AB SCIENCE

# Corporate Presentation

March 2025

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## 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 : 57.794.294 (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

# AB Science has three platforms, platform 1with masitinib, in phase 3, primarily centered around neuro-degenerative diseases, platform 2 with AB8939 in AML and platform 3 with new discovery projects

| Platform | Drug | Therapeutic area | Indication | Development Stage |
|---|---|---|---|---|
| Tyrosine Kinase Inhibitor | Masitinib (Oral) | Neuro-degenerative Diseases (NDD) | Amyotrophic Lateral Sclerosis | Phase 3 |
| | | | Progressive Forms of Multiple Sclerosis | Phase 3 |
| | | | Alzheimer's Disease | Phase 3 |
| | | Mast Cell Diseases | Indolent Systemic Mastocytosis | Phase 3 |
| | | | Mast Cell Activation Syndrome | Phase 2 |
| | | Blood diseases | Sickle Cell Disease(1) | Phase 2 |
| Oncology Platform | AB8939 (IV) | Hematology | Acute Myeloid Leukemia (AML) | Phase 1 |
| | AB12319 (oral) | Oncology | Sarcoma, Solid Tumors | Preclinical |
| Drug Discovery Platform | | Target 1: undisclosed for neurodegenerative diseases<br>Target 2: undisclosed for neurodegenerative diseases | | Drug Discovery |

(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 PLATEFORM

## Target Product Profile

*Amyotrophic Lateral Sclerosis*

*Multiple Sclerosis*

*Alzheimer's Disease*

*Other indications*

*Intellectual Property*

# Masitinib is an orally-administered kinase inhibitor selectively targeting mast cells and macrophages

## Masitinib targets mast cells

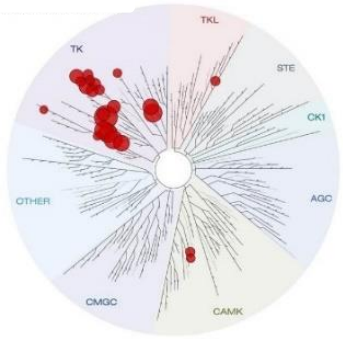
- Masitinib is a potent and selective inhibitor of c-Kit, Lyn, and Fyn kinases. These kinases play critical roles in the activation of mast cells
- Mast cells are a target in neurodegenerative diseases, inflammatory diseases and in oncology

## Masitinib targets macrophages/microglia

- Masitinib is a potent and selective inhibitor of MCSFR-1
- Macrophages are a target in oncology. Microglia are a target in amyotrophic lateral sclerosis and Alzheimer's disease.

## Masitinib is orally administered

| Kinase inhibition profile of masitinib | | | |
|---|---|---|---|
| **Cellular Target** | Molecular Target | $IC_{50}$ [nM] | Kd [µM] |
| **Mast cells** | KIT wild-type (WT) | 20 | 0.008 |
| | FYN | 240 | 0.14 |
| | LYN | 225 | 0.061 |
| **Macrophages / Microglia** | MCSFR-1 | 90 | 0.0076 |





- Dubreuil 2009, PLoSONE.4(9):e7258; AB Science. Davis 2011, Nat Biotechnol; 29(11):1046

# Masitinib's dual-targeting strategy, targeting mast cells and macrophages, is uniquely positioned to realize this therapeutic potential in neurodegenerative diseases (NDDs)

**Microglia and mast cells are at the cutting edge of research regarding NDDs, with a consensus that drugs aimed at these targets will have strong therapeutic potential**

- Innate immune cells, including mast cells, are potential contributors to neuropathology. JK (2021)
- Regulating microglia functions might represent a strategy to develop future therapies aimed at counteracting brain degeneration in MS, AD, ALS. Muzio L (2021)
- Mast cells exert profound effects on their microenvironment and/or activation of microglia, which, in turn, are implicated in neurodegeneration. Jones MK (2019)

**Masitinib has demonstrated neuroprotective benefits in three challenging NDDs, showing that targeting microglia and mast cells is a valid strategy**

- ALS: Masitinib exerts neuroprotection in both central and peripheral nervous systems [8–14]
- AD: Masitinib is distinguished from other AD drugs by its multi-faceted action against neuroimmune cells and signaling pathways (e.g., FYN) [15–20]
- Progressive forms of MS: Masitinib targets the innate immune components of progressive MS. [21–24]

[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.
[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.

*Target Product Profile*

**Amyotrophic Lateral Sclerosis**

*Multiple Sclerosis*

*Alzheimer's Disease*

*Other indications*

*Intellectual Property*

# In ALS, all competitive programs with different approaches failed and Masitinib is today the most advanced compound in clinical development with a validated scientific approach and positive clinical data

**Drugs Approved in US or EU**

| Drug | Sponsor |
|---|---|
| Riluzole | Generic |
| Radicava | Mitsubishi Tanabe |
| Tofersen | Biogen |

- Approved by the FDA in 1995 and EMA in 1997 with modest OS benefit
- Approved by the FDA in 2017; not approved by EMA
- Limited OS benefit and the only positive study had a less severe baseline function score than masitinib's studies
- Failed primary endpoint on functional benefit
- Benefit only demonstrated on surrogate endpoint (NfL)
- Limited target patient population (~2% of ALS patients)

**Confirmatory Phase 3**

| | |
|---|---|
| Masitinib | AB Science |

- Novel and validated mechanism of action
- +12 months OS benefit on top of Riluzole in the proposed Ph3 population
- Acceptable safety profile by regulator

**Recently Failed Late-Stage Clinical Studies**

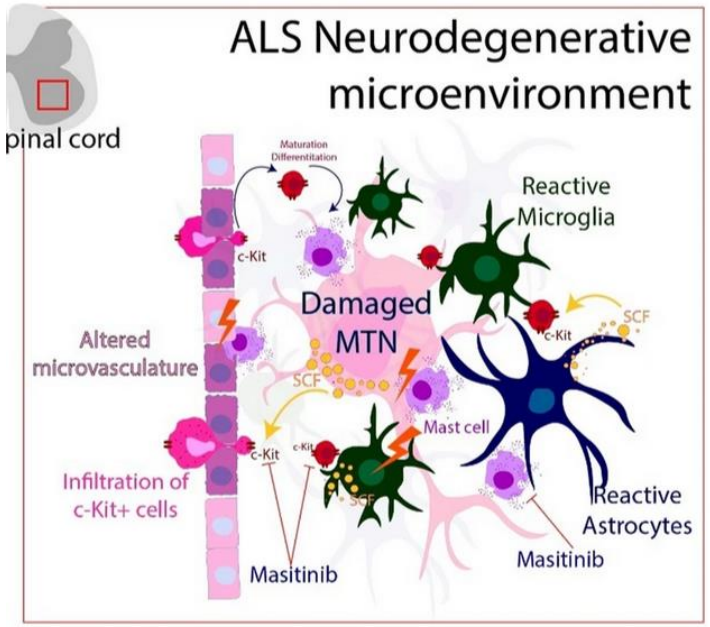
| Recent Failures | | Mechanism of Action |
|---|---|---|
| 2024 | Edaravone *(Ferrer)* | Reduction of oxidative stress *(Unknown MoA)* |
| 2024 | Relyvrio *(Amylyx)* | Reduction of oxidative stress *(Unknown MoA)* |
| 2024 | Tauroursodeoxycholic Acid *(Academic)* | Reduction of oxidative stress *(Inhibitor of ER stress)* |
| 2024 | SAR443820 *(Sanofi)* | Reduction of microglia activity *(Inhibitor of RIPK1)* |
| 2024 | Utreloxastat *(PTC Therapeutics)* | Reduction of oxidative stress *(15-Lipoxygenase inhibitor)* |
| 2025 | DNL343 *(Denali Therapeutics)* | Targeting of TDP43 protein agregrates *(Activator of EIF2b)* |
| 2025 | Verdiperstat *(Biohaven)* | Reduction of oxidative stress *(Myeloperoxidase inhibitor)* |
| 2025 | Zilucoplan *(UCB Pharma)* | Tissue damage and cell death *(Complement C5 inhibitor)* |

# Masitinib has a proven mechanism of actions acting via mast cells inhibition and microglia modulation, as published in several peer-reviewed journals

## There is a Strong Scientific Rationale

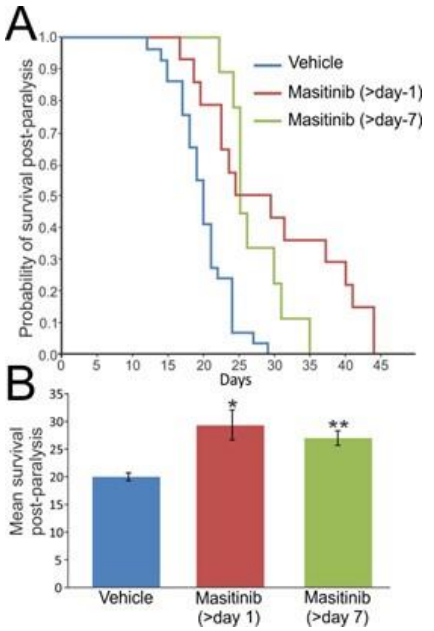
**Masitinib exerts a protective effect on the central nervous system by targeting microglia**

**Masitinib exerts a protective effect on the peripheral nervous system by targeting mast cells**

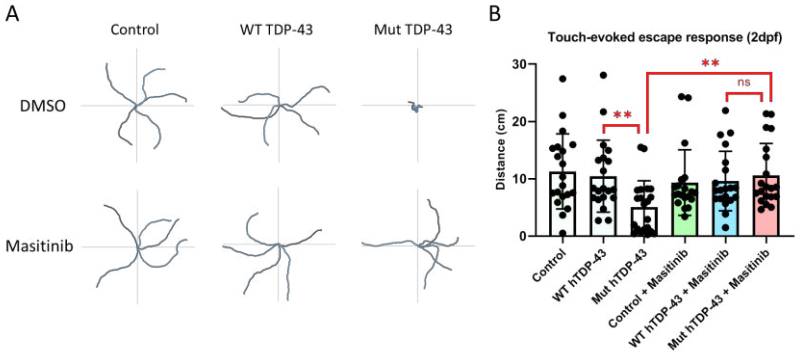



## There is a Well Demonstrated Mechanism of Action

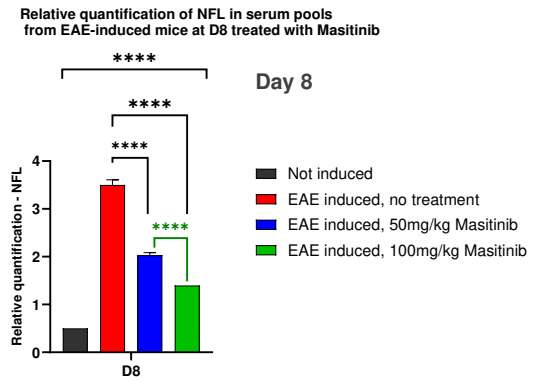
**Masitinib treatment initiated 7 days after paralysis onset prolonged survival by 40 % in in SOD1 model**




**Masitinib restored motor function in a zebrafish model of mutant TDP-43 overexpression**




**Masitinib lowered blood levels of neurofilament light (NfL) in a neurodegenerative disease model***




Díaz-Amarilla P., et al., Proc Natl Acad Sci U S A. 2011 Nov 1;108(44) ; Trias, E., et al., JCI Insight, 2017. **2**(20) ; Trias, E., et al. J Neuroinflammation, 2016. **13**(1): p. 177 ; Trias, E., et al.. JCI Insight. 2018. **3**(19).

# Phase 2B enrolled 394 patients with broad inclusion criteria and evaluated Masitinib after 48 weeks of treatment. The primary analysis was preplanned in the population defined as "Normal" progressors, following an early protocol amendment

## Design

**Design:**

Double blind, placebo controlled, 2-parallel groups

**Standard of care:** Riluzole

**394 patients enrolled**

- Masitinib 4.5 mg/kg/day + riluzole : 130 patients
- Masitinib 3.0 mg/kg/day + riluzole : 131 patients
- Placebo + riluzole : 133 patients

**Primary endpoint:**

- Change in the ALSFRS-R score at 48 weeks (ΔALSFRS-R)

**Duration:** 48 weeks

## Main inclusion criteria

- Probable, or definite ALS, sporadic or familial ALS, without restriction on baseline ALSFRS-R score
- Stable dose of riluzole for at least 30 days prior to screening
- Patients with disease duration ≤ 36 months
- Patients with FVC ≥ 60%

## Statistical analysis

**Two distinct populations were differentiated:**

- 'Normal Progressors': rate <1.1 points/month — **84% of trial patients**
- 'Fast Progressors': rate ≥ 1.1 points/month — **16% of trial patients**

- Rate of ALSFRS-R progression from first symptom to randomization (points/month):

**Efficacy analyses were conducted in a stepwise manner**

- Fixed sequence method, to control the global family-wise error rate at the 0.05 level for the primary analysis for each dose.

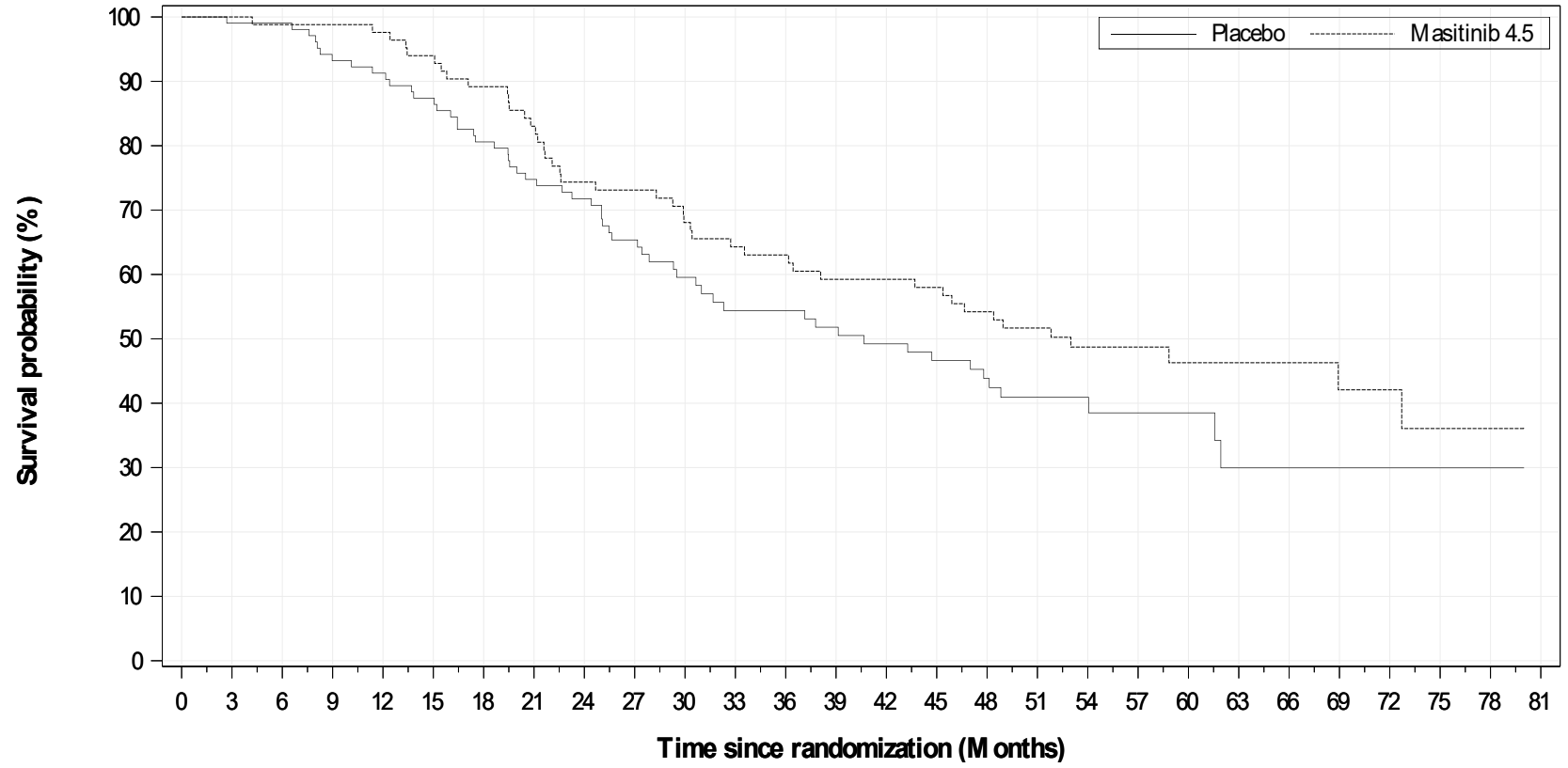
| | STEP | POPULATION |
|---|---|---|
| **Primary Analysis** | 1 | Normal Progressor; Masitinib 4.5 mg |
| **Move to next step if previous step is positive** | 2 | Normal Progressor; Masitinib 3.0 mg |
| | 3 | Normal + Fast Progressors; Masitinib 4.5 mg |
| | 4 | Normal + Fast Progressors; Masitinib 3.0 mg |

# A first phase 2B/3 (394 patients) met its primary analysis, slowing down functional decline at week 48, and generated a strong hypothesis for confirmatory phase 3 with the identification of an optimal population (normal progressor prior to loss of function)

| | | **AB10015 - Primary Analysis Population** (Normal Progressors) | **AB10015 – Subgroup Analysis** (Patients with ALS prior to any loss of function =86% of Normal Progressors) |
|---|---|---|---|
| **ΔALSFRS-R (primary endpoint)** (mLOCF – pirmary analysis) | **Diff. of mean** | **3.39** | **4.04** |
| | p-value | **0.0157** | **0.0065** |
| **ΔALSFRS-R (primary endpoint)** (Copy Increment in Reference - CIR) | Diff. of mean | **2.68** | **3.13** |
| | p-value | **0.0462** | **0.0308** |
| **Combined Assessment of Function and Survival (CAFS)** | Relative benefit | + 14.8% | **+ 20.2%** |
| | P-value | 0.0776 | **0.0290** |
| **Quality of Life (ALSAQ-40)** (CIR) | Diff. of mean | -6.04 [-11.51;-0.57] | **-6.22 [-12.27;-0.17]** |
| | p-value | 0.0305 | **0.044** |
| **Forced Vital Capacity (FVC)** (CIR) | Diff. of mean | 5.85 [-0.98;12.67] | **7.59 [0.41;14.77]** |
| | p-value | 0.0931 | **0.0384** |
| **Median Progression Free Survival** | Gain | + 4 months | **+ 9 months** |
| | Median [95% CI] | 20 [14; 30] vs 16 [11; 19] | 25 [17, NE] vs 16 [11, 19] |
| | p-value log rank | 0.0159 | **0.0057** |
| **Median OS (Long-term) (censoring of placebo at time of switch to masitinib)** | Gain | + 6 months | **+ 12 months** |
| | Median [95% CI] | 46 [33; 69] vs 40 [30; 49] | 53 [36; NE] vs 41 [30; 54] |
| | p-value log rank | 0.0761 | **0.0192** |

- **Phase 3 design** in patients with ALS prior to any loss of function **reviewed by FDA and EMA**
- **Phase 3 protocol approved by FDA and EMA** (Step 1 of CITS harmonization)

# In particular, in this population prior a complete loss of function, a significant survival benefit of +12 months was observed based on long-term follow-up




| Analysis | Gain in OS Median [95% CI] | p-value log rank |
|---|---|---|
| **Prior to any complete loss of function**<br>(subgroup, ALSFRS>0 on any item), Masitinib 4.5 vs placebo<br>OS analysis from baseline (censoring of placebo patients at time of switch to masitinib) | **+ 12 months**<br>53 [36; NE] vs 41 [30; 54] | 0.0192 |

# Following patients under compassionate use program, we observe very long-term survivors that are not explained by the published model that predicts survival based on baseline characteristics

**A large proportion of patients treated with masitinib 4.5 mg/kg/day have a survival duration of more than 5 years from onset**

Normal + Fast Progressors initially randomized in M4.5 treatment arm

| Survival Duration | Masitinib 4.5 mg/kg/day (N=128) |
|---|---|
| **Alive > 5yrs** | **55 (43.0%)** |
| Alive > 6yrs | 47 (36.7%) |
| Alive > 7yrs | 29 (22.7%) |
| Alive > 8yrs | 14 (10.9%) |

* 22.7 % of patients entered the compassionate-use (CU) program

**Survival for these patients is not explained by the published model that predicts survival based on baseline characteristics**

Comparison of overall observed survival with ENCALS predicted data
**Normal + Fast Progressors** initially randomized in M4.5 treatment arm
**and alive more than 5 years from onset**

| Survival Duration | Masitinib 4.5 mg/kg/day (N=55) |
|---|---|
| Observed overall survival (average in months) | 87 |
| ENCALS predicted overall survival (average in months) | 45 |
| **Average benefit over ENCALS predicted (in months)** | **42** |

# In its benefit-risk assessment, EMA considered the safety of Masitinib acceptable in ALS

## Masitinib Safety Benefits from a Large Database

**Number of Patients Randomized in Masitinib Treatment Arms**
**Safety Population**

| Safety population | | Patients exposed to Masitinib | | | | |
|---|---|---|---|---|---|---|
| | All | ≤ 3 months | More than 3 months | More than 6 months | More than 1 year | More than 2 years |
| **All** | **4,318** | **1,674** | **2,644** | **1,924** | **1,255** | **560** |
| Healthy Volunteers | 96 | 96 | 0 | 0 | 0 | 0 |
| **Non-Oncology subjects** | **2,184** | **565** | **1,619** | **1,307** | **958** | **453** |
| Oncology subjects | 2,038 | 1,013 | 1,025 | 617 | 297 | 107 |
| | | | | | | |
| *ICH Topic E1 requirements for non-orphan drugs* | *1,500* | | | *300-600* | *100* | |

## Masitinib Safety is Deemed Acceptable in ALS

**CHMP Latest Assessment Report**

Conclusion on clinical safety

*"Having considered the data from masitinib studies, the safety profile of mentioned medicinal product is considered acceptable";*

# 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

Taylor & Francis
Taylor & Francis Group

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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

Correspondence: Jesus S. Mora, M.D., ALS Unit, Unidad de ELA, Hospital San Rafael, c/Serrano, 199, Madrid 28016, Spain.
Email: sanrafael.neurociencias@hsjd.es
*AB10015 STUDY GROUP collaborators (non-author investigators) listed in Supplementary Table 1.

Supplemental data for this article can be accessed here.

*(Received 23 December 2018; revised 10 May 2019; accepted 4 June 2019)*

ISSN 2167-8421 print/ISSN 2167-9223 online 
DOI: 10.1080/21678421.2019.1632346

*Therapeutic Advances in Neurological Disorders* — *Original Research*

## 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

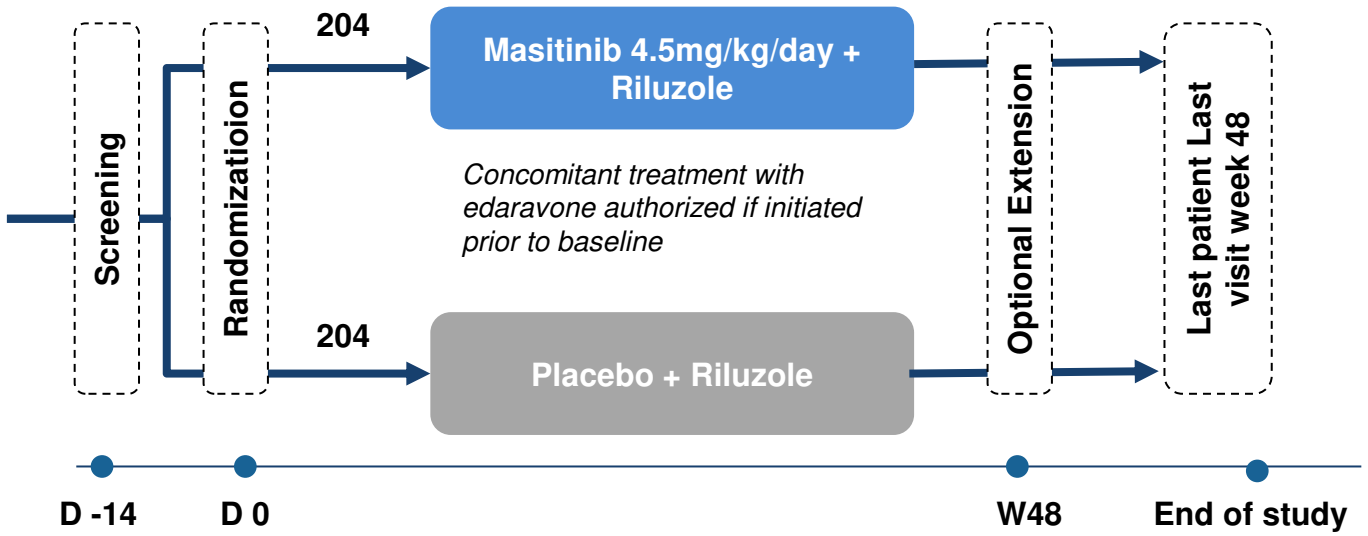
Received: 25 February 2021; revised manuscript accepted: 17 June 2021.

*Ther Adv Neurol Disord*
2021, Vol. 14: 1–16
DOI: 10.1177/17562864211030365



Correspondence to:
**Albert C. Ludolph**
Department of Neurology, University of Ulm, Oberer Eselsberg 45, Ulm 89081, Germany
German Center for Neurodegenerative Diseases, Ulm, Germany
albert.ludolph@rku.de
**Olivier Hermine**
Department of Hematology, Necker Hospital, University of Paris, 149 Rue de Sèvres, Paris 75015, France
AB Science, Paris, France
Laboratory of Cellular and Molecular Mechanisms of Hematological Disorders and Therapeutic Implication, Imagine Institute, INSERM UMR 1163 and CNRS ERL 8254, Hôpital Necker, Paris, France
ohermine@gmail.com
**Jesus S. Mora**
ALS Unit, Hospital San Rafael, Madrid, Spain
**Walter G. Bradley**
Department of Neurology, University of Miami School of Medicine, Miami, FL, USA
**Delia Chaverri**
**María Hernández-Barral**
**Javier Mascias**
ALS Unit, Department of Neurology, University Hospital La Paz-Carlos III, Madrid, Spain
**Josep Gamez**
Neurology Department

# A confirmatory phase 3 has been authorized by FDA and harmonized protocol has been approved through step 1 of CTIS




**Duration :**
- 48 weeks, Open label treatment after week 48

**Sample size**
- 408 patients, Masitinib 4.5 mg/kg/day vs placebo, Randomization 1:1

**Primary endpoint**
- CAFS (FDA), Change in ALSFRS-R (EMA)

**Main secondary endpoints**
- PFS, Quality of life, OS

**Surrogate endpoint**
- NfL, Biomarkers

*Target Product Profile*

*Amyotrophic Lateral Sclerosis*

**Multiple Sclerosis**

*Alzheimer's Disease*

*Other indications*

*Intellectual Property*

# There is a tremendous unmet need in progressive MS, with no approved drugs for non-active secondary progressive MS and one for primary progressive MS

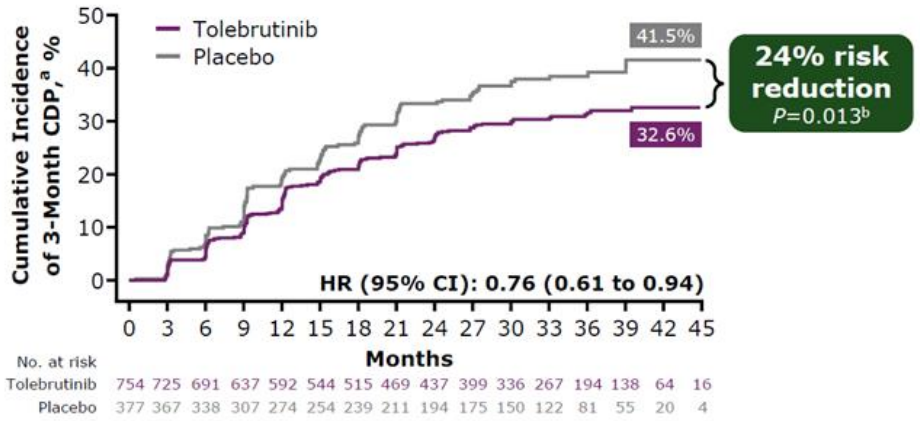
- Vast majority of drugs are effective only in active MS patients because these drugs stop immune attacks (active inflammation) but cannot repair myelin damage or protect nerves
- Ocrevus is indicated in specific forms of primary progressive MS (PPMS), for the treatment of adult patients with early PPMS in terms of disease duration and level of disability, and with imaging features characteristic of inflammatory activity

| | Manufacturer | Label | | | | First approved |
|---|---|---|---|---|---|---|
| | | PPMS | Non-active SPMS* | Active SPMS | RRMS | |
| **Distribution of patients** *(Estimated Nbr of patients Europe + USA)* | | **15%** *(~ 150 000)* | **35%** *(~ 350 000)* | **10%** *(~ 90 000)* | **40%** *(~ 400 000)* | |
| **Total number of drugs registered** | | **1** | **0** | **15** | **16** | |
| Mayzent (siponimod) | Novartis | | | X | X | 2019 |
| Vumerity (diroximel fumarate) | Alkermes / Biogen | | | X | X | 2019 |
| Ocrevus (ocrelizumab) | Roche / Genentech | X | | X | X | 2017 |
| Mavenclad (cladribine) | EMD Serono / Merck | | | X | X | 2017 |
| Plegridy (peginterferon beta-1a) | Biogen | | | X | X | 2014 |
| Tecfidera (dimethyl fumarate) | Biogen | | | X | X | 2013 |
| Aubagio (Teriflunomide) | Sanofi-Aventis | | | X | X | 2012 |
| Gilenya (fingolimod) | Novartis | | | X | X | 2010 |
| Extavia (interferon beta-1b) | Novartis | | | X | X | 2008 |
| Tysabri (natalizumab) | Biogen | | | X | X | 2004 |
| Lemtrada (alemtuzumab) | Sanofi / Genzyme | | | X | X | 2001 |
| Rebif (interferon beta-1b) | Serono | | | X | X | 1998 |
| Avonex (interferon beta-1a) | Biogen | | | X | X | 1996 |
| Copaxone (glatiramer acetate) | Teva Pharms | | | X | X | 1996 |
| Betaferon / Betaseron (interferon beta-1b) | Bayer Healthcare | | | X | X | 1993 |

**Masitinib positioning**

# The recent success of tolebrutinib in secondary progressive MS, a BTK inhibitor targeting microglia, validates the strategy of targeting microglia, although BTKi have a safety class effect

**Tolebrutinib***
**24% risk reduction of time to 3 months confirmed disability progression**




- Tolebrutinib demonstrated a significant effect on time to 3-month CDP

➢ **BTKi target Microglia**

** ECTRIMS 2024 Presentation #O136*

**BKT inhibitors Safety Class Effect**

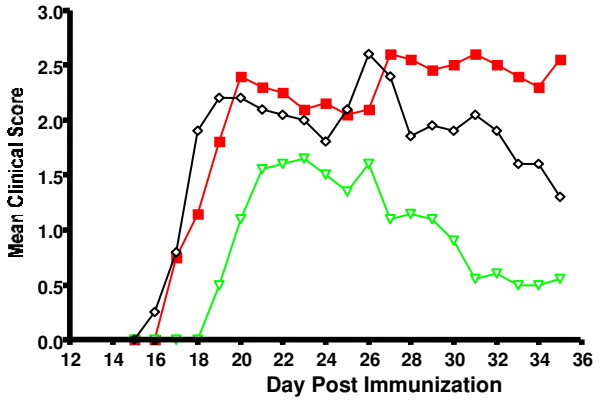
- **Cardiac toxicity** established (hypertension and sudden death reported)
- **Life-threatening liver toxicity** (one death following liver transplant due to liver injury)
- **Infections due to the targeting of B-cells**

- De-risking of the scientific approach targeting innate immunity in progressive MS
- Opportunity for drugs with improve Benefit/risk ration

# Masitinib's targeting of the innate immune system showed activity in animal model of multiple sclerosis

## In EAE mouse model of MS, masitinib showed significant reduction in disease.

**The potential of masitinib in MS was explored using a MOG-EAE model** (MOG-induced experimental allergic encephalomyelitis). It is established that mast cells are necessary for the full manifestation of disease in this model [Secor VH et al. j Exp Med 2000;191(5):813–821]




Control (vehicle)
Masitinib (25 mg/kg)*
Masitinib (12.5 mg/kg)*

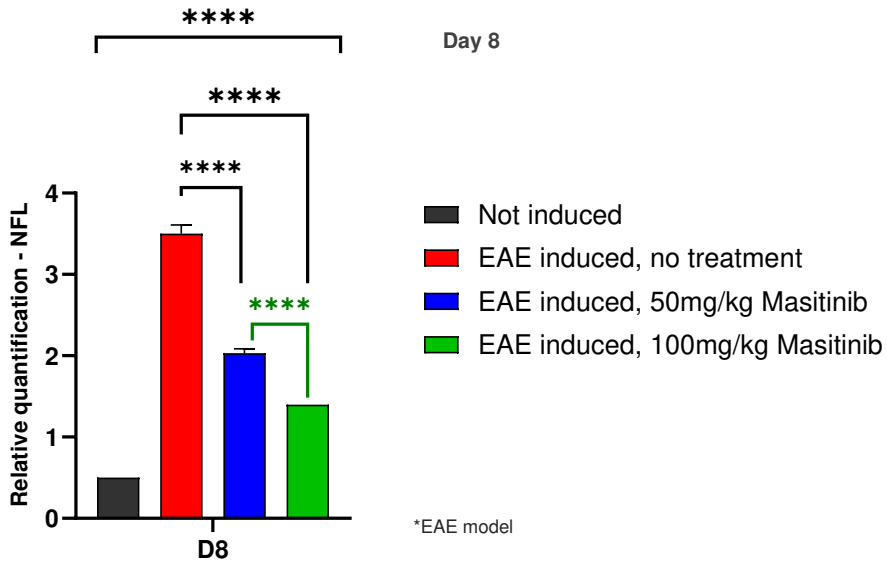
Mice were scored daily by visual assessment of symptoms on a scale of 0-5 where:

- 1 denotes a flaccid tail
- 2 denotes hind limb weakness
- 3 denotes hind limb paralysis
- 4 denotes an inability to right from supine;
- 5 indicates death

Masitinib administered daily from day 0. * 25 mg in mice is equivalent to approximately 2mg in human

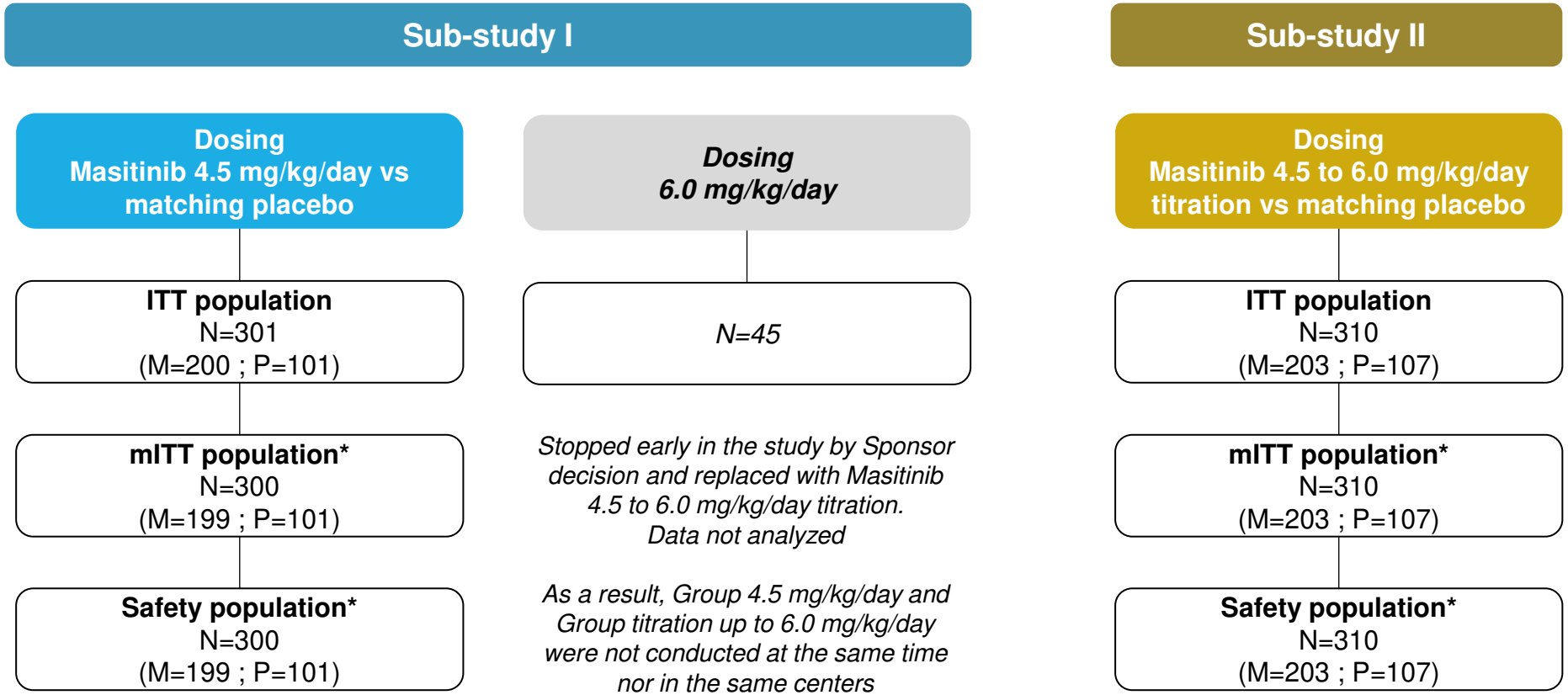
## Masitinib lowered blood levels of NfL in a EAE model

**Relative quantification of NFL in serum pools from EAE-induced mice at D8 treated with Masitinib**




*EAE model

# Phase 2B/3 enrolled 656 patients

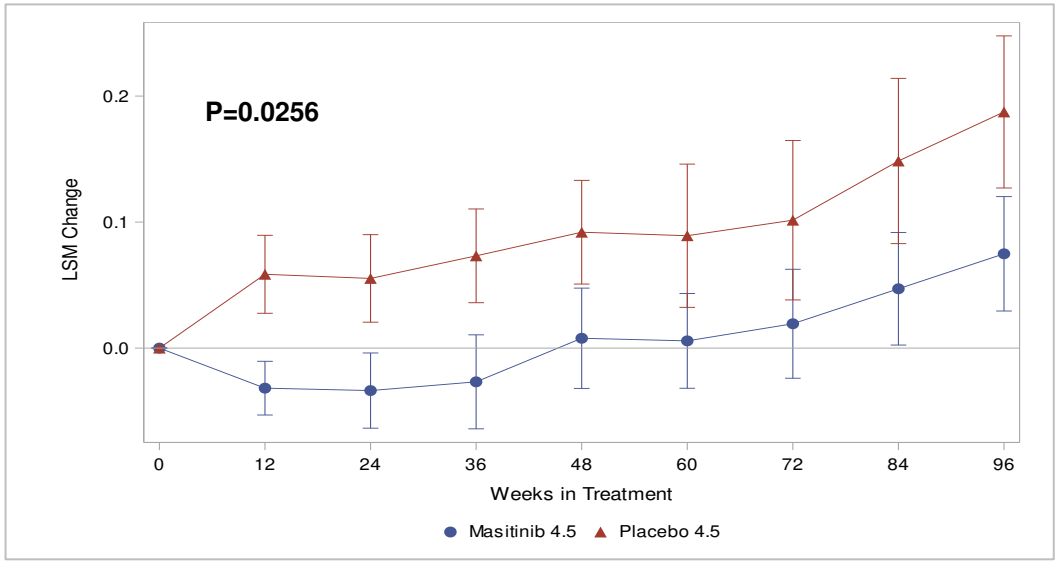



* All randomized patients (ITT) who took at least one dose of study treatment (masitinib/placebo).

Efficacy analyses were performed in the mITT population

# 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*)**



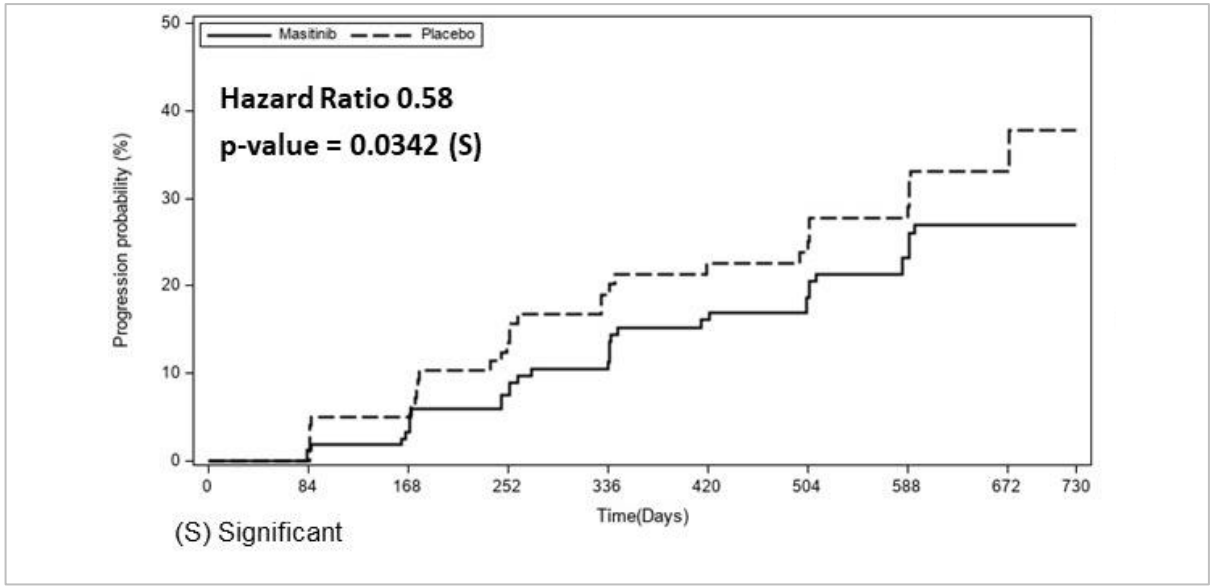

* Change in EDSS

**Patients were enrolled at advanced disease stage**

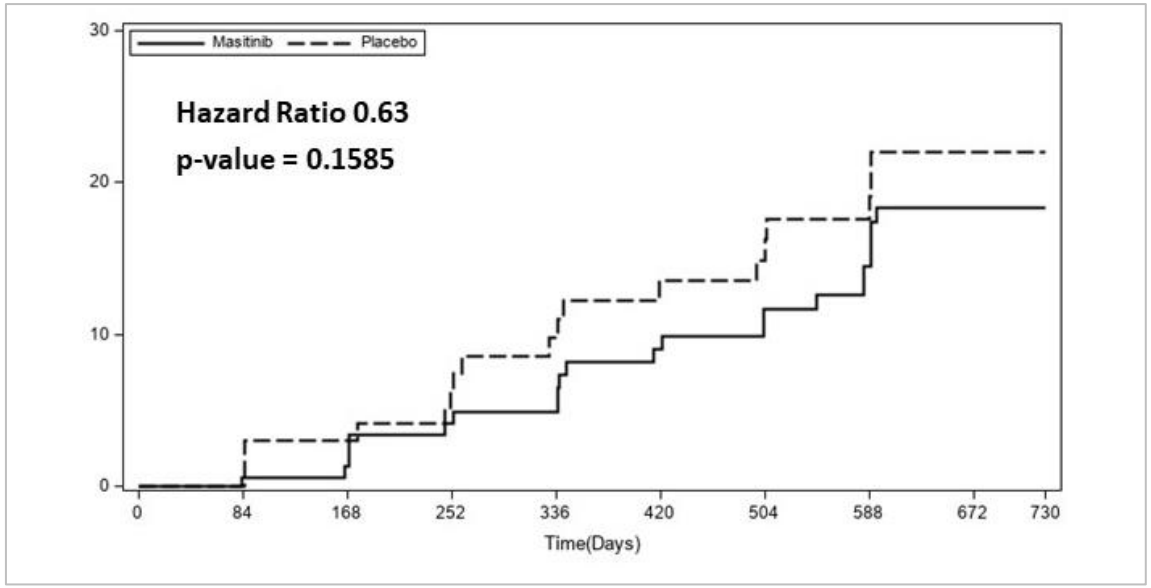
- Median age (years) : 50.0 (both masitinib and placebo)
- Median duration of first MS Symptom (yrs) : 12.4 masitinib and 12.2 placebo
- Median EDSS Score : 5.5 (both masitinib and placebo)
- % of patients with EDSS score of 6 : 49.0% masitinib and 47.5% placebo

# Phase 2B 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 (12 weeks)**




**37% risk reduction of time to confirmed disability progression (12 weeks)**



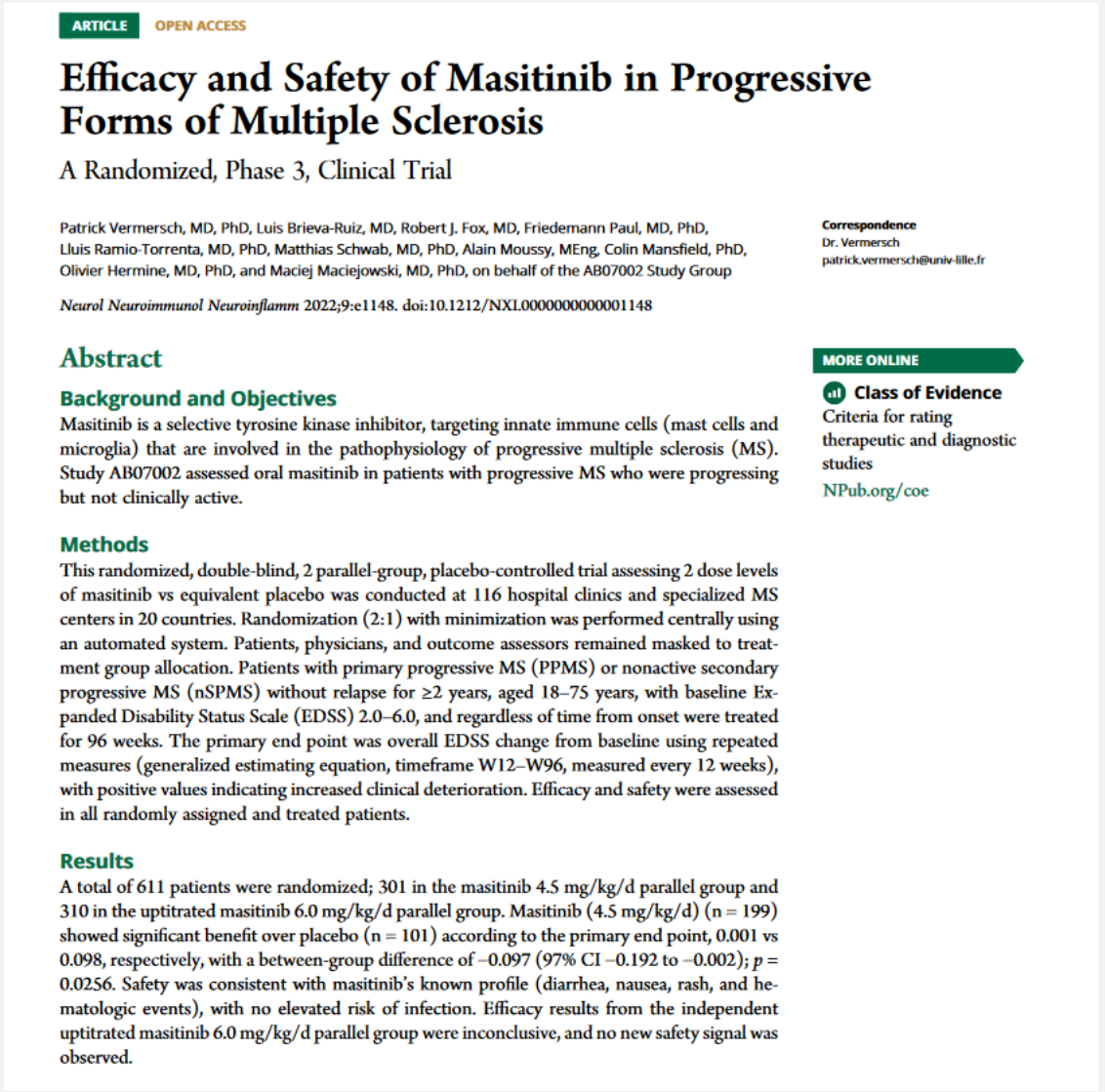
# Masitinib has the potential to become a best-in-class drug for PPMS and nSPMS comparison of 3-month confirmed disability progression

**Time to confirmed disability progression (CDP)**

| Drug | Study Size (patients) | Type of Progressive MS | Hazard Ratio | Reduction in risk of CDP |
|---|---|---|---|---|
| Masitinib 4.5 mg/kg/day | 300 | PPMS and nSPMS | • 3-month CDP : 0.63 | • 37% (NS) |
| Tolebrutinib | 1,131 | nSPMS | • 3-month CDP : 0.76 | • 24% (S) |
| Ocrelizumab | 732 | PPMS | • 3-month CDP : 0.76 | • 24% (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

# 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

Patrick Vermersch, MD, PhD, Luis Brieva-Ruiz, MD, Robert J. Fox, MD, Friedemann Paul, MD, PhD, Lluis Ramio-Torrenta, MD, PhD, Matthias Schwab, MD, PhD, Alain Moussy, MEng, Colin Mansfield, PhD, Olivier Hermine, MD, PhD, and Maciej Maciejowski, MD, PhD, on behalf of the AB07002 Study Group

**Correspondence**
Dr. Vermersch
patrick.vermersch@univ-lille.fr

*Neurol Neuroimmunol Neuroinflamm* 2022;9:e1148. doi:10.1212/NXI.0000000000001148

### 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.

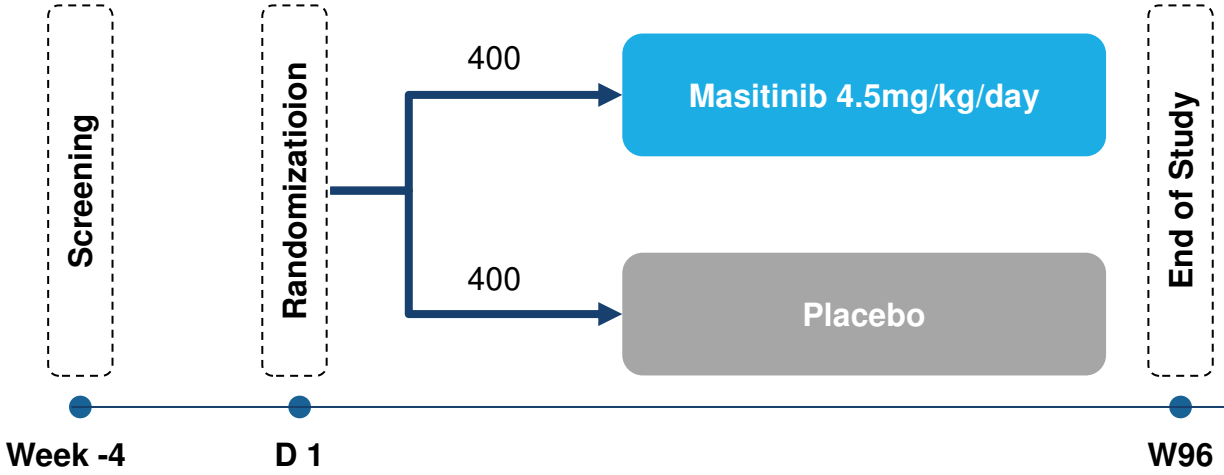
#### Results

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

# Confirmatory phase 3 study is authorized by FDA and key European countries




**Primary endpoint**

- Time to confirmed EDSS progression

**Main secondary endpoints**

- Change in EDSS from baseline considering all measurements from baseline up to Week 96
- Time to EDSS score of 7.0
- Brain MRI Assessments

**Main inclusion criteria:**

**The study will enroll PPMS and exclusively SPMS patients without superimposed inflammation documented by MRI at baseline in order to exclude inflammatory brain lesions at inclusion**

- PPMS and nSPMS, stratified
- Onset of symptoms at least five years before inclusion
- No relapse diagnosed at least two years before inclusion (according to the 2017 revised McDonald's criteria)
- EDSS score progression ≥1 point with no improvement during 2 years before screening
- **Absence of T1 Gadolinium-enhancing brain lesions as measured by MRI**
- EDSS score of [3.0 to 6.0] inclusive

**Study Status**

**Confirmatory phase 3 study design has been discussed with FDA and EMA**

**Approved countries**

- Bulgaria, France, Germany, Greece, Italy, Netherlands, Poland, Norway, Portugal, Spain, Sweden, United Kingdom
- USA

**Approved sites:** 67

*Target Product Profile*

*Amyotrophic Lateral Sclerosis*

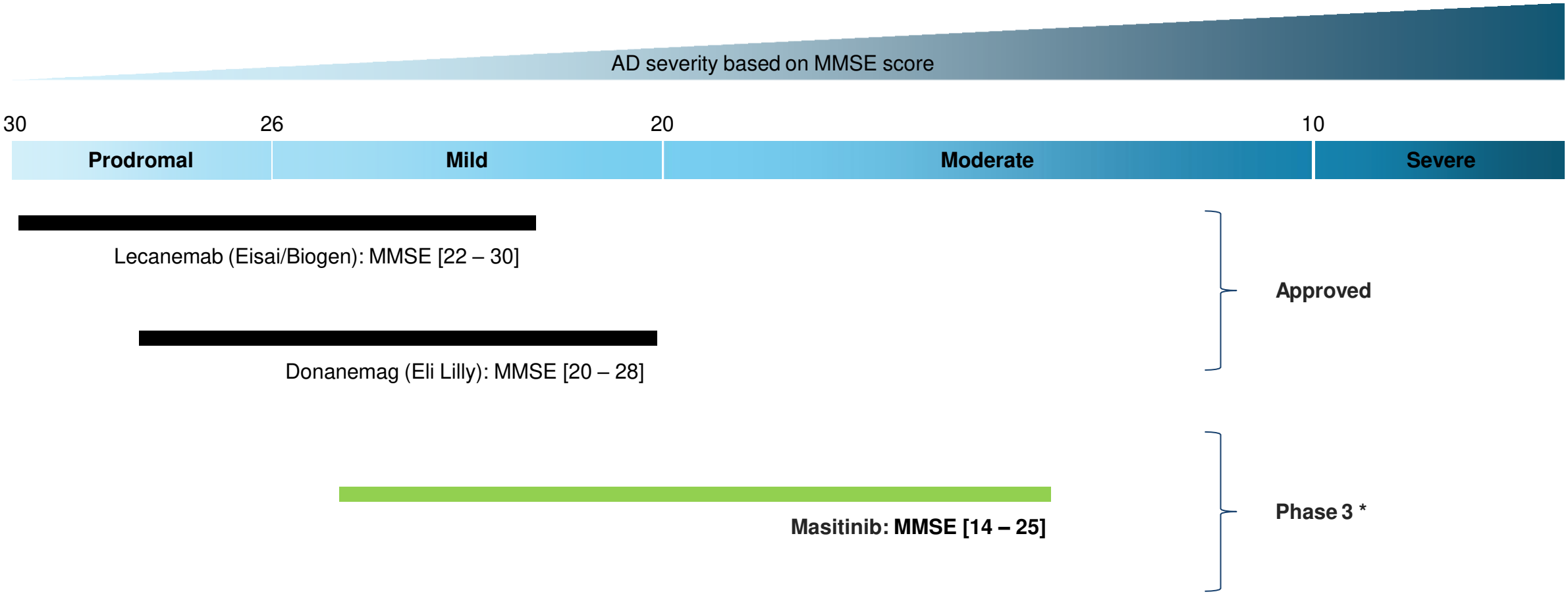
*Multiple Sclerosis*

**Alzheimer's Disease**

*Other indications*

*Intellectual Property*

# Masitinib is developed in more advanced forms of Alzheimer's disease as compare with biologics recently approved




- Confirmatory phase 3 study is authorized by FDA and key European countries and to be started

# Masitinib has a differentiating positioning

**Strategy**

Main Strategy 1
**beta amyloid plaques**

| Approved Drugs | Sponsor |
|---|---|
| Donanemab (Kisunla) | Eli Lilly |
| Lecanemab (Leqembi) | Eisai / Biogen |

- Currently the main strategy for early AD
- Class-effect warning for amyloid-related imaging abnormalities (ARIA)
- ARIA can be life-threatening (swelling in areas of the brain that usually resolves over time, though some people may have seizure)
- The objective of next generation drugs is to reduce ARIA

Main Strategy 2
**Tau protein aggregate**

| Failed Studies | Sponsor |
|---|---|
| Zagotenemab | Eli Lilly |
| Semorinemab | Roche |
| Tilavonemab | AbbVie |
| Bepranemab | UCB |

- No approved treatment base on this strategy
- Multiple failures in phase 3
- Reducing tau tangles in the brain (as seen in imaging) often did not translate to cognitive or functional improvements

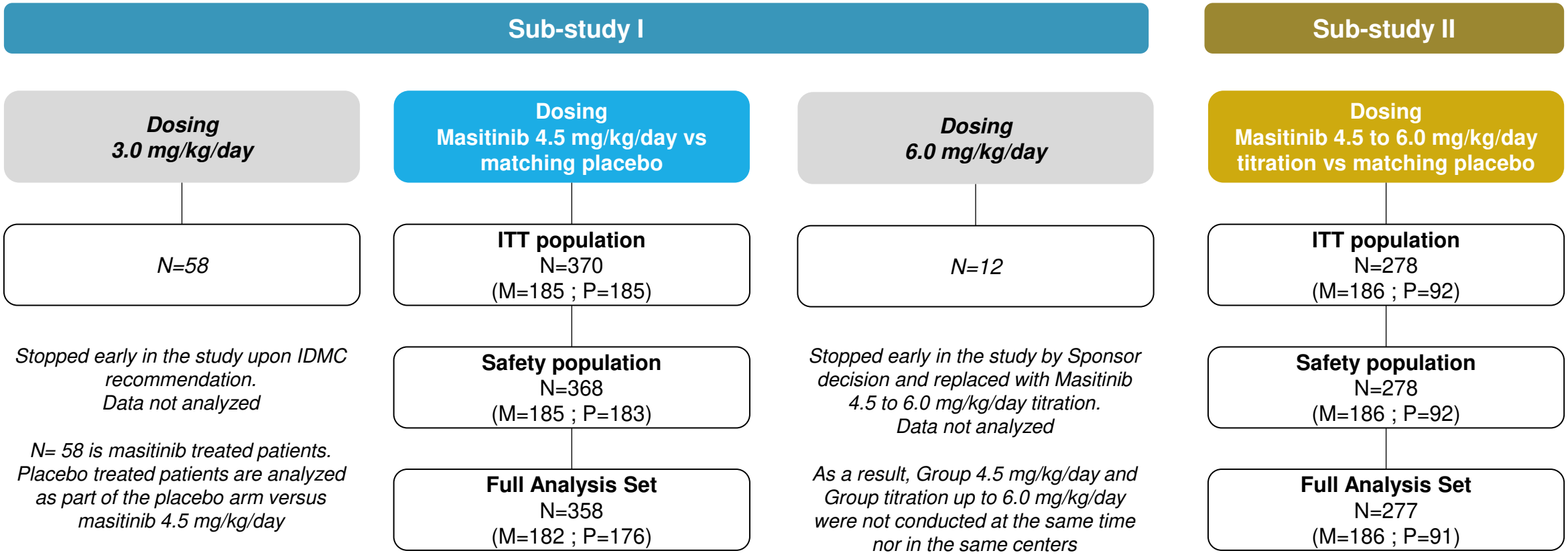
Other Strategies

| Positive Phase 3 | Sponsor |
|---|---|
| Masitinib | AB Science |

- Targets microglia and mast cells, which is a unique MoA in AD complementary to anti beta amyeloid and anti tau strategies
- Masitinib could be combined with anti beta amyeloid or anti tau treatments in early and mild AD to become first of class combo treatment

| Failed Studies | Sponsor |
|---|---|
| Simufilam | Cassava Sciences |
| CT1812 | Shine |

# Phase 2B/3 enrolled 718 patients from 118 sites in 21 countries




**Full Analysis Set :** Exclusion from ITT population of 13 patients

- Patients from sites with critical GCP violations at 2 sites as highlighted by audit report and internal report (n=6)
- Patients with no treatment intake (n=2)
- Patients with baseline ADL or Cog scores that do not correspond to the medical history, with documented letter from investigator to exclude them from primary analysis, validated by steering committee (n=3)
- Patients with caregiver that changed during the main period, with documented letter from investigator to exclude them from primary analysis, validated by steering committee (n=2)

# 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**

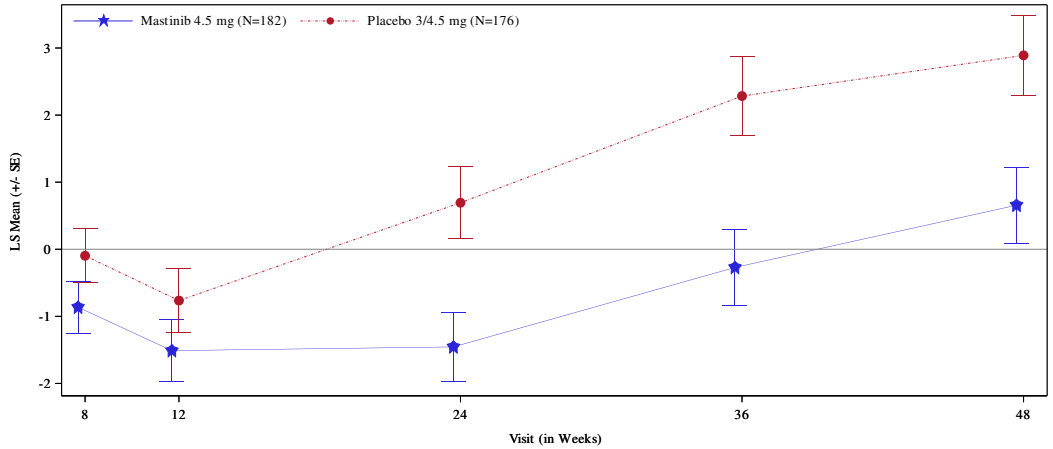
| Treatment | n | LS Mean (95% CI) | LS Mean Difference (97.51% CI) | p-value |
|---|---|---|---|---|
| Masitinib 4.5 mg/kg/day + memantine and anticholinesterase | 182 | **1.01** (-0.48, 2.50) | **1.82** (-0.15, 3.79) | **0.0381** |
| Placebo + memantine and anticholinesterase | 176 | **-0.81** (-2.36, 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 | | | | |
| 0.0871 | 0.1590 | 0.0003 | <.0001 | 0.0007 |

# 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

Bruno Dubois[1*], Jesús López-Arrieta[2], Stanley Lipschitz[3], Doskas Triantafyllos[4], Luiza Spiru[5,6], Svitlana Moroz[7], Olena Venger[8], Patrick Vermersch[9], Alain Moussy[10], Colin D. Mansfield[10], Olivier Hermine[10,11,12*], Magda Tsolaki[13] for the AB09004 Study Group Investigators

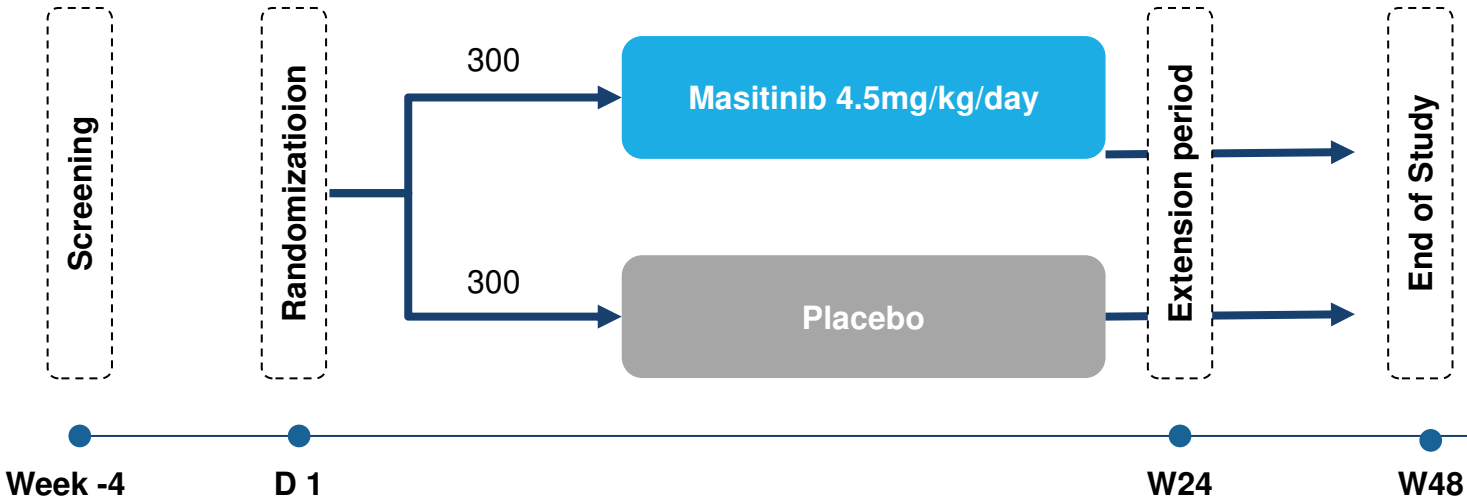
**Abstract**

**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.

# Confirmatory phase 3 study is authorized by FDA and key European countries




**Primary endpoint**

- Change from baseline in ADCS-ADL score at week 24, and
- Change from baseline in ADAS-Cog 11 score at week 24

**Main secondary endpoints**

- Time to severe dementia (MMSE<10)
- Change from baseline in ADCS-ADL and ADAS-Cog score at week 48

**Main inclusion criteria**

- Patients with clinical diagnosis of Alzheimer's disease based on cognitive impairment and daily functional dependency at screening visit
- Patients with ADCS-ADL score at screening visit and baseline visit < 73
- Patients with MMSE ≥ 14 and ≤ 25 at screening visit and baseline visit

**Study Status**

**Confirmatory phase 3 study design has been discussed with FDA and EMA**

**Approved countries**

- Belgium, Bulgaria, Czech Republic, France, Germany, Greece, Hungary, Ireland, Italy, Poland, Portugal, Romania, Slovakia, Spain, Sweden, United Kingdom
- USA

**Approved sites:** 91

*Target Product Profile*

*Amyotrophic Lateral Sclerosis*

*Multiple Sclerosis*

*Alzheimer's Disease*

**Other indications**

*Intellectual Property*

# 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**

**SCD is a major public health challenge**

- SCD affects 1 in 13 Black or African-American babies and approximately **100,000 Americans** [1]
- **Multiple severe multi-organ complications: Pain crisis** leading to hospitalization, **Vaso-Occlusive Crises** (VOC, Blood flow blocked by sickled cells), **Infection**, [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

- Global market size : From $2.7 billion (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** and **high costs** (> 2 million USD per patient)
- Recently, 4 new symptomatic treatments have been registered by the FDA, including **two recently revoked (crizanlizumab, voxelotor**), 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 **revoked** |

*[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)<br>▪ 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<br>▪ Phase 2 in non-hospitalized patients | ▪ Expected Read-out : 2024<br>▪ Expected Read-out : 2024 |

*Target Product Profile*

*Amyotrophic Lateral Sclerosis*

*Multiple Sclerosis*

*Alzheimer's Disease*

*Other indications*

**Intellectual Property**

# Masitinib IP rights are secured through use patent until 2037 in ALS and up to 2041 in MS and AD

| Scope | Protection | Title | Reference | Duration of protection |
|---|---|---|---|---|
| Multiple Sclerosis | Use patent | Treatment of multiple sclerosis with masitinib | WO2011131705 | 2031 |
| | | Masitinib for the treatment of a multiple sclerosis patient subpopulation | WO2021165472 | 2041 |
| Amyotrophic Lateral Sclerosis | Use Patent | Use of masitinib for treatment of an amyotrophic lateral sclerosis patient subpopulation | WO2017162884 | 2037 |
| | Orphan Drug Status | Treatment of amyotrophic Lateral Sclerosis | FDA - 15-4694<br>EMA - EU/3/16/172 | FDA – 7 years as of approval<br>EMA – 10 years as of approval |
| Alzheimer's Disease | Use patent | Masitinib for the treatment of Alzheimer's disease (subpopulations) | WO2022129410A1 | 2041 |

## In addition, regulation provides up to 7.5 years and possibly 8 years data exclusivity in the USA and 8 years data exclusivity and up to 11 years market protection in the EU

- **USA : Up to 7.5 years and possibly 8 years data exclusivity**
  - 5-year protection as of FDA approval based on Hatch-Waxman Act, and to **up to 7.5 years protection in practice**
  - **8 Years protection if Masitinib is approved for a new use, formulation, dosage form, route of administration**
- **EU : Up to 11 years market protection**
  - **10 years protection** as per Regulation (EC) No 726/2004, medicinal products for human use benefit from an eight-year period of data protection and a ten-year period of marketing protection
  - **11 years protection if masitinib is approved in a new indication**

# AB8939 PLATEFORM

**Target Product Profile**

*Pharmacology Data*

*Phase 1 Preliminary Safety and Efficacy*

*Preliminary Activity in MECOM*

*Intellectual Property*

# AB8939 is a next generation synthetic microtubule destabilizer and targeted stem cell ALDH1/2 inhibitor with key differentiating factors for treatment of refractory/relapsing acute myeloid leukemia (AML)

## Scientific Rationale

**Cancer cells and Microtubule**

- *Microtubules are critical for cell division*
- *Microtubule targeting chemotherapies are gold standard in many cancers, but, subjected to multidrug resistance (efflux by PgP) and are degraded by myeloperoxidase (produced by cancer cells) in AML*

**Cancer stem cells and ALDH**

- *ALDH plays critical role in cancer stem cells*
- *AML cells with high ALDH activity are more resistant to chemotherapeutic agents*
- *ALDH is over-expressed in MECOM*

## AB8939 Target Product Profile

### 1. BLOCKING PROLIFERATING LEUKEMIA CELLS THROUGH MICROTUBULES

- AB8939 destabilizes microtubules
- AB8939 is not subjected to multidrug resistance (no PgP binding)
- AB8939 is not degraded by myeloperoxidase

### 2. TARGETING OF LEUKEMIA CANCER STEM CELLS THOUGH ALDH

- AB8939 inhibits ALDH1
- AB8939 favors the bone marrow repopulation of normal progenitors

### 3. TREATMENT OF REFRACTORY/RELAPSING AML

- AB8939 has activity seen across refractory AML cell lines
- AB8939 has an additive effect with cytarabine, azacitidine and venetoclax
- AB8939 has shown a signal of efficacy in AML with MECOM gene rearrangement, a subset of patients that show extreme resistance to chemotherapies

### 4. LOW HEMATOLOGICAL TOXICITY

- AB8939 shows absence of hematological toxicity based on clinical data

## Targeted Indications

**Acute Myeloid Leukemia:**

- **relapsed or refractory patients**

**and**

- **AML patients with MECOM gene rearrangement**

# AB8939 has a potential to improve treatment of relapsed / refractory AML

| | | Relapsed / refractory AML (R/R AML) * | |
|---|---|---|---|
| | **Line 1** | **Line 2** | **Line 3** |
| **Patients eligible to high dose chemotherapy** | Anthracyclines + cytarabine + targeted therapies (IDH/FLT3) | High dose chemotherapy or Low dose chemotherapy | **No approved drug**<br>**Low dose chemotherapy or**<br>**Best supportive care** |
| **Patients ineligible to high dose chemotherapy** | Hypomethylating agents (azacitidine / venetoclax) + targeted therapies (IDH/FLT3) | **No approved drug**<br>**Low dose chemotherapy or**<br>**Best supportive care** | **No approved drug**<br>**Best supportive care** |

*AB8939 current positioning in AML*

* One Menin inhibitors recently registered for R/R AML patients with KMT2Ar rearrangement or NPM1 mutation

Anthracyclines = Daunorubicin or Idarubicin
Cytarabine = Ara C
Azacitidine = Vidaza
Venetoclax = Venclyxto

# The objective is to position AB8939 combination treatment to be the standard of care in refractory/relapsing AML, which represents a market size potential above EUR 2 billions per annum, including EUR 100 millions for AML with MECOM gene rearrangement

| Region | Incidence Case (1) | % Relapse or Refractory (2,3) | % Insured Patients (4) | Drug Price (€) | Market Size (per in in Mio EUR) |
|---|---|---|---|---|---|
| USA / CANADA | 23,700 | 50% | 90% | 100,000[5] | 1 000 000 |
| EUROPE | 27,600 | | 90% | 60,000 | 770 000 |
| APAC | 27,800 | | 30% | 60,000 | 250 000 |
| INDIA | 11,000 | | 30% | 60,000 | 100,000 |
| LATAM | 7,200 | | 30% | 60,000 | 65 000 |
| MENA | 3,900 | | 30% | 60,000 | 35 000 |
| **TOTAL** | **90,200** | | | | **2 200 000** |

EUROPE = EU27 + Norway + United Kingdom + Switzerland ; APAC = Australia, People's Republic of China , Japan, New Zealand, Singapore, Taiwan ; LATAM = Argentina, Brazil, Chile, Colombia, Costa Rica, Mexico ; MENA = Algeria, Bahrain, Egypt, Israel, Kuwait, Morocco, Oman, Qatar, Saudi Arabia, Tunisia, United Arab Emirates.


(1) Zhou, Y et al. Global, regional, and national burden of acute myeloid leukemia, 1990–2021: a systematic analysis for the global burden of disease study 2021. Biomark Res 12, 101 (2024).
(2) Ravandi F. Relapsed acute myeloid leukemia: Why is there no standard of care Best Pract Res Clin Haematol. 2013;26(3):253-9
(3) Walter RB et al. Resistance prediction in AML: analysis of 4601 patients from MRC/NCRI, HOVON/SAKK, SWOG and MD Anderson Cancer Center. Leukemia (2015) 29:312–20. .
(4) Estimated
(5) Choi M. et al. Costs per patient achieving remission with venetoclax-based combinations in newly diagnosed patients with acute myeloid leukemia ineligible for intensive induction chemotherapy. Journal of Managed Care & Specialty Pharmacy Volume 28, Number 9. https://doi.org/10.18553/jmcp.2022.22021

*Target Product Profile*

**Pharmacology Data**

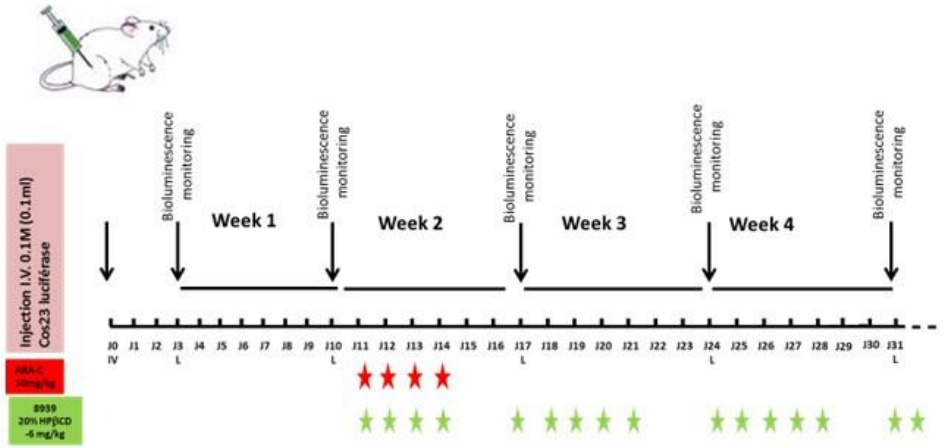
*Phase 1 Preliminary Safety and Efficacy*

*Preliminary Activity in MECOM*

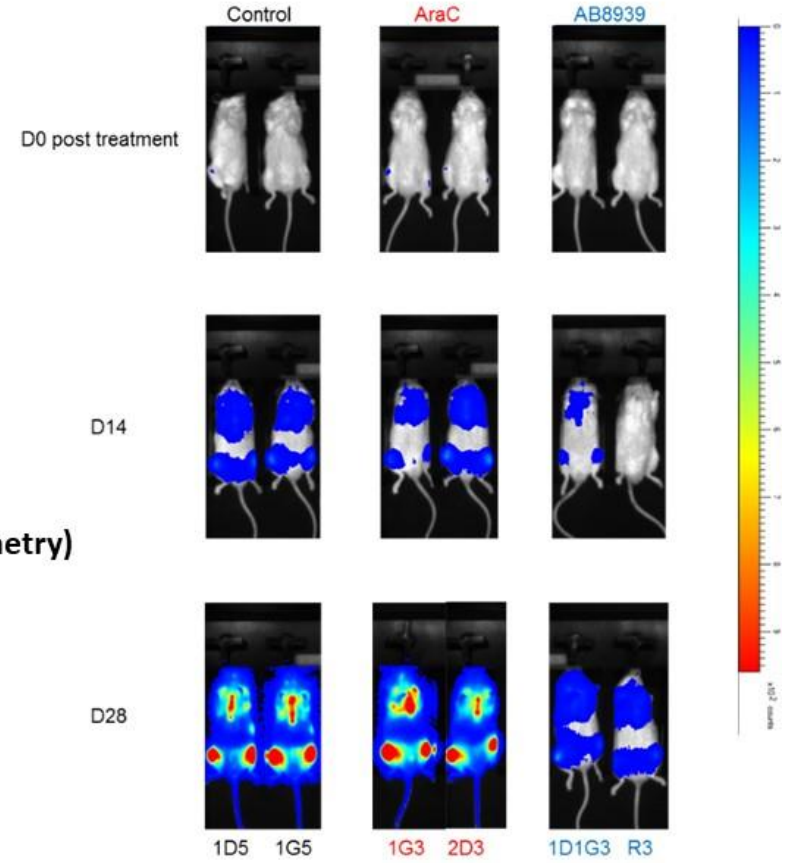
*Intellectual Property*

# AB8939 eradicates blasts in Blood and Bone Marrow in 5-AraC-resistant (Cytarabine) PDX

**A. Study design**

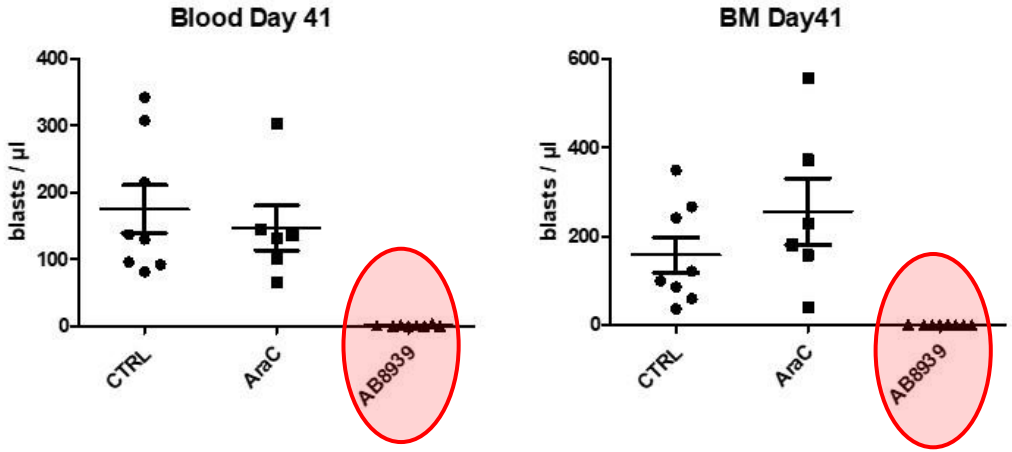



**B. Bioluminescence monitoring**



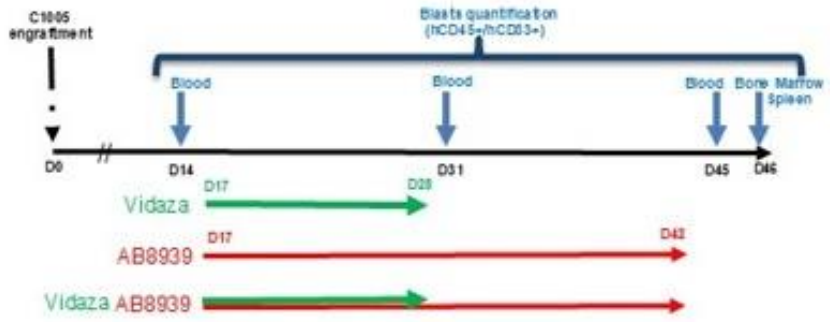

***Red luminescence detects cancer cells***

**C. Blasts quantification in blood and bone marrow (hCD45+, flow cytometry)**

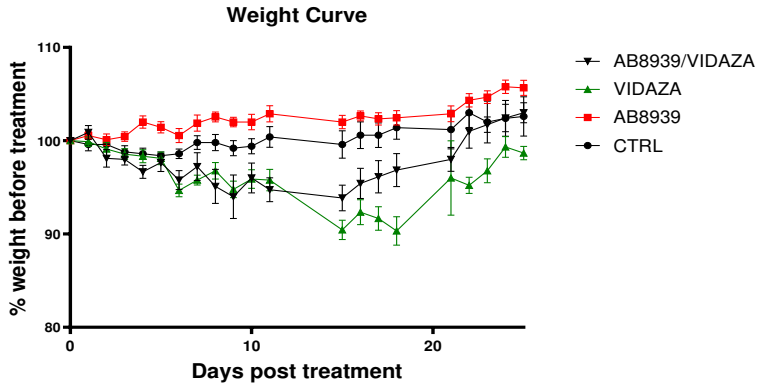


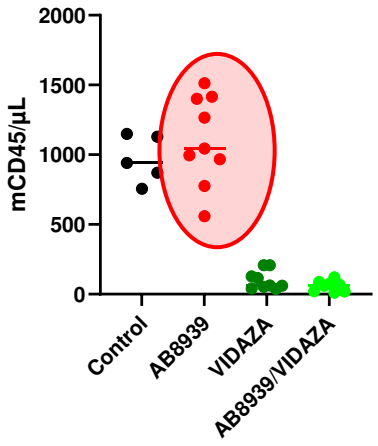
# AB8939 increase survival and has an additive effect in combination with reference treatment Azacitidine

A. Study Design



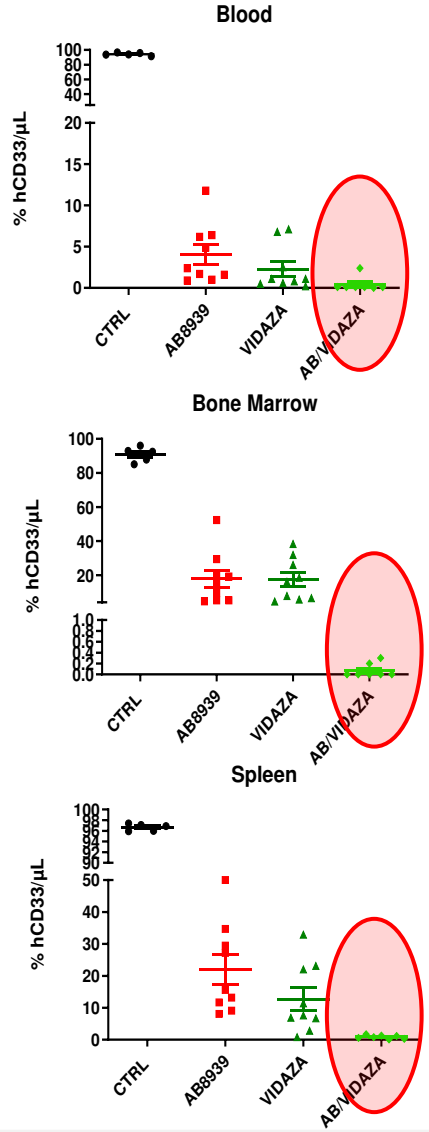

B. Unlike Vidaza, AB8939 does not induce any hematotoxicity



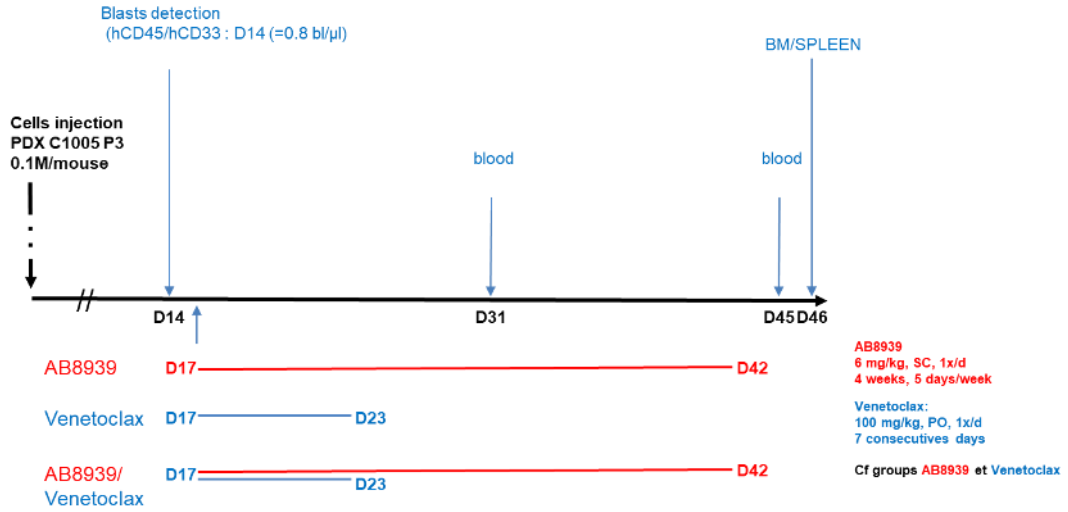

C.

- **AB8939/ vidaza combination allows the clearing of leukemia blasts in blood, spleen and bone marrow (C) without adding toxicities.**

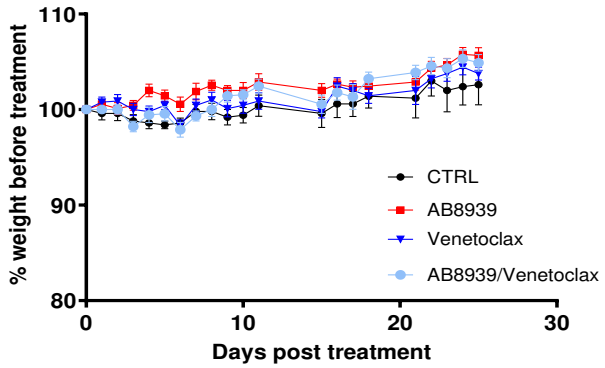


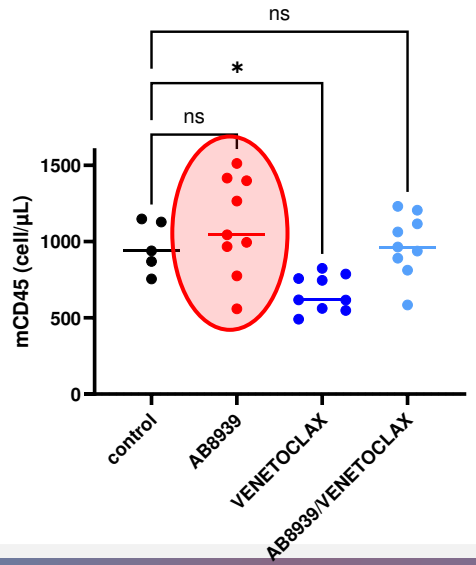
# AB8939 increase survival and has a potential additive effect in combination with reference treatment Venetoclax

A. Study Design



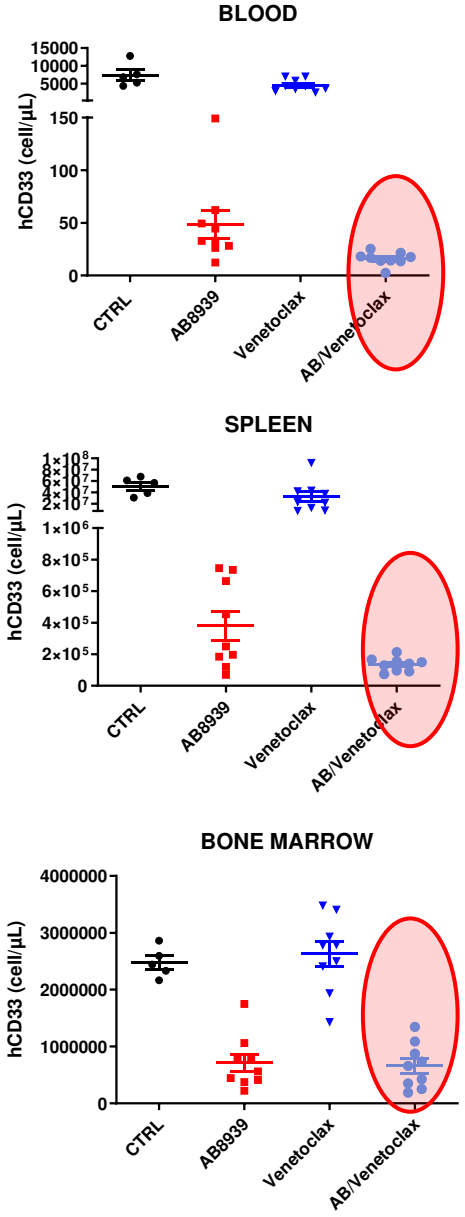

**B. AB8939 monotherapy or combined with Venetoclax is well-tolerated: absence of any toxicity (left: weight curves) or hematotoxicity (right: hematopoietic progenitors mCD45)**




**C.**

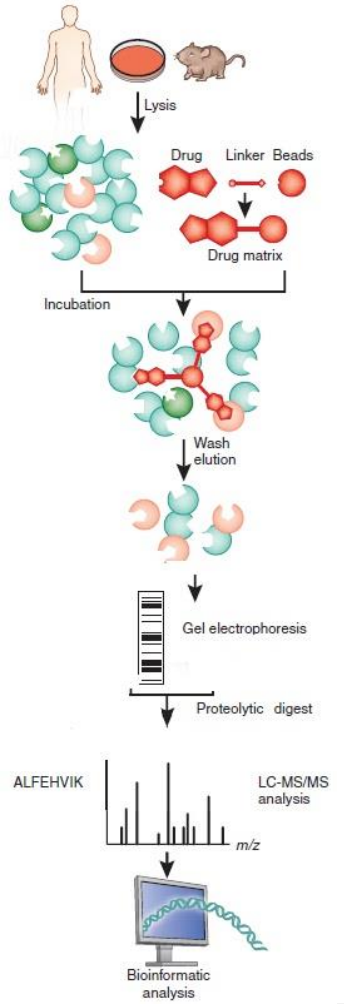
**AB8939/ Venetoclax combination allows the clearing of leukemia blasts in blood, spleen and bone marrow without adding toxicities.**



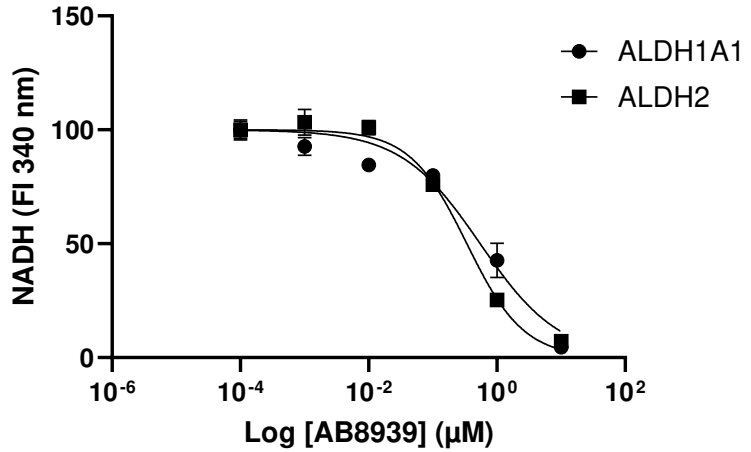
# ALDHs expression is a hallmark of cancer stem cells (CSCs) and AB8939 is an inhibitor of ALDH1/2

- Reverse proteomic analysis revealed ALDHs as main AB8939 interactors

- Preliminary *in vitro* studies have shown that AB8939 inhibits both recombinant ALDH1A1 and ALDH2 with a sub-micromolar potency



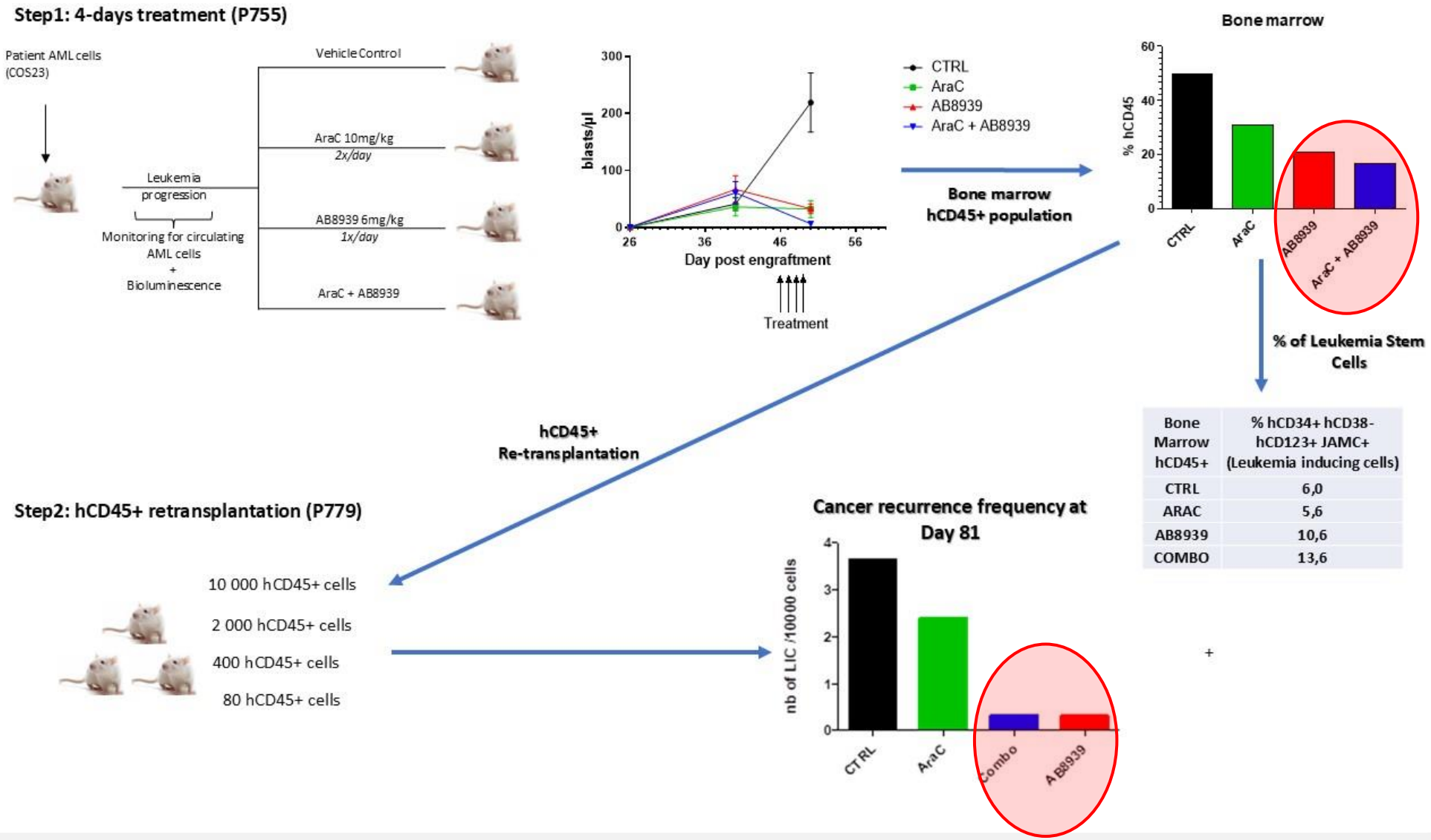

| Accession number | Gene | AB8939 beads peptides count | Control beads peptides count | Ratio 8939/control |
|---|---|---|---|---|
| **Experiment 1 (Pool of 33 cell lines lysates)** | | | | |
| P05091 | ALDH2 | 34,5 | 1 | 34,5 |
| P47895 | ALDH1A3 | 4,5 | 1 | 4,5 |
| P30837 | ALDH1B1 | 7 | 1 | 7 |
| P00352 | ALDH1A1 | 2 | 1 | 2 |
| **Experiment 2 (CLS354-4 cell lysate)** | | | | |
| P30837 | ALDH1B1 | 60 | 1 | 60 |
| P05091 | ALDH2 | 178 | 4 | 45 |
| P47895 | ALDH1A3 | 102 | 33 | 3 |
| P30838 | ALDH3A1 | 7 | 3 | 2 |




| | ALDH1A1 | ALDH2 |
|---|---|---|
| $IC_{50}$ (nM) | 500 | 340 |
| R squared | 0,96 | 0,99 |

# AB8939 eradicates Leukemia Cancer Stem Cells in a human PDX AML model

- Preliminary AB8939 treatment eradicates most of leukemia cells in the bone marrow (step 1).
- AB8939 reduces the re-occurrence of leukemia following re-transplanted of leukemia cells indicating that AB8939 treatment eradicates both leukemic blast and leukemia cancer stem cells(Step 2).
- AB8939 is likely to kill highly dividing blasts through microtubule disruption while it kills resting cancer Stem cells through inhibition of ALDHs.




| Bone Marrow hCD45+ | % hCD34+ hCD38- hCD123+ JAMC+ (Leukemia inducing cells) |
|---|---|
| CTRL | 6,0 |
| ARAC | 5,6 |
| AB8939 | 10,6 |
| COMBO | 13,6 |

*Target Product Profile*

*Pharmacology Data*

**Phase 1 Preliminary Safety and Efficacy**

*Preliminary Activity in MECOM*

*Intellectual Property*

# The objective of the phase 1 is to determine the maximum tolerated dose (MTD) for three different cycles of AB8939

**Step 1**

**MTD* 3 DAYS**
**AB8939 alone**

***Completed***
***28 patients randomized***
*(some patients received several cycles at increased dose following observed clinical benefit)*

| # | Dose | Patients | DLT | |
|---|---|---|---|---|
| 1 | 0.9 mg/m$^2$ | 3 | 0 | |
| 2 | 1.8 mg/m$^2$ | 3 | 0 | |
| 3 | 3.6 mg/m$^2$ | 3 | 0 | |
| 4 | 6.0 mg/m$^2$ | 3 | 0 | |
| 5 | 9.0 mg/m$^2$ | 3 | 0 | |
| 6 | 12.0 mg/m$^2$ | 3 | 0 | |
| 7 | 16.0 mg/m$^2$ | 3 | 0 | |
| **8** | **21.3 mg/m$^2$** | **4** | **1** | **MTD 3D** |
| 9 | 28.3 mg/m$^2$ | 3 | 2 | |

**Step 2**

**MTD 14 DAYS**
**AB8939 alone**

***On-going***
***Near completion***

| # | Dose | Patients | DLT |
|---|---|---|---|
| 1 | 16.0 mg/m$^2$ | 7 | 1 |
| 2 | 21.3 mg/m$^2$ | On-going | |

**Step 3**

**MTD 14 DAYS**
**AB8939 Combination**

**Next Steps**

- **AB8939 + Venetoclax / Azacitidine**
- **AB8939 + Venetoclax + Azacitidine**

*Target Product Profile*

*Pharmacology Data*

*Phase 1 Preliminary Safety and Efficacy*

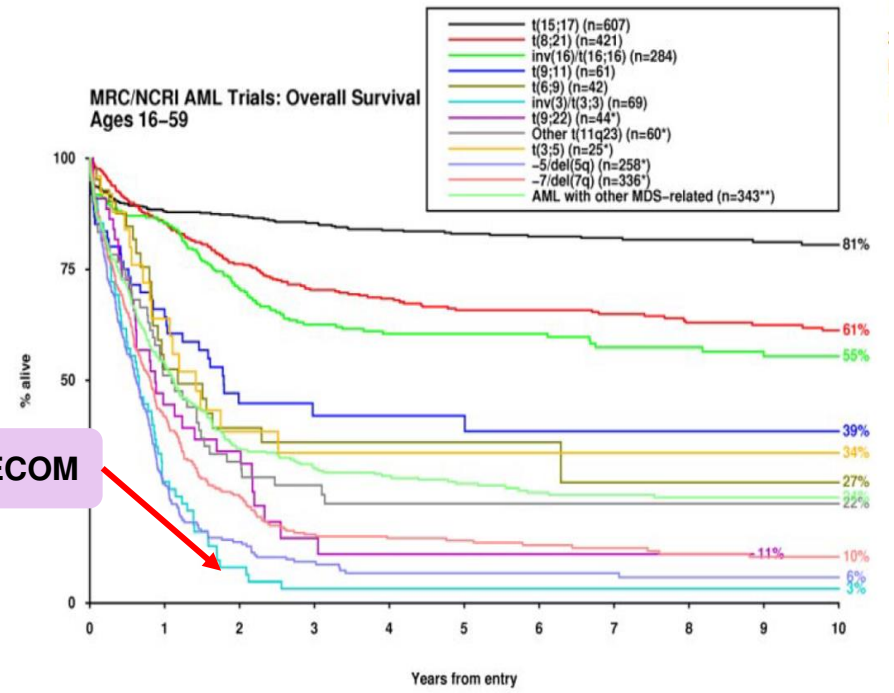
**Preliminary Activity in MECOM**

*Intellectual Property*

# MECOM is associated with a dismal outcome, with short survival and only 14% response rate[1] in relapsed or refractory setting

## AB8939 has shown activity on MECOM rearrangement, based on non-clinical data and early clinical data with 50% response rate observed

**Impact of cytogenetic entities recognized in 2008 WHO classification24 on survival .**




MECOM

*Excluding patients with t(15;17), t(8;21), inv(16), t(9;11), t(6;9),inv(3)/t(3;3).
**Excluding patients with any other abnormalities listed previously.

**Non clinical *in vitro* evidence**

- **50% response rate in *in-vitro* tests**

In-vitro, AB8939 was effective (IC50 of 50nM and 13nM) against 2 out of 4 patient blasts with MECOM rearrangement

| Drug sensitivity (IC50 µM) in MECOM Karyotype | | | | |
|---|---|---|---|---|
| Patient ID | AML type | AraC | AB8939 | Azacitidine |
| 1135 | M0 | >20 | >2 | 49,90 |
| 1156 | M0 | >20 | >5 | >50 |
| C1005 | M1 refractory | 4,1 | 0,05 | NT |
| C1012 | M4 refractory | 7,9 | 0,013 | 9,7 |

**Clinical evidence in MECOM**

- **50% response rate in early phase 1**

2 out of 4 patients with MECOM after 1 cycle of 3 days or 14 days AB8939 treatment below the MTD

| Patient ID | AB8939 | Best Response |
|---|---|---|
| ES-12-001 | 0,9 mg/m$^2$, 3 days | Early discontinuation |
| ES-07-001 | 1.8 mg/m$^2$, 3 days, | Response (BM blast from 55% to 5%) |
| ES-07-002 | 16 mg/m$^2$, 14 days | Stable disease |
| GR-04-001 | 16 mg/m$^2$,14 days | Response (BM blast from 13% to 3%) |

*Target Product Profile*

*Pharmacology Data*

*Phase 1 Preliminary Safety and Efficacy*

*Preliminary Activity in MECOM*

**Intellectual Property**

# 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. AB Science is the sole proprietary holder of AB8939 and its family of compounds

| Protection | Exclusivity period | Enforcement |
|---|---|---|
| Orphan drug status | 7-year protection as of FDA approval<br><br>10-year protection as of EMA approval | ▪ **Granted in the USA**<br>▪ To be filed with EMA |
| Composition of Matter patent | Until February 2036 | ▪ **Granted** (United States / Europe / China / Hong Kong / Japan / South Korea / India / Mexico / Israel / Brazil / South Africa / Russia / Australia) |
| Second Medical Use patent | Until February 2044 (if granted) | ▪ **PCT patent application** filed for AML subpopulation with chromosome abnormality |