AB SCIENCE

Corporate Presentation

April 2024

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Overview

Management Team

ALAIN MOUSSY
Co-founder and CEO

Former strategic consultant at Booz, Allen & Hamilton and former Head of Corporate Development at Carrefour. President of AFIRMM, association of mastocytosis patients

OLIVIER HERMINE, MD, PhD
Co-founder and Chairman of Scientific Committee

Member of the French Académie des Sciences and author of 700 international publications

CHRISTIAN FASSOTTE, MD
Chief Medical Officer

Medical Doctor. 30 years of experience, including executive position at Sanofi for Medical, Regulatory Affairs and R&D

LAURENT GUY
Chief Financial Officer

Former positions in the banking industry (Société Générale and Paribas) and strategy consulting (Accenture).

Stock Information

- Listed on Euronext Compartment B
- ISIN : FR0010557264
- Tickers : AB.PA (Reuters) ; AB:FP (Bloomberg)
- Ordinary shares : 58,866,203 (https://www.ab-science.com/investors/regulated-information/monthly-disclosure-of-total-outstanding-shares-and-voting-rights/)
- Website : https://www.ab-science.com/
- Head Office : Paris, France

Core Pipeline

AB Science has two platforms, with masitinib in phase 3, primarily centered around neuro-degenerative diseases, and with microtubule destabilizer agents (MDAs) in haemato-oncology

Platform	Drug	Therapeutic area	Indication	Preclinical	Phase 1	Phase 2	Phase 2B	Confirmatory Phase 3
Tyrosine Kinase Inhibitor	Masitinib (Oral)	Neuro-degenerative Diseases (NDD)	Amyotrophic Lateral Sclerosis					
			Progressive Forms of Multiple Sclerosis					
			Alzheimer's Disease					
		Mast Cell Diseases	Indolent Systemic Mastocytosis					
			Mast Cell Activation Syndrome					
		Blood diseases	Sickle Cell Disease(1)					
		Viral Diseases	COVID-19					
Microtubule Destabilizer Agent	AB8939 (IV)	Hematology	Acute Myeloid Leukemia (AML)					
	ABXXXX (oral)	Oncology	Sarcoma, Solid Tumors					

(1) Collaborative programme with Assistance Publique - Hôpitaux de Paris (AP-HP) as sponsor, publicly funded as part of the "hospital-university health research " projects under the Future Investment Programme.

Masitinib Platform - Partnership

Partnership of masitinib platform with a pharmaceutical company is expected in 2024

Scope:
All options are considered

- Indications : from single indication to all indications
- Geography : from single country to global

Process:
Moving as per plan

- Top advisors (bankers, consultants) hired to implement the process
- Expected to be completed in 2024

Masitinib Platform – Validated MoA based on Modulation of the Neuroimmune System

Innmune cells (microglia and mast cells) are at the cutting edge of research regarding the pathophysiological mechanisms of NDDs, with a consensus that drugs aimed at these targets will have strong therapeutic potential

- Sandhu JK (2021) 'Decoding Mast Cell-Microglia Communication in Neurodegenerative Diseases'
  - *Innate immune cells, including mast cells, are potential contributors to neuropathology, mainly by losing their homeostatic functions and gaining pathogenic functions.*
  - *Mast cell-microglia cross-talk might contribute to neuroinflammation and neurodegeneration.*
- Muzio L (2021) 'Microglia in Neuroinflammation and Neurodegeneration: From Understanding to Therapy'
  - *Regulating microglia functions during disease pathology might represent a strategy to develop future therapies aimed at counteracting brain degeneration in multiple sclerosis, Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis.*
- Jones MK (2019) 'Mast Cells in Neurodegenerative Disease'
  - *Mast cells exert profound effects on their microenvironment and neighboring cells including behavior and/or activation of microglia, which, in turn, are implicated in neuroinflammation, neurogenesis and neurodegeneration.*
  - *Mast cells have emerged as potential key players in both neuroinflammation and neurodegenerative diseases.*

References
[1] Mado H, et al. Int J Mol Sci. 2023;24(3):1861. [2] Sandhu JK, et al. Int J Mol Sci. 2021;22(3):1093. [3] Muzio L, et al. Front Neurosci. 2021;15:742065. [4] Hagan N, et al. Cell Death Dis. 2020;11(10):904. [5] Jones MK, et al. Front Cell Neurosci. 2019;13:171. [6] Long JM, et al. Cell. 2019;179(2):312-339. [7] Skaper SD, et al. Front Cell Neurosci. 2018 Mar 21;12:72.

Masitinib Platform – Validated MoA based on Modulation of the Neuroimmune System

Masitinib has demonstrated neuroprotective benefits in three challenging NDDs, showing that targeting microglia and mast cells is a valid strategy across a broad range of indications, and that masitinib's dual-targeting strategy is uniquely positioned to realize this therapeutic potential

- Amyotrophic lateral sclerosis (ALS) – Masitinib exerts neuroprotection in both central and peripheral nervous systems via selective kinase inhibition that modulates the functionality of different cells implicated in ALS pathogenesis [8–14]
  - *Ketabforoush AHME (2023) 'Masitinib: The promising actor in the next season of the ALS treatment series'*
  - *Trias E (2018) 'Mast cells and neutrophils mediate peripheral motor pathway degeneration in ALS'*
- Alzheimer's disease (AD) – Masitinib is distinguished from other AD drugs by its multi-faceted action against neuroimmune cells and signaling pathways (e.g., FYN) that are specifically implicated in the pathogenesis of AD [15–20]
  - *Lin CJ (2023) 'Mast cell deficiency improves cognition and enhances disease-associated microglia in 5XFAD mice'*
  - *Schwabe T (2020) 'Shifting paradigms: The central role of microglia in Alzheimer's disease'*
- Progressive forms of multiple sclerosis (MS) – Masitinib targets the innate immune components of progressive MS. This mechanism of action is different from and potentially complementary to other drugs being developed in MS, such as BTK inhibitors, which target B cells [21–24]
  - *Mahmood A (2022) 'Microglia as therapeutic targets for central nervous system remyelination'*
  - *Pinke KH (2020) 'Should mast cells be considered therapeutic targets in multiple sclerosis?'*
  - *Kamma E (2022) 'Central nervous system macrophages in progressive MS: relationship to neurodegeneration and therapeutics'*

[8] Ketabforoush AHME, et al. Biomed Pharmacother. 2023;160:114378. [9] Kovacs M, et al. Acta Neuropathol Commun. 2021;9(1):136. [10] Trias E, et al. Glia. 2020;68(6):1165-1181. [11] Harrison JM, et al. Neurobiol Dis. 2020;145:105052. [12] Trias E, et al. JCI Insight. 2018;3(19):e123249. [13] Trias E, et al. JCI Insight. 2017;2(20):e95934. [14] Trias E, et al. J Neuroinflammation. 2016;13(1):177. [15] Lin CJ, et al. Cell Rep. 2023;42(9):113141. [16] Harcha PA, et al. Int J Mol Sci. 2021;22(4):1924. [17] Leng F et al. Nat Rev Neurol. 2021;17(3):157-172. [18] Li T, et al. J Alzheimers Dis. 2020;76(4):1339-1345. [19] Schwabe T, et al. Neurobiol Dis. 2020;143:104962. [20] Folch J, et al. Expert Rev Neurother. 2015 May 11:1-10. [21] Kamma E, et al. J Neuroinflammation. 2022;19(1):45. [22] Mahmood A, et al. Curr Opin Pharmacol. 2022;63:102188. [23] Pinke KH, et al. Neural Regen Res. 2020;15(11):1995-2007.. [24] Vermersch P, et al. BMC Neurol. 2012;12:36.

Masitinib in Amyotrophic Lateral Sclerosis

ALS - Status & Positioning

In ALS, no drug has generated a consensus based on definitive evidence of efficacy

Confirmatory Phase 3 Status

- Preceded by first phase 2B/3 positive and published[1]
- Confirmatory phase 3 study is authorized by FDA and key European countries and is on-going

Masitinib Positioning

- Like masitinib, the final registration of the most advanced compounds are dependent on the success of their confirmatory phase 3

Oral Edaravone	▪ Approved in the USA ▪ Not approved in the EU ▪ Failed confirmatory phase 3 (Ferrer)
Relyvrio (Amylyx)	▪ Approved in the USA ▪ Conditional approved in Canada ▪ Not approved in the EU ▪ Failed confirmatory phase 3
Tofersen (Biogen)	▪ Accelerated approval in the USA ▪ Conditional approved in EU ▪ Genetic forms of ALS (>5%)

1. Mora 2020 ; Mora 2021.

ALS – Positioning

Market research from top advisory firm hired for partnership indicates that if masitinib is approved, it can become the standard of care in ALS and can generate substantial revenue in the USA and the EU

Market size potential (USA/EU)

*While ALS market is dynamic, we forecast masitinib could **capture $3.8Bn peak sales under base case assumptions***

Positioning in case of registration with same results as phase 2B/3

*Overall, we believe if **masitinib phase 3** confirms **expected efficacy** then it can become the standard of care in ALS*

KOLs estimate masitinib could capture market share of up to ~70%

ALS – Conditional Marketing Authorization

Decision from EMA on conditional marketing authorization for masitinib in ALS is expected in Q2 2024 and decision from Health Canada on NOC/c reconsideration is expected in Q3 2024

EMA

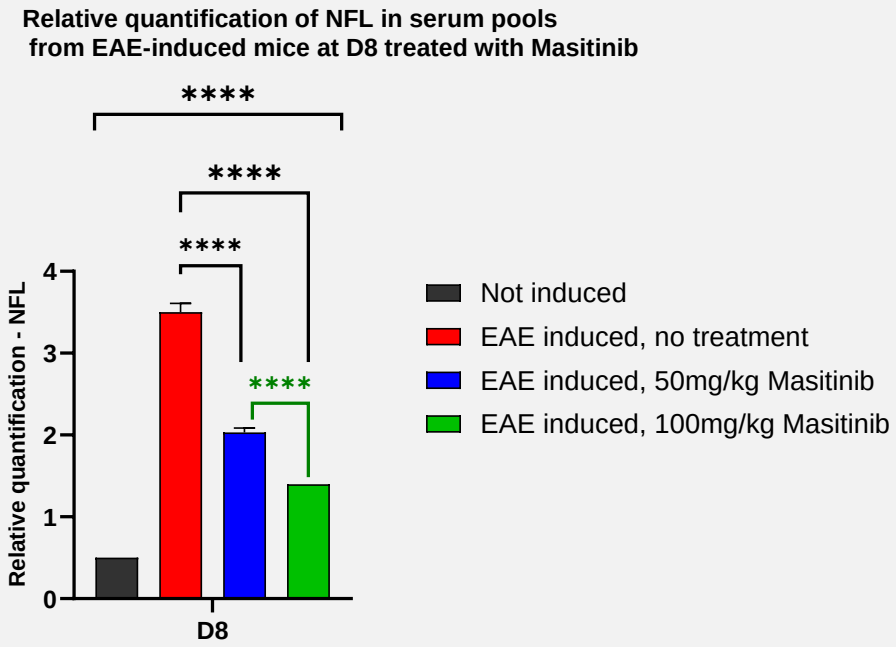
- Application filed in August 2022
- Whereas an Oral Explanation was planned in January, CHMP proposed that AB Science submit a written response to the List of Outstanding Issues at D195 of the procedure, instead of addressing these issues through the Oral Explanation, which is unusual
- Decision expected in end of Q2 2024

Health Canada

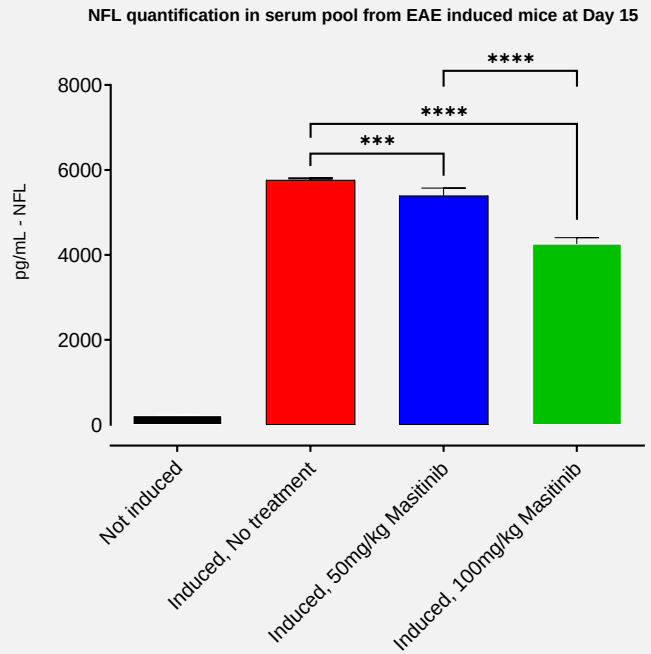
- Health Canada has issued a Notice of Deficiency-Withdrawal (NOD/w)
- AB Science intends to submit a Request for Reconsideration
- Reconsideration process involves new assessors and offers the possibility to have an opinion from a panel of experts
- Decision expected in end of Q3/Q4 2024

Masitinib has demonstrated ability to lower blood levels of neurofilament light (NfL) in a neurodegenerative disease model (EAE model)

Day 8



Day 15



Evaluation of masitinib activity in on a neurodegenerative disease model (i.e., experimental autoimmune encephalomyelitis, EAE, induced in C57BL/6 mice) with analysis of change in neurofilament light (NfL) concentration over time

ALS - Phase 2B/3

Phase 2B/3 demonstrated with masitinib 4.5 mg/kg/day a significant delay of disease progression over a 48-week period in the primary analysis population and significant OS benefit in subgroup of patients with moderate ALS

Normal Progressors (Primary Endpoint) : 27% slowing of functional deterioration

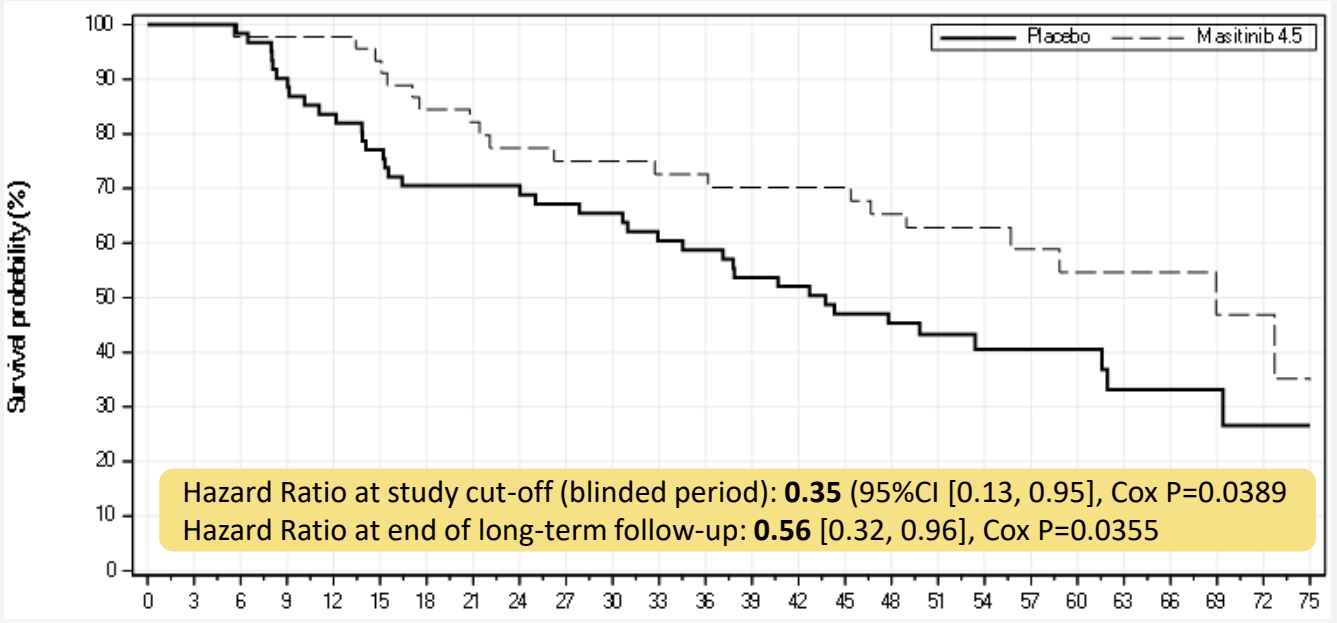
PRIMARY ANALYSIS
Absolute change from baseline to week 48 in ALSFRS-R
masitinib 4.5 mg/kg/day – Normal Progressors

Treatment group	Difference of means	[95% CI]	p-value
Primary Analysis			
LOCF Method	3.39	[0.65;6.13]	0.0158
Sensitivity analyses imputing all missing data			
Multiple Imputation Model (Proc MI)	3.44	[0.54; 6.33]	0.020
Multiple Imputation with Penalty (J2R)	2.80	[0.15; 5.46]	0.0386

* Defined as Normal Progressors with baseline score ≥ 2 on each ALSFRS-R item

+ 25 months in median OS for patients with moderate ALS

POST-HOC SUBGROUP ANALYSIS
Kaplan–Meier survival curves from pivotal phase 3 study long-term survival analysis in Moderate ALS patients* - Masitinib 4.5 mg/kg/d – June 2020 cut-off)

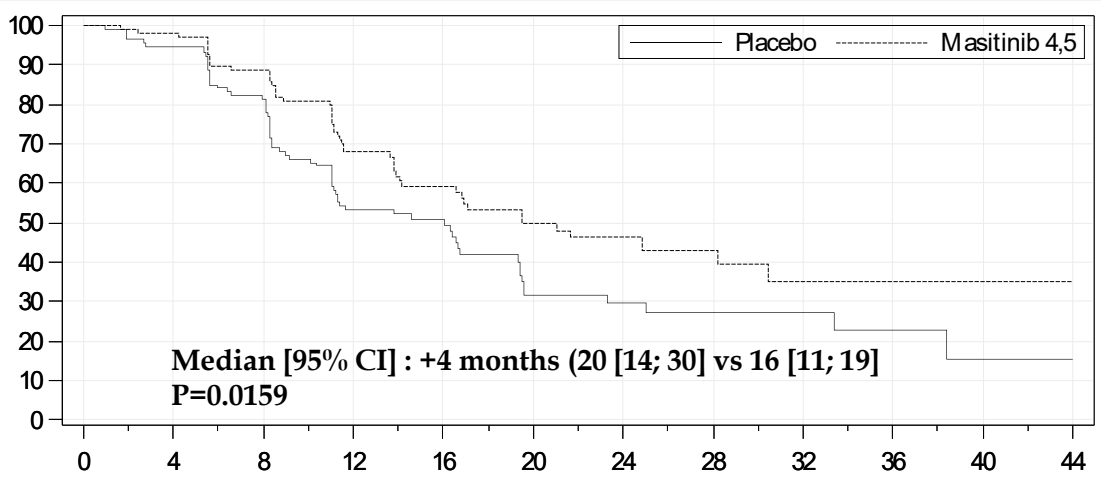


65% reduction of risk of death

ALS - Phase 2B/3

Benefit on functional score (ALSFRS-R) was supported by improvement in secondary endpoints in (time to disease progression or death (PFS), quality of life, and respiratory function)

25% delay in disease progression (PFS): +4 months



PFS (Progression Free Survival) is a time to event endpoint, with the event defined as the earliest between death or a 9-point deterioration of ALSFRS-R from baseline

28% improvement in quality of life

ALSAQ-40 score – Masitinib 4.5 mg/kg/day – Normal Progressors

Treatment group	LS Mean	Diff.of means [95% CI]	p-value
Control	27.2	-7.8 [-13.45;-2.06]	0.0078
Masitinib 4.5 mg/kg/d	19.4		

Quality of Life Component	Diff. of means [95% CI]	p-value
Eating and drinking	-13.70 [-22.14; -5.26]	0.0016
Activities of daily living and independence	-10.23 [-17.68; -2.78]	0.0074
Communication	-9.21 [-17.36; -1.07]	0.0269
Physical mobility	-7.53 [-15.06; -0.01]	0.0497
Emotional reactions	-2.85 [-10.14; 4.44]	0.4418

22% improvement in respiratory function

FVC – Masitinib 4.5 mg/kg/day – Normal Progressors

Treatment group	LS Mean	Diff.of means [95% CI]	p-value
Control	-33.99	7.55 [0.75;14.32]	0.0296
Masitinib 4.5 mg/kg/d	-26.45		

ALS - Phase 2B/3

There is a consistent pattern across key efficacy endpoints of increasing treatment effect with decreasing baseline severity

Increasing benefit

Consistent Pattern

Population (ΔFS<1.1, not including fast progressors)		Moderate / Severe / Very Severe ALS * (step 3) (Alsitek 4.5=106; PBO=114)	Moderate / Severe ALS * (step 2) (Alsitek 4.5=85; PBO=104)	Moderate ALS * (step 1) (Alsitek 4.5=45; PBO=62)
ΔALSFRS-R mLOCF primary analysis	**Diff. of mean**	**3.39**	**4.04**	**4.68**
	% delay in progression	-27%	-31%	-42%
	p-value	0.0157	0.0065	0.0176
ΔALSFRS-R Multiple Imputation sensitivity analysis	**Diff. of mean**	**3.44**	**3.52**	**3.94**
	p-value	0.020	0.027	0.068
ΔALSFRS-R Jump to Reference sensitivity analysis	**Diff. of mean**	**2.80**	**3.01**	**3.33**
	p-value	0.0386	0.0404	0.0882
Median PFS	**Gain in Median PFS**	**+ 4 months**	**+ 9 months**	**+ 13 months**
	Median [95% CI]	20 [14; 30] vs 16 [11; 19]	25 [17, NE] vs 16 [11, 19]	30 [22, NE] vs 17 [11, 33]
	p-value	0.0159	0.0057	0.0597
Median OS (Long term follow-up)	**Gain in Median OS**	**+ 6 months**	**+10 months**	**+ 25 months**
	Median [95% CI]	46 [33, 69] vs 40 [30, 48]	53 [36, NE] vs 43 [31, 49]	69 [45, NE] vs 44 [33, 62]
	p-value (Log Rank)	0.1054	0.0395	0.0477
	Reduced risk of death	23%	30%	44%
	Hazard Ratio [95% CI]	0.773 [0.55, 1.10]	0.699 [0.48, 1.03]	0.555 [0.32, 0.96]
	p-value (Cox)	0.1489	0.0695	0.0355

PBO = Placebo. ΔFS = ALSFRS-R progression rate calculated from disease-onset to baseline. ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised. LSM = Least-squares means difference from baseline. ΔLSM = Between treatment-arm difference of LSM. 95% two-sided confidence intervals [95%CI]

* Moderate ALS : ΔFS<1.1, ≥2 each baseline ALSFRS-R item ; Moderate and Severe ALS: ΔFS<1.1, ≥1 each baseline ALSFRS-R item ; Moderate, Severe, and Very Severe ALS: FS<1.1, any baseline ALSFRS-R score

ALS - Phase 2B/3

Results from phase 2B/3 and long-term survival were published in two peer-reviewed journals

Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 2020; 21: 5–14

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RESEARCH ARTICLE

Masitinib as an add-on therapy to riluzole in patients with amyotrophic lateral sclerosis: a randomized clinical trial

Abstract

Objective: To assess masitinib in the treatment of ALS. *Methods:* Double-blind study, randomly assigning 394 patients (1:1:1) to receive riluzole (100 mg/d) plus placebo or masitinib at 4.5 or 3.0 mg/kg/d. Following a blinded transition from phase 2 to phase 2/3, a prospectively defined two-tiered design was implemented based on ALSFRS-R progression rate from disease-onset to baseline (ΔFS). This approach selects a more homogeneous primary efficacy population ("Normal Progressors", ΔFS < 1.1 points/month) while concurrently permitting secondary assessment of the broader population. Primary endpoint was decline in ALSFRS-R at week-48 (ΔALSFRS-R), with the high-dose "Normal Progressor" cohort being the prospectively declared primary efficacy population. Missing data were imputed *via* last observation carried forward (LOCF) methodology with sensitivity analyses performed to test robustness. *Results:* For the primary efficacy population, masitinib ($n = 99$) showed significant benefit over placebo ($n = 102$) with a ΔALSFRS-R between-group difference (ΔLSM) of 3.4 (95% CI 0.65–6.13; $p = 0.016$), corresponding to a 27% slowing in rate of functional decline (LOCF methodology). Sensitivity analyses were all convergent, including the conservative multiple imputation technique of FCS-REGPMM with a ΔLSM of 3.4 (95% CI 0.53–6.33; $p = 0.020$). Secondary endpoints (ALSAQ-40, FVC, and time-to-event analysis) were also significant. Conversely, no significant treatment-effect according to ΔALSFRS-R was seen for the broader "Normal and Fast Progressor" masitinib 4.5 mg/kg/d cohort, or either of the low-dose (masitinib 3.0 mg/kg/d) cohorts. Rates of treatment-emergent adverse events (AEs) (regardless of causality or post-onset ΔFS) were 88% with masitinib 4.5 mg/kg/d, 85% with 3.0 mg/kg/d, and 79% with placebo. Likewise, rates of serious AE were 31, 23, and 18%, respectively. No distinct event contributed to the higher rate observed for masitinib and no deaths were related to masitinib. *Conclusions:* Results show that masitinib at 4.5 mg/kg/d can benefit patients with ALS. A confirmatory phase 3 study will be initiated to substantiate these data.

Keywords: Clinical trials, therapy, tyrosine kinase inhibitor, masitinib

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*AB10015 STUDY GROUP collaborators (non-author investigators) listed in Supplementary Table 1.

Supplemental data for this article can be accessed here.

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Long-term survival analysis of masitinib in amyotrophic lateral sclerosis

Jesus S. Mora, Walter G. Bradley, Delia Chaverri, María Hernández-Barral, Javier Mascias, Josep Gamez, Gisella M. Gargiulo-Monachelli, Alain Moussy, Colin D. Mansfield, Olivier Hermine and Albert C. Ludolph

Abstract

Background: A randomized, placebo-controlled phase III study (AB10015) previously demonstrated that orally administered masitinib (4.5 mg/kg/day) slowed rate of functional decline, with acceptable safety, in amyotrophic lateral sclerosis (ALS) patients having an ALS Functional Rating Scale-revised (ALSFRS-R) progression rate from disease onset to baseline of <1.1 points/month. Here we assess long-term overall survival (OS) data of all participants from study AB10015 and test whether a signal in OS is evident in an enriched patient population similar to that prospectively defined for confirmatory study AB19001.
Methods: Survival status of all patients originally randomized in AB10015 was collected from participating investigational sites. Survival analysis (using the multivariate log-rank test and Cox proportional hazards model, with stratification factors as covariates) was performed on the intention-to-treat population and enriched subgroups, which were defined according to initial randomization, baseline ALSFRS-R progression rate and baseline disease severity.
Results: A significant survival benefit of 25 months ($p = 0.037$) and 47% reduced risk of death ($p = 0.025$) was observed for patients receiving 4.5 mg/kg/day masitinib ($n = 45$) *versus* placebo ($n = 62$) in an enriched cohort with ⩾2 on each baseline ALSFRS-R individual component score (i.e. prior to any complete loss or severe impairment of functionality) and post-onset ALSFRS-R progression rate <1.1 (i.e. exclusion of very fast progressors) [median OS of 69 *versus* 44 months, respectively; hazard ratio, 0.53 [95% CI (0.31–0.92)]]. This corresponds to the population enrolled in confirmatory phase III study, AB19001.
Conclusions: Analysis of long-term OS (75 months average follow-up from diagnosis) indicates that oral masitinib (4.5 mg/kg/day) could prolong survival by over 2 years as compared with placebo, provided that treatment starts prior to severe impairment of functionality.
This trial was registered at www.ClinicalTrials.gov under identifier NCT02588677 (28 October 2015).

Keywords: clinical trials, masitinib, therapy, tyrosine kinase inhibitor

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Masitinib in Multiple Sclerosis

Multiple Sclerosis – Status & Positioning

There is no approved drugs for non-active SPMS and only one for PPMS, and masitinib stands-out as the only non BTKi into phase 3

Confirmatory Phase 3 Status

- Preceded by first phase 2B/3 positive and published[1]
- Confirmatory phase 3 study is authorized by FDA and key European countries and to be started

Masitinib Positioning

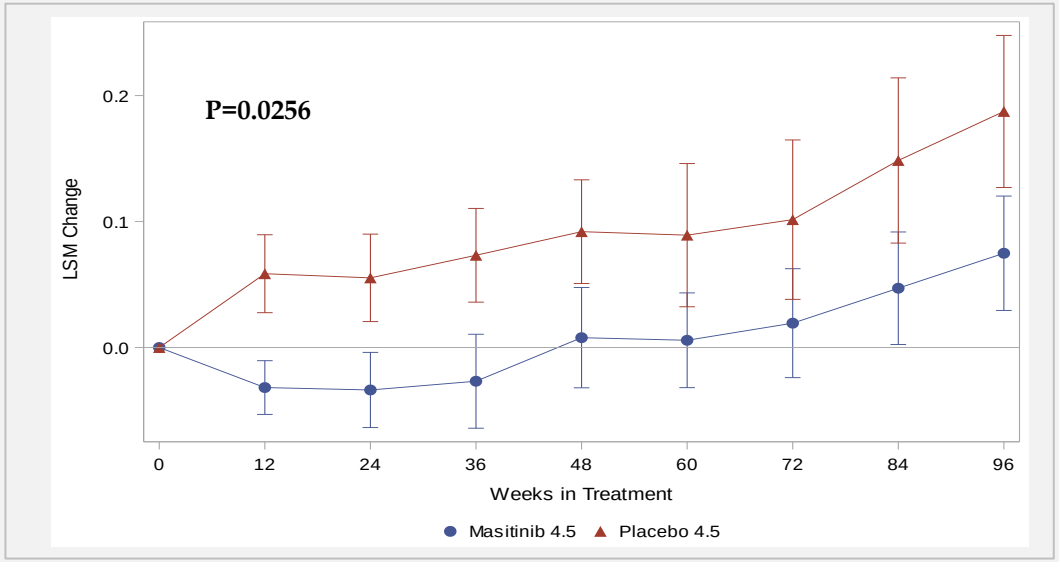
- Primary Progressive MS accounts for 15 % of the total MS market and Non-active primary progressive MS accounts for 35 % of the total MS market
- Only Ocrevus (Roche) is approved in primary progressive MS
- In progressive forms of MS*, front runners in phase 3 are BTK inhibitors and masitinib
  - BTKi : - Target B-cells and microglia
    - Tolebrutinib (Sanofi) and Fenebrutinib (Roche)
  - Masitinib : Targets mast cells and microglia
- BTKi had issues recently
  - Tolebrutinib & Fenebrutinib on FDA hold due to liver injury.
  - Evobrutinib (Merck) phase III missed its primary endpoint in RRMS
- *"This situation potentially paves the way for masitinib to emerge as a standout oral option in the landscape" ((GLOBE NEWSWIRE)*

1. Vermersch 2022.

* Primary progressive MS and Non-active primary progressive MS

Phase 2B/3 demonstrated a significant benefit on disability progression with masitinib 4.5 mg/kg/day in patients with advanced stage of the disease

Significant reduction in progression on EDSS (Primary Endpoint*)



Patients were enrolled at advanced disease stage

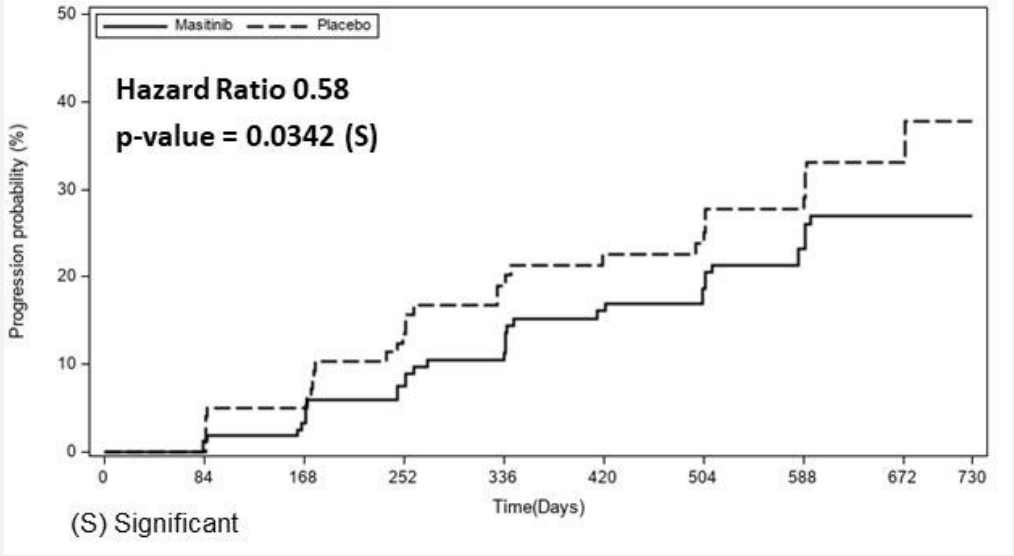
- Median age (years) : 50.0 (both masitinib and placebo)
- Median duration of first MS Symptom (yrs) : 12.4 masitinib and 12.2 placebo
- Median EDSS Score : 5.5 (both masitinib and placebo)
- % of patients with EDSS score of 6 : 49.0% masitinib and 47.5% placebo

* Change in EDSS

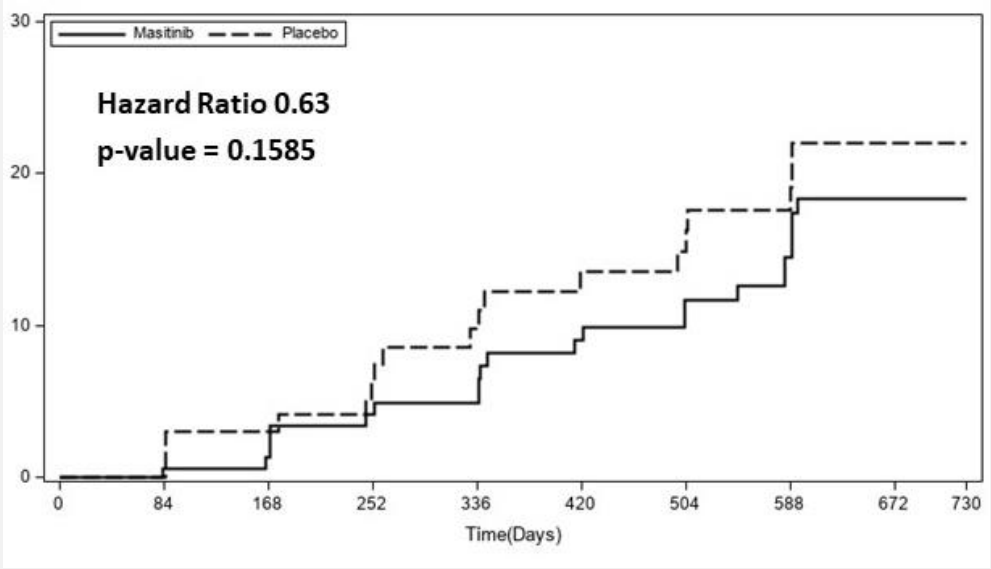
Multiple Sclerosis – Phase 2B/3

Phase 2B/3 demonstrated a significant reduction of risk of first disability progression by 42% and a reduction of risk of confirmed (12-week) disability progression by 37%

42% risk reduction of time to disability progression



37% risk reduction of time to confirmed disability progression



Multiple Sclerosis – Phase 2B/3

Masitinib has the potential to become a best-in-class drug for PPMS and nSPMS

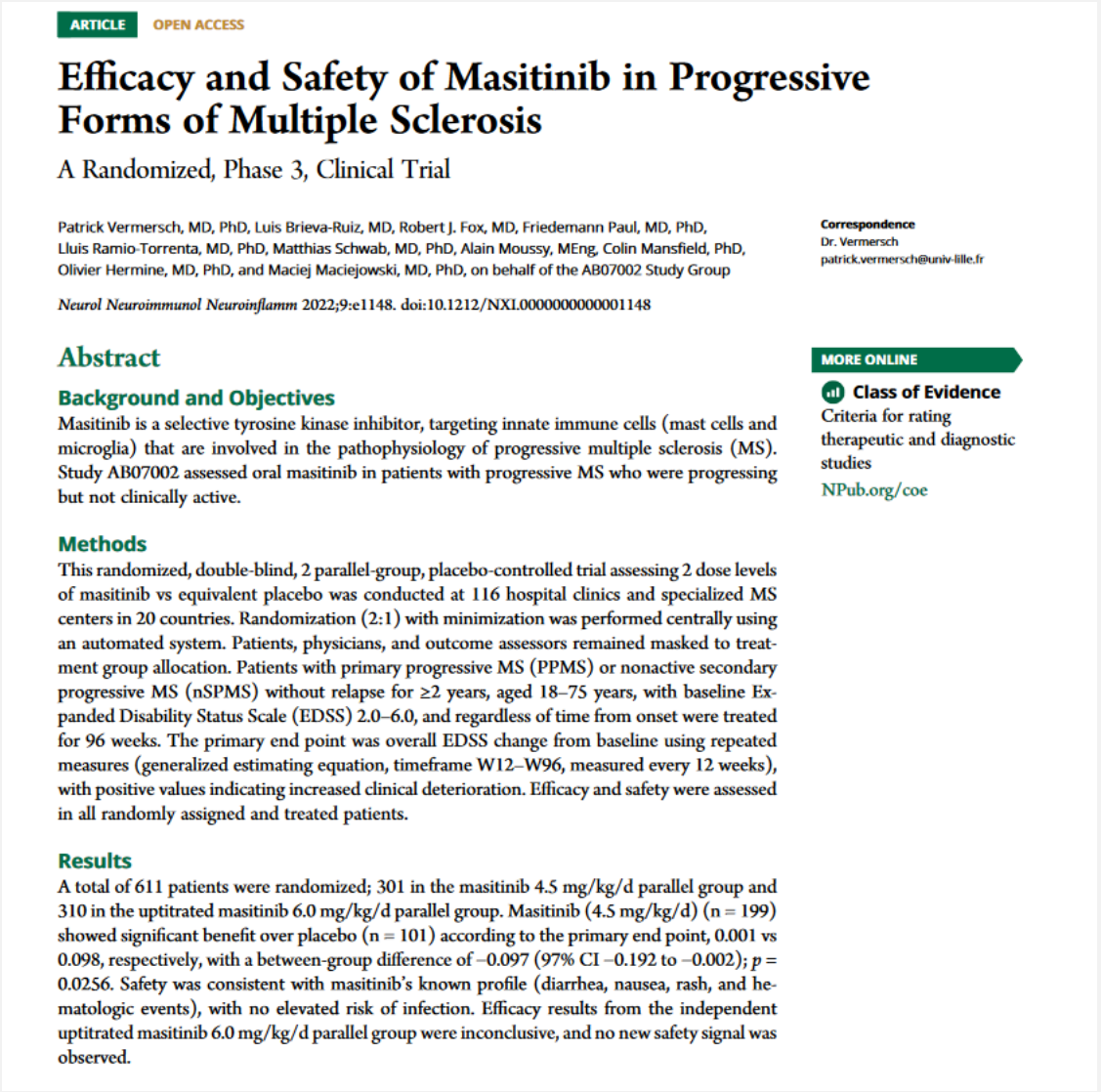
Time to confirmed disability progression

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 (effectdrivenby active)	21% (S)

S: Statistically Significant. NS : Not Statistically Significant
In masitinib study, time to confirmed disability progression was a secondary endpoint and the study was not powered to demonstrate significant effect on this endpoint

Multiple Sclerosis – Phase 2B/3

Results from phase 2B/3 were published in peer-reviewed journal



ARTICLE OPEN ACCESS

Efficacy and Safety of Masitinib in Progressive Forms of Multiple Sclerosis

A Randomized, Phase 3, Clinical Trial

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Abstract

Background and Objectives

Masitinib is a selective tyrosine kinase inhibitor, targeting innate immune cells (mast cells and microglia) that are involved in the pathophysiology of progressive multiple sclerosis (MS). Study AB07002 assessed oral masitinib in patients with progressive MS who were progressing but not clinically active.

Methods

This randomized, double-blind, 2 parallel-group, placebo-controlled trial assessing 2 dose levels of masitinib vs equivalent placebo was conducted at 116 hospital clinics and specialized MS centers in 20 countries. Randomization (2:1) with minimization was performed centrally using an automated system. Patients, physicians, and outcome assessors remained masked to treatment group allocation. Patients with primary progressive MS (PPMS) or nonactive secondary progressive MS (nSPMS) without relapse for ≥2 years, aged 18–75 years, with baseline Expanded Disability Status Scale (EDSS) 2.0–6.0, and regardless of time from onset were treated for 96 weeks. The primary end point was overall EDSS change from baseline using repeated measures (generalized estimating equation, timeframe W12–W96, measured every 12 weeks), with positive values indicating increased clinical deterioration. Efficacy and safety were assessed in all randomly assigned and treated patients.

Results

A total of 611 patients were randomized; 301 in the masitinib 4.5 mg/kg/d parallel group and 310 in the uptitrated masitinib 6.0 mg/kg/d parallel group. Masitinib (4.5 mg/kg/d) (n = 199) showed significant benefit over placebo (n = 101) according to the primary end point, 0.001 vs 0.098, respectively, with a between-group difference of −0.097 (97% CI −0.192 to −0.002); p = 0.0256. Safety was consistent with masitinib's known profile (diarrhea, nausea, rash, and hematologic events), with no elevated risk of infection. Efficacy results from the independent uptitrated masitinib 6.0 mg/kg/d parallel group were inconclusive, and no new safety signal was observed.

MORE ONLINE

Class of Evidence
Criteria for rating therapeutic and diagnostic studies
NPub.org/coe

Masitinib in Alzheimer’s Disease

AD - Status & Positioning

Masitinib is the only drug into confirmatory phase 3 developed in mild and moderate Alzheimer

Confirmatory Phase 3 Status

- Preceded by first phase 2B/3 positive and published[1]
- Confirmatory phase 3 study is authorized by FDA and key European countries and to be started

Masitinib Positioning

- Theoretical market for drugs in mild and moderate AD (masitinib positioning) estimated to be $50 billion and increasing to $100 billion by 2030[2]
- Drugs are positioned according to severity measured with MMSE
  - Prodromal AD: MMSE >26
  - Mild AD: MMSE [21 ; 26]
  - Moderate AD: MMSE [10 ; 20]
- Two drugs have been approved in early AD with a different positioning from masitinib
  - Lecanemab (Eisai/Biogen): MMSE [22 – 30]
  - Donanemag (Eli Lilly): MMSE [20 – 28]
- Three therapeutic strategies are pursued
  - β–Amyloid plaque : Approved in early AD
  - Tau protein : No positive phase 3 at this time
  - Immune response and neuro-inflammation : Leading drugs starting phase 3
    - Blarcamesine (Anavex) in early AD: MMSE [20 – 28]
    - Masitinib in mild/moderate AD: MMSE [14 – 25]

1. Dubois 2023.
2. 8 million patients in EU and USA, six month treatment period, 70% insurance coverage, annual drug price of €15k in the EU and $20k in the USA

AD – Phase 2B/3

Phase 2B/3 study demonstrated a significant reduction in cognitive impairment based on ADAS-COG (p=0.0003) and improvement on daily activity based on ADCS-ADL (p=0.0381) with masitinib 4.5 mg/kg/day

Significant effect on cognitive function after 24 weeks of treatment

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)		

Significant effect on daily activity after 24 weeks of treatment

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

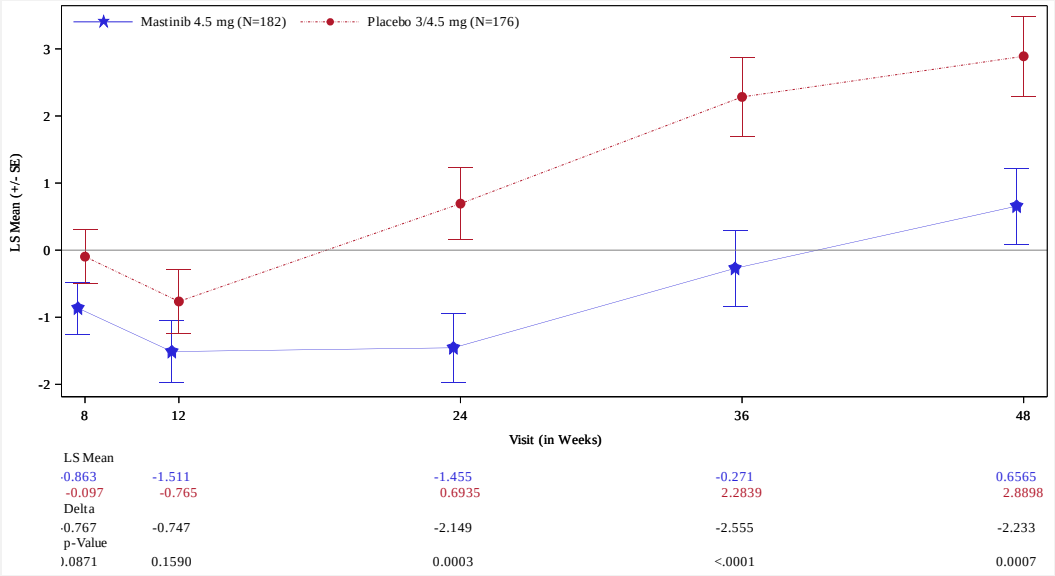
Treatment	n	LS Mean (95% CI)	LS Mean Difference (97.51% CI)	p-value
Masitinib 4.5 mg/kg/day + memantine and anticholinesterase	182	**1.01** (-0.48, 2.50)	**1.82** (-0.15, 3.79)	**0.0381**
Placebo + memantine and anticholinesterase	176	**-0.81** (-2.36, 0.74)		

Clinically relevant benefit because on top of standard of care (memantine & anticholinesterase)

The treatment effect on COG was sustained at week 48

Significant effect on cognitive function after 48 weeks of treatment

LSM of ADAS-Cog Change from Baseline - Masitinib 4.5 versus Placebo (Full Analysis Set Population)



LS Mean				
-0.863	-1.511	-1.455	-0.271	0.6565
-0.097	-0.765	0.6935	2.2839	2.8898
Delta				
-0.767	-0.747	-2.149	-2.555	-2.233
p-Value				
.0871	0.1590	0.0003	<.0001	0.0007

AD – Phase 2B/3

Results from phase 2B/3 were published in peer-reviewed journal

Dubois *et al. Alzheimer's Research & Therapy* (2023) 15:39
https://doi.org/10.1186/s13195-023-01169-x

Alzheimer's
Research & Therapy

RESEARCH Open Access

Masitinib for mild-to-moderate Alzheimer's disease: results from a randomized, placebo-controlled, phase 3, clinical trial

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Abstract

Background Masitinib is an orally administered tyrosine kinase inhibitor that targets activated cells of the neuroimmune system (mast cells and microglia). Study AB09004 evaluated masitinib as an adjunct to cholinesterase inhibitor and/or memantine in patients with mild-to-moderate dementia due to probable Alzheimer's disease (AD).

Methods Study AB09004 was a randomized, double-blind, two parallel-group (four-arm), placebo-controlled trial. Patients aged ≥50 years, with clinical diagnosis of mild-to-moderate probable AD and a Mini-Mental State Examination (MMSE) score of 12–25 were randomized (1:1) to receive masitinib 4.5 mg/kg/day (administered orally as two intakes) or placebo. A second, independent parallel group (distinct for statistical analysis and control arm), randomized patients (2:1) to masitinib at an initial dose of 4.5 mg/kg/day for 12 weeks that was then titrated to 6.0 mg/kg/day, or equivalent placebo. Multiple primary outcomes (each tested at a significance level of 2.5%) were least-squares mean change from baseline to week 24 in the Alzheimer's Disease Assessment Scale - cognitive subscale (ADAS-cog), or the Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory scale (ADCS-ADL). Safety for each masitinib dose level was compared against a pooled placebo population.

Results Masitinib (4.5 mg/kg/day) (n=182) showed significant benefit over placebo (n=176) according to the primary endpoint of ADAS-cog, −1.46 (95% CI [−2.46, −0.45]) (representing an overall improvement in cognition) versus 0.69 (95% CI [−0.36, 1.75]) (representing increased cognitive deterioration), respectively, with a significant between-group difference of −2.15 (97.5% CI [−3.48, −0.81]); p<0.001. For the ADCS-ADL primary endpoint, the between-group difference was 1.82 (97.5% CI [−0.15, 3.79]); p=0.038 (i.e., 1.01 (95% CI [−0.48, 2.50]) (representing an overall functional improvement) versus −0.81 (95% CI [−2.36, 0.74]) (representing increased functional deterioration), respectively). Safety was consistent with masitinib's known profile (maculo-papular rash, neutropenia, hypoalbuminemia). Efficacy results from the independent parallel group of titrated masitinib 6.0 mg/kg/day versus placebo (n=186 and 91 patients, respectively) were inconclusive and no new safety signal was observed.

Masitinib in other indications

Masitinib Platform – Sickle Cell Disease

SCD is the largest monogenic disease worldwide, with a disproportionate burden on Black communities and masitinib will address severe form of SCD

Major Health Problem

SCD is a group of inherited red blood cell disorders

- A genetic mutation causes red blood cells to turn sickle shaped, getting stuck in small blood vessels, causing pain and serious complications, and to die early

SCD is a major public health challenge

- SCD affects 1 in 13 Black or African-American babies and approximately **100,000 Americans** [1]
- In some areas of Saudi Arabia, SCD affects up to 2.6% of the population [2].
- **Multiple severe multi-organ complications: Pain crisis** leading to hospitalization, **Vaso-Occlusive Crises** (VOC, Blood flow blocked by sickled cells), **Infection**, such as flu, meningitis, and hepatitis, **Acute Chest Syndrome** (ACS, Blood flow blocked in the lungs), and **Stroke** (Blood flow blocked in the brain) [1]
- **SCD is a life-threatening disease**
  - Total SCD deaths put at 376,000 for 2021, 'cause-specific' estimate was 34,400 [3]
  - 1 in 4 patients have a stroke by age 45 [4]
  - In the USA, the median age at death is 43 years [1]

Growing Market, driven by the high cost of novel drugs and rising awareness

- SCD treatment global market size is projected to grow from $2.7 billion in 2023 to **$9.8 billion by 2030** (20.1% CAGR)
- Treatment for SCD can be curative based on gene therapy, but this option remains **extremely limited** (Estimated 1% of SCD patients) due unresolved **safety challenges** (chemotherapy pre-treatment, associated with long hospitalization , risk of infection, risk of repro-toxicity), and **high costs** (> 2 million USD per patient)
- Recently, 4 new symptomatic treatments have been registered by the FDA, including one recently revoked (crizanlizumab), and significant unmet need still remains

Drug / Pharma		Reg Status
Deferiprone	Chiesi	FDA 2011, EMA 1999
L-glutamine	Emmaus Life Sciences	FDA 2017, EMA rejected
Crizanlizumab	Novartis	FDA 2019, EMA revoked
Voxelotor	Pfizer & Global Blood Ther.	FDA 2019 ; EMA 2022

[1] Center For Disease Control and Prevention (CDC); [2] Jast *ania 2011, Ann Saudi Med; [3] GBD 2021 Sickle Cell Disease Collaborators. Lancet Haematol. 2023; [4] Mortality Rates and Age at Death from Sickle Cell Disease: U.S., 1979–2005*

Masitinib Platform – Sickle Cell Disease

Phase 2 of masitinib as a new treatment of SCD for patients harboring a specific biomarker is funded through public collaborative program

Scientific Rationale

- Mast cells appear to play a critical role for the severe forms of SCD
- Masitinib has demonstrated in an SCD mouse model survival benefit and protection from acute lung injuries and mast cell infiltration

Funding

- Funding of 9.2 million Euros distributed among the partners
- AB Science remains free to carry out, as it sees fit, any potential phase 3 development following the success of phase 2

Phase 2 Objectives

▪ Part 1 : Biomarker	Identify and validate biomarkers for patients responsive to masitinib treatment
▪ Part 2 : Phase 2	Demonstrate the efficacy of masitinib in the treatment of acute and chronic complications of sickle cell disease in patients identified based on biomarkers

Refer to AB Science press release date 27 November 2023

Masitinib Platform – Other programs

Masitinib pipeline in oncology and inflammatory diseases can add value to the neurology platform

Therapeutic area	Indication	Results	Development Status
Mast Cell diseases	**Indolent systemic mastocytosis**	▪ First phase 3 completed (135 patients) ▪ Significant reduction in symptoms (pruritus, flushes, depression, asthenia)	▪ Confirmatory phase 3 ongoing
	Mast cell activation syndrome (MCAS)	▪ None	▪ Phase 2 study ongoing
Viral diseases	**Covid-19**	▪ Phase 2 in hospitalized patients ▪ Phase 2 in non-hospitalized patients	▪ Expected Read-out : 2024 ▪ Expected Read-out : 2024

AB8939

MDA Platform – AB8939

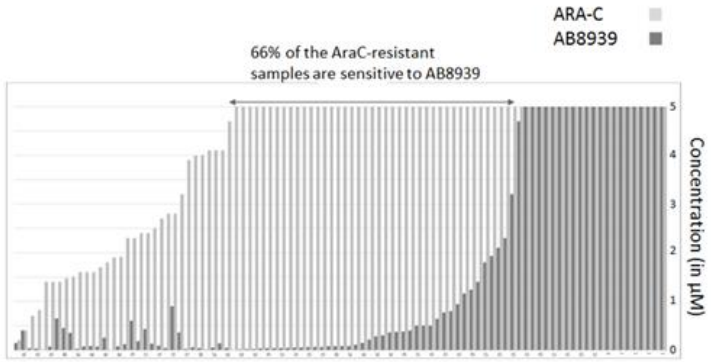
AB8939 has the potential to improve AML treatment based on its original mechanism of action

Scientific rationale

- Microtubule is a validated target and is a gold standard in many cancers (paclitaxel, vincristine, vinblastine…)
- Unlike other MDAs, AB8939 is not a transported by PgP/BRCP efflux pumps
- Unlike other MDAs, AB8939 is not a deactived by myeloperoxydase

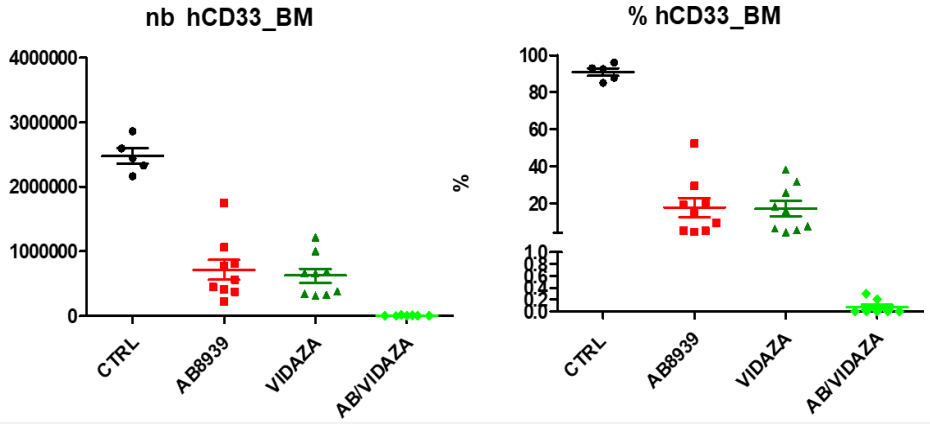
Ex-vivo data

- ~70% of blasts isolated from a cohort of 99 AML patients at diagnosis are sensitive to AB8939 (IC_{50}<1 µM), but only ~30% are sensitive to standard Ara-Cytidine-based chemotherapy



In-vivo data

- AB8939 has strong activity in Ara-C resistant PDX model
- AB8939/azacitidine combination allows the clearing of leukemia blasts in bone marrow without adding toxicities



MDA Platform – AB8939 Phase I

MTD has been reached in Step 1 of Phase 1 and key agencies have authorized to proceed with Step 2

Step 1

MTD* 3 DAYS
AB8939 alone

- Dose 1: 0.9 mg/m²
- Dose 2: 1.8 mg/m²
- Dose 3: 3.6 mg/m²
- Dose 4: 6.0 mg/m²
- Dose 5: 9.0 mg/m²
- Dose 6: 12.0 mg/m²
- Dose 7: 16.0mg/m²

- Extra doses added

Step 2

MTD 14 DAYS
AB8939 alone

- Dose 1: MTD3d- 1
- Dose 2: MTD3d

Step 3

MTD 14 DAYS
AB8939 + Azacitidine

- Dose 1: MTD14d- 1
- Dose 2: MTD14d

Step 4

MTD 28 DAYS
AB8939 alone

- Dose 1: MTD14d- 1
- Dose 2: MTD14d

- Phase 1 (steps 1 to 4) is expected to be completed in 2024
- Phase 2 will be initiated in 2025 with a the intention to design the study to support accelerated approval

Highlights of Step 1

- Neutrophil count are stabilized or even increased, which is unusual for a cytotoxic agent and could make AB8939 eligible as a chronic treatment in high-risk myelodysplastic syndrome (MDS)
- We observed a response in a MECOM rearrangement, which is a very aggressive subset of patients

Patent protection

Masitinib - Patents

Masitinib intellectual property rights are secured until 2037 in ALS, potentially up to 2041 in MS and AD

Method of use patents

Title	Reference	Duration	Status
Use of masitinib for treatment of an amyotrophic lateral sclerosis patient subpopulation	WO2017162884	2037	**Granted** USA, Europe, China, Japan, South Korea, Canada, Israel, Mexico, Singapore, Australia, New Zealand, Russia, South Africa, Hong Kong
Masitinib for the treatment of a multiple sclerosis patient subpopulation	WO2021165472	2041	**Pending** USA, Europe, China, Japan, South Korea, Canada, Australia, Israel
Masitinib for the treatment of AD	WO2022129410A1	2041	**Pending** USA, Europe, China, Japan, South Korea, Canada, Israel, Mexico, Australia, South Africa, Brazil

Orphan drug status granted by both EMA and FDA for masitinib in ALS

AB8939 - Patents

AB8939 intellectual property rights in AML are secured until 2036 through a ‘composition of matter’ patent and potentially until 2044 in AML with chromosome abnormality through a ‘second medical use’ patent

Protection	Item	Duration of protection	Status
Patent on composition of matter	Patent on composition of matter has been filed and delivered.	Until 2036	Delivered
Patent on Phase 1 ‘second medical use’	Provisional patent application filed for AML subpopulation with chromosome abnormality	Until 2044	Filed
Orphan drug status	AB8939 has been granted orphan drug designation by the FDA	Exclusivity of 7 years	Delivered