

Web-Conference Clinical Development Update

January 2025

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The background of the slide is a microscopic image of a cell culture. It shows a dense population of cells, likely fibroblasts, with a light blue/purple hue. The cells are mostly rounded and have a granular appearance. There are several distinct clusters or islands of cells, particularly in the upper left and lower right areas, which are more densely packed than the surrounding monolayer. The overall texture is somewhat irregular and porous.

MASITINIB PLATFORM

Masitinib's dual-targeting strategy, targeting mast cells and microglia/macrophages, is uniquely positioned to realize this therapeutic potential in neurodegenerative diseases



- **AB Science was the pioneer in discovering the role of the innate immune system in Neuro-Degenerative Diseases (NDD)**
- **Today, microglia and mast cells, two critical cells of the innate immune system, are at the cutting edge of research regarding NDDs, with a consensus that drugs aimed at these targets will have strong therapeutic potential**
- **Masitinib has demonstrated neuroprotective benefits in three challenging NDDs, Amyotrophic Lateral Sclerosis (ALS), Alzheimer's Disease (AD) and progressive forms of Multiple Sclerosis (MS), contributing to the demonstration that targeting microglia and mast cells is a valid clinical strategy**
- **Masitinib, a phase 3 clinical asset, is a credible drug candidate for ALS, AD and progressive MS**

[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.



Masitinib in Amyotrophic Lateral Sclerosis

In ALS, all recent studies failed and Masitinib is now the most advanced compound in clinical development

Drugs Approved in US or EU

Drug	Sponsor
Riluzole	Generic
Radicava /Edaravone	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
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- 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

Edaravone (New Oral formulation)	Ferrer
Relyvrio/Albrioza	Amylyx
TUDCA (Tauroursodeoxycholic Acid)	Academic Consortium
RIPK1 (SAR443820)	Sanofi / Denali Therapeutics
DNL343 (eIF2B Agonist)	Denali Therapeutics
Utreloxastat	PTC Therapeutics
Reldesemtiv	Cytokinetics



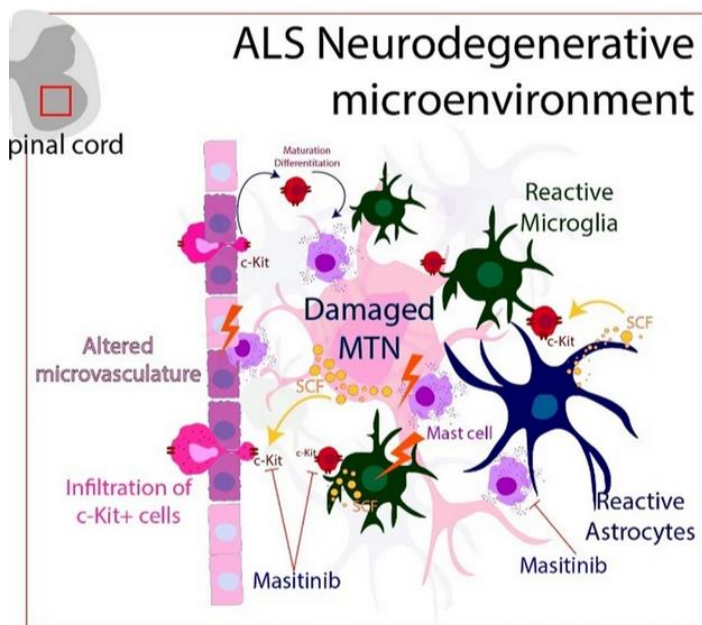
Mid/Late-stage programs failed

Masitinib has a unique and innovative mechanism of actions acting in the innate immune system, as demonstrated in several peer-reviewed journals

There is a Strong Scientific Rationale

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

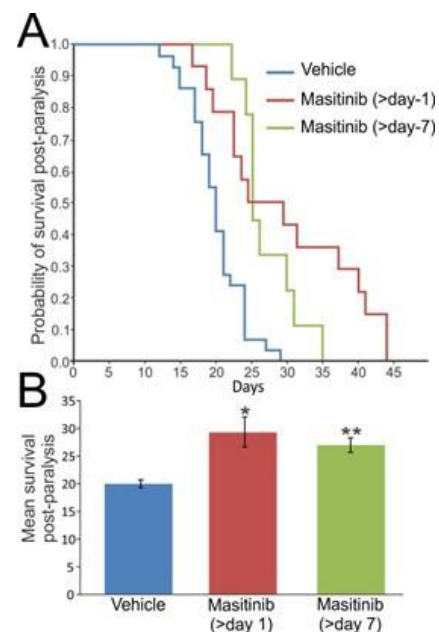
Masitinib exerts a protective effect on the peripheral nervous system by targeting mast cells



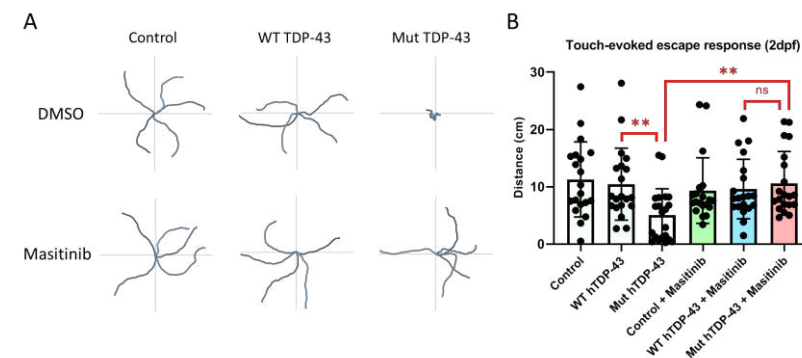
Díaz-Amarilla P., et al., Proc Natl Acad Sci U S A. 2011 Nov 1;108(44); Trias, E., et al., JCI Insight, 2017. 2(20); Trias, E., et al. J Neuroinflammation, 2016. 13(1): p. 177; Trias, E., et al., JCI Insight. 2018. 3(19).

There is a Well Demonstrated Mechanism of Action

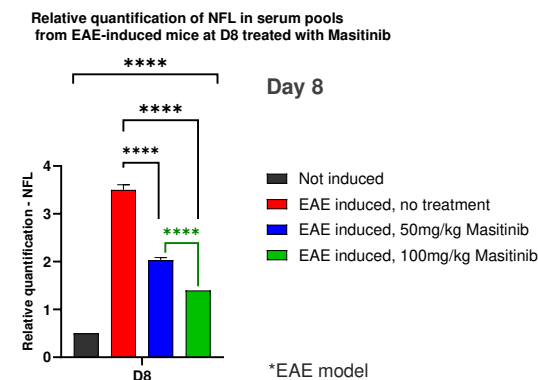
Masitinib treatment initiated 7 days after paralysis onset prolonged survival by 40 % in in SOD1 model



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*



Phase 2B/3 (AB10015) generated consistent results in the primary analysis population, slowing down functional decline at week 48 based on non-LOCF methods



Change from baseline to week 48 in ALSFRS-R (primary endpoint)	Rule for Imputation of Missing Data	Primary Analysis Population (Normal Progressors ; M4.5 vs P)		Reduction in slope
LOCF method (Primary Analysis)	Last observation collected is carried forward to week 48 timepoint	Diff. of mean	3.39	27%
		p-value	0.0157	

mITT population. N= 113 (placebo) and 105 (Masitinib 4.5 mg/kg/day)

Change from baseline to week 48 in ALSFRS-R (primary endpoint)	Rule for Imputation of Missing Data	Primary Analysis Population (Normal Progressors ; M4.5 vs P)		Reduction in slope
Copy Increment in Reference - CIR	<ul style="list-style-type: none"> CIR assumes progressive return to placebo at the time of discontinuation CIR is adapted to disease modifying treatment 	Diff. of mean	2.67	20%
		p-value	0.0462	
Jump to Reference Analysis (JTR) for discontinuations due to Lack of Efficacy/ Toxicity/Travel	<ul style="list-style-type: none"> JTR gives 2 penalties: i) a brutal alignment to placebo at the time of discontinuation, ii) then to follow the slope of placebo JTR is adapted to symptomatic treatment 	Diff. of mean	2.82	21%
		p-value	0.0372	

mITT population. N= 113 (placebo) and 105 (Masitinib 4.5 mg/kg/day)

There was a disbalance in a subset (14%) of the study population (defined as patients with a complete loss of function in at least one individual component of the ALSFRS-R)

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

When analyzing study AB10015 without this bias, 86% of the patient remains for which there is an optimum benefit across all endpoints

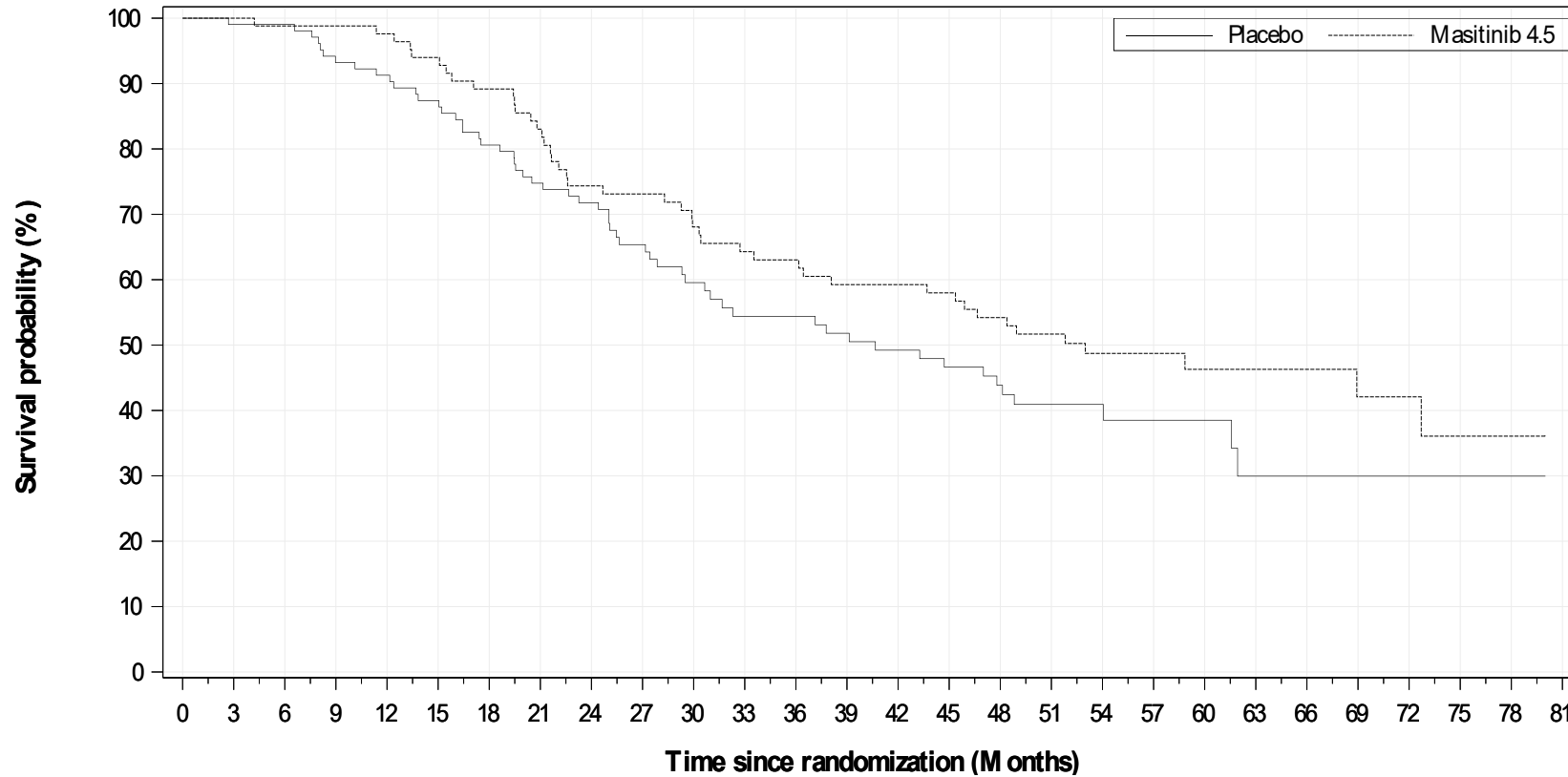
Differential treatment effect in the subgroup 'patients with ALS prior to any loss of function' as compared with the primary efficacy population

		AB10015 Primary Analysis Population (Normal Progressors)	AB10015 Patients with ALS prior to any loss of function (Subgroup)
ΔALSFRS-R (primary endpoint) (mLOCF – primary 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	2.67	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
ALSAQ-40 (CIR)	Diff. of mean	-6.04 [-11.51;-0.57]	-6.22 [-12.27;-0.17]
	p-value	0.0305	0.044
FVC (CIR)	Diff. of mean	5.85 [-0.98;12.67]	7.59 [0.41;14.77]
	p-value	0.0931	0.0384
Median PFS	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

Population consistent with masitinib mechanism of action, which is not expected to regenerate motor-neurons

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

Overall Survival - KM Curves - Patients prior to any complete loss of function - Masitinib 4.5 vs placebo



Analysis

Prior to any complete loss of function

(subgroup, ALSFRS>0 on any item), Masitinib 4.5 vs placebo

OS analysis from baseline (censoring of placebo patients at time of switch to Masitinib)

**Gain in OS
Median [95% CI]**

+ 12 months
53 [36; NE] vs 41 [30; 54]

**p-value log
rank**

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

EMA decision not to grant conditional marketing authorization based on result from first study AB10015 does not affect the pathway to registration for masitinib in ALS

Data are Robust despite Negative Opinion for Conditional marketing authorization

- Study AB10015, as a single pivotal study, is not enough to register conditionally
- Study AB10015 is considered as hypothesis generating study
- Masitinib safety is deemed acceptable by EMA for ALS indication

- Study AB10015 has generated strong hypothesis for confirmatory study
- Registration will be based on the result of phase 3 confirmatory study

AB19001 study is slow to recruitment due to design features. Instead of amending the study, FDA and EMA recommend the initiation of a new study

Main Obstacles

- 3 months run-in period before randomization without investigational treatment in order to exclude fast progressors, making recruitment very difficult
- Moderate ALS only (Baseline functional score ≥ 2 on each ALSFRS-R items)
- No concomitant treatment with edaravone approved in the USA and Relyvrio previously approved in the USA, making recruitment in the USA very difficult
- Blinded Extension at week 48, preventing access to active treatment upon completion of the protocol period, making recruitment more difficult
- 2 masitinib doses tested, 4.5 mg/kg/day (Confirmatory) and 6.0 mg/kg/day (exploratory)

AB Science discussed with FDA and EMA the possibility to amend the protocol in order to remove these four obstacles

FDA and EMA recommend the initiation of a new study

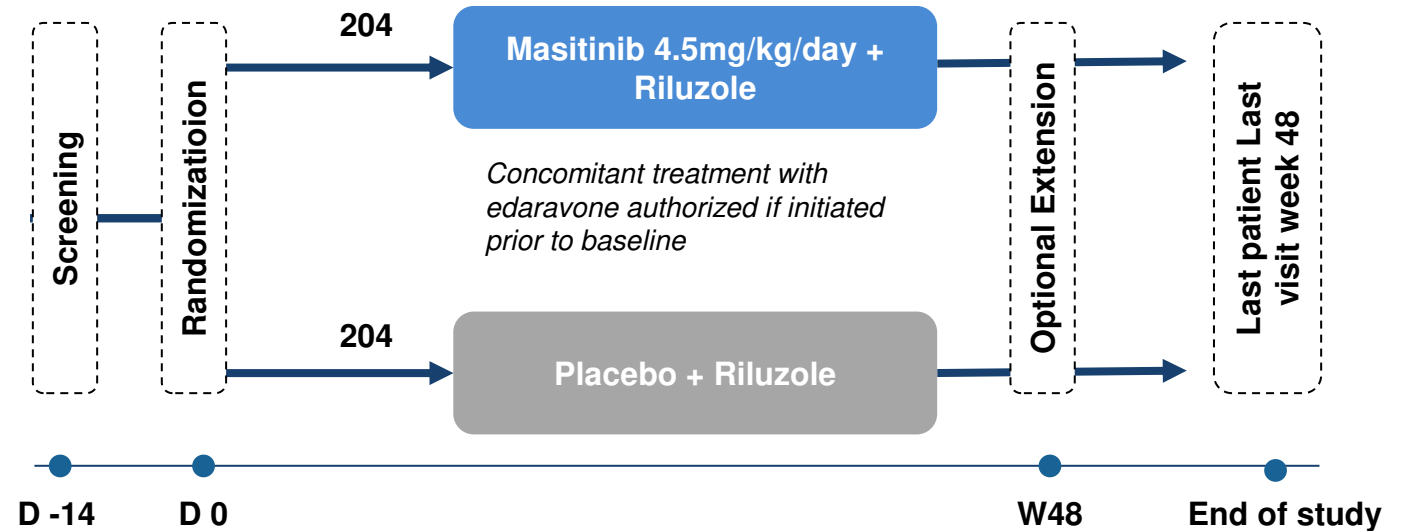
AB Science is following FDA and EMA recommendation

AB Science is following the recommendation from EMA and FDA and will launch a new confirmatory study AB23005



Main Changes

- No run-in period
- Moderate + Severe ALS (Baseline functional score ≥ 1 on each ALSFRS-R item)
- Authorized concomitant treatment with Edaravone in the USA and riluzole
- Open label Extension at week 48
- Testing of 4.5 mg/kg/day dosing only
- 408 patients, randomization 1:1



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

The design of the new confirmatory study is optimized based on hypotheses generated with phase 2B/3 and will enroll patients prior to loss of function and excluding fast progressors in order to maximize efficacy

Limitations identified in AB10015 study

Study AB10015 excluded Fast Progressors through protocol amendment

Study AB10015 included patients with loss of function*

Study AB10015 had no stratification on baseline severity, only minimization

Optimizations made on AB23005 study

Exclusion of Fast progressors is pre-specified

Exclusion of patients with loss of function*

Stratification based on baseline ALSFRS-R

* Patients with a score of 0 on at least one of the 12 items of the ALSFRS-R score

The design is also optimized based on conservative sample size assumptions for CAFS as primary endpoint for FDA SAP

Study AB10015 was not powered for CAFS but there was a trend of treatment effect

CAFS	Primary Analysis Population (Normal Progressors)
Relative benefit	+ 14.8%
P-value	0.0776



Significant effect on CAFS achieved with patients prior to loss of function (n=92)

CAFS	Patients with ALS prior to any complete loss of function
Relative benefit	+ 20.2%
P-value	0.0290

Optimization

Sample size 2x greater than the minimum required for the same treatment effect

- For the AB10015 study, statistical significance was achieved in normal progressors prior to loss of function using 92 patients per arm
- By contrast, study AB23005 will include 204 patients per arm

Treatment effect assumption lower than actually achieved for CAFS

- In study AB10015, the CAFS relative benefit for normal progressors prior to complete loss of function was 20.2%
- In contrast, AB23005 sample size is based on a relative benefit in CAFS of 14%, which corresponds to what was observed for the normal progressor population in study AB10015

The new confirmatory phase 3 study has been discussed with FDA and EMA and approved, securing the pathway to registration

Phase 3 approval

- Phase 3 design discussed and approved by FDA and EMA
- Phase 3 study submitted and approved by FDA
- Phase 3 study submitted to EMA's Clinical Trials Information System (CTIS) and approved
 - CTIS provides harmonized assessment of clinical trials in the European Union
 - Harmonized protocol has been approved (step 1)
- Once new confirmatory phase 3 is approved, study AB19001 will become supportive and exploratory for dose-range evaluation



Benefits

- It is essential for potential partners that we follow agencies recommendations
- Securization of the pathway to registration with a design validated by FDA and EMA
- Phase 3 study much easier to enroll
- Possibility for the potential partner to execute the phase 3 from the start

The feasibility shows enrolment of 683 patients from 86 sites per 12-month period. Confirmatory study plans to enroll 400 patients which can be done in less than 12 months

With 400 patients to enroll, study can be completed in 24 months

- 12 months enrolment
- 12 months treatment period

Study completion feasible within 2 years

Pre-selected sites in retained countries		
	Number of Sites	Enrolment per 12 Month
USA	36	262
EU	43	352
Belgium	1	10
Denmark	1	7
France	6	21
Germany	8	82
Greece	3	36
Italy	13	123
Latvia	1	7
Norway	1	10
Portugal	1	6
Slovenia	1	5
Spain	5	34
Sweden	2	11
Other Non EU	6	57
Argentina	5	47
Serbia	1	10
Total	85	671

A microscopic image of brain tissue stained with a blue dye, likely hematoxylin. The image shows a dense population of cells with prominent nuclei. In the center, there is a distinct, darker blue, irregularly shaped area that appears to be a lesion or a region of abnormality. The overall texture is granular and cellular.

Masitinib in Multiple Sclerosis

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 <i>(Estimated Nbr of patients Europe + USA)</i>		15% <i>(~ 150 000)</i>	35% <i>(~ 350 000)</i>	10% <i>(~ 90 000)</i>	40% <i>(~ 400 000)</i>	
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**

*: Non-active SPMS is a stage of MS that follows relapsing-remitting multiple sclerosis and that is characterized with an EDSS score progression ≥ 1 point without any relapse in the last 2 years.

Masitinib has a unique and innovative mechanism of actions acting in the innate immune system, as demonstrated in several peer-reviewed journals

There is a Strong Scientific Rationale

The innate immune system can play a critical role in the progressive forms of MS

- Progressive forms of MS (PPMS and non active SPMS) are predominantly driven by self-perpetuating innate immunity-related inflammation that has become contained within the CNS [1-5].
- Microglia and mast cells are types of innate immune cells present in the CNS that are strongly associated with pathophysiology of MS [6-8].
- Targeting innate immunity-related MS disease progression via modulation of mast cells and activated macrophage/microglia may slow or prevent worsening of disability in progressive MS.

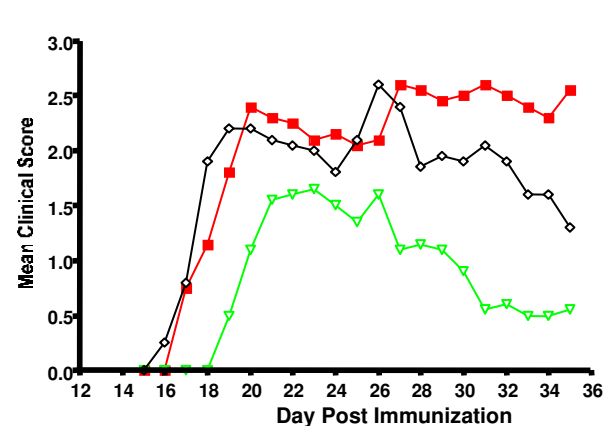
References

[1] Stys PK, et al. F1000Res. 2019;8:F1000 Faculty Rev-2100; [2] Hendriksen E, et al. Neurosci Biobehav Rev. 2017 Aug;79:119-133; [3] Fani Maleki A, et al. Front Cell Neurosci. 2019;13:355; [4] Skaper SD, et al. Front Cell Neurosci. 2018;12:72; [5] Skaper SD, et al. Immunology. 2014 Mar;141(3):314-27; [6] Brown MA, et al. Front Immunol. 2018;9:514; [7] Jones MK, et al. Front Cell Neurosci. 2019 Apr 30;13:171; [8] Luo C, et al. Neuropsychiatr Dis Treat. 2017 Jun 26;13:1661-1667

masitinib has a Well Demonstrated Mechanism of Action

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)

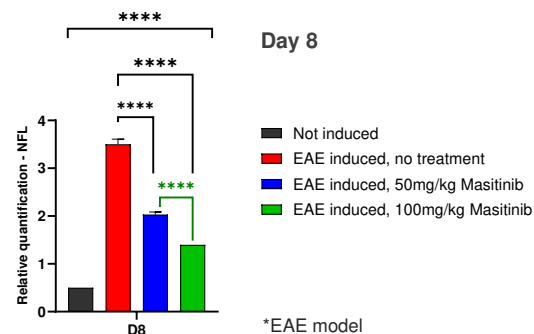
Mice were scored daily by visual assessment of symptoms on a scale of 0-5 where:

- 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

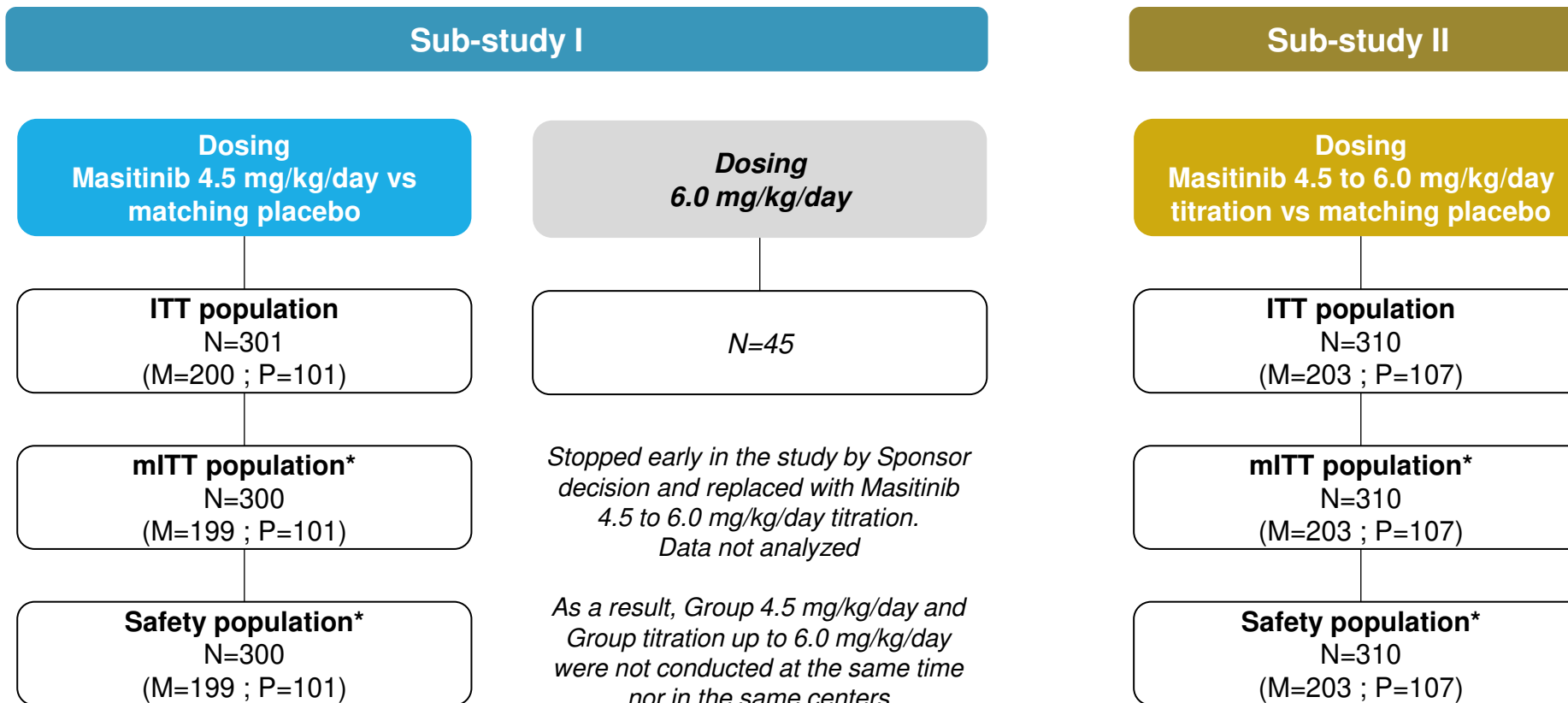
Masitinib administered daily from day 0. * 25 mg in mice is equivalent to approximately 2mg in human

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

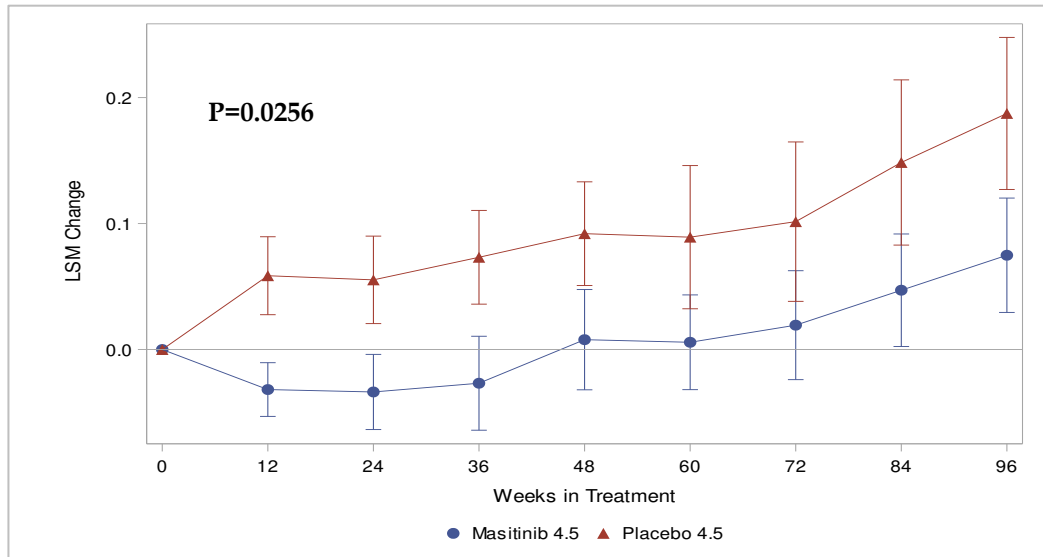


* All randomized patients (ITT) who took at least one dose of study treatment (masitinib/placebo).

Phase 2B/3 primary analysis 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



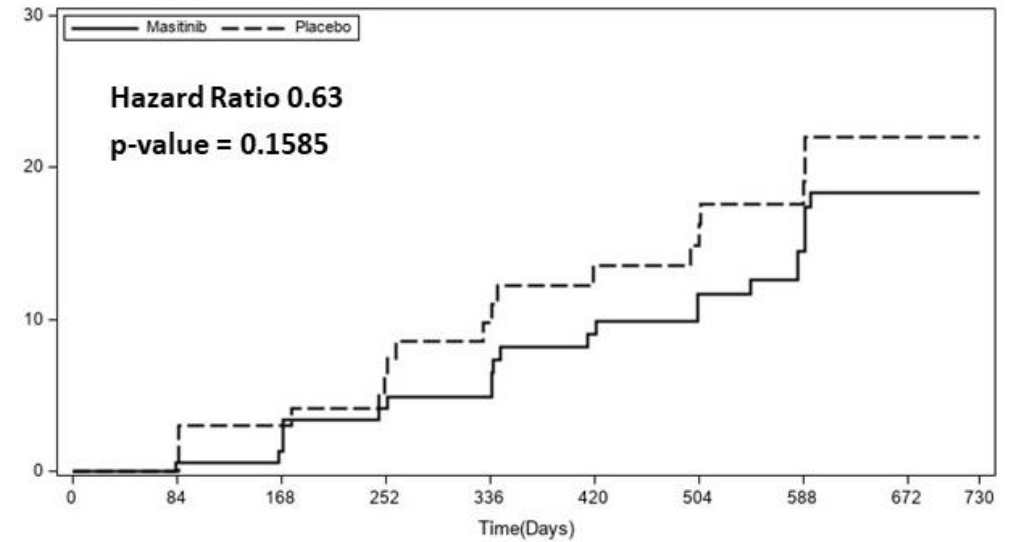
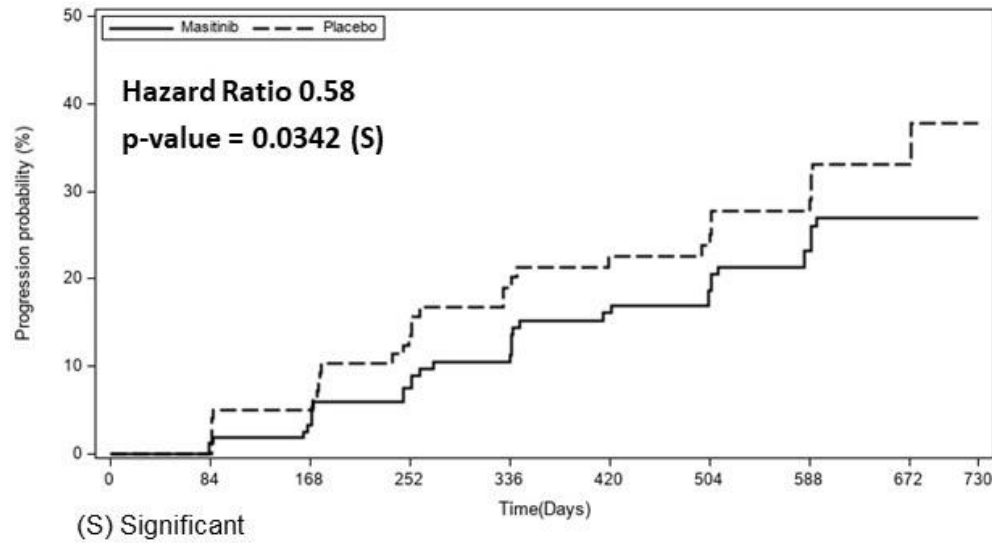
* Change in EDSS

- 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/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%

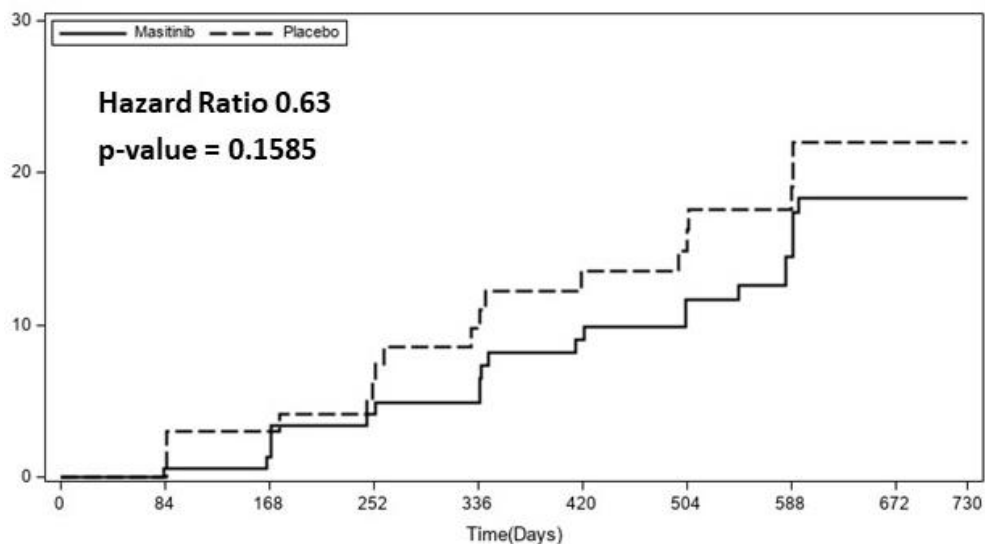
42% risk reduction of time to disability progression

37% risk reduction of time to confirmed disability progression



The recent success of tolebrutinib in secondary progressive MS, a BTK inhibitor targeting microglia, validates the strategy of targeting microglia, and although head-to-head comparison is not possible, results with masitinib are promising

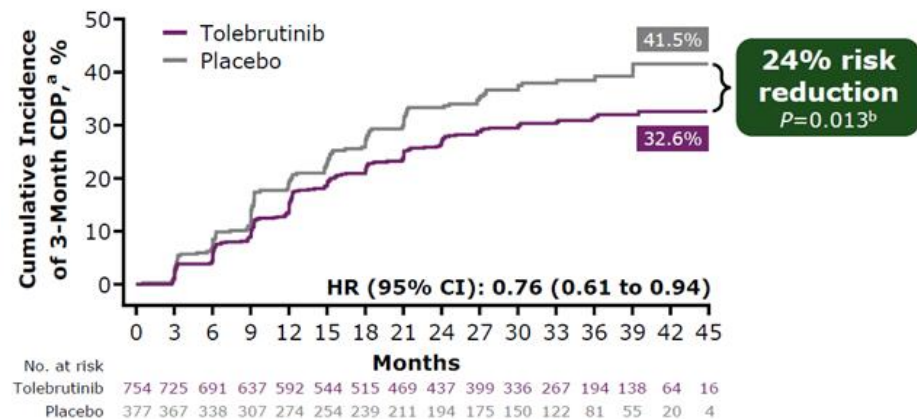
Masitinib
37% risk reduction of time to 3-months confirmed disability progression



Masitinib benefit achieved before year 2

↑
2 years

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



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

Tolebrutinib benefit achieved between year 2 and year 3

↑
3 years

**AB07002 (NCT01433497)

*ECTRIMS 2024 Presentation #O136

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

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



Patrick
Vermersch

❖ **The clinical data are supported by the mechanism of action of masitinib**

- RRMS and active SPMS are predominantly driven by peripheral adaptive immunity (e.g. B cell and T cell lymphocytes), whereas progressive forms of PPMS and nSPMS are predominantly driven by self-perpetuating innate immunity-related inflammation.
- Masitinib is the first drug targeting mast cells and microglia and has a distinctive and relevant mechanism of action.

❖ **The results are very promising**

- Masitinib significantly delays disability progression measured by average change in EDSS either in absolute value or ordinal change
- Probability of having either more disease improvements or fewer disease progressions is significantly increased by 39% with masitinib
- Time to first progression is significantly delayed by 42% and time to confirmed progression is delayed by 37%
- The safety profile appears acceptable in the targeted indication.



Robert
Fox

❖ **The results are very promising**

- A significant delay in EDSS progression, including time to EDSS 7.0, is a marker of a relevant benefit in MS.
- The treatment-effect was consistent across the 2 disease phenotypes - PPMS and nSPMS
- Safety profile appears quite acceptable



Friedemann
Paul

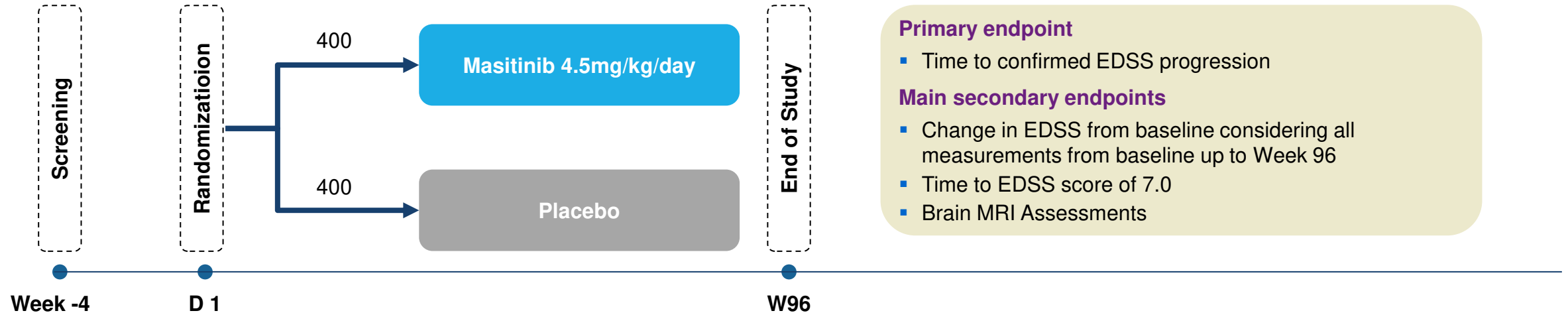
❖ **The targeting of the innate immunity is a new and promising strategy**

- Masitinib has a unique mechanism of action by selectively targeting both mast cells and microglia.
- This study shows for the first time that targeting the innate immune cells has a beneficial impact on the course of the disease.

❖ **The results are very promising**

- The study demonstrated a sustained benefit of EDSS change over a two year duration, with benefit observed as early as week 12.
- A 37% reduction of the risk of confirmed disability progression is very relevant from a medical standpoint.
- Masitinib safety profile seems suitable for long-term administration, because it is not immunosuppressive.

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

- 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

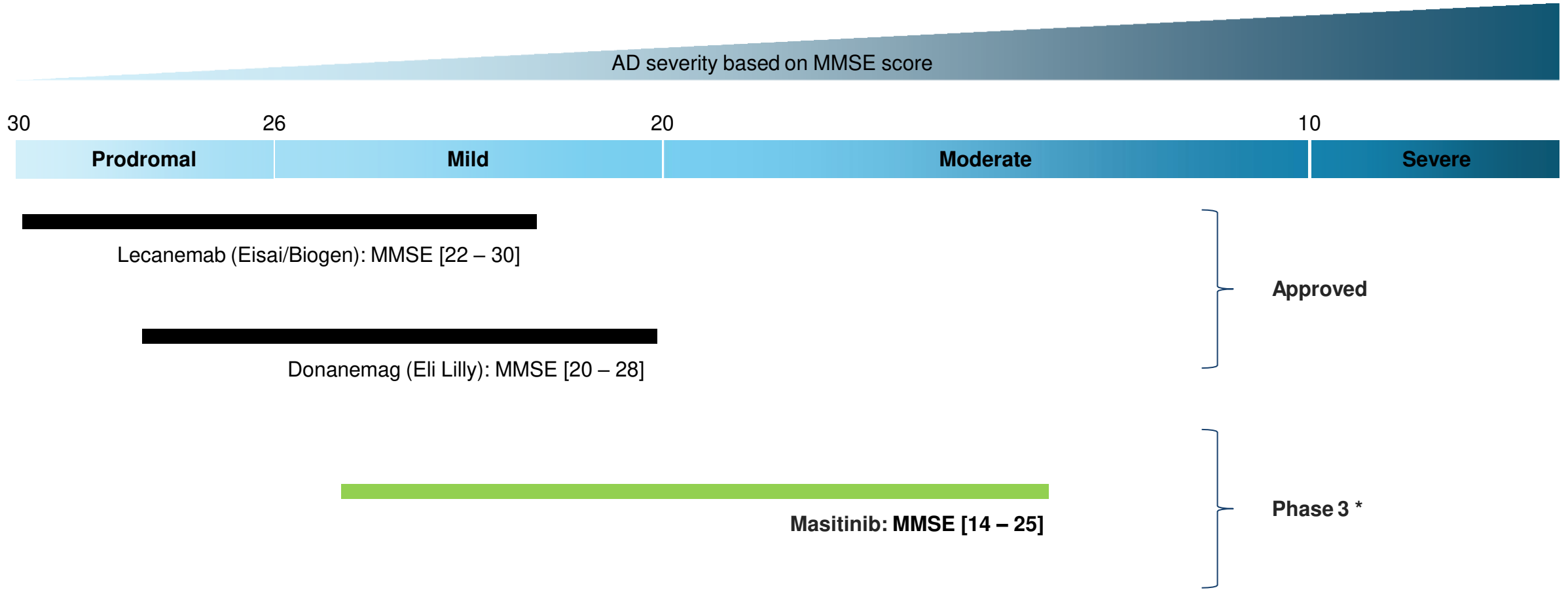
- Bulgaria, France, Germany, Greece, Italy, Netherlands, Poland, Norway, Portugal, Spain, Sweden, United Kingdom
- USA

Approved sites: 67

A microscopic image of brain tissue, likely stained with hematoxylin and eosin (H&E), showing numerous cells with dark nuclei and lighter cytoplasm. A prominent, dense, blue-stained area is visible in the upper left quadrant, possibly representing a region of inflammation or a specific pathological feature. The overall image has a light blue overlay.

Masitinib in Alzheimer's Disease

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

Main approaches

- Target the two visible aggregates, beta amyloid and Tau
- Reduce ARIA associated with this strategy

- Masitinib targets microglia and mast cells, which is a unique MoA in AD complementary to anti beta amyloid and anti tau strategies
- Masitinib could be positioned in three different settings

Differentiating features of masitinib in AD, leading to several positioning options

Single agent

- Mild & Moderate AD
- Comparing (ADAS-Cog and ADCS ADL) for masitinib versus placebo

Combined with amyloid-targeting drugs

- Mild AD, not previously treated (or only with lecanemab or donanemab), ApoE ϵ 4 non-carriers or heterozygotes, with positive amyloid PET
- Comparing (ADAS-Cog and ADCS ADL) for masitinib + registered anti-amyloid therapy versus anti-amyloid therapy

Adjuvant to amyloid-targeting drugs

- Mild & Moderate AD, achieving negative positive amyloid PET following treatment with registered amyloid-targeting drugs
- Comparing (ADAS-Cog and ADCS ADL) for masitinib versus placebo

The mode of action of masitinib in AD is based on four pathways, which may have a synergistic effect

Modulation of Microglia

- Microglia is involved in the neuro-inflammation in AD
- Masitinib blocks microglia through inhibition of MCSFR-1 kinase

Protection of Synapses

- Synapses are altered in AD
- Masitinib promotes recovery of synaptic markers in mice model of AD

Inhibition of Tau protein

- Tau protein aggregates in the physiopathology of AD
- Masitinib inhibits FYN kinase, a kinase that is phosphorylating Tau
- Masitinib prevent the accumulation of amyloid fibrill in hippocampus of young mouse model of AD

Control of Mast Cell (MCs) activity

- Mice depleted from MCs do not develop symptoms of AD
- Masitinib blocks MCs activation through inhibition of c-Kit, LYN, and FYN kinases
- β -amyloid plaques activate mast cells
- Transgenic AD mice treated by masitinib are protected for cognition impairment

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)

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

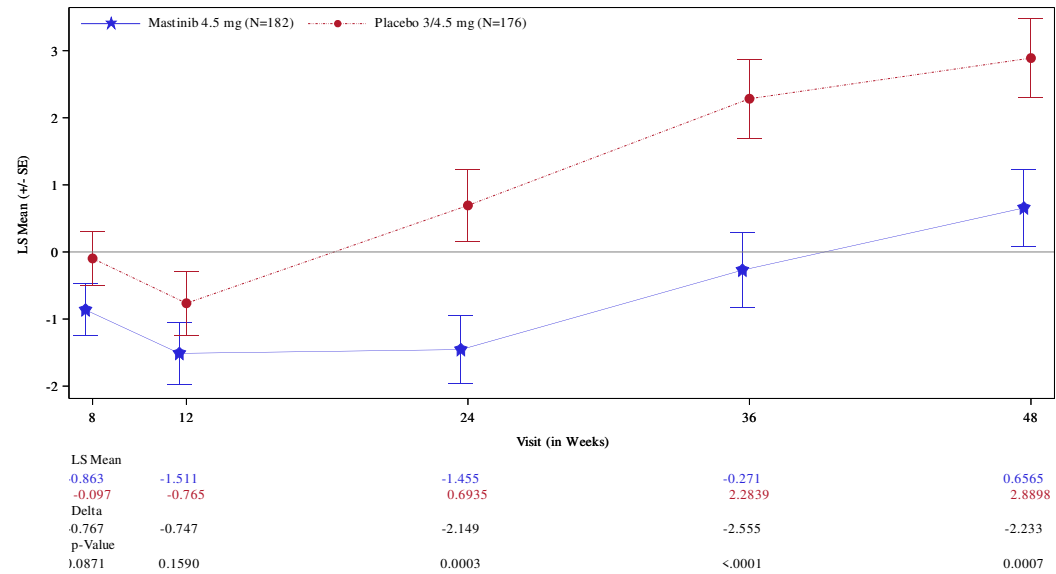
Change in ADCS-Adl - ANCOVA Analysis (Full Analysis Set) - M4.5 vs Placebo

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)		

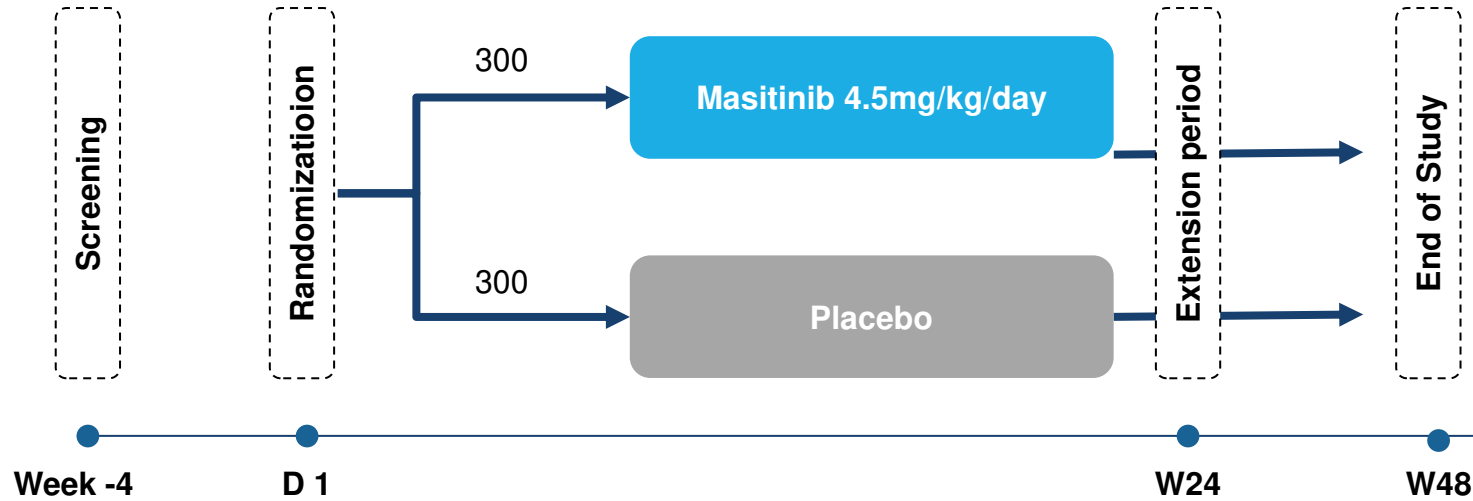
Clinically relevant benefit because on top of standard of care (memantine & anticholinesterase)

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)



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

The background of the slide is a microscopic image of brain tissue. It features a dense field of cells, likely neurons, stained in shades of light blue and pink. The cells are arranged in a somewhat regular pattern, with some larger, more prominent cells and smaller, more numerous ones. The overall appearance is that of a histological section of neural tissue.

Intellectual Property in Neuro-degenerative Diseases

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	Status
Multiple Sclerosis	Use patent	Treatment of multiple sclerosis with masitinib	WO2011131705	2031	Granted USA
		Masitinib for the treatment of a multiple sclerosis patient subpopulation	WO2021165472	2041	Pending
Amyotrophic Lateral Sclerosis	Use Patent	Use of masitinib for treatment of an amyotrophic lateral sclerosis patient subpopulation	WO2017162884	2037	Granted
	Orphan Drug Status	Treatment of amyotrophic Lateral Sclerosis	FDA - 15-4694 EMA - EU/3/16/172	FDA – 7 years as of approval EMA – 10 years as of approval	Granted
Alzheimer's Disease	Use patent	Masitinib for the treatment of Alzheimer's disease (subpopulations)	WO2022129410A1	2041	PCT Application

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**

A microscopic view of brain tissue, likely a histological section, showing numerous cells with dark nuclei and lighter cytoplasm. The image is overlaid with a semi-transparent blue filter. The text is positioned in the lower-left quadrant of the image.

Market Potential in Neuro-degenerative Diseases

Masitinib has blockbuster potential in neuro-degenerative diseases

	ALS	Progressive forms MS	Mild to moderate Alzheimer's Disease
Global disease Prevalence	<ul style="list-style-type: none"> 6 per 100.000 	<ul style="list-style-type: none"> 115 per 100.000 for MS 	<ul style="list-style-type: none"> 1.000 per 100.000 for ALZ
Targeted label with masitinib	<ul style="list-style-type: none"> ALS patients with no complete loss of function 	<ul style="list-style-type: none"> PPMS and nSPMS 	<ul style="list-style-type: none"> Mild to moderate forms of Alzheimer's Disease
% of patients targeted in the disease	<ul style="list-style-type: none"> 85% 	<ul style="list-style-type: none"> 35% 	<ul style="list-style-type: none"> 50%
Expected market share in the label	<ul style="list-style-type: none"> 50% 	<ul style="list-style-type: none"> PPMS : 10% nSPMS : 10% Overall: 10% 	<ul style="list-style-type: none"> Mild AD : 5% Moderate AD : 20% Overall : 12,5%
% of patients covered by insurance	<ul style="list-style-type: none"> 90% 	<ul style="list-style-type: none"> 90% 	<ul style="list-style-type: none"> 90%
Annual treatment price	<ul style="list-style-type: none"> EUR : 80K€ US : 140K€ 	<ul style="list-style-type: none"> EUR : 60K€ US : 80K€ 	<ul style="list-style-type: none"> EUR : 20K€ US : 30K€
Annual peak sales (EUR + US)	<ul style="list-style-type: none"> ~1bn 	<ul style="list-style-type: none"> ~1,5bn 	<ul style="list-style-type: none"> [2,5bn – 5bn]

The background of the slide is a microscopic image of cells, likely from a tissue sample, showing various cell types and structures in shades of blue and white. The cells are densely packed and vary in size and shape, with some showing distinct nuclei and others appearing more rounded or elongated. The overall appearance is that of a histological section.

Summary on Masitinib Clinical Development in Neuro-degenerative Diseases

Amyotrophic Lateral Sclerosis

- New confirmatory study AB23005 simplified for enrolment and targeting best responders for masitinib will be initiated in line with recommendation of FDA and EMA
- Design validated by FDA and EMA
- Confirmatory study authorized by FDA
- Secure pathway to registration with agencies
- Facilitate discussion with partners
- First study AB10015 generated strong hypothesis on patients normal progressor and prior to any complete loss of function with significant +12 months survival
- Long term follow up shows 53% of patients surviving more than 5 years, with a +36 months benefit over ENCALS prediction
- Some patients survived from 10 to 15 years and continue to take treatment

Progressive Forms of Multiple Sclerosis

- MoA targeting microglia reinforced after BTK success
- Targeting mast cells add to the efficacy since mast cells activate microglia and directly acts on myelin degradation
- Masitinib Hazard Ratio of EDSS progression compared with BTK inhibitor Hazard Ratio published shows that masitinib is competitive
- KOL are very supportive of masitinib program

Alzheimer's Disease

- Targeting the innate immune reaction stands out in addition to main strategy with amyloid or tau targeted therapies
- Masitinib is the only drug that generated positive results in moderate Alzheimer
- Masitinib could be combined with biologics in early and mild Alzheimer

More globally

- The failure of multiple programs for decades reinforces the value of masitinib approach to target the innate immune reaction through modulation of microglia and mast cells
- The unmet needs is immense
- The markets are huge with potential sales exceeding billions in each indication
- Masitinib IP rights are secured through use patent until 2037 in ALS and up to 2041 in MS and AD

A microscopic view of a blood smear showing numerous sickle cells. The cells are characterized by their crescent or sickle shape, which is a result of the abnormal hemoglobin (HbS) in sickle cell disease. The cells are densely packed and vary in size and shape, with some showing a distinct sickle morphology. The background is a light blue color, typical of a Giemsa-stained blood smear.

Masitinib in Sickle Cell Disease

SCD remains a major public health challenge, with limited treatment options

Curative option

- **Allogeneic hematopoietic stem cell transplantation with a matched sibling donor (MSD)**
- **Gene therapy (CRISPR/Cas9)**



- Less than 15% of patients have suitable donor
- Only 10% eligible patients receive HSCT
- Overall, <2% of SCD population treated

Drug	Sponsor
Casgevy	Vertex
Lyfgenia	Bluebird Bio



- High price (>2 million USD) and limited access
- Occurrence of Hematologic malignancy with Lyfgenia

Approved treatment

Drug	Sponsor
Ferriprox	Chiesi



- Used to reduce iron overload from blood transfusions
- Box Warnings: Agranulocytosis, neutropenia

Revoked or un-approved drugs

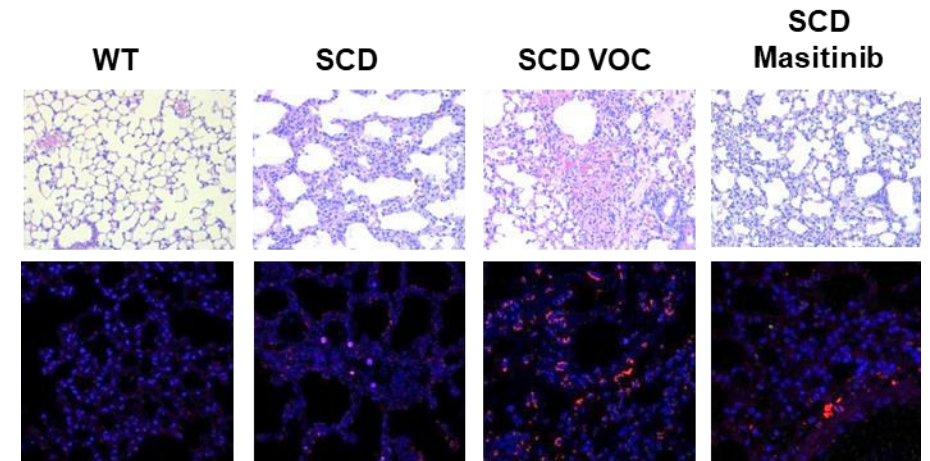
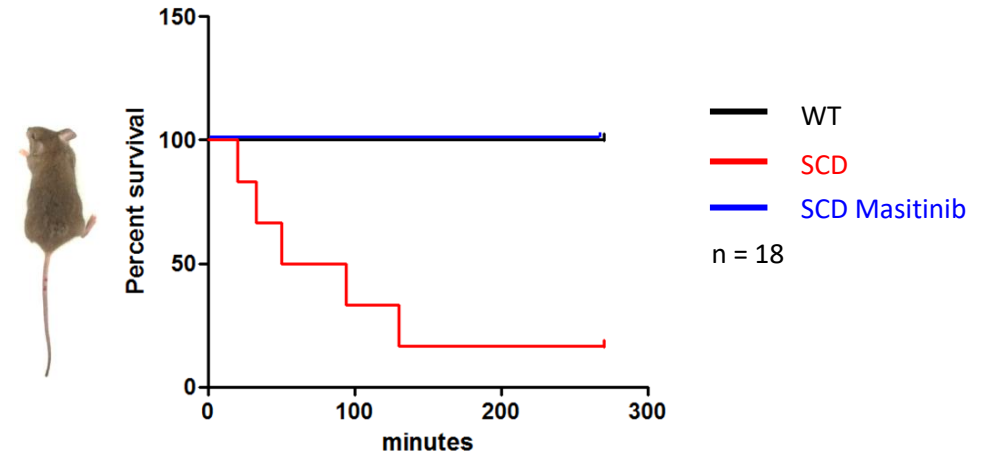
Drug	Sponsor
Xyndari	Emmaus Life Sciences
Adakveo	Novartis
Oxbryta	Pfizer

ROLE OF MAST CELLS

- Mast cells and basophils in the pathophysiology of SCD ⁽¹⁾
- Mast cells mediates pain in SCD ⁽²⁾
- Mast cells are involved in SCD complications ⁽²⁾

IN-VIVO RESULTS WITH MASITINIB

- Masitinib has demonstrated survival benefit in an SCD mouse model
- Masitinib protects from acute lung injuries and mast cell infiltration in an SCD mouse model
- Masitinib has been shown in other conditions to have clinical benefit in complications associated with SCD



1 Allalli, Maciel et al Blood. 2022.

2. Allalli, Maciel et al Blood advance 2021, British J Hematol 2019

1 collaborative program is on-going, aiming to develop in phase 2 masitinib as a new treatment of SCD for patients harboring a specific biomarker

Collaborative program

- 6 partners (4 academic, 2 industrial partners)

ASSISTANCE
PUBLIQUE  HÔPITAUX
DE PARIS

 Université
Paris Cité

institut
imagine
GUÉRIR LES MALADIES GÉNÉTIQUES

Inserm
La science pour la santé
From science to health



codoc

- Funding of 9.2 million Euros distributed among the partners

Objectives

- 2025 **Identify and validate biomarkers** highlighting the role of mast cells and basophils in orchestrating acute and chronic complications of sickle cell disease
- 2026 Demonstrate in a **phase 2 clinical trial** the efficacy of masitinib in the treatment of acute and chronic complications of sickle cell disease in patients identified based on biomarkers

The background of the slide is a microscopic image of cells, likely red blood cells, stained with a light blue dye. The cells are densely packed and have a characteristic biconcave disc shape. The overall color palette is light blue and white.

FINANCING OF DEVELOPMENT PROGRAM

AB Science has three platforms, platform 1 with 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⁾
Oncology Platform	AB8939 (IV)	Hematology	Acute Myeloid Leukemia (AML)	Phase 1
	ABXXXX (oral)	Oncology	Sarcoma, Solid Tumors	Preclinical
Drug Discovery Platform		Target 1: undisclosed for neurodegenerative diseases 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.

AB Science raised 5 millions euros in Q4 2024, which provides financial runway for more than 12 months



Financing Strategy

Masitinib

- **Neuro-degenerative diseases : Financing through partnership**
- **Sickle Cell Disease : Financing of phase 2 through RHU collaborative program with APHP (9.2M€)**

AB8939


- **Phase 1 : Financing through equity**
- **Phase 2 : Financing through equity or partnership**

**Drug Discovery
Platform**

- **Financing through equity**

AB Science has a debt of 3.7M€ related to PGE (Prêt Garanti par l'Etat) and intend to negotiate a stand-still clause



- 
- Allocation of current resources to R&D program exclusively
 - Delay PGE repayment until after partnership agreement or registration