



Corporate Presentation

July 2024

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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 : 588 707,03 (<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.

Next expected Milestones

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

The background of the slide is a microscopic image of cells. It features a dense population of cells with light blue, oval nuclei. Interspersed among these are several larger, more irregularly shaped cells with a pinkish-purple hue, possibly representing different cell types or a specific staining technique. The overall texture is granular and cellular.

MASITINIB PLATFORM

Masitinib Platform – Drug Profile

Orally-administered kinase inhibitor selectively targeting mast cells and macrophages

Masitinib targets mast cells

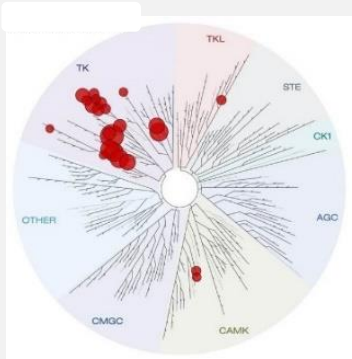
- Masitinib is a potent and selective inhibitor of c-Kit, Lyn, and Fyn kinases. These kinases play critical roles in the activation of mast cells
- Mast cells are a target in neurodegenerative diseases, inflammatory diseases and in oncology

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



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

Innate immune 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.*

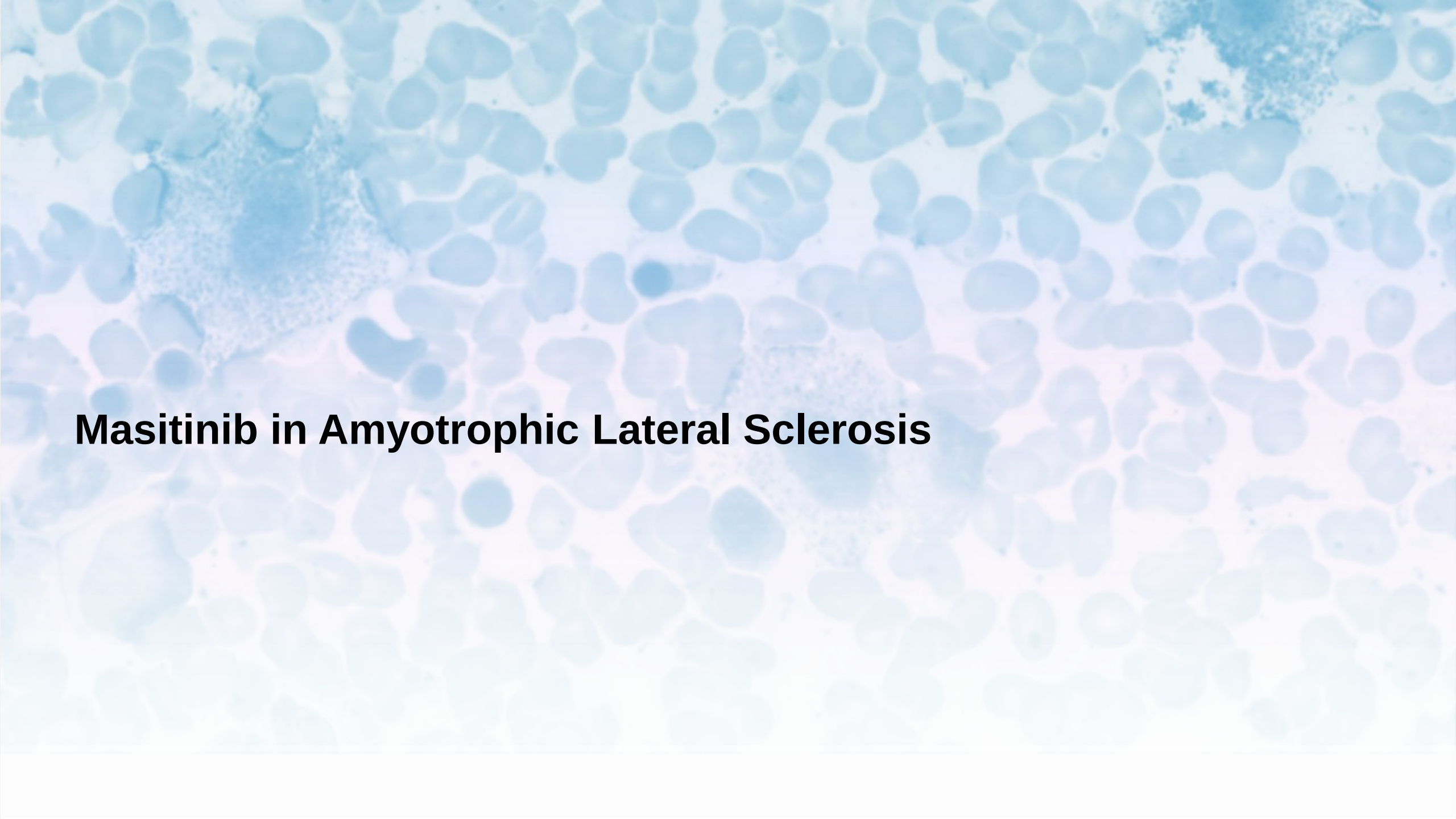
References

[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'*

The background of the slide is a microscopic image of tissue, likely a histological section. It shows numerous cells with prominent, dark blue nuclei and lighter blue cytoplasm and extracellular matrix. The cells are densely packed, and the overall color palette is dominated by various shades of blue and light purple, typical of hematoxylin and eosin (H&E) staining.

Masitinib in Amyotrophic Lateral Sclerosis

ALS - Status & Positioning

In ALS, no drug except riluzole has generated a consensus based on definitive evidence of efficacy, there is a need for combination of treatments due to the multifactorial nature of the disease

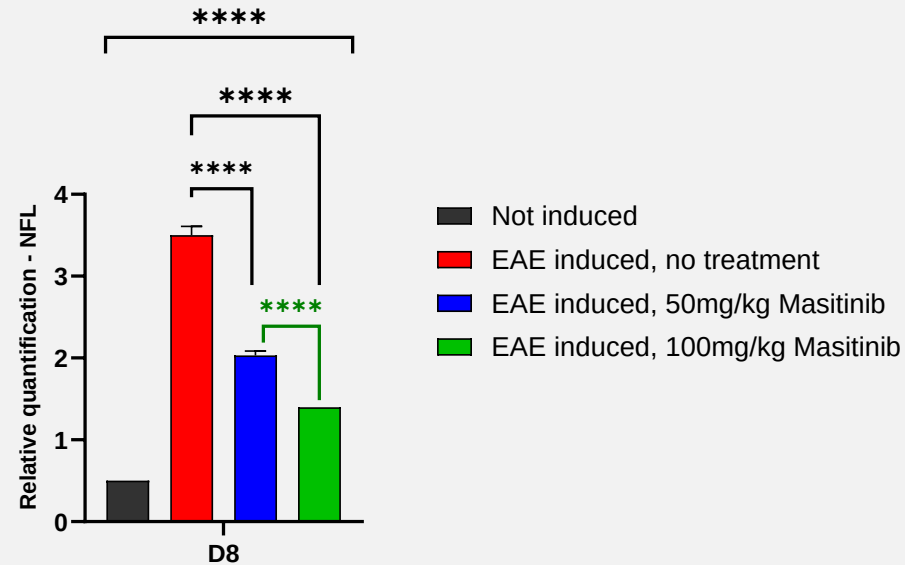
Drug	MA Holder / Sponsor	Mechanism of action	FDA Status	Heath Canada Status	EMA Status	Current clinical development
Riluzole	Generic	Unknow	Approved	Approved	Approved	None
Edaravone (IV/Oral)	Mitsubishi Tanabe	Anti-oxidative stress	Approved	Approved	Rejected	None
Edaravone (New Oral formulation)	Ferrer	Anti-oxidative stress	Failed phase 3			Stopped
AMX0035	Amylyx	Anti-apoptotic	Withdrawn	Withdrawn	Rejected	Failed confirmatory phase 3
Tofersen	Biogen	Gene therapy (familial 2% of patients)	Accelerated approval granted		CMA granted	Confirmatory phase 3 on-going
Masitinib	AB Science	Anti-inflammatory & immunomodulation (microglia & mast cells)	Not filed	NOC/c under reconsideration	CMA under review	Confirmatory phase 3 on-going

Multiple Sclerosis - Pharmacology

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

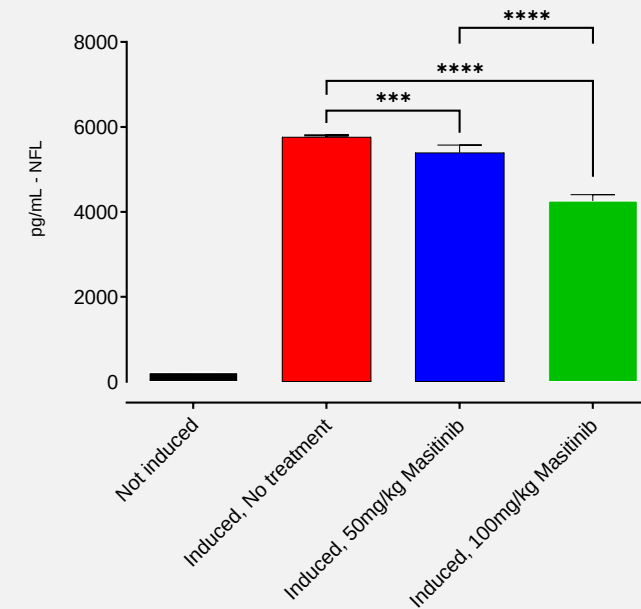
Day 8

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



Day 15

NFL quantification in serum pool from EAE induced mice at 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

Masitinib clinical development plan in ALS

The development program in ALS consists of AB10015 phase 2B/3 study (published) and AB19001 phase 3 confirmatory study

Phase	Study code	Design	Dose Tested	Primary endpoint	Patient target	Related publications
2B/3	AB10015 (NCT02588677)	Prospective, double-blind, placebo-controlled, parallel groups study	- Masitinib 3.0 mg/kg/day + Riluzole - Masitinib 4.5 mg/kg/day + Riluzole - Placebo + Riluzole	Change in the ALSFRS-R score at 48 weeks (Δ ALSFRS-R)	394	Mora, 2020 Mora, 2021
3	AB19001 (NCT03127267)	Prospective, double-blind, placebo-controlled, parallel groups study	- Masitinib 4.5 mg/kg/day + Riluzole - Masitinib 6.0 mg/kg/day + Riluzole - Placebo+ Riluzole	Change in the ALSFRS-R score at 48 weeks (Δ ALSFRS-R)	495	

Mora JS, et al. Amyotroph Lateral Scler Frontotemporal Degener. 2020;21(1-2):5-14

Mora JS, et al. Ther Adv Neurol Disord. 2021;14:17562864211030365

Phase 2B/3 – Design

Study AB10015 had broad inclusion criteria and evaluated masitinib after 48 weeks of treatment

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 (Δ ALSFRS-R)

Duration: 48 weeks

Main inclusion criteria

- 1) Probable, or definite ALS, sporadic or familial ALS, without restriction on baseline ALSFRS-R score
- 2) Stable dose of riluzole for at least 30 days prior to screening
- 3) Patients with disease duration $\leq$ 36 months
- 4) Patients with FVC $\geq$ 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
1	Normal Progressor; Masitinib 4.5 mg*
2	Normal Progressor; Masitinib 3.0 mg
3	Normal + Fast Progressors; Masitinib 4.5 mg
4	Normal + Fast Progressors; Masitinib 3.0 mg

*Primary Efficacy Population

Phase 2B/3 – Primary analysis

Masitinib (4.5) demonstrated a significant benefit in patients defined as Normal Progressors (ALSFRS-R progression of <1.1 point/ month), which was the population for primary analysis

Normal Progressor (Primary Efficacy Population): 27% slowing of functional deterioration

**Absolute change from baseline to week 48 in ALSFRS-R – Primary Efficacy
Analysis Masitinib 4.5 mg/kg/day – Normal Progressor**

Treatment group	LS Mean	Difference of means [95% confidence interval]	p-value
Active control	-12.63	3.39 [0.65;6.13]	0.0158
Masitinib 4.5 + riluzole	-9.24		

Sensitivity Analyses	Difference, [95% CI]	p-value
J2R Lack of Efficacy/ any AE	2.8 [0.15; 5.46]	0.0389
J2R Lack of Efficacy/ any AE/Travel	2.82 [0.16;5.48]	0.0376
J2R 'Full Penalty'	2.31 [-0.17;4.80]	0.0678
Tipping-Point analysis, 76% penalty	2.48 [0.00, 4.96]	0.0498
CIR 'Full Penalty'	2.67 [0.03 , 5.32]	0.0477

Phase 2B/3 – Secondary endpoint

The primary endpoint analyses were supported by multiple key secondary endpoints

Significant ALSAQ40 benefit based on the most conservative imputation methods

Masitinib 4.5 mg/kg/day – Normal Progressors

	Analysis	Difference, [95% CI]	p-value
ALSAQ-40	Multiple Imputation with J2R	-5.99 [-11.55;-0.44]	0.0343

There was a significant PFS benefit (+ 4 months) with a p=0.0159

Masitinib 4.5 mg/kg/day – Normal Prog. PFS analysis

Treatment group	N	Median months [95% CI]	Wilcoxon p-value
Placebo	113	16 [11; 19]	0.0159
Masitinib 4.5	105	20 [14; 30]	

Event Free Survival (EFS), defined as the earliest between progression, tracheostomy, ventilation, gastrostomy, or death event, remained statistically significant (p=0.01), showing a median benefit of +3 months

Masitinib 4.5 mg/kg/day – Normal Prog. EFS analysis

Treatment group	N	Median months [95% CI]	Wilcoxon p-value
Placebo	113	11 [10; 17]	0.0162
Masitinib 4.5	105	14 [12; 20]	

PTVGFS: Progression Tracheostomy Ventilation Gastrostomy Free Survival

CAFS is close to significance with P value = 0.07 although study was not designed for CAFS as a primary endpoint

Masitinib 4.5 mg/kg/day – Normal Prog. CAFS analysis

Treatment group	N	Mean Score	Difference of means	p-value
Placebo	113	100.77	14.95	0.0776
Masitinib 4.5	105	115.72		

Phase 2B/3 – Secondary endpoint – Overall Survival

There was a trend of + 6 month increase in median overall survival

OS analysis was performed, censoring placebo patients at the time they switched to masitinib treatment.

This retreatment is essential because OS was significantly improved for placebo patients who switched to masitinib 4.5mg/kg/day as compared with placebo patients who did not switch

Analysis of Overall survival (placebo switch vs no switch to masitinib)

Treatment group	N	Median months [95% CI]	Wilcoxon p-value
Placebo	53	62 [49; NE]	0.0367
Masitinib 4.5	25	69 [44; NE]	

Masitinib 4.5 mg/kg/day – Normal Prog. OS analysis (censoring of placebo patients at time of switch to masitinib - ITT)

With that retreatment, there was a trend in survival improvement (+ 6 months) with a p=0.0761

Treatment group	N	Median months [95% CI]	Wilcoxon p-value
Placebo	114	40 [30; 49]	0.0761
Masitinib 4.5	106	46 [33; 69]	



Consistency of treatment effect measure with ALSFRS-R, PFS, and OS

Phase 2B/3 – Subgroup Analysis “ALS prior to complete loss of function in any individual component of the ALSFRS-R



There was a disbalance in a subset of the study population (defined as patients with a complete loss of function in at least one individual component of the ALSFRS-R (i.e., a score of zero on any item)), because ALSFRS-R score was minimized but not stratified by category of severity

Distribution of patients with complete loss of function in at least one individual component of the ALSFRS-R in the primary analysis population

A greater proportion of patients with any complete loss of function were randomized in the masitinib arm (20%) as compared with the control arm (8%)

Normal Progressor	Placebo N=113	Masitinib 4.5 mg/kg/d N=105
ALS <u>with complete loss of function</u> in any individual component of the ALSFRS-R (score of zero on any item)	8.0%	20.0%

The disease severity in patients with any complete loss of function was higher in the masitinib arm

Population	Stat	Placebo	Masitinib 4.5 mg/kg/d
1 item with score 0	n [Q]	8 [8]	10 [10]
2 items with score 0	n [Q]	0	7 [10]
3 items with score 0	n [Q]	0	3 [9]
4 items with score 0	n [Q]	1 [4]	1 [4]
Total	n [Q]	9 [12]	21 [33]

The bracketed [Q] represents the number of items with a 0-score. Some patients (n) had a 0-score (Q) in more than one item

Phase 2B/3 – Subgroup Analysis “ALS prior to complete loss of function in any individual component of the ALSFRS-R

The treatment effect is clearly increased in patient prior to any complete loss of function, even when considering both normal and fast progressors

Differential treatment effect (M4.5 vs placebo)		Primary analysis Population (Normal Progressors)	Subgroup prior to any loss of function (Normal	Patients prior to any loss of function (Normal + Fast)
ΔALSFRS-R (CIR)	Diff. of mean	2.68	3.13	2.76
	p-value	0.0462	0.0308	0.0538
CAFS	Relative benefit	14.8%	20.2%	18.4%
	P-value	0.0776	0.0290	0.0346
ALSAQ-40 (CIR)	Diff. of mean	-6.04	-6.22	-6.74
	p-value	0.0305	0.044	0.0235
FVC (CIR)	Diff. of mean	5.85	7.59	7.79
	p-value	0.0931	0.0384	0.0369
Median PFS	Gain	+ 4 months	+ 9 months	+ 5 months
	Median [95% CI]	20 [14; 30] vs 16 [11; 19]	25 [17, NE] vs 16 [11, 19]	20 [14; 30] vs 15 [11; 19]
	p-value log rank	0.0159	0.0057	0.0183
Median OS (Long-term) (censoring of placebo at time of switch to masitinib)	Gain	+ 6 months	+ 12 months	+ 8 months
	Median [95% CI]	46 [33; 69] vs 40 [30; 49]	53 [36; NE] vs 41 [30; 54]	46 [30; 69] vs 38 [29; 49]
	p-value log rank	0.0761	0.0192	0.0684

Clinical data from the subgroup are exceptionally strong due to the consistency and magnitude of effect across endpoints

The CHMP confirmed that the safety of masitinib is deemed acceptable

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



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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 (Δ FS). This approach selects a more homogeneous primary efficacy population (“Normal Progressors”, Δ FS < 1.1 points/month) while concurrently permitting secondary assessment of the broader population. Primary endpoint was decline in ALSFRS-R at week-48 (Δ ALSFRS-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 Δ ALSFRS-R between-group difference (Δ LSM) 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 Δ LSM 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 Δ ALSFRS-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 Δ FS) 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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 *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

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Neurology Department

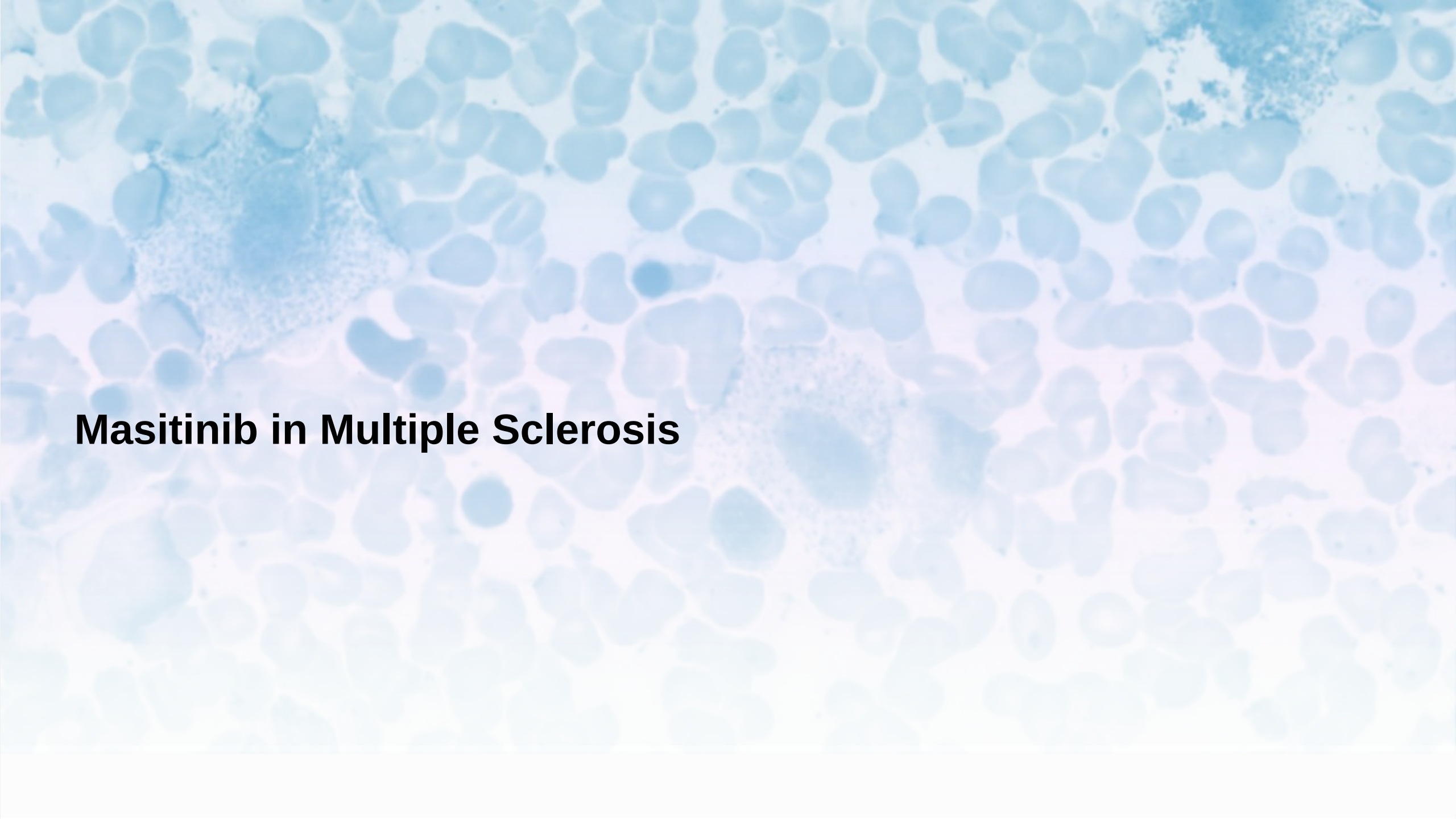
At this stage, negative opinion received on the application for conditional marketing authorization of masitinib in the treatment of ALS

Status with EMA

- EMA adopted a trending toward a negative opinion
- AB Science intends to request a re-examination

Status with Health Canada

- Health Canada has issued a Notice of Non-Compliance-Withdrawal (NON/w)
- AB Science submitted a Request for Reconsideration, which has been accepted



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 published¹
- Confirmatory phase 3 study is authorized by FDA and key European countries and to be started

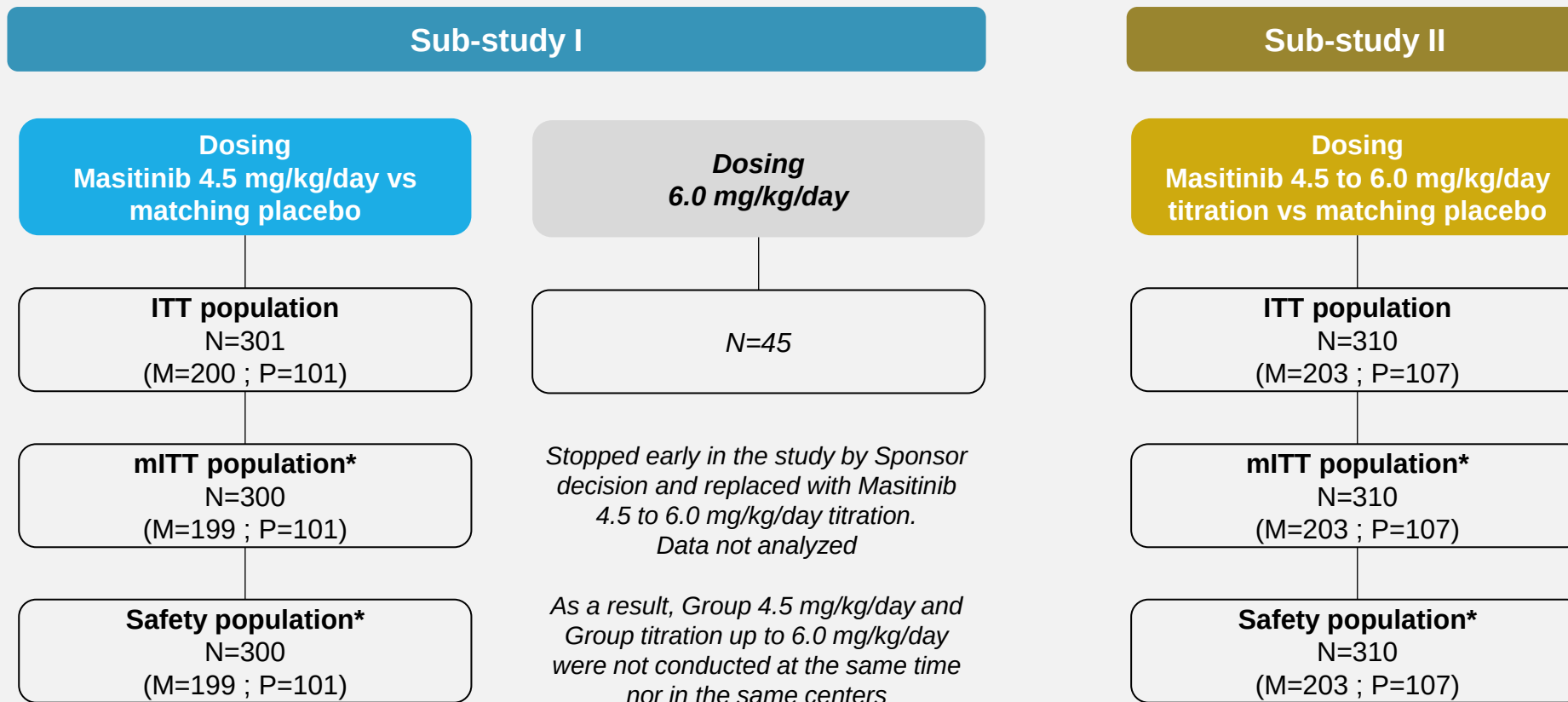
Masitinib Positioning

- 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 enrolled 656 patients

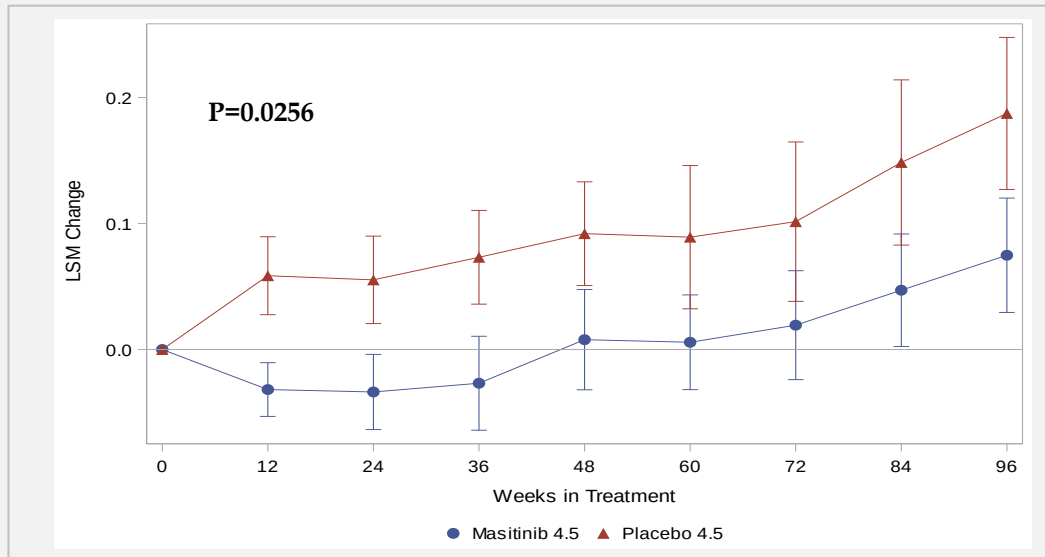


* All randomized patients (ITT) who took at least one dose of study treatment (masitinib/placebo).

Multiple Sclerosis – Phase 2B/3

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

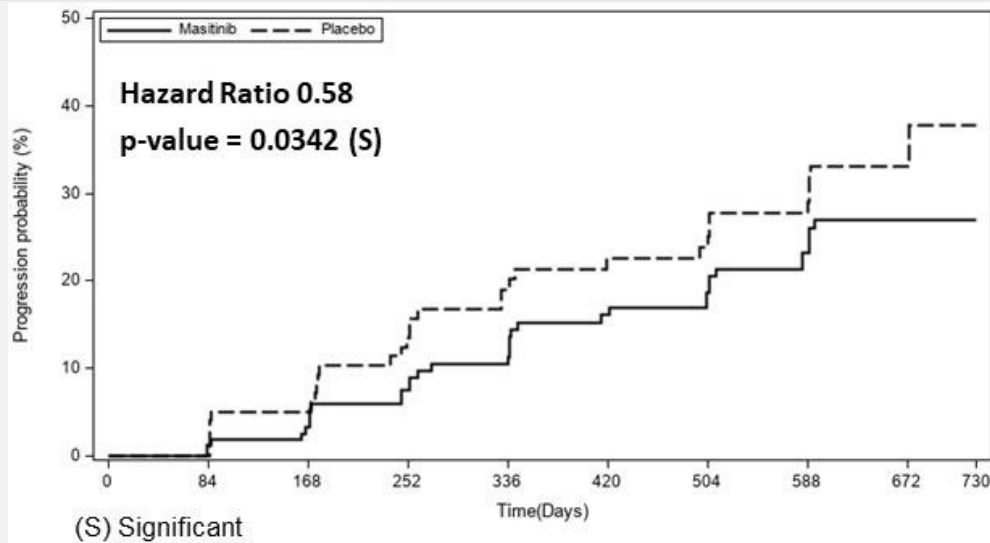
- Median age (years) : 50.0 (both masitinib and placebo)
- Median duration of first MS Symptom (yrs) : 12.4 masitinib and 12.2 placebo
- Median EDSS Score : 5.5 (both masitinib and placebo)
- % of patients with EDSS score of 6 : 49.0% masitinib and 47.5% placebo

* Change in EDSS

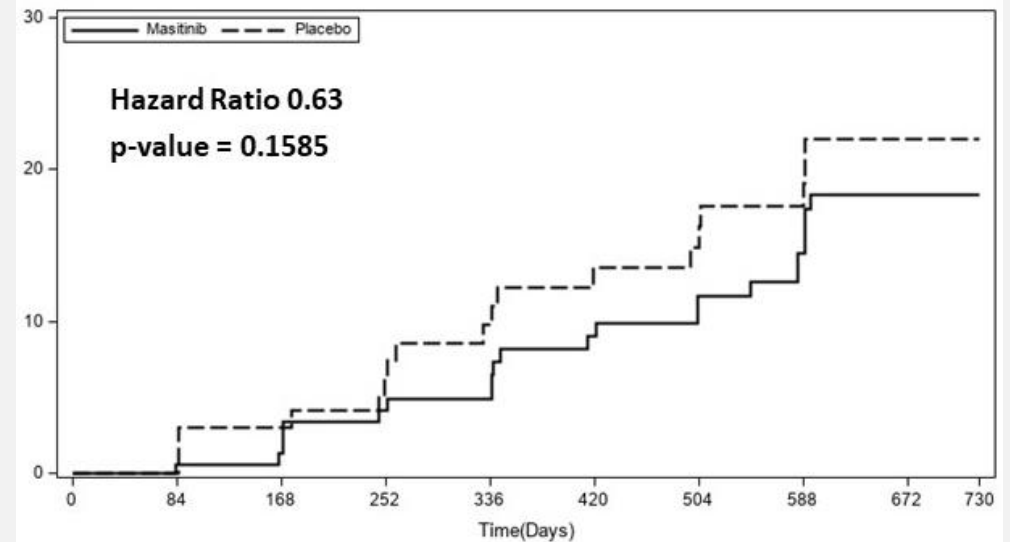
Multiple Sclerosis – Phase 2B/3

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 (effect driven by 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

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, Luis 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

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

Correspondence
Dr. Vermersch
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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

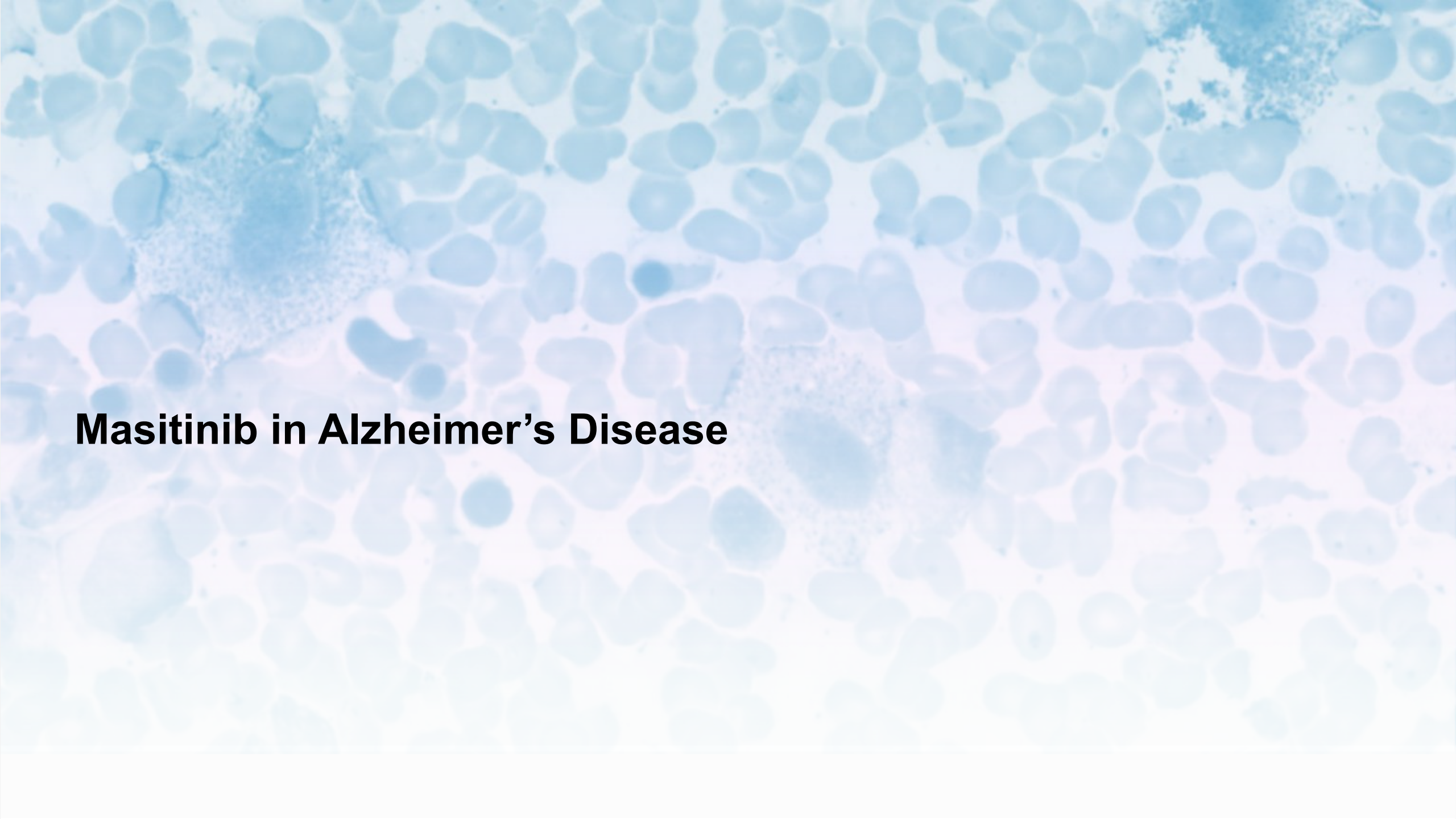
A total of 611 patients were randomized; 301 in the masitinib 4.5 mg/kg/d parallel group and 310 in the uptitrated masitinib 6.0 mg/kg/d parallel group. Masitinib (4.5 mg/kg/d) ($n = 199$) showed significant benefit over placebo ($n = 101$) according to the primary end point, 0.001 vs 0.098, respectively, 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](https://npub.org/coe)

The background of the slide is a microscopic image of cells, likely from a blood smear or tissue section. It features numerous light blue, oval-shaped cells with thin borders, densely packed together. There are also some darker, more irregularly shaped cells and clusters of cells, particularly in the upper left and lower right areas, which might represent different types of cells or pathological changes. The overall color palette is a range of light blues and whites.

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 published¹
- 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 2030²
- 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 enrolled 718 patients from 118 sites in 21 countries

Sub-study I

Dosing
3.0 mg/kg/day

N=58

*Stopped early in the study upon IDMC recommendation.
Data not analyzed*

*N= 58 is masitinib treated patients.
Placebo treated patients are analyzed
as part of the placebo arm versus
masitinib 4.5 mg/kg/day*

Dosing
Masitinib 4.5 mg/kg/day vs
matching placebo

ITT population
N=370
(M=185 ; P=185)

Safety population
N=368
(M=185 ; P=183)

Full Analysis Set
N=358
(M=182 ; P=176)

Dosing
6.0 mg/kg/day

N=12

*Stopped early in the study by Sponsor decision and replaced with Masitinib 4.5 to 6.0 mg/kg/day titration.
Data not analyzed*

As a result, Group 4.5 mg/kg/day and Group titration up to 6.0 mg/kg/day were not conducted at the same time nor in the same centers

Sub-study II

Dosing
Masitinib 4.5 to 6.0 mg/kg/day
titration vs matching placebo

ITT population
N=278
(M=186 ; P=92)

Safety population
N=278
(M=186 ; P=92)

Full Analysis Set
N=277
(M=186 ; P=91)

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)

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)		

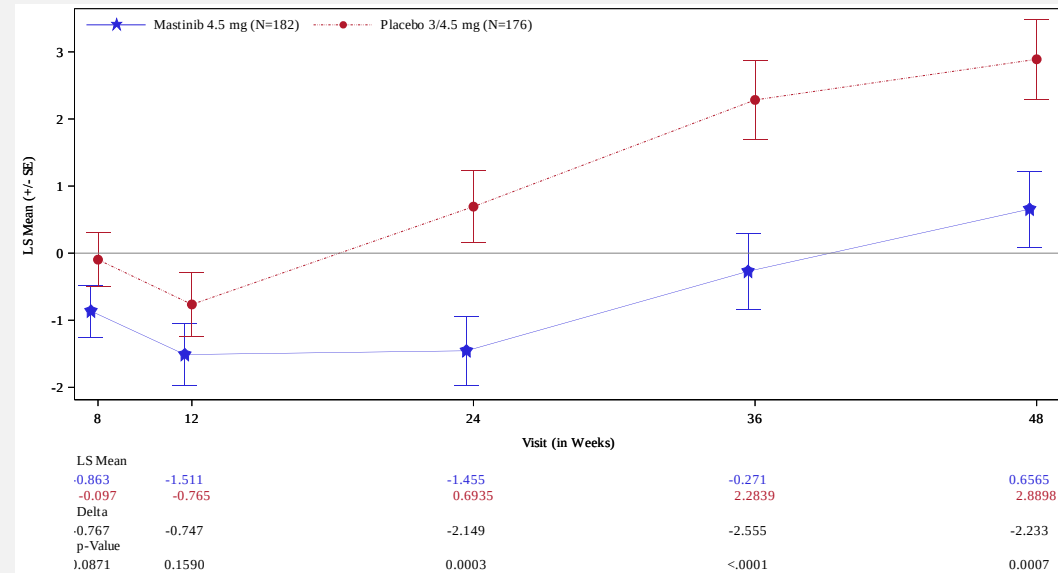
Clinically relevant
benefit because on top
of standard of care
(memantine &
anticholinesterase)

AD – Phase 2B/3

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)



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

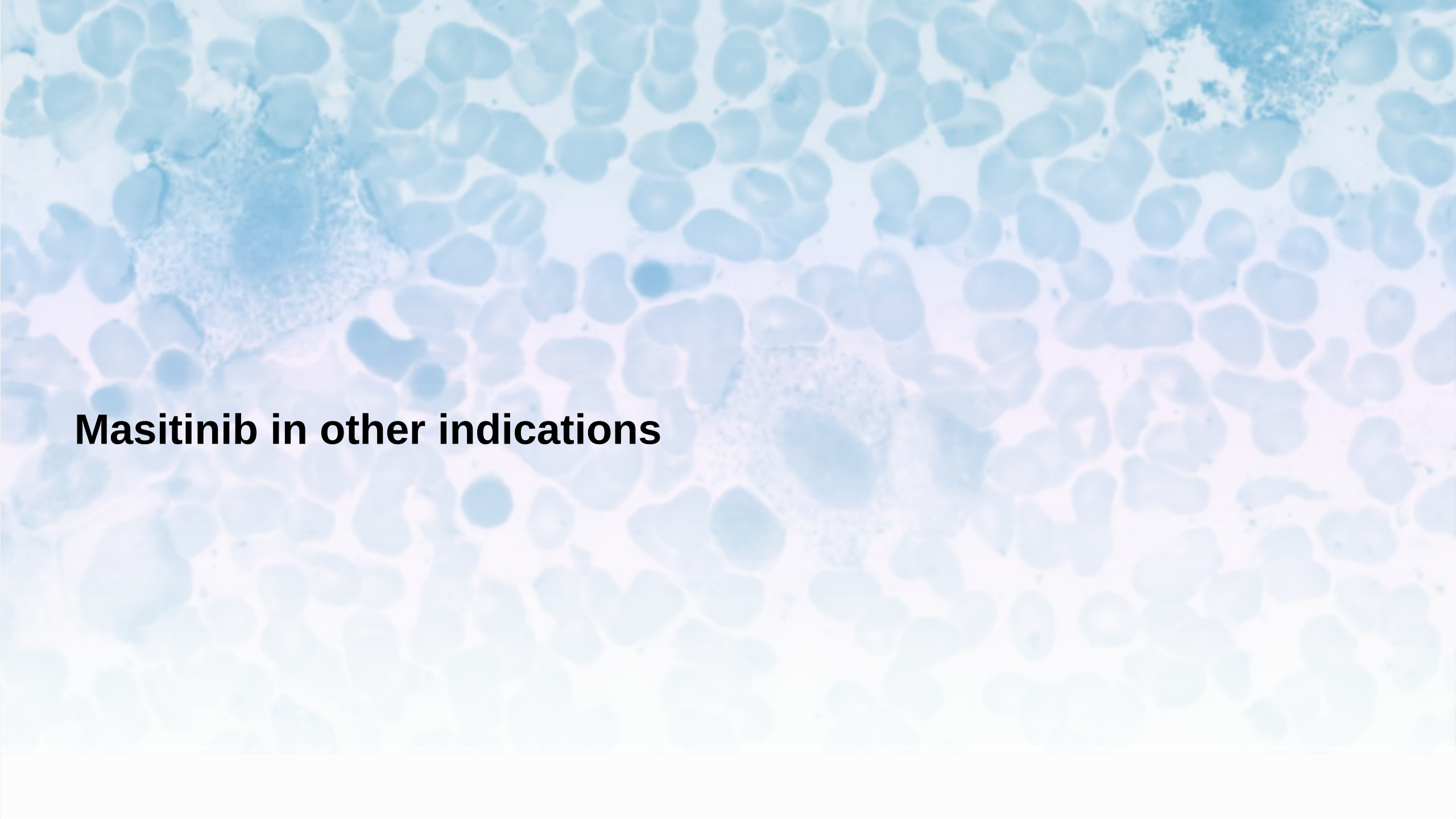
Bruno Dubois^{1*}, Jesús López-Arrieta², Stanley Lipschitz³, Doskas Triantafyllos⁴, Luiza Spiru^{5,6}, Svitlana Moroz⁷, Olena Venger⁸, Patrick Vermersch⁹, Alain Moussy¹⁰, Colin D. Mansfield¹⁰, Olivier Hermine^{10,11,12*}, Magda Tsolaki¹³ for the AB09004 Study Group Investigators

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.

The background of the slide is a microscopic image of a tissue sample, likely a bone marrow smear. It shows numerous cells with large, round, blue-stained nuclei and some lighter, granular cytoplasm. There are also some darker, more densely stained areas, possibly representing clusters of cells or specific cellular components. The overall color palette is dominated by light blue and white, with some darker blue and pinkish tones.

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 to unresolved **safety challenges** (chemotherapy pre-treatment, associated with long hospitalization, risk of infection, risk of reprotoxicity), 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] Jastania 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

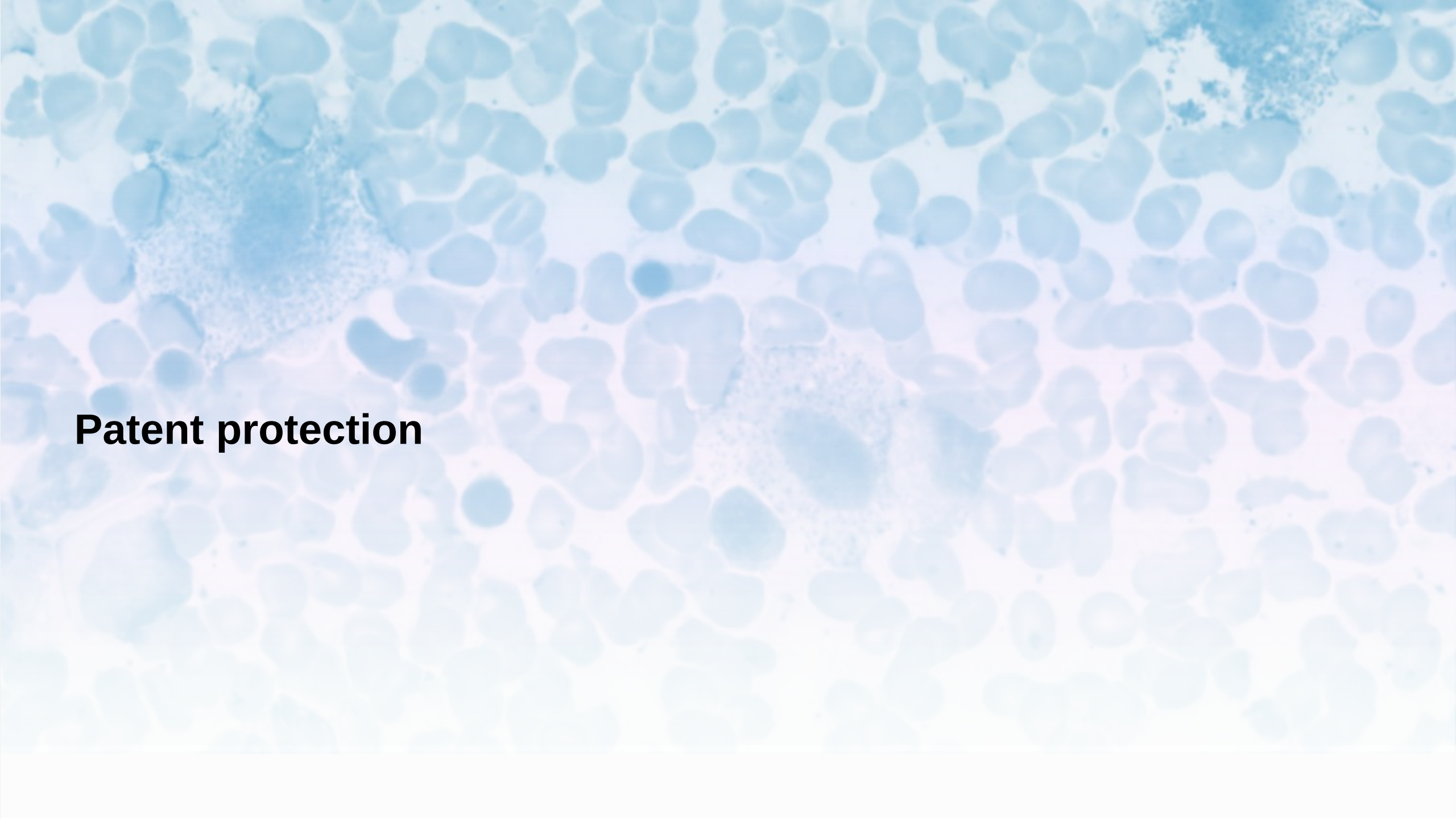
Phase 2 Objectives

- 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

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

The background of the slide is a microscopic image of cells. It features a dense population of cells with light blue, oval-shaped nuclei. Interspersed among these are several larger cells with more prominent, darker blue nuclei and some pinkish cytoplasm or surrounding medium. The overall texture is granular and cellular.

Patent protection

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

The background of the slide is a microscopic image showing a dense population of cells. Most cells are stained a light blue color, while others are stained a light pink color. The cells appear to be of various sizes and shapes, typical of a blood smear or a tissue section. The text "AB8939 PLATFORM" is centered over the image in a bold, black, sans-serif font.

AB8939 PLATFORM

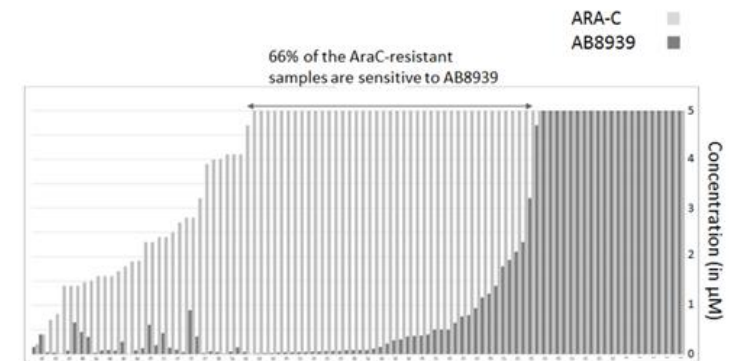
AB8939 has the potential to improve AML treatment based on its original mechanism of action

Scientific rationale

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

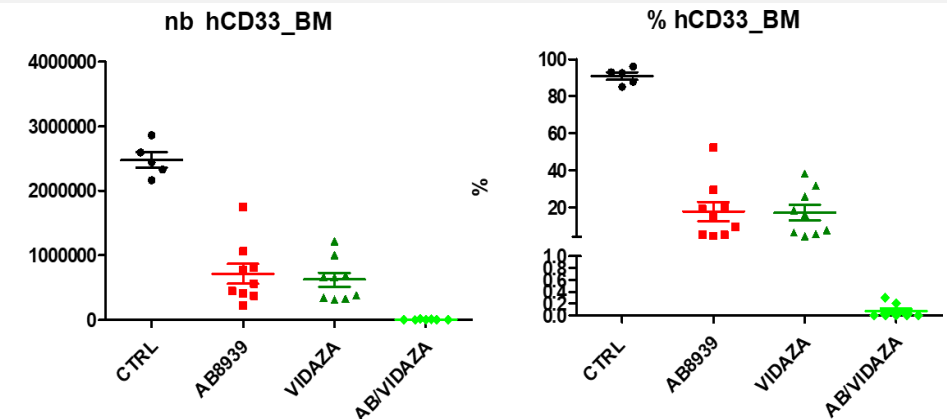
Ex-vivo data

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



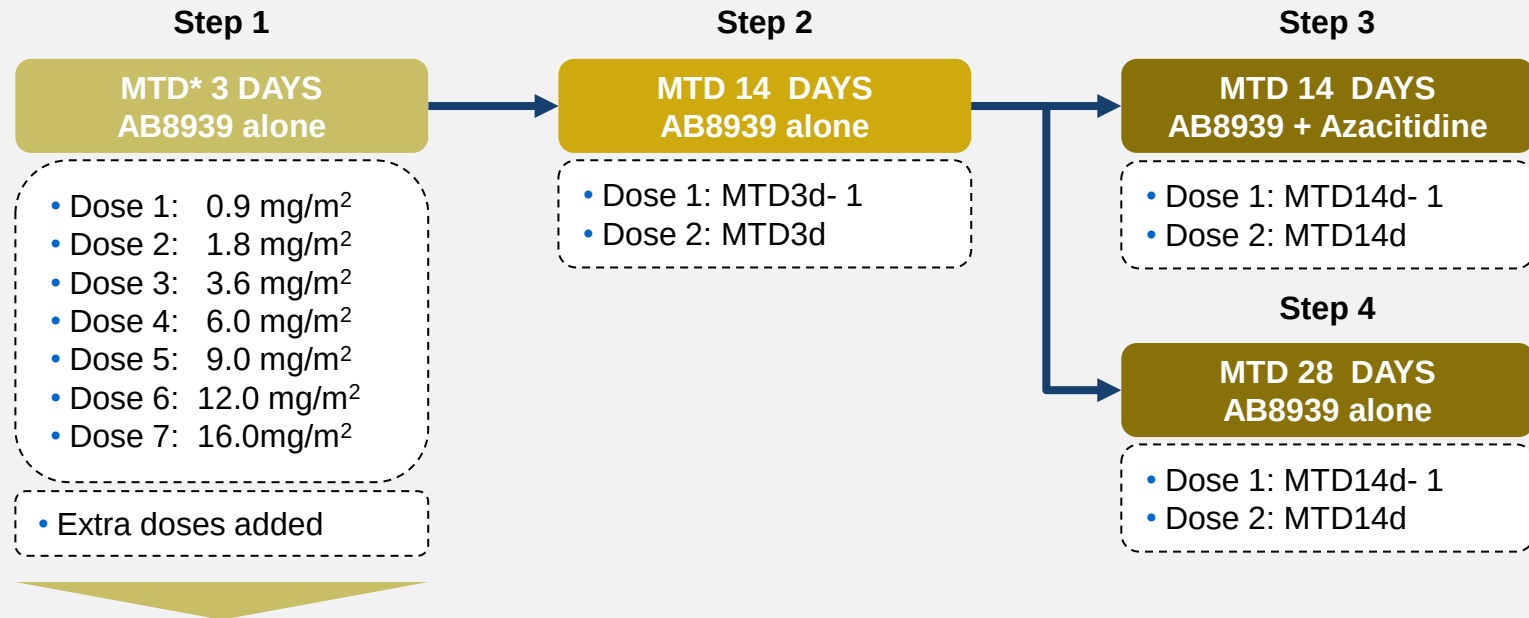
In-vivo data

- 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

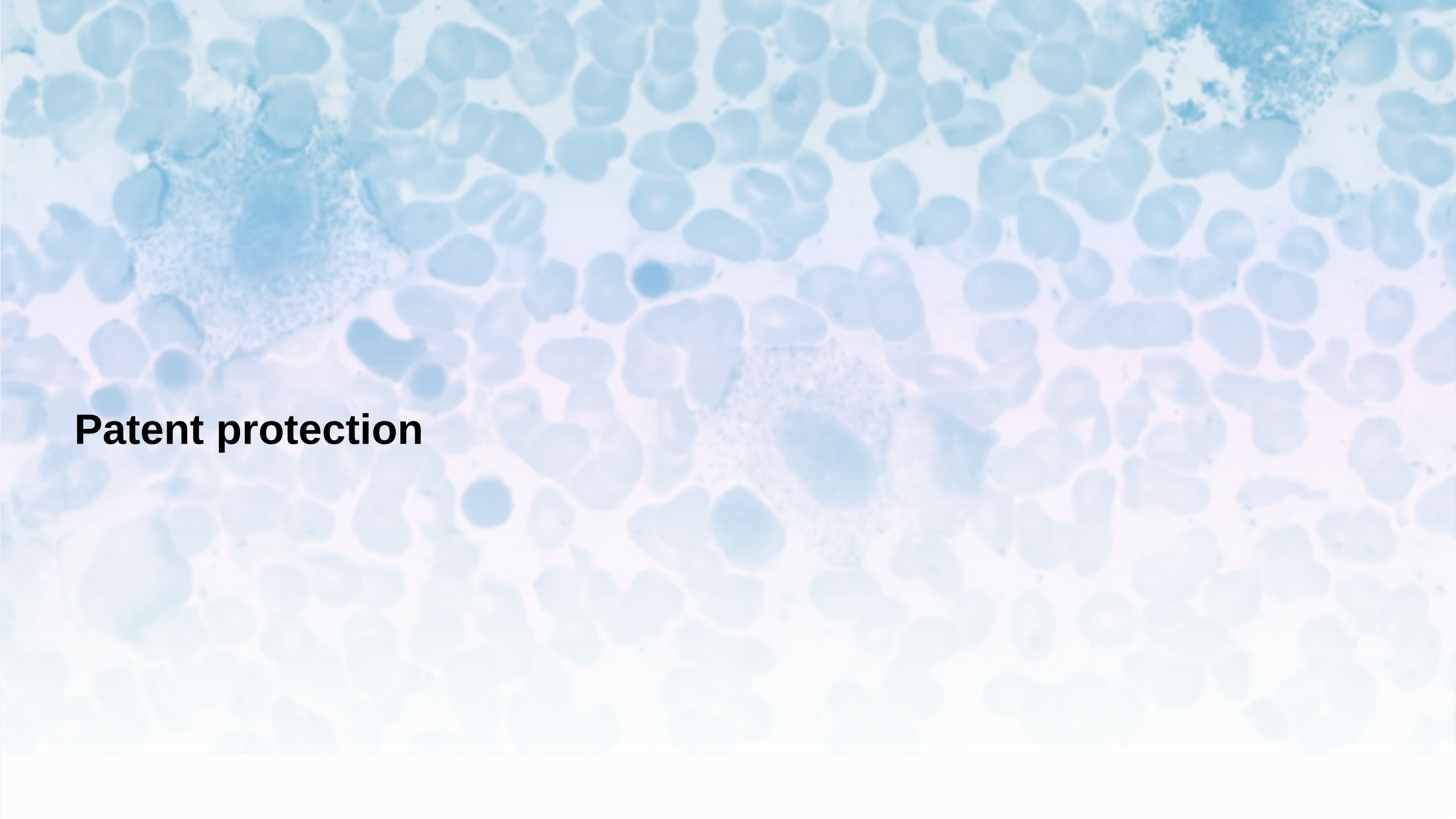
MTD has been reached in Step 1 of Phase 1 and key agencies have authorized to proceed with Step 2



- 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

The background of the slide is a microscopic image showing a dense population of cells. Most cells are stained a light blue color, while others are stained a light pink color. The cells vary in shape and size, with some appearing more rounded and others more elongated. The overall texture is granular and complex, typical of a histological or cytological preparation.

Patent protection

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