the outside and the inside of the cell. To do this, they are associated with a whole series of more or less complex transport mechanisms that allow either the passage of the component or the transfer of information. This is signal transduction, which refers to the mechanism by which extracellular information is translated into one or more intracellular responses.



Source : Yaqing He et al , Membranes 2021, 11, 736.



Source : https://www.e-cancer.fr/Patients-et-proches/Se-faire-soigner/Traitements/Therapies-ciblees-et-immunotherapie-specifique/Therapies-ciblees-

This specific "information" will therefore trigger a "specific intracellular response that will act on one or more of the signaling pathways that regulate essential mechanisms such as proliferation, migration and differentiation[38]. Intracellular mechanisms amplify information and activate a series of biochemical reactions in cells to produce a global response: cell signaling. Any inconsistency in the transmission of this signal automatically leads to abnormal communication. Thus, transient modification of proteins (reversible phosphorylation) plays a key role in the regulation of cellular functions (proliferation, intracellular displacement, metabolism, cell death, inflammation).[39]

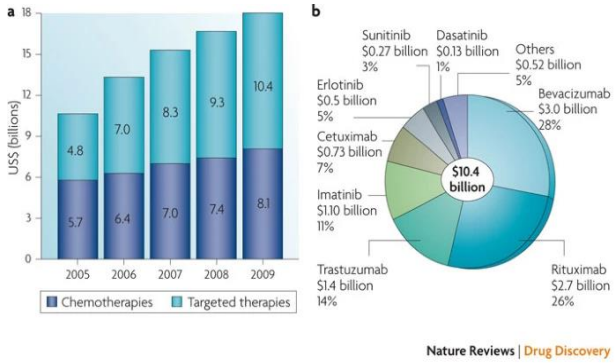
[32] Reber L. et al. Stem cell factor and its receptor c-Kit as targets for inflammatory diseases. *Eur J Pharmacol* 2006; 533: 327–40.
[33] Tests U. Kit mutations in cancer and their treatment with protein kinase inhibitors. *Drugs Fut.* 2008; 33: 161–174.
[34] Anastassiadis, T., et al. "Comprehensive assay of kinase catalytic activity reveals features of kinase inhibitor selectivity." *Nat Biotechnol* . 2011; 29(11): 1039-45.
[35] Davis, M. I., et al. "Comprehensive analysis of kinase inhibitor selectivity." *Nat Biotechnol*. 2011 ; **29**(11): 1046-51.
[36] Dubreuil P, et al. Masitinib (AB1010), a potent and selective tyrosine kinase inhibitor targeting KIT. *PLoS ONE*. 2009; 4 (9):e7258.
[37] Marech I, et al. Masitinib (AB1010), from canine tumor model to human clinical development: Where we are? *Crit Rev Oncol Hematol* 2014; 91(1):98-111.
[38] Charrin, S., Alcover, A. Role of ERM (ezrin-radixin-moesin) proteins in T lymphocyte polarization, immune synapse formation and in T cell receptor-mediated signaling. *Front Biosci*. 2006; 11,1987–1997,
[39] Ardito, F., et al. The crucial role of protein phosphorylation in cell signaling and its use as targeted therapy (Review). *Int. J. Mol. Med.* 2017; 40, 271–280.

The development of knowledge in cell signaling, particularly tumors, has led to the emergence of new drugs, which meet the generic term "targeted therapy", because they act in a specific way on molecular targets.

7.1 Targeted Therapies: Acting at the Molecular Level

These signaling pathways have therefore become the therapeutic targets of targeted therapies. These act through two distinct mechanisms. First, outside the cell, monoclonal antibodies (CAs), by binding to the ligand or directly blocking the receptor, prevent the interaction of a ligand with its receptor and thus the activation of the signaling cascade downstream of the receptor. Whereas inside the cell, small kinase-inhibiting molecules exert their effect by directly blocking the receptor's signaling pathways.

As can be seen in the following figure, which shows the evolution of sales of anti-cancer drugs in the USA between 2005 and 2009, distinguishing between chemotherapy and targeted therapy. While sales increased over the period, most of this growth was due to the increasing adoption of targeted therapies. In 2009, U.S. sales of targeted cancer therapies reached $10.4 billion, nearly twice as much as in 2005, and their market share increased from 46% in 2005 to 56% in 2009.



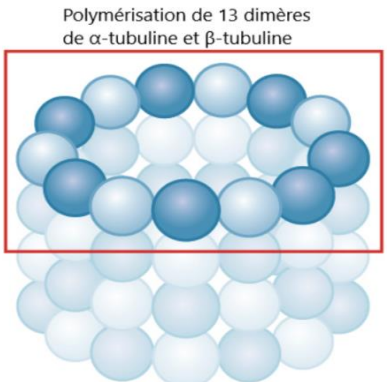
Source : Targeted cancer therapies, Aggarwal, Nature Reviews Drug Discovery

Targeted therapies are now part of what is known as "precision medicine". A term that refers to a medicine based on treatments based on an ever more intimate understanding of the biological mechanisms leading to the appearance and development of tumors. Its objective is to offer the patient a treatment adapted to the abnormalities of the pathology. However, as we have just mentioned, targeted therapies and precision medicine are mainly the prerogative of oncology. Thus, there are 58 protein kinase inhibitors registered with the FDA, but only a small number (between 7 and 9) of these molecules have been registered in non-cancer indications, such as *sirolimus*, *tofacitinib* or *fedratinib* in indications such as kidney transplantation, rheumatoid arthritis or myelofibrosis. Their potential is virtually untapped in neuroscience.

8 A new microtubule destabilizing agent: AB8939

Molecules that disrupt the dynamics of microtubules and tubulin have been chemotherapeutic cancer treatments for many years[40]. Indeed, given the central role played by microtubules in a variety of functions essential for cell life such as cell division, mitotic bundle formation, maintenance of cell morphology, motility, intracellular transport, motility, and cell signaling[41] , drugs, targeting tubulin, are certainly among the most useful and widely used molecules. However, their clinical activity is often limited by the emergence of multidrug resistance (MDR).
A microtubule is made up of tubulin proteins arranged in a tube, comparable to a straw, and each tubulin protein consists of two subunits, α-tubulin, and β-tubulin (see figure below left). Microtubules (MTs) are the essential components of the cytoskeleton, which is a network of proteins located in the cytoplasm of any cell. This backbone, which largely maintains the integrity of the cell, includes several types of proteins: actin microfilaments, intermediate filaments and microtubules.

[40] Jordan MA, Wilson L. Microtubules as a target for anticancer drugs. *Nat Rev Cancer*. 2004; 4(4):253–265.
[41] Nogales E. Structural insights into microtubule function. *Annu Rev Biochem* 2000; 69:277–302.



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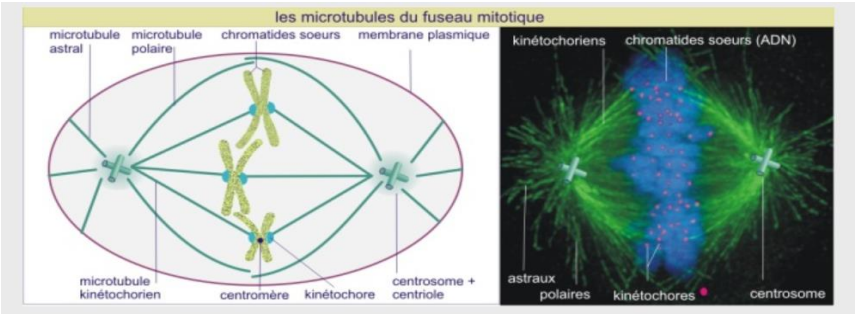
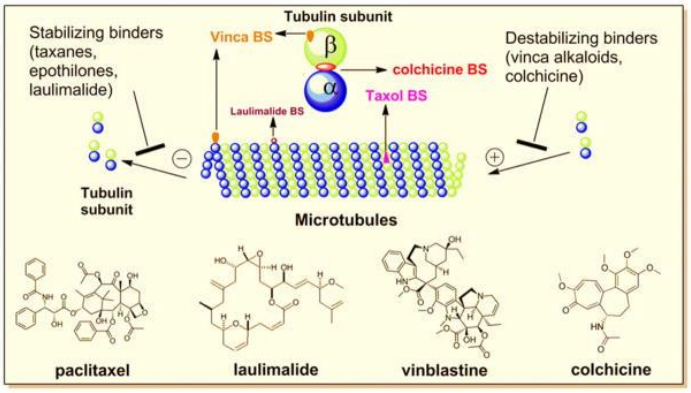


Source : *https://ressources.unisciel.fr/biocell/chap4/co/module_Chap4_23.html*

Microtubules are therefore extremely dynamic structures within the cell, which can grow and decrease rapidly with the addition or removal of tubulin dimers. It is therefore this centrality of TM functions and the polymerization dynamics of tubulin that have made it an interesting target for anti-cancer drugs[42]. To this end, a whole chemistry of "mitotic spindle poisons"[43] has been developed.



In recent years, microtubule targeting agents (MTAs) have attracted a lot of interest from scientists[44] and the pharmaceutical industry, as they offer several angles of approach for cancer therapies. Today, the number of binding sites for agents interacting with microtubules is considered to be between 4 and 6. Thus, as can be seen in the figure above, we distinguish:

- *Laulimalide*, with its own binding site, which promotes tubulin-microtubule assembly.
- *Taxanes* along with *paclitaxel* and *docetaxel*, which also promote tubulin stabilization, are widely used in the treatment of lung, breast, ovarian and bladder cancers.
- Vinca-alkaloids (alkaloids derived from periwinkle), including *vinblastine*, *vincristine* and *vinorelbine*, which, despite a high affinity for tubulin, induce a depolymerization of microtubules.
- The other two sites listed are that of *maytansine* (cf. ADC Trastuzumab emtansine) also on subunit β and that of *pironetine*, the only one on subunit α.
- *Colchicine* also induces the depolymerization of microtubules. Its binding site (CBS, colchicine binding site) is different since it is located at the aβ-tubulin intradimer. It results in the formation of a curved tubulin dimer and due to physical crowding between colchicine and α-tubulin, which inhibits the assembly of microtubules[45].

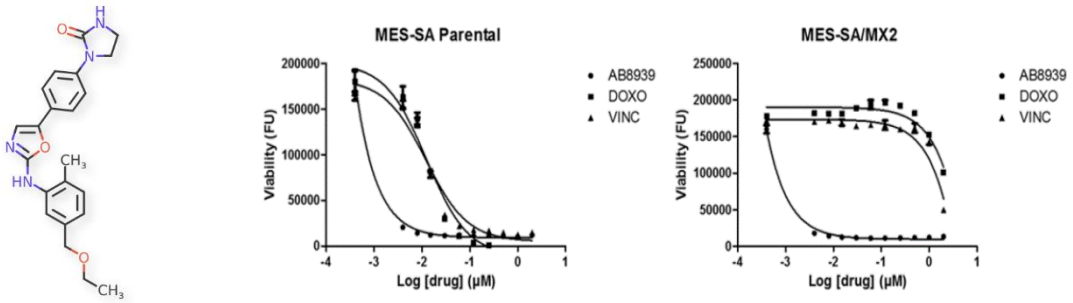
All of these families of molecules all have an action on TM, but they are also natural products initially extracted from different plants (blue periwinkle, maytenus, yew bark or needles). Thus, the clinical efficacy of periwinkle taxanes and alkaloids is often limited by elimination and regulatory mechanisms such as ATP-binding cassette-mediated drug efflux pumps, including P-glycoprotein (PgP), breast cancer-resistant proteins (BCRP), and multidrug-resistant proteins (MRP1 or MRP2). Tumor cells with overexpression of τηε χλασσ III b-tubulin isoform are also resistant to these agents. Many authors show that colchicine site-binding inhibitors (CBSIs) are insensitive to resistance mechanisms such as ABC transporters, the PgP efflux pump, MRP1 and MRP2.

[42] Jordan MA. Mechanism of action of antitumor drugs that interact with microtubules and tubulin. *Curr Med Chem Anticancer Agents* 2002; 2: 1–17.
[43] Thesis P Hannewald: Natural substances binding to tubulin: Implementation of mass spectrometry screening
[44] Lafanechère L. The microtubule cytoskeleton : An old, validated target for novel therapeutic drugs. *Front. Pharmacol*. 2022; 13969183
[45] Ravelli RB, et al. Insight into tubulin regulation from a complex with colchicine and a stathmin-like domain. *Nature.* 2004;428:198–202.

This suggests that the development of anti-tubulin agents targeting the colchicine binding site could overcome the limitations associated with existing tubulin inhibitors and improve clinical outcomes[46]. Thus, the therapeutic interest of this class led to numerous efforts to develop these CBSI agents, which also had the advantage of acting on the tumor vascular system (cf. CA-4P, Combrestatin A4 Phosphate or Fosbretabulin™). Several common traits may explain some of the MDR insensitivity observed with AB8939.
First of all, AB8939, unlike many of the MTA drugs in the pharmacopoeia, is a synthetic molecule. Secondly, it belongs to the class of molecules that bind to the colchicine binding site (CBSi), which has been shown to be useful against MDR.

8.1 AB8939: Robust preclinical data

AB Science's goal with AB8939 was to design an ultra-selective drug with strong antiproliferative properties and an acceptable safety profile with minimal cardiac or neuronal toxicity. AB8939 is therefore a small synthetic molecule, with a novel structure, inhibiting the colchicine binding site. This compound therefore inhibits tubulin by binding to CBS can bypass P-glycoprotein (PgP) and myeloperoxidase (MPO)-mediated resistance, thus conferring a significant advantage over traditional tubulin inhibitors as shown in the right side of the figure below. Indeed, tested in cell lines (MES-SA and MES-SA/MX2) known to be resistant. These human sarcoma-derived cell lines are multidrug-resistant to taxanes and vinca alkaloids.



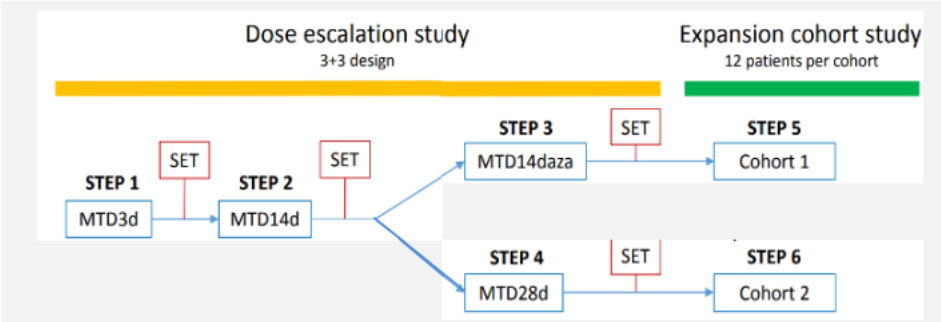
Source : AB Science, IEF

As can be seen in the figure, AB8939 reduces the viability and proliferation of MESSA cells as a function of its concentration and this inhibition is maintained over time (6 days). In addition, preclinical results show that AB8939 was not a substrate for PgP in the same way as docetaxel or verapamil. In vitro, AB8939 has been tested on cell lines of different origins, in which the molecule has demonstrated its ability to induce microtubule depolymerization and at very low concentrations. The antiproliferative potential was therefore evaluated in 19 bloodstream cancer lines as well as other types of solid tumors. Particularly positive responses were obtained with doxorubicin-resistant acute myeloid leukemia (AML) lineages.

Then, several experiments were conducted in mouse models to demonstrate the efficacy and safety of AB8939. Patient-derived xenograft (PDX) models with AML resistant to *cytarabine* and *azacitidine*, two standard chemotherapies for the treatment of AML, were chosen. The data show that AB8939 is 100 times more potent than *doxorubicin* (*adriamycin*), which is a reference drug in this indication. Indeed, AB8939 significantly reduced blast concentration in blood (38 days post-transplant), bone marrow (BM), and spleen (52 days post-transplant) compared to *azacitidine* (Vidaza®), a widely used AML-hypomethylating agent[47][48]. Similarly, when cytarabine-resistant PDX is used, AB8939 significantly reduced blast *concentration* in blood and bone marrow (41 days post-transplant) and decreased tumor growth compared to *cytarabine*. In addition, AB8939 is not deactivated by the enzyme myeloperoxidase, which is an advantage over periwinkle alkaloids (*vincristine* or *vinblastine*).

This body of relevant data on AB8939 in Acute Myeloid Leukemia (AML), where cancer cells proliferate rapidly, prompted the FDA to grant AB Science orphan drug designation to AB8939 in the indication and to authorize the conduct of a first phase I/II clinical trial. This AB18001 study (NCT05211570) entitled "Phase I/II Study to Evaluate the Safety, Pharmacokinetics and Efficacy of Daily Injection of AB8939 in Patients With Refractory/Relapsed AML" is a multi-step study. The first is a dose-escalation study to determine the safety and tolerability of intravenous AB8939 in patients with AML or in patients with refractory myelodysplastic syndrome (MDS).

[46] Perez EA. Microtubule inhibitors: Differentiating tubulin-inhibiting agents based on mechanisms of action, clinical activity, and resistance. *Mol Cancer Ther.* 2009; 8:2086–95.
[47] Goubard A, et al. In Vivo Assessment of the Next Generation Microtubule-Destabilizing Agent AB8939 in Patient-derived Xenograft Models of Acute Myeloid Leukemia. *Blood* 2019; 134 (Supplement_1): 5142.
[48] Humbert M, et al. Anticancer Activity of a Highly Potent Small Molecule Tubulin Polymerization Inhibitor, *AB8939. Blood*. 2019; 134 (Supplement_1): 2075.

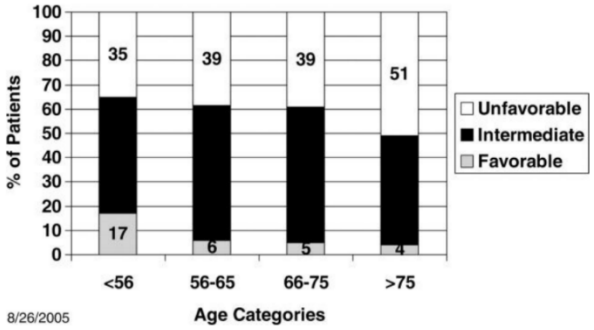


Source: The Company, IEF

In addition, this first part will determine the optimal dose for the second stage of the dose expansion study, which aims to determine the timing of a Phase II trial in patients with refractory or relapsed AML and to provide an early assessment of the efficacy (response rate) of AB8939.

8.2 Preliminary Results and Positioning

At the end of the clinical trial, the complete data should help guide future clinical studies for AB8939 and most certainly refine the positioning of the molecule in the AML landscape. Indeed, in this pathology due to an excessive development of immature stem cells, there is still a reference treatment, based on induction chemotherapy (anthracycline + azacitidine, Cytarabine™), followed by a maintenance period. However, the results observed depend on the age of the patients and their general condition. For example, a recent retrospective study[49] of trials carried out within the Southwest Oncology Group shows that aging induces a transformation of the conditions favorable to AML treatment.



Source : Appelbaum, F.R. et al. Age and acute myeloid leukemia. Blood. 2006; 107(9): 3481-3485

In this retrospective study of 968 adults, older patients with AML had poorer performance, lower white blood cell counts, and a lower percentage of blasts in the bone marrow. Multiple drug resistance was found in 33% of AMLs in patients younger than 56 years of age, compared to 57% in patients over 75 years of age. The percentage of patients with favorable cytogenetics decreased from 17% in patients younger than 56 years of age to 4% in patients older than 75 years of age. In contrast, the proportion of patients with unfavorable cytogenetics increased from 35% in those under 56 years of age to 51% in those over 75 years of age. The biology and clinical responses observed support age-specific assessments when evaluating therapies for AML.

In patients <60 years of age, whose state of health excluding leukemia is good, the protocol involves inductive chemotherapy, then consolidating before allogeneic hematopoietic cell transplantation (AlloHCT) if necessary in the event of a relapse. This treatment option provides satisfactory results in 70% of patients who have complete remission at the end of the first phases of chemo and have a long-term survival rate of 30 to 40%. On the other hand, for older patients (>60 years old) and in poor physical condition (frails), unable to withstand overly aggressive chemotherapeutic treatments, the remission rate collapses to 40% and decreases with age. And bone marrow transplant (AlloHCT) procedures, post-consolidation are proving difficult.

[49] Appelbaum, F.R. et al. Age and acute myeloid leukemia. *Blood*. 2006; 107(9): 3481-3485.

	Line 1	Line 2	Line 3
Patients eligible to high dose chemotherapy	Anthracyclines + Ara-C (Patients without FLT3 AML) Anthracyclines + Ara-C + FLT3 inhibitor (Patients with FLT3 AML)	High dose chemotherapy	**No approved drug** **Salvage Therapy or low dose chemotherapy**
Patients ineligible to high dose chemotherapy	Hypomethylating agents (azacitidine / decitabine / venetoclax)	**No approved drug** **Salvage Therapy or low dose chemotherapy**	**No approved drug** **Salvage Therapy or low dose chemotherapy**

Spring:

As can be seen in the previous figure, these patients have few therapeutic alternatives available to them. Therefore, the first indication for AB8939 will be acute myeloid leukemia (AML), as a second-line or even third-line treatment for frail patients and as a third-line treatment for refractory/relapsed patients after two lines of treatment. This is because cytarabine (Ara-C), the current standard chemotherapy for the treatment of AML, has significant drug resistance phenomena. In addition, the advantageous mechanistic characteristics of AB8939 mean that it is potentially applicable to a large number of other oncology indications currently treated with microtubule inhibitor drugs (such as periwinkle taxanes and alkaloids) and in particular other hematological cancers (ALL, MM, CML, CLL). The strategy envisaged is to position AB8939 in patients with cytogenetic abnormalities that make them insensitive to first-line therapy.

9 Markets, Benchmarks and Opportunities

AB Science, with masitinib, addresses markets of different sizes and opportunities, but always in pathologies with few or no therapeutic alternatives and with a differentiating mechanism of action.

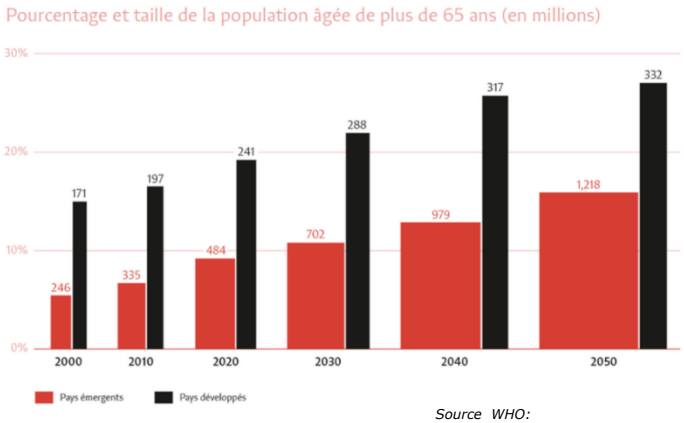
9.1 Rapidly changing global markets

Thus, the global market for neurodegenerative diseases (MND) is, according to various marketing research firms, booming. According to Mordor Intelligence, it would increase from $51.45 billion in 2023 to $72.63 billion in 2038 with a growth rate over the period considered of 7.14%. While for Future Market Insight, the market would evolve with a growth rate of 7% per year from $43.7 billion in 2021 to $92 billion in 2032. North America accounts for 42.2% of the MND market, due in particular to a high prevalence of Alzheimer's disease (6.5 million individuals with Alzheimer's-type dementia) and a drug market that is more advantageous than the others in terms of price. It is followed by Europe, which is also seeing a significant increase in the prevalence of MNDs. Europe is estimated to have generated nearly $11.5 billion in revenue in 2021. All these estimates converge on a significant and rapid growth of the MND market in the coming years and a shift of the epicenter that is expected to shift, towards middle-income countries.

This is due to the general ageing of the world's population, which affects both developed countries and low- and middle-income countries. Indeed, according to the World Health Organization (WHO), between 2015 and 2050, the proportion of individuals aged 60 and over will almost double, from 12% to 22%.[50] In addition, the pace of ageing is much faster than in the past, with a marked shift to low- and middle-income countries, with two-thirds of people aged 60 and over living in these countries by 2050. As can be seen in the figure below, emerging markets are expected to have more than one billion people over the age of 65. As a result , dependency ratios and higher public health costs are rising in both developed and emerging countries. According to the WHO, nearly 55 million people are now living with some form of dementia with an incidence of nearly 10 million new cases per year.

In terms of global prevalence, Alzheimer's disease is most certainly the MND that affects the most people on the planet today. Indeed, it is estimated that 10% of the world's population of individuals over the age of 65 would be affected, i.e. nearly 35 million people.

[50] https://www.who.int/fr/news-room/fact-sheets/detail/ageing-and health#:~:text=Entre%202015%20et%202050%2C%20la,de%20moins%20de%20cinq%20ans.

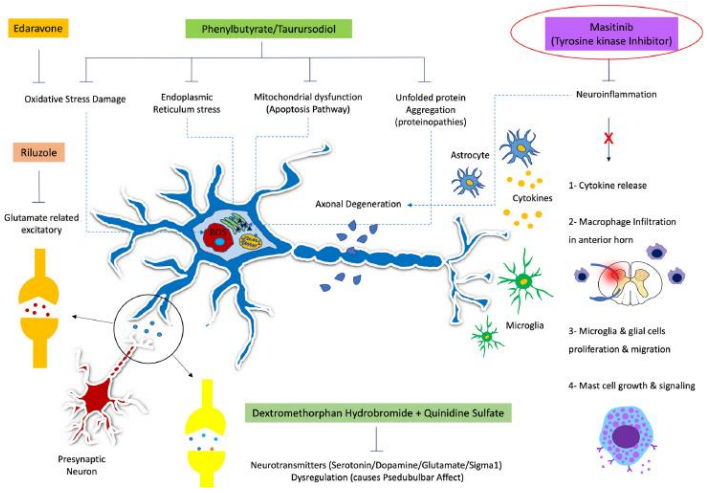


Source WHO:

With masitinib, AB Science is also addressing the market for the treatment of mast cell conditions, with a particular focus on indolent systemic mastocytosis and mast cell activation disorders, two markets characterized by high average annual growth rates. These pathologies, which, according to a recent scientific article, are "Often seen, rarely recognized... ", now benefit from a better understanding of their pathophysiological mechanisms and therapeutic targets. Moreover, in 2023, the first molecule, the first specific treatment for systemic mastocytosis and more particularly for its indolent form, was registered. Although AB Science is still in early stages of development for the use of masitinib in sickle cell disease, the market for treatments for this condition is also a significant market globally.

9.2 ALS: a very active regulatory authority

In 2021, global sales of ALS products accounted for more than $651 million, including both anti-ALS drugs and medical equipment (ventilators, feeding tubes, mobility aids, etc.) used during the progression of the disease. It is expected to increase by 6.2% over the period 2022-2030. In 2030, the market value is expected to be $901.7 million.



Although considered a rare disease, it affects 450,000 people worldwide, including 30,000 people in the United States alone, and therefore has significant market potential. There is currently no cure for this disease, with a growing demand for therapeutic alternatives that modify the course of the pathology. Despite a low average life expectancy of patients between 2 and 5 years, the cost of ALS care in the United States stands at nearly $6 billion. The standard of care remains riluzole, a molecule registered in 1995, and there is no new standard that is agreed upon today despite several molecules registered in recent years by the FDA. *Riluzole* is thought to prevent neuronal death by antagonizing glutamate receptors and reducing its ecotoxicity. In September 2022, PB-TURSO (AMX0035 or Relyvrio®), a combination of sodium phenylbutyrate and taurursodiol, was registered with the FDA on the basis of a 24-week (NCT03127514 study [51]).

[51] S. Paganoni, S. et al., Effect of sodium phenylbutyrate/taurursodiol on tracheostomy/ventilation-free survival and hospitalization in amyotrophic lateral sclerosis: long-term results from the CENTAUR trial, J. Neurol., Neurosurg. Psychiatry. 2022; 93 (8): 871–875.

This treatment has not been approved in Europe and a confirmatory phase III study is ongoing (NCT05021536), but with a duration of 48 weeks. We will therefore have to wait for the results of this study to know if the efficacy of this treatment is confirmed with the doubling of the evaluation period. Biogen's antisense oligonucleotide molecule, *tofersen,* was approved in May 2023 by the FDA with accelerated approval and in February 2024 by the EMA with conditional registration. This molecule is only effective in the early stages of ALS, and for familial forms mutated on the SOD1 gene (< 5% of patients). Therefore, it does not compete with masitinib. In addition, this efficacy appears to be associated with relatively large adverse effects[52]. Care for patients in advanced ALS ranges from $145,000 for *edaravone* to $185,000 for *tofersen*. The ALS treatment market has yet to be conquered, and given the multifactorial nature of the disease, it appears necessary to combine treatments in ALS. Masitinib is the most advanced compound for the strategy targeting microglia and mast cells, following the questioning of the strategy targeting the RIPK1 kinase and the recent failure of a clinical study (NCT05237284).

9.3 MS: A Paradigm Shift to Progressive Forms

Global sales of MS products in 2022 were more than $25.2 billion. According to marketing research firm Fortune Business Insight, the market is expected to grow at an annual rate of 4.76% between 2023 and 2030, reaching $34.9 billion at the end of the period. Multiple Sclerosis (MS) is one of the leading causes of neurological disability in young adults, which explains the large size of the global market. Estimates show that 2.8 million people are now affected worldwide, with a marked increase in the prevalence of RRMS and PPMS. Thus, the primary progressive multiple sclerosis treatment market is expected to grow at an annual growth rate of 14.7% for the period 2022-2031, leading it from $828.4 million in 2022 to more than $3.2 billion (2031). Of the 2.8 million people affected, it is estimated that nearly 50% have progressive forms, including 10% of primary progressive forms.

In addition to the standard of care that has long been the three beta interferons (IFN β: Avonex™, Betaferon™, Rebif™) and glatiramer acetate (Copaxone™), the majority of molecules targeting RRMS are found in the first line of treatment, such as *teriflunomide (*Aubagio™) initially developed by Sanofi for rheumatoid arthritis, Gilenya™ (*fingolimod* Novartis), a sphingosine-1-phosphate receptor modulator or Tecfidera™ (*dimethyl fumarate*), But none of these molecules supports progressive forms (primary and/or secondary), with the exception of Roche's Ocrevus™, registered since May 2018, with the FDA, in the treatment of primary progressive forms of MS as well as in recurrent forms[53, 54]Tags: This humanized monoclonal antibody directed against the CD20 protein present on the surface of B lymphocytes, is estimated to have generated nearly $3.5 billion in sales in the first half of 2023. This first molecule modifying the course of MS was marketed at $75,102 (wholesale purchase price), or $90,122 consumer price, much cheaper than *fingolimod* (Gilenya™, $126,813), *ofatumumab* (Kesimpta™, $114,297) or *alemtuzumab* (Lemtrada™, $142,213).

While there is now consensus on the immune track in the etiology of MS, it remains confined to immunity acquired by targeting B lymphocytes. This is evidenced by the interest in Bruton's tyrosine kinase (BTK), which is involved in the B lymphocyte molecular signaling pathway. As a result, a targeted therapy approach has been developed with several BTK-inhibiting molecules such as *Sanofi's* tolebrutinib or Roche's *fenebrutinib*, following what had been done in oncology (cf. *ibrutinib*, *acalabrutinib*, *zanubrutinib).* However, the inhibition of BTKs is often associated with adverse effects (cardiovascular and hepatic toxicity problems) that hinder their development (cf. the suspension of the phase 3 studies, PERSEUS in PPMS and HERCULES). In addition, Roche is also developing a BTK inhibitor, *fenebrutinib*, as a best-in-class treatment of Ocrevus in PPMS, with a Phase III clinical trial (FENtrepid) to compare the efficacy and safety of fenebrutinib to Ocrevus™ (*ocrelizumab*).

9.4 AD: Modernizing the Therapeutic Approach

The market for therapeutic products for Alzheimer's disease is also a fast-growing market, growing from $2.2 billion in 2020 to $13.7 billion in 2035. The growth rate for this period would be 20%. An increase in incidence, linked to the ageing of the population, is observed in many countries associated with a significant cost in terms of public health are certainly the main drivers of this growth. In the United States, there are nearly 6.2 million people over the age of 65 suffering from AD. All estimates agree that nearly 13.8 million people will be sick in 2050. AD is the sixth leading cause of death in the U.S. and the fifth leading cause of death for people over 65 years of age. Since there is no drug treatment that can cure Alzheimer's disease, the standard of care is limited to treatments that relieve symptoms. But the introduction of a new therapeutic class, anti-Ab antibodies, which inhibit the accumulation and formation of b-amyloid plaques, is transforming the therapeutic landscape, while adding an element of growth to this market.

[52] T.M. Miller, et al., Trial of Antisense Oligonucleotide Tofersen for SOD1 ALS, N. Engl. J. Med. 2022; 387(12): 1099–1110.
[53] P.S. Sorensen, M. Blinkenberg. The potential role for ocrelizumab in the treatment of multiple sclerosis: current evidence and future prospects Ther Adv Neurol Disord, 2016; 9; 44-52.
[54] OCREVUS (ocrelizumab), immunosuppressive (progressive early MS). Haute Autorité de Santé, https://www.hassante.fr/jcms/c_2863557/fr/ocrevus-ocrelizumab-immunosuppresseur-sep-d-emblee-progressive.

To date, the FDA has registered three types of drugs:

- cholinesterase inhibitors (Aricept™, Exelon™, Razadyne™)
- memantine (Namenda™), an NMDA receptor antagonist, to treat cognitive symptoms (memory loss, confusion, mood disorders, problems with thinking and reasoning).
- anti-amyloid agents with disease-modifying therapies (Disease-Modifying Therapies): Aduhelm™ (*aducanumab*), Leqembi™ (*lecanemab*).

However, there is consensus on the need to initiate treatment as early as possible, well before the first signs of dementia appear in the prodromal stage or mild cognitive impairment (MCI). The goal for these therapies is, if not to cure, at least to slow down the progression to dementia. Thus, in 2021 and 2023, the FDA approved the marketing of molecules of the anti-Ab antibody class in prodromal or mild forms of the disease, such as *aducanumab* (Aduhelm™), which has now been discontinued, or *lecanemab* (Leqembi™) from Eisai/Biogen. The latter molecule is available at an annual price of $26,500. However, these two monoclonal antibodies, which aim to reduce the accumulation of amyloid peptides, have been registered but with modest clinical efficacy and worrying benefit/risk ratios. Moreover, on January 31, 2024, Biogen and Eisai decided to stop the production and marketing of *aducanumab* (Aduhelm™). A decision that could have serious consequences for the b-amyloid track, after the failures of *gantenerumab* and *crenezumab*. Today, masitinib is increasingly interested in reducing neuroinflammation by acting on mast cell kinases and is supported by scientific advances. It also offers a therapeutic alternative to patients with mild to moderate impairments who were previously left in a state of therapeutic uncertainty.

9.5 Mast cell diseases

Within the large mast cell disease market, which includes mast cell-related cancer pathologies, AB Science is targeting the indolent systemic mastocytosis (ISM) treatment market, which is expected to show strong growth (MAGR: 6.2%) over the period 2023-2033. This market was $437.4 million in 2023 and is expected to reach $797.8 million in 2033. This growth takes into account a better understanding of the pathophysiology of this condition, including the involvement of mast cell tyrosine kinase KIT and its mutations. The other element that could boost the growth of this market is the emergence and approval of new therapeutic alternatives. In 2023, the first specific treatment for systemic mastocytosis and more specifically for its indolent form, *avapritinib* (Ayvakit™) from BluePrint Medicines, was registered with the FDA. This selective KIT mutated tyrosine kinase inhibitor D816V, initially registered in advanced gastrointestinal tumors (GIST) in 2020, has had its approval extended to aggressive mastocytosis and then to indolent systemic mastocytosis. While the price for avapritinib in GIST remains high ($384,000), due to the chronicity of MSI, the life expectancy of mastocytosis patients, we estimate (like the "Seeking Alpha" website) that the price of this molecule should be significantly reduced ($192,000). Until now, the standard treatments for MSI focused on relieving symptoms and reducing mast cell activation and therefore the release of "intramastocyte" mediators. These standard supportive treatments included antihistamines and medications to manage symptoms such as itching and flushing. However, medical needs remain, particularly for the refractory and/or relapsed or non-mutated segment of the population (10%-15% of patients with systemic mastocytosis). Indeed, resistance to tyrosine kinase inhibitors can occur as a result of the selection of clones resistant to carriers of TKI resistance mutations from KIT or PDGFRA. In addition, it appears that Ayvakit™ at the doses used has toxicities since a significant proportion of patients in the EXPLORER trial (~50%) had grade ≥ 3 adverse effects including ascites, pleural effusions, cognitive impairment. This would explain why the company is currently developing a new generation of the inhibitor for mutated KIT, *elenestinib* with an improved safety profile, as well as an inhibitor for the non-mutated (wild-type) form of tyrosine kinase KIT, BLU-808, which is still in the preclinical phase. Similarly, Cogent Biosciences has *bezuclastinib* for MSI, in phase II in the SUMMIT study (patients with non-advanced systemic mastocytosis) with a safety profile that appears to be superior to *avapritinib*, for at least equal efficacy.

Thus, we believe that there are still real opportunities for masitinib, which not only targets the "normal" form (wild-type of KIT) but is also active on other tyrosine kinases present in the mast cell such as LYN, FYN, opening the possibility for alternative approaches for this rare disease which is characterized by an aberrant accumulation of mast cells in a variety of tissues and organs. As in MND, the care paradigm, based mainly on supportive care, is evolving towards treatments, which, by acting on the essential element of the disease, namely the mast cell, induce profound changes in the evolution of the disease (cf. DMT). Although BluePrint has the significant advantage of being a first mover in this market, we believe that AB Science can be a player in the field.

9.6 Sickle cell anemia

Hereditary and genetic, this condition is very widespread, with it estimated that it will affect nearly 400,000 births per year worldwide by 2050. In France alone, in 2015, with 466 children affected, or 1 child affected in 1736 births, it is the most common genetic disease in our country. The prevalence increased significantly in the overseas departments (1/499 individuals) and in the Paris region (1/765 individuals), a major emigration area. This pathology appeared in Africa and India before becoming very present in America (West Indies, Brazil, etc.). According to marketing analyst firm Expert Market Research, the global sickle cell treatment market was $3.4 billion in 2020 and is expected to reach $8.5 billion by 2026. There are several factors that support this increase, such as the increasing prevalence of sickle cell disease, increased awareness of the disease, increased spending on health infrastructure in developing countries, and the emergence of innovative treatments. Sickle cell disease is estimated to affect more than 100,000 people in the United States and about 20 to 25 million people worldwide, mostly people of African, Middle Eastern and Indian descent. However, estimates of global incidence are not considered reliable, as many new cases come from regions where medical care is not readily available, often leading to chronic underdiagnosis (Source: Sickle-Cell.com).

For example, in countries such as Cameroon, the Republic of Congo, Gabon, Ghana and Nigeria, the prevalence of sickle cell disease can be as high as 20-30% of the population, and even as high as 45% in some parts of Uganda. Due to lack of access to medical resources, more than 90% of children with sickle cell disease in some of these areas do not survive to adulthood, with the majority of children with the most severe form of the disease dying before the age of five, usually as a result of infection or severe blood loss. This is why the World Health Organization and the United Nations have recognized the importance of this disease as a global health problem (Source: World Health Organization). Much progress in treating the disease has yet to be made in countries with high levels of poverty. Thus, the increasing awareness about treatments for the disease and the expected improvement in healthcare infrastructure in Africa are expected to provide lucrative growth opportunities to the market (Source: Sickle-Cell.com).

The standard of care for sickle cell disease is treatment that reduces symptoms and prevents the occurrence of complications (antibiotics, folic acid, transfusions + hydroxyurea). However, several new molecules have been registered but do not solve the medical need, which remains important. In 2017, *L-glutamine* (Endari™), an antioxidant that reduces oxidant damage to red blood cells and is used to treat pain associated with vaso-occlusive crises, was registered by the FDA (but not by the EMA). In 2019, the monoclonal antibody *crizanlizumab* (Adakevo™) was registered by the FDA and EMA for the reduction of vaso-occlusive crises and pain reduction, but following the failure of the confirmatory study, the MA was revoked by the EMA and its use also remains very limited [1]. Finally, the FDA (2019) and EMA (2022) registered *voxelotor* (Oxbryta™), used in the treatment of hemolytic anemia in sickle cell patients. It should be noted, however, that the use of these treatments remains low[55]. In 2023, the FDA approved two gene therapies, Casgevy™ from Vertex and Lyfgenia™ from Bluebird Bio. These treatments are curative, but their use is associated with significant risks (impact on fertility, hematologic malignancies, and their prices are simply prohibitively expensive, $2.2 million and $3.1 million, respectively. In fact, the only affordable cure today remains bone marrow transplantation, which by providing "new healthy stem cells" will result in healthy blood cells (RBCs). However, the use of this treatment is limited by the availability of compatible donors.

9.7 AML, SMD: AB8939 can reduce resistance.

The global AML treatment market was valued at some $2.3 billion in 2022, according to marketing research firm GlobalData, and is expected to grow at a CAGR of 4% through 2032. For Mordor Intelligence, the market momentum would be 10.15% CAGR from $1.83 billion in 2024 to $2.97 billion in 2029. Despite these disparities, the market is growing and benefits from the high incidence and prevalence of AML due most certainly to the aging of the population, but also to advances in molecular biology, genomics and pharmacology that make it possible to segment leukemias in an ever more relevant way. The prevalence of AML in Western countries is estimated to be around 40,000 cases in Europe and 20,000 in the United States. Among AML patients, it is estimated that about 50% will not benefit from a stem cell transplant and will relapse. It is a serious, life-threatening condition in which the majority of patients face a very poor prognosis and is also the most common cause of leukemia-related mortality. AML represents an unmet medical need, with limited therapeutic options for refractory or overly frail patients, often elderly, who cannot benefit from the potentially curative but highly toxic standard of care. The situation is the same for patients who have relapsed after an initial complete response.

The treatment paradigm for AML has been constantly changing for several years, thanks to the contributions of genomics and phenotypic differentiation. Indeed, first-line "7+3" chemotherapy or the single use of a hypomethylating agent (*decitabine* or *azacitidine*) are a thing of the past. Since 2017, a number of innovative molecules have been registered with the FDA targeting either specific segments of AML or patients with specific mutations.

[55] Cronin RM, et al. Unadjusted rate of medication use for the entire SCD population (US). *Blood Adv.* 2023 Jul 11; 7(13).

Three FLT3 inhibitors have been approved by the FDA for FLT3-mutated AML: Rydapt™ (April 2018) and Vanflyta™ (July 2023) for first-line patients eligible for intensive chemotherapy, and Xospata™ (November 2018) for relapsed/refractory patients. The other registered molecules target other components of the system such as the CD33 protein with the Mylotarg™ antibody or the BCL-2 protein with Vencletax™. In October 2023, the FDA registered Servier's Tibsovo™ (*ivosidenib*) for patients with relapsed/refractory myelodysplastic syndromes with an IDH1 mutation.

AML is the primary target for AB8939, but we believe that myelodysplastic syndromes (MDS) should be the second. Indeed, there is a real pathophysiological proximity between these two pathologies, since in 30% of cases, AML is the result of MDS. A proximity, which is reinforced by similar treatment regimens. Furthermore, with a higher prevalence of MDS than AML, we believe that it may be prudent to develop AB8939 in AML and MDS in parallel in order to maximize the chances of the drug candidate being approved by the market and benefiting from commercial potential. In 2019, according to Datamonitor, the number of cases in the United States amounted to 238,000 people with an average prevalence increasing by 3.1% per year to reach 313,500 in 2028. Considered rare forms of blood cancer or hematologic malignancies, they are characterized by a deficiency of healthy blood cells, probably due to inefficient production of blood cells associated with dysplasia, production of abnormal cells. The standard of care for MDS is allogeneic stem cell transplantation (HSCT). However, for high-risk MDS that are not eligible for HSCT, the use of hypomethylating agents such as *azacitidine* is recommended. However, the survival expectancy of these patients on *azacitidine* is low (2 years), often without a cure, with a non-negligible risk of progression into AML (30%). The FDA has approved only three MDS agents: *azacitidine*, *decitabine*, and an immunotherapy, *lenalidomide,* all of which are also indicated for AML. However, a certain number of patients may find themselves in therapeutic wandering, when transplantation or transfusion associated with growth factors (GCSF, GM-CSF, erythropoietin), or chemotherapy are unsuccessful. AB Science's positioning with AB8939 could reduce therapeutic wandering in the second and third line, while improving the therapeutic window with a new molecule that is less sensitive to resistance mechanisms, particularly for high-risk MDS. On the other hand, an effective new therapy that is likely to also improve the five-year survival rate, addressing the elimination and control of residual disease as part of consolidation could be an opportunity for AB8939.

9.8 From competitive sectors to numerous licensing and M&A

The registration of the different molecules in MNDs (Radicava™, Relyvrio™ in ALS, Aduhelm™ in AD) has led to renewed interest in the MND sector. This interest extends to development partnerships as well as takeovers by major pharmaceutical companies. Indeed, for them, the ageing of the population, the prevalence and especially the incidence of MND appear to be real opportunities for product portfolios sometimes threatened by patent losses. In addition, scientific advances that are leading to a better understanding of pathophysiological mechanisms give rise to the hope that new molecules will have an impact on the evolution of these pathologies (DMT).

9.8.1 Licensing: growing amounts

We have listed (table below) in a non-exhaustive manner a number of partnership, collaboration and licensing agreements in the field of neurodegenerative diseases and neurology between companies of different sizes. Paying particular attention to a number of reference deals with Phase III compounds. They were carried out by companies with different maturities and on distinct segments of neuroscience (psychiatric diseases, neurodegenerative diseases). The amounts and criteria of the partnership are highly dependent on the general transaction climate. So in 2021, the deals have overall amounts much higher than in 2022 and 2023, probably because we were coming out of the Covid epidemic globally and the pharmaceutical industry was looking to strengthen its pipelines. Given the early clinical failures, however, we anticipate that licensees will become increasingly selective, only interested in candidates with compelling data.

Some recent licensing agreements in the field of neuroscience

Date	Licensee	Licensor	Molecule (Target)	Indications	Phase	Upfront (MC)	Equity (MC)	Milestones (MC)	Royalties (%)	Total deal value (MC)
déc-23	Dr. Reddy's Laboratoiries	Coya Therapeutics	COYA 302	ALS	PC	7,4		669,7		677,1
oct-23	Roche	Ionis	RNA	AD & HD	PC	59,3				59,3
sept-23	Viropharma	Intellect Neurosciences	OX1 (anti-oxydant molecule)	Friedreich's Ataxia	I/II	6,4		118,7	10%	125,1
juil-23	BMS	Evotec	EVT8683 (Late Stage discovery programs)	NDD	PC	39,6				39,6
juil-23	BMS	Prothena	PRX005 (MTBR)	AD & HD	I	54,4		556,2		610,6
mai-23	UCB	ClearPoint Neuro	Gene Therapy delivery	Neurology	PC					0,0
févr-23	Karuna Therapeutics	Goldfinch Bio	Transient receptor potential canonical 4 and 5 (TRPC4/5) channel agents	Neurology (Anxiety disorders)	PC			514,2		514,2
juil-22	Biogen	Alectos Therapeutics	AL01811, GBA2 Inhibitor	PD	PC	14,8		699,6		714,5
déc-21	Alto Neurosciences	Total Brain ltd	iSpot-D research data	Neurology	PC	0,5				0,5
nov-21	BioThera Solutions	Biogen	BAT-1806	RA	III	29,7				29,7
nov-21	Zai Laboratories	Karuna Therapeutics	KarXT (muscarinic agonist)	Psychiatric disorders	III	34,6		150,3		184,9
sept-21	Spark Therapeutics	NeuEx Cell Therapeutics	Gene Therapy delivery	HD	PC					187,9
sept-21	BMS	Evotec	EVT8683	NDD	option	19,8		247,2		267,0
sept-21	Otsuka Pharmaceuticals	Sunovion Pharmaceuticals	SEP-363856, SEP-4199, SEP-378614 & SEP-380135	Psychiatry & Neurology	I/II/III	267,0		613,1		880,1
août-21	Ipsen	Exicure	Spherical nucleic acids	HD, Angelman Syndrome	PC	19,8		988,8		1 008,5
août-21	Roche	Shape Therapeutics	RNA & Gene therapy	AD, PD	PC					2 966,6
juil-21	GSK	Alector	AL001 & AL101 (mAb-progranulin)	NDD	III	692,2		1 507,8		2 200,0
juil-21	Biogen	InnoCare Pharma Ltd	orelabrutinib (BTKi)	MS	II	123,6		803,9		927,6
mars-21	Otsuka Pharmaceuticals	Perception Neurosciences	PCN-101 (R-Ketamine)	Depressive disorders	I/II	19,8				19,8

Source IE Finance

Indeed, large pharmaceutical companies are constantly looking for innovations that increasingly originate in relatively small biotechnology companies, if not academic research teams. This is evidenced by the case of BAN2401 (*lecanemab),* originally developed at BioArtic AB, a small Swedish company.

9.8.2 M&A: an increased appetite for neuroscience and oncology

In recent years, we have seen a return of the appetite of large pharmaceutical laboratories for small biotechnology companies, or start-ups with either a portfolio in several neuroscientific indications, or with an active ingredient registered or in the process of being approved by regulatory agencies. In the last quarter of 2023, we have seen several transactions of this type, the most recent and most emblematic of which is certainly the acquisition of Karuna Therapeutics by Bristol-Meyer-Squibb for $13.8 billion ($14 billion). Karuna's KarXT™ is a novel mechanism of action antipsychotic (muscarinic receptor M1/M4 agonist), which has a Marketing Authorization Application (NDA) accepted for review by the FDA with a PDUFA (Prescription Drug User Fee Act) date set for September 26, 2024. KarXT is also being tested for registration as an adjunctive treatment for schizophrenia and for the treatment of psychosis in patients with Alzheimer's disease.

Some recent transactions in the field of neuroscience

Date	Acquéreur	Cible	Actitvité	Stage	CA Cible (MC)	Valeur du Deal (MC)	Ratio (Deal/CA)	Cash	Ratio (Deal/Cash)
déc-23	BMS	Karuna Therapeutics	Schizophrenia, AD Psychosis, Bipolar disorders	P3	10,4	13 844,1	1 325,8	1 285,5	10,8
déc-23	BMS	Rayze Bio	Oncology (Radiopharmaceuticals)	P3	NS	4 054,3	NS	560,7	7,2
déc-23	AbbVie	Cerevel Therapeutics	Schizophrenia, PD	P3	NS	8 603,1	NS	1 242,9	6,9
nov-23	Merck & Co	Caraway Therapeutics	Modulation Lysosomal storage PND (TRPML1)	P3	NS	603,2	NS	0,0	NS
oct-23	AbbVie	Mitokinin	DMT for Parkinson's Disease		NS	538,9	NS	0,0	NS
oct-23	Roche	Telavant	Immunology & Inflammatory	P2/3	NS	7 020,9	NS	NS	NS
oct-23	BMS	Mirati	Oncology	P2/3	37,8	5 735,4	151,8	1 087,7	5,3
sept-23	Acino	M8 Pharmaceuticals	Pharmaceuticals	Market	20,8		NS	NS	NS
sept-23	Otsuka	Mindset Pharma	Psychedelic medications	Market	5,2	54,5	10,6		NS
août-23	Harmony Biosciences	Zynerba	Rare neurological drugs		NS	138,4	NS	54,2	2,6
juil-23	Novartis	Dtx Pharma	Charcot-Marie-Tooth's Disease (CMT1A)	PC	NS	494,4	NS	113,7	4,3
juil-23	Biogen	Reata Pharmaceuticals	Neurologic	PC	22,4	7 218,7	321,6	41,8	172,6
juin-23	Eli Lilly	Dice Therapeutics	Immunology & Inflammatory	P1/2	NS	2 373,3	NS	567,8	4,2
mars-23	EIP Pharma	CervoMed (ex-Diffusion Pharmaceuticals)	Devices	Market	NS	9,9	NS	10,0	1,0
nov-22	Kriya Therapeutics	Redpin Therapeutics	Gene therapy for CNS (Epilepsy)	PC	NS	NS	NS	NS	NS
août-22	Neurocrine Biosciences	Diurnal	neurology specialities	Market	5,1	55,9	11,0	1,2	48,4
juil-22	Ultragenyx Pharmaceuticals	GeneTx	Angelman Syndrome	P1/2	NS	74,2	NS	NS	NS
juin-22	GSK	Affinivax	Vaccins		NS	3 263,2	NS	NS	NS
juin-22	BMS	Turning Point Therapeutics	Repotrectinib (TKI)	P3	30,5	4 054,3	133,0	908,0	4,5
mars-22	AbbVie	Syndesi Therapeutics	Neuroscience	P1/2	NS	988,9	NS	16,8	58,8
févr-22	Biohaven Pharmaceuticals	Channel Biosciences	Neurosciences	P2/3	NS	2 966,6	NS	50,1	59,2
janv-22	UCB	Zogenix	Epilepsy	Market	80,8	1 878,8	23,3	62,0	30,3

Source : IE Finance

Although the above table does not seek to be exhaustive, the transactions listed represent an overall value of €64 billion with an average and median agreement value of €3.2 billion and €2.13 billion respectively. Based on the ratios, we see that buyers value their targets at an average of 282x sales and 29.7x cash. These ratios show that major laboratories are looking for new molecules and new growth opportunities, and ready to invest in pipelines that have been set up or are in the process of being set up (see the Karuna/BMS, Cerevel/AbbVie or Mirati/BMS operations).

10 Financial Items

10.1 Strong growth in 2022 and H1 2023 in line

AB Science's final financial statements for the 2022 financial year show a turnover of €0.96 million, mainly made up of sales of Mastivet™, a veterinary version of masitinib against canine mastocytosis. Operating expenses increased by 9.6% to €16.89 million for the 2022 financial year compared to €15.41 million in 2021.

R&D expenses increased by 18.8% to €13.34 million (+€2.11 million) allocated to the various clinical studies conducted by the company in both neurodegenerative diseases and oncology. This increase is mainly due to the intensification of clinical studies, since for its lead molecule, masitinib, several confirmatory trials have been authorized by both the FDA and the EMA. On the other hand, marketing expenses and administrative expenses remained relatively stable at €0.480 million and €3.04 million respectively. All this leads to an operating loss of €15.9 million, up 15.4% compared to December 31, 2021, when it stood at €13.8 million. Despite a positive financial result of €2.32 million, the net loss amounted to €13.61 million, a reduction of nearly 6% compared to €14.46 million on December 31, 2021. As of December 31, 2022, the company ended FY22 with a cash position of €7.27 million.

Simplified income statement 2021 – 2022 and H1 2023 vs. H1 2022

en M€	2021	2022	en % de var	S1 2022	S1 2023	en % de var
Chiffre d'affaires	**1,607**	**0,958**	**-40,4%**	**0,629**	**0,448**	**-28,8%**
Subventions Exploitation	0,030	0,053	75,3%			
Autres Produits	1,031	1,061	2,9%			
Produits exploitation	**2,669**	**2,073**	**-22,3%**	**0,629**	**0,448**	**-28,8%**
Achats consommés	*0,72*	*0,30*	-58,2%	*0,16*	*0,22*	38,6%
Marge brute	**1,945**	**1,770**	**-9,0%**	**0,471**	**0,229**	**-51,4%**
Impôts et taxes	0,143	0,160	11,5%			
Salaires et Traitements	6,603	7,001	6,0%	3,570	3,551	-0,5%
Charges sociales	2,590	2,526	-2,5%	1,342	1,243	-7,4%
Autres charges externes	8,190	10,094	23,2%	5,122	4,285	-16,3%
Autres produits et charges d'exploitation	0,352	0,400	13,5%			
EBITDA	**-15,934**	**-18,409**	**15,5%**	**-9,563**	**-8,850**	**-7,5%**
Dépréciation et amortissements	0,602	0,859	42,6%			
EBIT	**-16,536**	**-19,268**	**16,5%**	**-9,563**	**-8,850**	**-7,5%**
Résultat financier	0,092	-0,622	-774,6%	2,424	-1,569	-164,7%
Résultat exceptionnel	-0,085	0,155	-281,4%	0,155	0,000	-100,0%
Résultat courant avant impôts	**-16,529**	**-19,736**	**19,4%**	**-6,984**	**-10,419**	49,2%
Impôts	-3,871	-4,008	3,5%			
Résultat Net de l'ensemble consolidé	**-12,691**	**-15,777**	**24,3%**	**-6,967**	**-10,360**	48,7%
Résultat Net part du groupe	**-12,691**	**-15,777**	**24,3%**	**-6,967**	**-10,360**	**48,7%**
TN	3,149	7,269	**130,8%**	7,27	14,786	
Résultat dilué/Action	**-0,848**	**-0,384**	**0,005**	**-0,148**	**-0,220**	**48,7%**
Nombre moyen pondéré d'actions	14,966	41,124		47,124	47,124	

Source : AB Science, estimations IE Finance

In fiscal 2023, AB Science has decided to focus its development strategy on prioritizing its current resources in the development of masitinib in ALS and the development of the microtubule platform with AB8939. In addition, AB Science has also chosen to seek partners for masitinib's non-rare disease indications, including progressive MS and mild-to-moderate Alzheimer's disease. This focus has also been accompanied by a job protection plan that has led the company to reduce its payroll by 41 of the 100 existing positions.

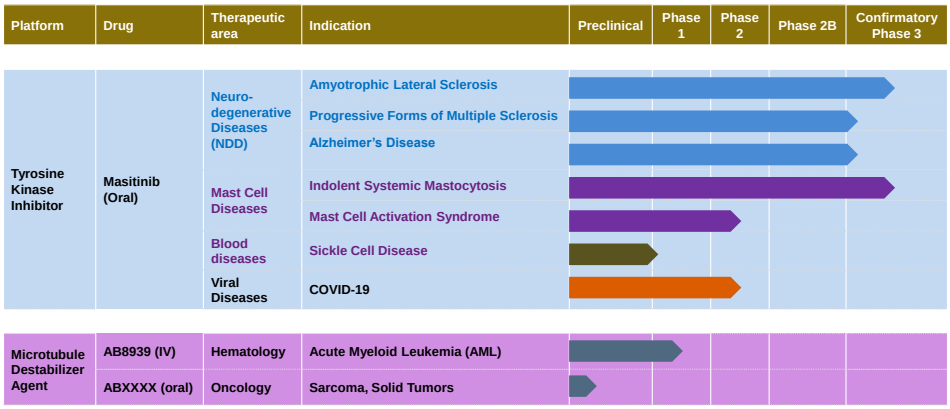
In addition, in the first half of 2023, supply disruptions of Masivet™, the veterinary form of masitinib, following a change in the synthesis process impacted AB Science's revenue, which fell by nearly 28.8%, to €448k compared to €62k in June 2022. Operating income (EBITDA) stood at -€8.85 million, an improvement of just over 7% (+7.5%) compared to a loss of €9.56 million in June 2022. Overall, operating expenses decreased by 8.8% to €9.3 million from €10.2 million in June 2022. The various contributions show that marketing expenses decreased by 13.8%, while administrative expenses remained stable at €1.65 million. While R&D fell by 10.9% (-€0.89 million) from €8.01 million in June 2022 to €7.21 million in June 2023. This decline is the result of an increase in the CIR and a differential in the valuation of certain warrants issued in payment of R&D services. On the other hand, At the same time, personnel expenses were maintained at €5.34 million compared to €4.98 million on June 30, 2022 with a significant and "exceptional" contribution from payment in shares. The financial result showed a loss of €1.57 million, resulting from an increase in financial expenses (-€2.61 million) due to the modification of the bond contract and its restatement (-€98 million) as well as interest on loans (-€0.95 million) and the discounting of conditional advances (-€0.65 million). Financial income (+€1.04 million) is due to the de-recognition of the ADPC's debt following their cancellation and the recognition of new shares. Net loss amounted to -€10.36 million compared to -€6.97 million, an increase of 48.7%.

10.2 A global go-to-market strategy

10.2.1 A well-stocked pipeline

AB Science's pipeline is based on two technological and scientific platforms. The first, historically, consists of discovering, developing and marketing tyrosine kinase inhibitors in a number of indications ranging from neurodegenerative diseases to sickle cell anemia, mast cell pathologies and viral pathologies such as Covid-19. Today it consists mainly of masitinib. All these pathologies have one thing in common: they involve mast cells, which generate and reinforce inflammatory phenomena. AB Science's other microtubule destabilizing agents platform is based on a first molecule: AB8939, which has a number of advantages over other molecules registered with regulatory agencies.

AB Science's Pipeline



Source : AB Science.

With such an extensive pipeline, the company finds itself in a situation that allows for multiple commercialization approaches. Thus for ALS, a rare indication for which it is estimated that there are 450,000 patients worldwide, including 30,000 in the USA and 3,000 in France, the market opportunity is such that AB Science could approach the market by "going it alone". Indeed, the reasons for such an approach are:

- ALS is a relatively concentrated market that should require only a small specialized marketing force, which we believe is within AB Science's reach.
- The relationships that exist between a number of KOLs and AB Science today and those developed during multicenter and international clinical trials necessarily contribute to the commercialization effort.

In contrast, for other MND indications, AB Science's business model is to seek a licensing partner at the earliest during the completion of confirmatory Phase III trials. The management team will strategically consider whether the company should enter into a licensing agreement in order to maximize shareholder value.

10.3 Indication-based marketing scenarios

10.3.1 SLA: alone or in partnership

We modelled two scenarios for the commercialization of masitinib, first in ALS. Scenario 1 in which AB Science goes it alone and scenario 2 in the event of a commercialization partnership with a pharmaceutical company.

Scenario N°1: This first "Stand Alone" scenario is based on the development and commercialization of masitinib in ALS by AB Science. This assumes that:

- Commercialization could begin in 2027 following the completion of Phase 3 confirmation and the entire registration process with various regulatory agencies (FDA, EMA, ANSM, Health Canada).
- All R&D fees (phase III confirmations pending) and registration fees with Canadian, American and European regulatory agencies

There are many reasons in favor of scenario 1.

- The ALS market is relatively concentrated, requiring only a "modest" marketing team, as there are few centers receiving ALS patients. According to the latest estimates from the US CDC and NINDS, the market opportunity is in the order of 30,000 people suffering from ALS in the US. In Canada, an estimated 3,000 people are affected, while in France, there are an estimated 6,000 cases of ALS
- The relationship established between some KOLs in the field and AB Science, during the development of the molecule as well as during clinical trials, also bodes well

ALS Mastinib	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033
France	0,0	0,0	0,0	1,7	3,1	4,6	7,0	10,5	10,5	10,59
EU-25	0,0	0,0	0,0	14,5	21,8	32,7	49,2	73,8	110,9	79,03
Canada	0,0	0,0	0,0	1,3	2,0	3,0	4,5	6,8	10,3	166,63
USA	0,0	0,0	0,0	14,6	22,0	33,1	49,8	74,8	112,5	184,56
Ventes totales	**0,0**	**0,0**	**0,0**	**32,2**	**48,9**	**73,5**	**110,4**	**166,0**	**244,2**	**440,8**

Source : AB Science, Estimations IE Finance

Scenario N°2: In the event of a marketing partnership with a pharmaceutical company, concerning ALS, it seems to us that this agreement could take place on the basis of the AB10015 study, the results of which are promising regardless of the ongoing conditional registration procedures. Our timeline for this agreement could be along these lines:

- Second semester 2024
- Partner participating in or covering the majority of the costs of the ongoing confirmatory Phase III trial in the U.S. and regulatory approval (€20 million as early as 2025)
- Partnership in FY24 (midway through Phase III in the U.S. - recruitment completed).

- Initial and milestone payments to AB Science for a total of €190 million over the period from FY26 to FY33 (in 2027 following the filing of the NDA (€56.7 million), in 2029 at the start of commercialization, €75.6 million).
- Revenue royalties start in FY27 at 9% (first 5 years) and then increase to FY32 to 15%.

ALS Mastinib	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033
France	0,0	0,0	0,0	3,5	5,2	7,9	11,9	18,0	27,1	40,9
EU-25	0,0	0,0	0,0	74,3	111,5	167,6	251,7	378,1	568,0	853,2
Canada	0,0	0,0	0,0	1,3	2,0	3,0	4,5	6,8	10,3	15,5
USA	0,0	0,0	0,0	73,2	110,1	165,5	248,8	374,1	562,4	845,5
Ventes totales	**0,0**	**0,0**	**0,0**	**152,3**	**228,9**	**344,0**	**517,0**	**777,0**	**1167,7**	**1755,0**
Revenus totaux AB Science	***0,0***	***20,0***	***0,0***	***70,4***	***20,6***	***106,5***	***46,5***	***69,9***	***175,2***	***301,0***

Source : AB Science, Estimations IE Finance

10.3.2 Indolent systemic mastocytosis

As mentioned above, the current prevalence of systemic mastocytosis in the United States is nearly 32,000 adult patients, 95% of whom are non-advanced. In Europe, based on an incidence of between 1 case per 7,700 individuals and 1/10,400 people, between 42,696 and 57,667 people are affected, i.e. an average of 50,181 patients. Systemic mastocytosis is therefore a rare disease for which patients are treated in well-identified centers. This is why we believe that AB Science can consider the possibility of approaching the market autonomously in "Stand Alone".

MSI Mastinib	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033
EU-26+UK	0,0	0,0	0,0	0,4	1,3	4,1	12,2	36,7	85,1	127,9
Amérique Nord	0,0	0,0	0,0	0,2	0,7	2,2	6,7	20,1	35,3	53,1
Ventes totales (EU + North America)	**0,00**	**0,00**	**0,00**	**0,70**	**2,09**	**6,29**	**18,90**	**56,84**	**120,42**	**181,04**

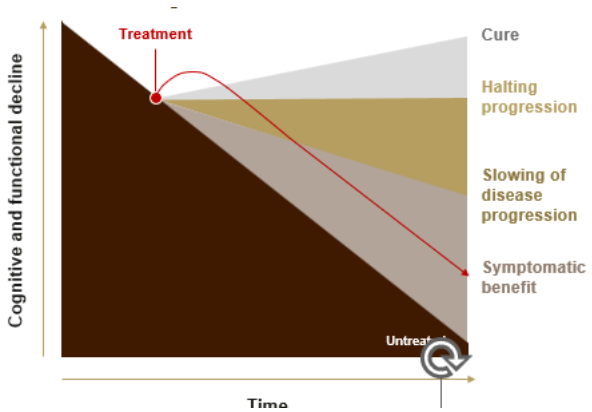
Source : AB Science, Estimations IE Finance

MSI mainly affects adults with dermatological, immunological (allergy) and gastrointestinal disorders. Current treatments seek to control the release of chemical mediators by mast cells. In fact, treatments are therefore individualized in order to prevent the appearance of anaphylactic shock, the aggravation of dermatological disorders as well as osteopenic and osteoporotic symptoms. For our marketing model, we believe that masitinib would be able to reach the market in 2027 simultaneously or with a very slight lag between Europe and the US, for an eligible population between these two markets of 41,090 people. With a market penetration of around 20%, given the competition existing in this market with *avapritinib*.

In addition, given the prices charged for active therapies in this indication ($192,000 annually for BluePrint's Ayvakit), annual prices for masitinib are expected to be €52,500 in Europe and about 30% more expensive in the US, i.e. €75,000. However, we believe that if the Phase III confirmatory phase III is successful in MSI, this market share could grow significantly as well as the price given the large number of molecules that have failed in these indications.
As a corollary to indolent systemic mastocytosis, AB Science is developing masitinib in a sister indication, Mast Cell Activation Syndrome (MAS), whose proximity to symptoms and treatments should allow the company to position itself quickly and easily in this market. As mentioned above, its recent inclusion in international consensus does not allow us to have an exact assessment of its epidemiology, in the scientific literature it is estimated that there is 17% of the population affected by this syndrome, a much higher prevalence than that of MSI.

10.3.3 MND: Possibilities for agreement for DMTs

For the two indications of neurodegenerative diseases (MND), multiple sclerosis (MS) and Alzheimer's disease (AD), the results of phase IIb/III showed that masitinib had a neuroprotective effect by reducing the mechanisms of inflammation in microglia and associated mast cells. This dual approach to neuroprotection and inflammation reduction is perfectly in line with the current problem of treatments that seek to modify the evolution of the disease (Disease-Modifying Treatment (DMT).



Indeed, recent successes (regulatory registrations) almost all point in the direction of treatments that are certainly not curative but modify the evolution of the pathology. In addition, the vast majority of these new treatments target the amyloid pathway. However, there are some incursions into the tau protein pathway. However, the proposed mechanism for the action of masitinib at the level of mast cells, microglia and therefore the innate immune system, represents a real therapeutic alternative, in particular because of the first results in MND (ALS, MS and AD) which show a modifying action on the evolution of these pathologies.

10.3.3.1 For MS, mainly progressive forms.

Indeed, by reducing the progression to disability in MS, masitinib influences the course of the pathology. In addition, masitinib is most effective when patients are in an early stage of MS. The mechanism of action and targets of masitinib are a third point of particular differentiation, proposing an approach and mechanism outside the current competitive landscape. Masitinib is comparable with the reference molecules (*ocrelizumab, siponimod*) in the treatment of primary progressive and secondarily progressive forms of MS, two forms of MS that occur independently of acute relapses.

Masitinib dans la SEP	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033
UE	0	0	0	0	11	20	35	52	78	118
Amérique Nord	0	0	0	0	13	23	40	60	90	135
Ventes totales (UE + Amérique Nord)	**0,0**	**0,0**	**0,0**	**0,0**	**24,4**	**42,7**	**74,7**	**112,1**	**168,3**	***252,5***
Paiements initiaux	0,0	25,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0
Paiements d'étapes	0,0	0,0	0,0	75,0	0,0	0,0	0,0	0,0	0,0	0,0
Royalties	0,0	0,0	0,0	0,0	3,7	6,4	11,2	16,8	25,2	37,9
Total Revenus AB Science	**0,0**	**25,0**	**0,0**	**75,0**	**3,7**	**6,4**	**11,2**	**16,8**	**25,2**	**37,9**

Source : AB Science, Estimations IE Finance

Following the example of what has been achieved between TG Therapeutics and Neuraxpharm Group on *ublituximab* (Briumvi™), a novel anti-CD20 drug approved in the US and Europe for relapsing forms of multiple sclerosis (MS), we believe that AB Science should be in a position to sign a license agreement based on the following assumptions for a total amount of €400 million as follows:

- Initial payment €50 million (€25 million upon signature and €25 million upon initiation of the confirmatory Phase 3 trial).
- Total milestone payments of €350 million based on clinical development, regulatory progress (MA application, MA received) and sales levels.
- A progressive royalty rate of 12% royalties on sales, which can increase up to 15% above one billion euros in sales.
- The full cost of confirmatory Phase III trials already approved by the FDA.

10.3.3.2 For AD, market size will take precedence.

Based on the Phase IIb/III results obtained by masitinib in the treatment of AD, the FDA and EMA have granted AB Science approval to conduct a confirmatory Phase III study. This trial is expected to confirm the reduction in the deterioration of disease cognition as well as an improvement in patients' daily activities. If these criteria are met, it will demonstrate the effect on the natural course of pathology (DMT) that the vast majority of players in the field are looking for. This is why we believe that AB Science is in a position to negotiate and sign a partnership or license agreement based on the results of Phase IIb/III and the future Phase 3 authorized by the FDA and EMA.

Masitinib in AD	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033
EU-26	0,0	0,0	0,0	0,0	44,9	78,6	137,6	206,5	309,9	465,0
Amérique Nord	0,0	0,0	0,0	0,0	122,3	214,1	374,9	562,5	844,1	1 266,7
Total Sales (EU + North America)	***0,0***	***0,0***	***0,0***	***0,0***	***167,2***	***292,7***	***512,5***	***769,0***	***1 154,0***	***1 731,7***

Source : AB Science, Estimations IE Finance

AB Science therefore has the opportunity to quickly initiate its confirmatory phase 3. However, the company is currently in discussions with potential partners with a view to licensing. Several scenarios are possible for AB Science. For example, if AB Science finds a partner willing to intervene immediately, a licensing agreement could be entered into before the start of the Phase III trial. Following the example of the agreements signed by BioArtic with Eisai and with AbbVie, respectively on Alzheimer's and Parkinson's diseases, we believe that AB Science should be in a position to sign a license agreement based on the following assumptions for an estimated total amount of €900 million:

- an initial payment of between €40 and €60 million.
- milestone payments broken down as follows:
  - initiation phase III de confirmation (80 M€)
  - NDA deposit (€80 million)
  - registration and commercialization (€160 million)
- a progressive royalty rate of 18 to 20% on sales (up to €502 million).

10.3.4 LMA and SMD: two more "Stand Alone" possibilities for AB Science

The relatively low prevalence of acute myeloid leukemia (AML) makes it a relatively rare disease and allows AB Science to consider the possibility of approaching the market autonomously in a "Stand Alone" manner. In fact, in

2018, in the USA, there were some 158,400 cases and according to epidemiologists, this prevalence is expected to increase by 0.7% per year to reach 169,000 in 2027. In Europe, AML is the most common acute leukemia in adults. It is estimated to affect 5/100,000 people (20,000 new cases/year).[56] Patients with AML have a five-year survival prognosis of between 54% and 14%, depending on their cytogenetics and risk category. In addition, this survival rate erodes sharply with the age of the patients, since at 75 years of age, it is less than 10%.[57]

LMA	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033
EU-26+UK	0,0	0,4	0,9	1,7	3,4	6,0	10,5	15,8	23,7	35,6
Amérique Nord	0,0	0,0	0,0	0,0	0,0	0,1	0,2	0,5	1,2	2,6
Total Sales (EU + North America)	**0,00**	**0,43**	**0,86**	**1,72**	**3,46**	**6,09**	**10,76**	**16,32**	**24,87**	**38,20**

Source : AB Science, Estimations IE Finance

AML mainly affects elderly subjects, who are often less tolerant of intense chemotherapy and whose cytogenetics are poorer. This has led to the definition of different categories of risk classes: high, medium and low on the basis of the determination of genetic and molecular factors. After diagnosis, the standard treatment for AML is more intense induction chemotherapy, followed by less intense post-remission/consolidation therapy to reduce the risk of recurrence. In the best-case scenario (50%), patients achieve complete remission and no longer have cancer. Patients at moderate or high risk often receive a stem cell transplant. Induction therapy usually consists of a combination of *cytarabine* and agents such as *anthracycline*, *etoposide*, *fludarabine*, *idarubicin* or *azacitidine*. In addition, treatment for CD33+ AML usually includes Mylotarg™, while mutated FLT3 AML is commonly treated with Rydapt™. However, the relapse rate is high in the order of 50%, sometimes even 55% after the 1st line of treatment. Within this refractory/relapsed population, approximately 30% of patients have an FLT3+ mutation with a poor prognosis.

Also in 2018, *gilteritinib* (Xospata™) was registered with the FDA for these refractory and relapsed (R/R) mutated patients. However, the non-FLT3 mutated or simply wild type R/R population fringe, i.e. nearly 20%, remains with significant unmet medical needs. In addition, the pathophysiology of MDS (Myelodysplastic Syndrome) is very close to AML, since in 30% it is subsequent to MDS. This closeness explains the similar treatment regimens. In addition, with a higher prevalence of MDS than AML, we agree with the company that it may be prudent to develop AB8939 in AML and MDS in parallel in order to maximize the chances of the drug candidate to be approved by the market and benefit from commercial potential. Considered a rare form of blood cancer or hematologic malignancies (hematopoietic stem cell disorders), they are characterized by a deficiency of healthy blood cells.

[56] ESMO Guidelines 2020 – Acute myeloid leukemia in adult patients: ESMO clinical practices guidelines for diagnosis, treatment, and follow-up.
[57] National Cancer Institute. Surveillance, Epidemiology, and End Results (SEER) Program. Cancer Stat Facts : Acute Myeloid Leukemia (AML). https://seer.cancer.gov/statfacts/html/amyl.html

11 Valorization

We have chosen several methods to add value to AB Science because the company is developing several platforms in multiple and complex indications such as neurodegenerative diseases with significant unmet medical needs. But also in mast cell pathologies such as MSI and SAM, characterized by significant mobilization and involvement of mast cells. Secondly, AB Science has an oncology-hematology platform with AB8939 indicated for the treatment of AML, MDS and certain solid tumors. Finally, AB Science has a new area of development with sickle cell anemia (Sickle Cell Disease), an indication in which masitinib has already demonstrated the relevance of its action.

11.1 Determining the discount rate

The discount rate corresponds to the average cost between the cost of equity and the cost of financial debt, weighted according to the importance of these two resources in the overall financing of the company. The cost of equity was determined on the basis of the CAPM model with a small cap risk premium, according to the following formula:

Cost of Equity = Rf +beta * (Rm-Rf) + Premium Small Caps

with Rf: risk-free rate (Rm-Rf): equity market premium

Indeed, given the size of the company, we allocate a small caps risk premium to the cost of equity. The Small Caps premium is determined according to 6 criteria, the evaluation of which is factual and objective. The rating scale for each criterion has 5 levels ranging from -- to ++. Each milestone increases 20 basis points to the cost of equity. The criteria are assessed as follows:

Criterion	Rating Scale				
	++	+	=	-	--
Corporate Governance[58]	4	3	2	1	0
Liquidity[59]	[66 % ; 100 %]	[33 % ; 66 %[	[15 % ; 33 % [	[5 % ; 15 % [	[0 % ; 5 % [
Gross margin size (€M)	[150 ; +∞ [	[100 ; 150[	[50 ; 100[	[25 ; 50[	[0 ; 25[
Operational Profitability	[25 % ; 100 %]	[15 % ; 25 % [	[8 % ; 15 % [	[3 % ; 8 % [	[0 % ; 3 % [
Gearing	] -∞ % ; -15 %]	] -15 % ; 15 %]	]15 % ; 50 %]	]50 % ; 80 %]	]80 % ; +∞ [
Customer Risk[60]	[0 % ; 10 %]	]10 % ; 20 %]	]20 % ; 30 %]	]30 % ; 40 %]	]40 % ; 100 %]

In the case of AB Science, we get the following matrix:

	++	+	=	-	--	Small Caps Premium
Corporate Governance						0,80%
Liquidity						0,60%
Size of turnover						1,00%
Operational Profitability						1,00%
Gearing						0,80%
Customer Risk						1,00%
TOTAL						**5,20%**

Therefore, based on a risk-free rate of 2.88 % (OAT TEC 10 – source: FactSet, Agency France Trésor), a risk premium of 6.4% (premium calculated by Market Risk Premia), a beta of 1.09, a small caps risk premium of 5.2% and with a financial leverage of 1.8%, the company's debt as at 3 January 2023, The discount rate is 14.8%.

Taux sans risque	Prime de risque	Beta	Prime Small Caps	Coût du Capital	Coût de la dette	Levier Financier	Taux d'impôts	WACC
2,88%	6,4%	1,09	5,2%	15,0%	4,9%	1,8%	25,0%	14,8%

Source : FactSet, Agence France Trésor, Fairness Finance, Market Risk Premia, Damodaran, estimations IEF

11.1.1 Probability of Approval (PoA) and Generic Assumptions

To assess the likelihood that a clinical-stage drug candidate in neurology will obtain marketing authorization, we use historical data on success rates in this area. The average probability of progress in Phase II neurology trials is 26.8%,

[58] The quality of corporate governance is assessed according to the following four criteria: separation of the functions of Chairman and General Management or functioning on the basis of a Supervisory Board and a Management Board; presence of independent members on the Board of Directors or the Supervisory Board; presence of censors or supervisory bodies; existence of specialized committees.
[59] Capital turnover rate over the course of a year.
[60] Share of gross margin represented by the 5 largest customers.

and in Phase III trials 53.1%. When the molecule is at the NDA stage, the probability of proceeding to approval is then 86.7%. The overall POA for a candidate since Phase II trials is approximately 12.34%.[61]

Probability of Success (PdS) of Phase Transitions

	Phase I à II	Phase II à III	Phase III à NDA	NDA à Approbation	PdA
Neurologie	47,7%	26,8%	53,1%	86,7%	**5,9%**
Allergie	56,4%	28,3%	64,7%	100,0%	**10,3%**
Hématologie	69,6%	48,1%	47,7%	92,0%	**14,7%**
Overall	52,0%	28,9%	76,8%	93,1%	**10,7%**

Source : BIO and QLS Advisors, IE Finance

In the other two areas of application of AB Science's drug candidates, namely mast cell diseases that we have linked to allergy and leukemias that we have chosen to associate with hematology, the transition rates of the clinical phases are given in the previous figure. The PdA for allergy that we will apply to mast cell diseases is 10.3%, while it is much higher for hematology at 14.7%.
However, interim data from the different trials showed good results and an excellent safety profile for Masitinib, suggesting that the drug candidate could be suitable for combination therapies in certain neurodegenerative indications. However, in order to be conservative, we therefore consider that the probability of success of Phase III Masitinib in these indications agrees with the usual values based on indications, for MSI and SAMA based on allergy PdS and for AB8939 in AML in agreement with the data obtained for hematology:

- Phase III – NDA transition in neurology: 53.1% for ALS, implying an overall PdA of 46.0% from the current stage of masitinib in this indication, beginning of phase II.
- Phase III – NDA transition in allergy: 64.7% for MSI, implying an overall PdA of 64.7%
- Phase I – Phase II transition in hematology: 69.9% leading to an overall PdA of 14.7% for masitinib in AML and 10.7% for masitinib in MDS.

11.2 rNPV

11.2.1 rNPV of masitinib in ALS (baseline scenario)

In our baseline scenario, we postulated that AB Science was pursuing the development of masitinib in a confirmatory Phase III phase. Then it marketed masitinib on a stand-alone basis by setting up a sales force that allowed it to approach the various centers treating this debilitating and fatal pathology. The US website "I am ALS" estimates that there are about 200 centers treating ALS in the United States and nearly a hundred in Europe (see European Networks to cure ALS, ENCALS). We therefore believe that it is possible for AB Science to build a sales force for both Europe and the USA (about fifty representatives). However, this will require a relatively large investment.

SLA Mastinib	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033
France	0,0	0,0	0,0	1,7	3,1	4,6	7,0	10,5	10,5	10,59
EU-25	0,0	0,0	0,0	7,1	10,7	16,0	24,0	36,1	54,2	81,5
Canada	0,0	0,0	0,0	0,6	0,9	1,4	2,1	3,2	4,8	7,3
USA	0,0	0,0	0,0	0,0	10,3	15,6	23,4	35,2	52,9	86,76
Ventes totales	**0,0**	**0,0**	**0,0**	**7,7**	**21,9**	**33,0**	**49,6**	**74,5**	**111,9**	**175,5**
Couts des ventes	0,0	0,0	0,0	1,1	2,6	3,3	4,0	4,5	4,5	7,0
Marge Brute	**0,0**	**0,0**	**0,0**	**6,6**	**19,3**	**29,7**	**45,6**	**70,0**	**107,5**	**168,5**
Dépenses opérationnelles	3,0	3,0	2,6	2,3	6,5	9,7	14,6	22,0	33,0	51,8
EBIT	-3,0	-3,0	-2,6	4,4	12,8	20,0	31,0	48,0	74,4	116,7
CIR /Impôts	-0,9	-0,9	-0,8	0,0	2,6	4,0	6,2	9,6	14,9	23,3
Capex	0,0	0,0	0,0	0,1	0,3	0,5	0,7	1,1	1,7	2,7
Depreciations/Amortissements	-0,1	0,0	0,0	0,1	0,4	0,6	0,9	1,3	2,0	3,1
Variation BFR	-0,5	-0,7	-0,4	0,0	-0,2	-0,2	-0,2	-0,1	-0,1	-0,1
Free Cash Flow opérationnels	-2,7	-2,8	-2,2	4,7	10,7	16,8	26,2	40,8	63,1	99,0
WACC	14,8%									
FCF opérationnels actualisés	-2,1	-1,9	-1,3	2,3	4,7	6,4	8,7	11,7	15,8	21,6
Valeur terminale	1 642,7									
Valeur terminale actualisée	243,6									
VAN	**309,7**									
PdS	46,04%									
NPV ajusté au risque	**142,6**									
Nb d'actions	51,07									
rNPV/Action	2,79									

Source : Estimations IE Finance

In this model, this Phase III concludes positively in 2025, leading the company to file an application for registration with the FDA in fiscal 2026. The probability of approval would be 46.04% corresponding to a Phase III-NDA transition of 53.1% and an NDA-Approval transition of 86.7%. Although over the past two years the number of approvals for alternative therapies in ALS has increased, the medical needs remain, especially in terms of neuroprotection, so we

[61] Clinical development success Rate and contributing factors 2011-2020. BIO, Pharma Intelligence and Quantitative Life Science (QLS Advisors)

assume a very conservative market share of 20% in Europe and the USA. In this conservative or baseline scenario, the risk adjusted NPV of masitinib in the treatment of ALS reaches €**142.6** million.

11.2.2 rNPV of masitinib in MSI (baseline scenario)

In the first indication of mast cell disease, in this case indolent systemic mastocytosis (ISM), our baseline scenario postulates that AB Science would be able to finalize the development and commercialize masitinib on a "Stand Alone" basis. Initially, the company would pursue the development of masitinib in confirmatory Phase III. Indeed, the quality of the phase 2 data and the continuation of the phase 3 confirmation in the MSI are all positive elements, allowing AB Science to calmly approach the possibility of a "Stand Alone" commercialization. By acquiring a sales force (which we estimate at around fifty people), AB Science would be able to address the different marketing markets (Europe and North America).

MSI Mastinib	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033
EU-26+UK	0,0	0,0	0,0	0,5	0,9	2,8	8,5	25,6	44,9	78,8
Amérique Nord	0,0	0,0	0,0	0,6	1,1	3,4	10,4	31,2	54,7	95,9
Ventes totales (EU + North America)	**0,00**	**0,00**	**0,00**	**1,04**	**2,09**	**6,28**	**18,88**	**56,78**	**99,60**	**174,70**
Ventes totales	**0,0**	**0,0**	**0,0**	**1,0**	**2,1**	**6,3**	**18,9**	**56,8**	**99,6**	**174,7**
COGS	0,0	0,0	0,0	0,1	0,3	0,6	1,5	3,4	4,0	7,0
Marge Brute	**0,0**	**0,0**	**0,0**	**0,9**	**1,8**	**5,7**	**17,4**	**53,4**	**95,6**	**167,7**
Dépenses opérationnelles	3,0	3,0	2,6	0,3	0,6	1,7	5,2	15,6	27,4	48,0
EBIT	-3,0	-3,0	-2,6	0,6	1,3	3,9	12,2	37,8	68,2	119,7
CIR /Taxes	-0,8	-0,9	-0,8	0,0	0,1	0,4	1,4	4,1	7,1	12,5
Capex	0,0	0,0	0,0	0,0	0,0	0,1	0,3	1,1	1,9	3,4
Depreciations/Amortissements	0,0	0,0	0,0	0,0	0,0	0,1	0,3	1,0	1,7	3,1
Variation BFR	-0,5	-0,7	-0,4	0,0	-0,2	-0,2	-0,2	-0,1	-0,1	-0,1
Financing	-0,5	-0,4	-0,1	2,4	0,0	0,0	0,0	0,0	0,0	0,0
Free Cash Flow opérationnels	-3,3	-3,2	-2,3	3,0	0,9	3,4	11,0	34,7	62,9	110,4
WACC	14,8%									
FCF opérationnels actualisés	-2,5	-2,1	-1,3	1,5	0,4	1,3	3,7	10,1	16,0	24,4
Valeur terminale	805,4									
Valeur terminale actualisée	119,5									
VAN	170,9									
PdS	64,70%									
VAN ajustée au risque	**110,56**									
Nb d'actions	51,07									
VANar/Action	2,16									

Source : Estimations IE Finance

In this basic model, the confirmatory Phase III in the treatment of MSI (severe forms of mastocytosis) concludes positively in the first half of 2025, leading the company to file an application for registration with the FDA in the second half of 2025. Based on the results of Phase II showing the efficacy and safety of masitinib, we believe that Phase III will be positive. By choosing the field of allergy because of the proximity of mast cell disorders to allergic phenomena and anaphylaxis, the probability of approval would be 64.7%, corresponding to a phase III-NDA transition of 64.7% and an NDA-Approval transition of 100%. Although a new molecule, Ayvakit™ from BluePrint Medicine, has recently been added to the therapeutic arsenal against mast cell diseases, particularly those with mutations affecting KIT type D816v, the medical needs remain, especially for mast cells whose function is not mutated (wild type). However, we assume a very conservative market share of 20% in Europe and 20% in the US, as well as annual prices of €52,500 in Europe and €75,000 in the US (prices well below those of avapritinib) given the recent arrival on the market of the BluePrint Medicines molecule. In this conservative or baseline scenario, the risk adjusted NPV of masitinib in the treatment of MSI reaches €**110.56** million.

11.2.3 rNPV of AB8939 in AML (baseline scenario)

For the new microtubule-destabilizing agent, AB8939, the first indication is acute myeloid leukemia (AML), which mainly affects an elderly population for whom the use of certain aggressive chemotherapies is prohibited. In addition, a certain number of these chemotherapy agents have to deal with resistance phenomena on the part of tumor cells, leading to increasingly high dosages, changes in molecules or significant toxicities. Thus, many medical needs remain and AB8939 with its various properties (insensitivity to induced resistance mechanisms, new mechanism of action, mast cell damage, in this case indolent systemic mastocytosis (SIM), our base case, postulates that AB Science would be able, once again, to finalize the development and market masitinib in "Stand Alone". Initially, the company would pursue the development of masitinib in confirmatory Phase III. Indeed, the quality of the phase 2 data and the continuation of the phase 3 confirmation in the MSI are all positive elements, allowing AB Science to calmly approach the possibility of a "Stand Alone" commercialization. By acquiring a sales force (which we estimate at around fifty people), AB Science would be able to address the different marketing markets (Europe and North America).

LMA AB8939	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033
Ventes totales	**0,0**	**0,0**	**0,0**	**0,0**	**0,0**	**12,9**	**22,6**	**34,0**	**51,0**	**76,8**
COGS	0,0	0,0	0,0	0,0	0,0	2,6	4,5	6,8	10,2	15,4
Marge Brute	**0,0**	**0,0**	**0,0**	**0,0**	**0,0**	**10,3**	**18,1**	**27,2**	**40,8**	**61,4**
Dépenses opérationnelles	2,2	5,0	5,0	0,0	0,0	5,8	10,2	15,3	23,0	34,6
EBIT	-2,2	-5,0	-5,0	0,0	0,0	4,5	7,9	11,9	17,9	26,9
CIR /Taxes	-0,6	-1,5	-1,5	0,0	0,0	1,5	2,6	4,0	6,0	9,0
Capex	0,0	0,0	0,0	0,0	0,0	0,2	0,4	0,5	0,8	1,2
Depreciations/Amortissements	0,0	0,0	0,0	0,0	0,0	0,2	0,4	0,6	0,9	1,3
Variation BFR	-0,5	-0,7	-0,4	0,0	-0,2	-0,2	-0,2	-0,1	-0,1	-0,1
Financing	-0,5	-0,4	-0,1	2,4	0,0	0,0	0,0	0,0	0,0	0,0
Free Cash Flow opérationnels	-2,7	-4,5	-3,9	2,4	-0,2	3,0	5,4	8,4	12,6	19,0
WACC	14,8%									
FCF opérationnels discountés	-2,3	-3,4	-2,6	1,4	-0,1	1,3	2,1	2,8	3,6	4,8
Valeur terminale	62,6									
Valeur terminale actualisée	9,3									
VAN	16,7									
PdS	14,69%									
FCF ajusté au risque	**2,45**									
Nb d'actions	51,07									
rNPV/Action	0,05									

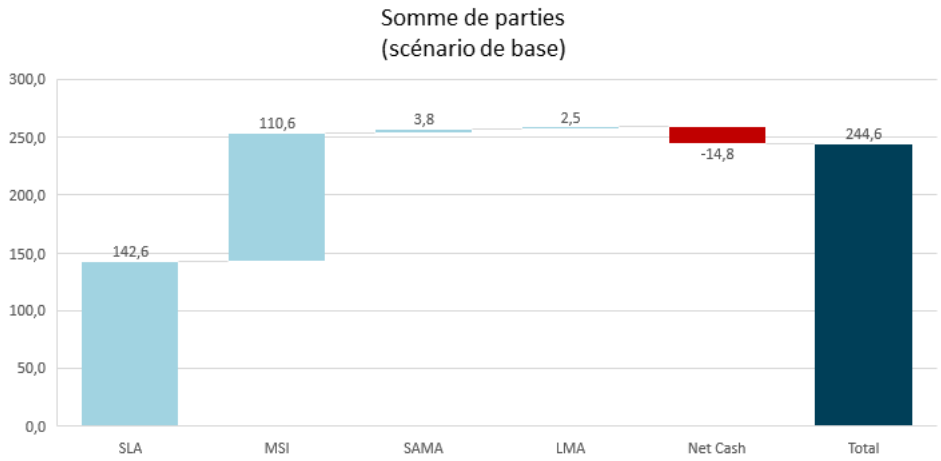
Source : Estimations IE Finance

In this basic model, the first preclinical and preliminary phase I results show the interest of AB8939 in certain indications such as AML, MDS and solid tumors such as sarcomas. However, as the progress of these projects is still preliminary, their contribution to the overall value of the company is low. Indeed, the overall probability of approval that we have chosen for this project is 14.7%, which represents the probabilities of the entire process from phase I to registration for a small molecule in hematology, i.e. 69.9%*48.1%*47; 7%*92.0%= 14.7%. Several new molecules have been registered in AML, including Daiichi Sankyo's *quizartinib* (Vanflyta™) as well as several other FLT3 inhibitors including *venetoclax* (Venclexta™). If these molecules are effective on cells carrying an Fms-bound tyrosine kinase 3 (FLT3) mutation, which are present in about 15 to 25% of AML with a higher percentage in the youngest patients (<60 years old). There are still significant medical needs for patients with other types of mutation such as IDH or for whom kinases are not mutated (wild type). Assuming a very conservative market share of 20% in Europe and 30% in the USA, the risk adjusted NPV of masitinib in the treatment of AML reaches **€2.45** million.

11.3 Sum of the Parts (PoP) (baseline scenario)

We value AB Science in our base case at €**244.6** million, or €**4.79** per share, mainly considering the ongoing progress in the development of masitinib in ALS (phase III ongoing), in MSI (phase III ongoing) as well as in the other mast cell pathology indication, SAM. The DTA platform, mainly driven by AB8939, is currently under development and only contributes very partially to the company's value today, in particular through the LMA indication.

Molecule	Indications	LOA	Royalties	Launch	Value (M)	Value/share
Masitinib						
	SLA	46%		2027	142,6	2,79
	MSI	65%		2028	110,6	2,16
	SAM	18%		2029	3,8	0,07
AB8939						
	LMA	15%		2029	2,5	0,05
		Sum			**259,4**	**5,08**
		Cash position			14,78	0,29
		Sum of parts			244,6	**4,79**



Source : Estimations IE Finance

11.4 Company DCF

Our DCF model for the baseline scenario is built over two time periods:

- An initial 10-year period in 2024E and 2033E, which should correspond to the start of marketing of masitinib in MSI (2026), then from 2027 to the commercialization of masitinib in ALS (2027);
- A second semi-explicit period of 10 years converging on the infinite period of cash flow stabilization.

The main assumptions of this scenario are as follows:

- **Sales:** sales of masitinib are growing very rapidly in two rare indications, ALS and MSI, in which AB Science is approaching the market in a "Stand Alone" manner. The growth rate is very fast, cumulatively 97.3% between 2024E and 2027E and then maintaining a virtually constant pace of 45.6% growth after 2028.
- **Operating profitability:** Although AB Science's objective is to break even quickly, the operating margin is not expected to turn positive until 2029E and is then expected to average 21% over the period 2029E – 2033E. Indeed, the strong growth in sales will make it possible to compensate for the significant expenses (marketing, SG&A). We should see a steady improvement in the operating margin over the years.
- **Investments:** in this model, investment levels are also kept constant over the period at 1% of turnover in order to maintain the company's level of innovation.
- **Corporate tax:** the tax rate is 25%
- **Working capital requirement:** 15% of sales
- **Discount rate:** In our model, we therefore apply a discount rate of 14.8% (see above).
- **Growth rate at infinity:** 1%

With a discount rate of 14.8%, we obtain the following free cash flow statement (in € million):

	2024E	2025E	2026E	2027E	2028E	2029E	2030E	2031E	2032E	2033E
Sales	1,0	1,1	1,2	10,1	25,5	54,1	101,8	181,3	287,2	465,7
EBIT	-6,3	-18,7	-19,3	-15,8	-8,0	8,8	43,0	101,7	180,7	316,6
Tax	-0,3	-0,3	-0,3	-0,3	-0,3	-0,3	10,5	25,2	45,0	78,9
Depreciation Provisions	0,1	0,1	0,1	0,1	0,1	0,1	0,1	0,1	0,1	0,1
Capital expenditure	0,0	0,0	0,0	-0,1	-0,3	-0,5	-1,0	-1,8	-2,9	-4,7
Change in WCR	-0,9	-0,8	-0,7	-0,6	-0,4	10,7	-0,5	0,0	0,9	2,2
Operating cash flow	-6,8	-19,1	-19,7	-16,1	-8,3	19,4	31,0	74,8	133,8	235,3
Discounted operating cash flow	-5,2	-14,7	-15,1	-12,3	-6,4	14,9	23,8	57,4	102,6	180,5

Source: IEFM estimates

Over the post-forecast period, we apply an infinite growth rate, in two stages, and obtain the following forecasts (in € million) adjusted to overall development risk (11%):

Discounted FCF 2024-2033	35,0
+ Discounted Terminal Value	248,0
+ Financial investments	0,1
+ Investments in associates	0,0
- Provisions	0,0
- Net financial debt	-12,9
- Minority interests	0,0
+ Discounted tax losses carried forward	-0,9
= Equity value pg (EV)	**215,6**
Number of shares	51,07
Value per share (EUR)	**4,22**

Source: IEFM estimates

Thus, the discounted free cash flow method shows an indicative value of equity of €269.2 million. However, considering the financing needs that we estimate will be necessary to complete the development of AB Science's indication pipeline between 2024 and 2028, i.e. €53.64 million, we obtain an equity value for AB Science of **€215.6 million,** i.e. **€4.22**/share.

11.5 Comparable

We chose a sample of companies active in the field of neurodegenerative disease (NDD) and oncology. However, there are relatively few companies active in the field of cancer prediction in the general population. Indeed, the vast majority of players target certain specific segments such as recurrence, treatment follow-up, and optimization of treatments according to the genetic profile of tumors and patients.

11.5.1 Choice of comparable

We have therefore chosen to constitute an initial sample of companies that develop products in several types of oncological and neurological indications. Thus, our sample consists of companies (Alkermes, Amylyx, Atara Biotherapeutics, Athira Pharma,)

Alkermes (ALKS). Founded in 1987, Alkermes Plc., is a biopharmaceutical company, discovering, developing and commercializing pharmaceutical products that address the unmet medical needs of patients in the fields of neuroscience and oncology. His portfolio focuses on alcohol dependence, opioid addiction, schizophrenia and bipolar I disorder. The company markets ARISTADA,™ VIVITROL™ and LYBALVI.™ Its 2022 revenue was $1.11 billion.

Amylyx Pharmaceuticals (AMLX). Founded in 2013 in Cambridge, MA, Amylyx Pharmaceuticals, Inc. is a commercial-stage biotechnology company that discovers and develops treatments for amyotrophic lateral sclerosis (ALS) and neurodegenerative diseases. Conditionally registered and marketed in Canada, ALBRIOZA™ and RELYVRIO™ in the USA, for the treatment of ALS in adults. This product would have generated $272.3 million in the first three quarters of 2023.

BluePrint Medicines (BPMC). Incorporated in 2008 in Massachusetts, formerly Hoyle Pharmaceuticals, which became BluePrint Medicines Corporation in 2011, this company develops genomics-based drugs for cancers and blood disorders. The company markets AYVAKIT,™ a KIT inhibitor for the treatment of systemic mastocytosis (SM) and gastrointestinal stromal tumors. As of December 31, 2022, its revenue stood at $204 million, including nearly $93 million in licensing and collaboration revenues.

Coya Therapeutics (COYA). Founded in 2020, in Texas, Coya Therapeutics, Inc. is a clinical-stage biotechnology company dedicated to developing medicinal products to modulate the function of regulatory T cells (Tregs). The Company's portfolio is primarily Treg-enhancing biologics, Treg-derived exosomes, and autologous Treg cell therapy. The lead treatment candidate is COYA 101, which has completed the Phase 2a clinical trial for the treatment of ALS.

Cytokinetics (CYTK). Active since 1997, the California-based company Cytokinetics focuses on the discovery, development and commercialization of muscle activators and inhibitors as potential treatments for debilitating diseases. Its drug candidates include *omecamtiv mecarbil*, a novel cardiac myosin activator that is in Phase III clinical trials in patients with heart failure, and *reldesemtiv*, a skeletal muscle troponin activator, which is in Phase III clinical trials to treat amyotrophic lateral sclerosis and spinal muscular atrophy. Its revenue in December 2022 was $94.6 million.

Deciphera Pharma (DCPH). Since 2003, Deciphera Pharmaceuticals has been a biopharmaceutical company focused on deciphering the main mechanisms of drug resistance that limit the rate and durability of response to existing cancer therapies. To this end, it is developing a drug candidate, QINLOCK,™ which is used for the treatment of GIST. Revenue for the year 2022 was $134 million.

Denali Therapeutics (DNLI). Originally known as SPR Pharma Inc., the company changed its name in 2015 to Denali Therapeutics Inc. This biopharmaceutical company is developing a portfolio of product candidates designed to cross the blood-brain barrier (BBB) in neurodegenerative diseases and lysosomal storage diseases. Its main small molecules that penetrate the brain are BIIB122/DNL151, SAR443820/DNL788 and DNL343. Its revenue in 2022 was $100 million, mostly from revenue from collaborations.

Gain Therapeutics (GANX). Founded in 2017, Gain Therapeutics, Inc. is a biotechnology company that researches and develops novel therapies to treat diseases caused by "protein misfolding." She focuses on rare genetic diseases and neurological disorders. Its lead candidate is GT-02287, for the treatment of Parkinson's disease GBA1.

TG Therapeutics (TGTX). Since 1993, in Morrisville, North Carolina, TG Therapeutics, Inc., a biopharmaceutical company, has focused on acquiring, developing, and commercializing novel treatments for B-cell diseases. It commercializes BRIUMVI™, an anti-CD20 monoclonal antibody for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS), including clinically isolated syndrome, relapsing-remitting disease and active secondary progressive disease in adults. The nine-month turnover of TG would be $140 million.

Voyager Therapeutics (VYGR). Voyager Therapeutics is a gene therapy biotechnology company applied to neurology. Voyager has an AAV TRACER™ capsid discovery platform that enhances the therapeutic window of neuronal gene therapy through low-dose blood-brain barrier penetration and optimized vectors. This platform powers many alliances, so in 2022, the company generated $40.9 million in collaboration revenue.

The table below summarizes the main aggregates, in € million, of the companies in our sample:

In EUR	CA 24E	CA 25E	CA 26E	EBE 24E	EBE 25E	EBE 26E	REX 24E	REX 25E	REX 26E
Alkermes	1 530,3	1 544,6	1 579,2	NS	NS	NS	429,6	410,2	448,0
Amylyx	483,1	579,3	648,4	NS	NS	NS	64,9	119,2	170,3
BluePrint Medicines	388,7	591,4	822,2	-321,8	-137,6	69,5	-311,7	-127,4	65,0
Coya Therapeutics	4,1	6,0	NS	NS	NS	NS	-6,2	-11,9	-23,1
Cytokinetics	14,2	165,2	549,6	-443,6	-279,9	-10,9	-439,0	-327,4	-59,9
Deciphera Pharma	199,1	262,9	382,0	NS	NS	NS	-204,4	-164,6	-68,1
Denali Therapeutics	64,2	152,5	207,0	-458,5	-402,8	-300,9	-458,5	-453,1	-367,4
Gain Therapeutics	0,3	0,9	0,2	NS	NS	NS	-22,8	-23,4	-30,7
TG Therapeutics	263,9	412,7	628,7	-5,1	51,1	231,0	-15,1	81,7	261,7
Voyager Therapeutics	37,7	60,7	60,8	-99,8	-98,9	-115,0	NS	-122,2	-124,1

Source: IE Finance based on FactSet as of 4/3/24

In EUR	Market cap.	Net debt 23	Minorities 21	EV
Alkermes	4 662,8	-401,3	0,0	4 261,5
Amylyx	1 170,4	-367,1	0,0	803,3
BluePrint Medicines	5 375,3	63,5	0,0	5 438,8
Coya Therapeutics	132,3	7,0	0,0	139,3
Cytokinetics	7 032,7	140,6	0,0	7 173,3
Deciphera Pharma	1 294,5	-280,3	0,0	1 014,2
Denali Therapeutics	2 679,0	-982,3	0,0	1 696,8
Gain Therapeutics	88,4	-18,9	0,0	69,5
TG Therapeutics	2 559,5	-106,7	0,0	2 452,8
Voyager Therapeutics	473,1	-210,6	0,0	262,5

Source: IE Finance based on FactSet as of 4/3/24

11.5.2 Valorization

The table below details the main stock market multiples of the peers in our sample, restated using the abbreviation "NS" for non-available securities.

	VE/CA 24E	VE/CA 25E	VE/CA 26E	VE/ EBE 24E	VE/ EBE 25E	VE/ EBE 26E	VE/REX 24E	VE/REX 25E	VE/REX 26E
Alkermes	2,8	2,8	2,7	NS	NS	NS	9,9	10,4	9,5
Amylyx	1,7	1,4	1,2	NS	NS	NS	12,4	6,7	4,7
BluePrint Medicines	14,0	9,2	6,6	-16,9	-39,5	78,2	-17,5	-42,7	83,6
Coya Therapeutics	34,4	23,2	NS	NS	NS	NS	-22,6	-11,7	-6,0
Cytokinetics	506,5	43,4	13,1	-16,2	-25,6	ns	-16,3	-21,9	-119,8
Deciphera Pharma	5,1	3,9	2,7	NS	NS	NS	-5,0	-6,2	-14,9
Denali Therapeutics	26,4	11,1	8,2	-3,7	-4,2	-5,6	-3,7	-3,7	-4,6
Gain Therapeutics	219,9	79,4	397,1	NS	NS	NS	-3,1	-3,0	-2,3
TG Therapeutics	9,3	NS	NS	NS	NS	NS	-162,6	30,0	9,4
Voyager Therapeutics	7,0	4,3	4,3	NS	NS	NS	NS	-2,1	-2,1

Source: IE Finance based on FactSet as of 1/2/24

The table below shows the induced valuations (in € million) based on the multiples applied on the basis of the current valuations of the sampled companies.

	CA 24E	CA 25E	CA 26E	EBE 24E	EBE 25E	EBE 26E	REX 24E	REX 25E	REX 26E	RN 24E	RN 25E
AB Science	1,0	1,1	1,2	-18,9	-19,1	-17,9	-19,3	-19,2	-18,0	-19,6	-19,5
Valorisation moyenne/action		1,13			NS			NS		NS	

Source: IE Finance based on FactSet as of 1/2/24

Thus, the approach using the method of comparable stock market multiples leads us to a valuation of **€1.13,** i.e. a capitalization of **€57.7 million.**

11.6 Synthesis (base scenario) and Other scenarios

The value of the company is determined by the different methods used (risk adjusted NPV, sum of parts, overall portfolio DCF and comparable methods). In total, the value for the base case is €3.79 per share, which reflects an upside potential of approximately 77.8% compared to the current level (€2.13), with additional potential if the company can execute its strategy (obtain accelerated and/or conditional registration for masitinib in ALS, complete its confirmatory clinical phases in SLA and MSI, enter into one or more partnerships with biopharmaceutical companies and raise additional capital in an efficient manner).

Methods	Value	Value/Action
Comp	57,75	1,13
rNPV	255,59	5,00
SOTP	244,64	4,79
DCF	215,60	4,22
Average	193,40	3,79

As previously stated, we expect the company to raise funds in 2024. It is important to note that there could be significant variability in results, influenced by factors such as stock price, market sentiment, and capital requirements. Therefore, we provide a sensitivity analysis incorporating different potential structures and their implications for our baseline scenario.

11.6.1 Partnerships on masitinib in MS and/or AD (Blue sky scenario)

For these two major indications in the world of neurodegenerative diseases, namely Multiple Sclerosis (MS) and Alzheimer's Disease (AD), AB Science is at a nodal point in the development of masitinib, as the company has been authorized by regulatory agencies to perform a confirmatory Phase III in order to strengthen the data from the Phase II (reduction of progression to disability for MS, reduction of AD-related cognitive impairment).

11.6.1.1 Multiple sclerosis.

Progressive multiple sclerosis (primary and secondary) represents a major market opportunity, as many players in the treatment of multiple sclerosis mainly target relapsing-remitting MS (85% of the overall population of people affected). Thus, there is still a medical need for the treatment of progressive forms, in particular the primary progressive form (i.e. about 15% of patients), against which only Roche Ocrevus™ is currently registered. Phase II data for Masitinib show that despite statistical non-significance (too small number of patients), masitinib would improve the risk of disability progression by about 37% (by reducing the values of the EDSS test) compared to "only" 24% with ocrelizumab and 21% for siponimod. In addition, this reduction in EDSS is confirmed at 3 months. However, there is still a phase III conformation to be done as requested by the FDA and EMA which granted the green light for such a study. At the end of phase III, if these results are confirmed, masitinib would have a much better efficacy profile than the leading molecule on the market today. We believe that AB Science can finalize a partnership with a major biopharmaceutical company based on its Phase II results and the ability to rapidly initiate a Phase III confirmation pre-approved by regulatory agencies. Several other players, with their Bruton's tyrosine inhibitors, have positioned themselves in the segment of primary progressive and secondarily progressive forms, such as Sanofi with *tolebrutinib,* Roche with *fenebrutinib.* Based on the agreement between TG Therapeutics and Neuraxpharm for the commercialization of ublituximab (Briumvi™)

Our assumptions for an MS agreement for masitinib:

- an initial payment of €50 million
- total milestone payments of €350 million, divided between Phase III of confirmation (one third of the total amount) and commercialization (two thirds of the total amount).
- a progressive royalty rate of 12% to 15% on sales.

11.6.1.2 Alzheimer's Disease

In Alzheimer's disease, the disease-modifying effect (DMT) that we see in the Phase IIb/III results should be confirmed in the confirmatory Phase III. However, the size of this type of trial is undergoing real inflation. For example, a recent article reported an average of 776 participants (range: 316 to 2046) and an average duration of 162 weeks (range: 73 to 309 weeks, including the recruitment period and the treatment period) for TMD trials[62]. In addition, the target market is particularly important, as nearly 6.8 million Americans are estimated to have AD and just as many Europeans. It is estimated that nearly 21.4% of patients have mild AD and 13.3% have moderate AD. If, on the other hand, it is estimated that 55% of these patients will "observe" this specific treatment modifying the evolution of their pathology, which leads to a little more than 1.7 million patients in the USA and 2.1 million patients in Europe (EU-26). Given the importance of the markets, we estimate that AB Science's partner will target around 5% of the market at peak sales, i.e. ~€2.8 billion. As an example of some deals in the field, we think of a relatively traditional structured agreement with an upfront payment, development milestone and commercial payments with royalties on sales. Like the agreements made in the field by which we will mention (Eli Lilly and AC Immune, Sanofi and Denali, AbbVie and Voyager Therapeutics or Takeda and Denali)

Our hypotheses could therefore be for an estimated total amount of €900 million:

- an initial payment of between €40 and €60 million.
- milestone payments broken down as follows:

[62] Cummings, J. et al. Alzheimer's disease drug development pipeline :2022. *Alzheimer's Dement.* 2022 ; 8(1) : e12295.

- initiation phase III de confirmation (80 M€)
- NDA deposit (€80 million)
- registration and commercialization (€160 million)

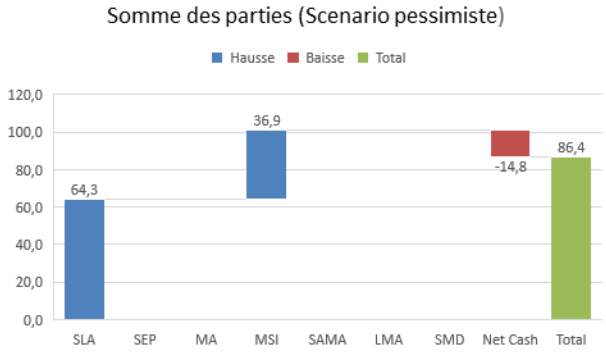
- a progressive royalty rate of 18 to 20% on sales (up to €502 million).

11.6.2 Other scenarios

Several scenarios lead us to the sensitivity analysis with a value of AB Science as a function of the successes of masitinib in MSI and SMA and in case of AB8939 in AML and MDS. Moreover, they are also a function of the company's ability to form partnerships.

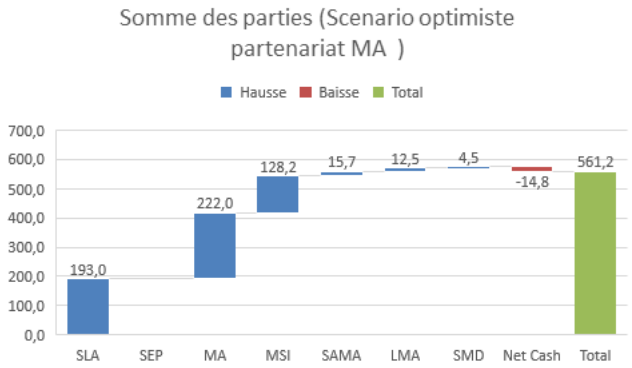
Bear case scenario.

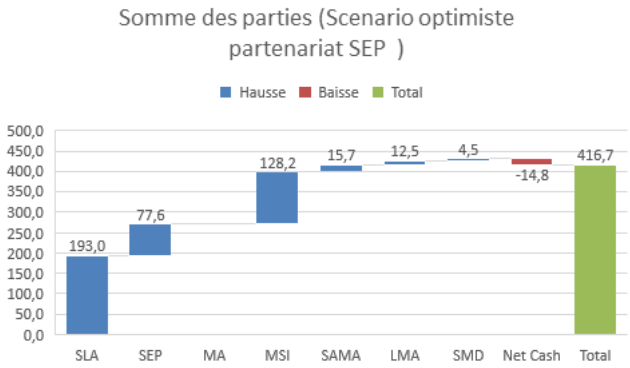
In our pessimistic scenario, AB Science succeeds in its Phase III confirmation in ALS, as well as in the MSI indication but with lower probabilities of success, which translates into a value of the sum of the projects of **€86.4 million**, or a value per share of **€1.98**, down 7% on the current value of the share.



Bull case scenario.

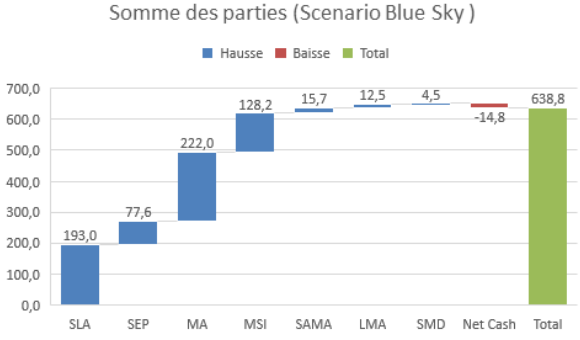
For our optimistic scenario, AB Science succeeds in its confirmatory phase III in ALS, in MSI and the company is able to sign a partnership in either MS or AD while continuing the development of AB8939 which translates into a value of the sum of the projects between €416.7 million and €561.2 million, i.e. a value per share between €8.2/share and €11.05/share.





Super Optimistic Scenario (Blue Sky)

For our optimistic scenario, AB Science succeeds in its confirmatory phase III in ALS, in MSI and the company is able to sign two partnerships, one in MS and the other in AD, while continuing the development of AB8939, which translates into a total value of **€638.8 million**, i.e. a value per share of **€12.57**, +489.3% on current levels.



12 Annexes

12.1 Intellectual property

With regard to intellectual property, the use of masitinib for therapeutic purposes is protected by several patent families guaranteeing commercial exclusivity until the end of 2042. In addition, in at least two indications, masitinib has been granted orphan drug status (exclusivity periods of 7 years in the USA and 10 years in Europe)

Indication	Duration	Orphan drug
Amyotrophic Lateral Sclerosis	2037	Yes
Multiple Sclerosis	2041	No
Alzheimer's Disease	2041	No
Indolent systemic mastocytosis	2036	Yes
Sickle-cell anemia	2040	Possible
Refractory metastatic prostate cancer	2042	No

The intellectual property rights of masitinib in ALS are secured until 2037 by several patents relating to the use of masitinib in the indication, an orphan drug status and filings issued in different countries

Protection	Subject	Duration	Status
Amyotrophic Lateral Sclerosis (ALS)	Treatment of ALS WIPO (PCT)	Until 2037	Issued
Country	Europe, USA, China, Japan, Eurasia, Israel, Mexico, Singapore, South Korea, Australia, New Zealand, South Africa,	Until 2037	Issued
Orphan drug status	FDA and EMA have granted masitinib orphan drug designation.	7-year exclusivity (USA) 10-year exclusivity (Europe)	Issued

The intellectual property rights of masitinib in MS are secured until 2041 by several patents for two second medical uses of masitinib in a subpopulation (PPMS and nSPMS).

Protection	Subject	Duration	Status
Material Composition	2-(3-aminoaryl)amino-4-aryl-thiazoles and their use as C-kit inhibitors	2023	Issued
Process	Process for synthesis of 2-aminothiazoles compounds as kinase inhibitors	2028	Issued
Process	Aminothiazole compounds as kinase inhibitors and methods of use thereof	2028	Issued
Process	Polymorphic form of a 2-amino (nitroaryl) thiazole derivative	2028	Issued
Second Medical Use	Treatment of Multiple Sclerosis with Masitinib	2031	Issued (USA)
Second Medical Use	Masitinib for the Treatment of a Subpopulation of Patients With Multiple Sclerosis	2041	PCT Application

In the field of AD, the intellectual property rights of masitinib are guaranteed until 2041 by, inter alia, a PCT application on the use of masitinib in subpopulations.

Protection	Subject	Duration	Status
Material Composition	2-(3-aminoaryl)amino-4-aryl-thiazoles and their use as C-kit inhibitors	2023	Issued
Process	Process for synthesis of 2-aminothiazoles compounds as kinase inhibitors	2028	Issued
Process	Aminothiazole compounds as kinase inhibitors and methods of use thereof	2028	Issued
Process	Polymorphic form of a 2-amino (nitroaryl) thiazole derivative	2028	Issued
Use for AD	Masitinib for the treatment of Alzheimer's disease (subpopulations)	2041	PCT Application

The intellectual property rights of AB8939 in the AML are secured until 2036 by a patent on the "composition of matter" and potentially until 2044 in the AML with chromosomal abnormality (MECOM) by a patent on the "second medical use".

Protection	Subject	Duration	Status
Composition of Matter (CoM)	CoM patent filed and granted	Until 2036	Issued
Second Medical Use	Filing of a provisional patent application for a subpopulation of AML with a chromosomal abnormality	Until 2044	Registered
Orphan drug status	The FDA has granted AB8939 orphan drug designation.	7-year exclusivity (USA)	Issued

12.2 Governance

12.2.1 Management & Executive Committee

- Alain Moussy, MBA. Co-founder and CEO. Founded AB Science. Former strategic consultant at Booz, Allen & Hamilton, and former head of development at Carrefour. President of AFIRMM, an association of mastocytosis patients. (Former strategic consultant at Booz, Allen & Hamilton, and former Head of Corporate Development at Carrefour. President of AFIRMM, association of mastocytosis patients)

- Laurent Guy, Chief Financial Officer, previously worked in the banking sector (Société Générale and Paribas) and in strategy consulting (Accenture). (Former positions in the banking industry (Société Générale and Paribas) and strategy consulting (Accenture)

- Christian Fassotte, MD. Medical Director. Medical Doctor. More than 30 years of experience, including leadership positions at Sanofi and Roche for medical, regulatory, and R&D affairs. 30 years of experience, including executive position at Sanofi for Medical, Regulatory Affairs and R&D

- Olivier Hermine, MD, PhD; Professor of Medicine, Member of the French Academy of Sciences and author of more than 700 international publications.

13 Summary of accounts

Simplified income statement

31/12 (M€) cpts sociaux	2021	2022	2023E	2024E	2025E	2026E
Turnover	1.63	0.95	0.93	0.99	1.1	1.19
Cost of sales	0.11	0.03	0.03	0.03	0.03	0.03
Marketing costs	0.49	0.48	0.48	0.48	0.48	0.48
Administration costs	3.58	3.04	3.04	3.04	3.04	3.04
R&D costs	11.23	13.35	13.35	13.35	13.35	13.35
EBIT	**-13.78**	**-15.95**	**-15.96**	-15.91	-15.8	-15.7
Net financial income	-0.62	2.33	3.33	4.33	5.33	6.33
Profit before tax	-14.4	-13.62	-12.64	-11.58	-10.47	-9.38
Taxes	-0.03	0	0	0	0	0
Net profit	-14.43	-13.63	-12.64	-11.59	-10.48	-9.38
	0.27	0.26	0.26	0.26	0.26	0.26
Net profit, Group share	-14.15	-13.37	-12.38	-11.33	-10.22	-9.12
Number of shares (in millions)	46.94	51.07	51.07	51.07	51.07	55.07
EPS (EUR per share)	-0.3	-0.26	-0.24	-0.22	-0.2	-0.17

Balance sheet – main aggregates

31/12 (M€)	2021	2022	2023E	2024E	2025E	2026E
ASSETS						
Intangible fixed assets	1.42	1.63	1.71	1.01	1.01	1.01
Tangible fixed assets	0.28	0.31	0.16	0.16	0.16	0.16
Long-term investments	1.38	1.03	0.76	0.16	0.16	0.16
Investments in associates						
Non-current asset	**3.08**	**2.97**	**2.63**	**1.34**	**1.34**	**1.34**
Inventories Merchandise	0.14	0.46	0.44	0.44	0.44	0.44
Advances, deposits paid/Orders						
Trade receivables	0.31	0.16	0.25	0.37	0.55	0.83
Other receivables	9.02	12.99	15.14	15.14	15.14	15.14
Deferred tax assets						
Prepaid expenses	0	0	0	0,00	0,00	0,00
Cash and cash equivalents	8.72	7.27	14.87	14.87	14.87	14.87
Current assets	**18.19**	**20.87**	**30.69**	**30.82**	**31.00**	**31.28**
TOTAL ASSETS	**21.77**	**23.84**	**33.32**	**32.15**	**32,34**	**32.62**
LIABILITIES						
Share Capital	0.47	0.47	0.47	0.47	0.47	0.47
Additional paid-in capital	233.92	233.93	248.87	233.93	234.93	235.93
Reserves and consolidated income	-257.52	-269.99	-269.99	-280.35	-280.35	-280.35
Other reserves	-0.07	-0.08	-0.08	-0.08	-0.08	-0.08
Shareholders' equity	**-23.2**	**-35.67**	**-20.73**	**-46.03**	**-45.03**	**-44.03**
Provisions (Risks and Expenses)	2.35	1.31	0	0	0	0
Bonds	0	7.05	7.05	7.05	7.05	7.05
Bank borrowings	6.69	11.55	11.55	11.55	11.55	11.55
Conditional advances	8.61	11.58	11.58	11.58	11.58	11.58
Trade payables	11.37	12.25	12.25	13.25	14.25	15.25
Tax and social security liabilities	4.22	6	6	6	6	6
Other liabilities	8.38	9.77	5.51	5.51	5.51	5.51
Total liabilities	39.26	53.03	53.94	54.94	55.94	57.94
TOTAL LIABILITIES	**21.27**	**23.84**	**33.32**	**32.16**	**32.34**	**32.62**

Statement of Cash Flows – Major Aggregates

31/12 (m€)	2021	2022	2023E	2024E	2025E	2026E
Earnings	-13.7	-17.78	-19.64	-18.77	-18	-16.96
Cashflow	-19.09	-17.9	-18.9	-17.6	-18.31	-18.94
Capital expenditure	-0.05	-0.05	-0.05	-0.06	-0.5	-1.27
Impact of working capital requirements variation	-0.04	11.57	0.14	-0.33	-0.18	-0.28
Free cashflow	-19.18	-6.38	-18.81	-17.99	-19	-20.49

Financial ratios

31/12 (€m)	2021	2022	2023E	2024E	2025E	2026E
EPS (€)	**-0.32**	**-0.42**	**-0.38**	**-0.36**	**-0.37**	**-0.39**
Market capitalisation (€m)	108.78	108.78	108.78	108.78	108.78	108.78
Enterprise value	95.84	154.95	155.03	168.56	151.9	158.04
P/E	-6.59	-6.58	-5.1	-5.59	-5.95	-5.72
EV/Sales	58.62	163.73	166.13	171.02	138.59	132.52
EV/Ebitda	-5.8	-8.2	-8.12	-9.42	-8.09	-8.14
EV/Ebit	-5.66	-8.04	-8.08	-9.37	-8.13	-8.18
Cashflow/Sales	NS	NS	NS	NS	NS	NS
Ebit/Sales	NS	NS	NS	NS	NS	NS
Net earnings/Sales	NS	NS	NS	NS	NS	NS
Gearing	NS	NS	NS	NS	NS	NS

14 Important Warnings

Definition of In Extenso Financing and Market Opinions and Course Objectives

The opinions mentioned by In Extenso Financement & Marché reflect the expected absolute return, over a horizon of between 6 and 12 months, for each stock considered, in local currency.

1. Strong Buy	The stock is expected to deliver an absolute return of more than +25%
2. Purchase	The stock is expected to deliver an absolute return of between +10% and +25%
3. Neutral	The stock is expected to move between +10% and -10%
4. Sale	The stock is expected to deliver an absolute underperformance of between -10% and -25%
5. Strong Selling	The stock is expected to achieve an absolute underperformance of more than -25%

Details of the methods used by In Extenso Financement & Marché to determine its price targets are available on the website www.genesta-finance.com.

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Participation of the analyst, In Extenso and/or its employees in the issuer's capital	Issuer's stake in In Extenso's share capital	Other significant financial interests between the issuer and In Extenso	Existence of a market maker or liquidity provider contract between the issuer and In Extenso	Remuneration of In Extenso by the issuer for the preparation of this financial analysis	Remuneration of In Extenso by the issuer in respect of services other than the preparation of this financial analysis	Communication of the financial analysis to the issuer prior to its dissemination
No	No	No	No	Yes	No	No

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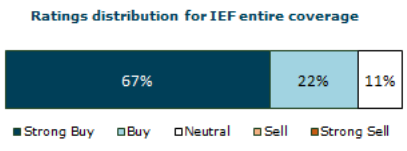
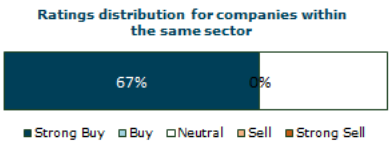
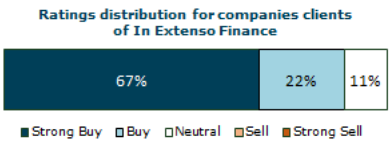
Historical opinions and price targets related to the stock over the last 12 months.

Date	Opinion	Course Objective
March 6, 2024	Initiation of Coverage	**€3.79**

Distribution of opinions







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