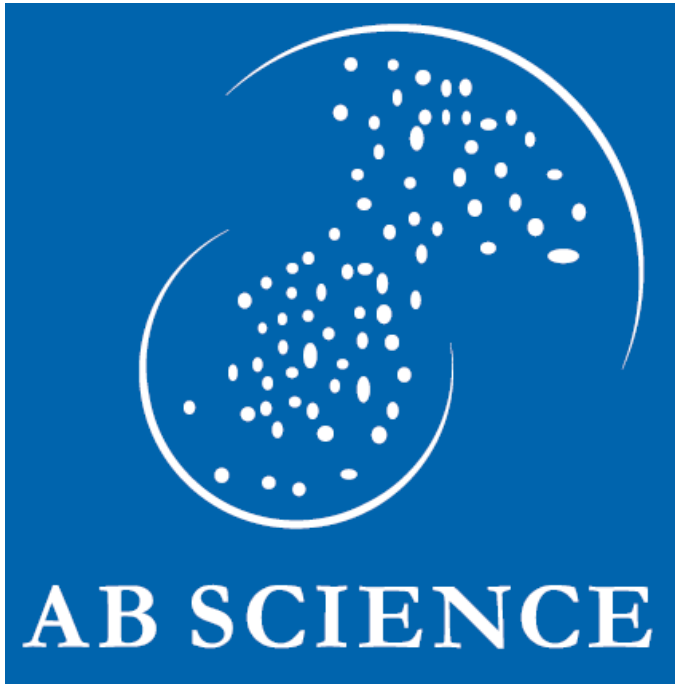

AB SCIENCE WEBCONFERENCE

MASITINIB IN PRIMARY PROGRESSIVE AND NON-ACTIVE SECONDARY PROGRESSIVE MULTIPLE SCLEROSIS

06 MARCH 2020

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AGENDA

- Introduction of participating experts
- Overview of multiple sclerosis
- Overview of masitinib clinical results
- Q&A

Participants

MS Experts

Patrick VERMERSCH, MD, PhD
Professor of Neurology at Lille University in France

Bob FOX, MD
Staff Neurologist at the Mellen Center for Multiple Sclerosis at Cleveland Clinic, USA

Friedemann PAUL, MD
Professor of Neurology at Charité Universitätsmedizin Berlin and Max Delbrueck Center for Molecular Medicine, Germany

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Chief Financial Officer

Olivier HERMINE, MD, PhD
Chief Scientific Officer and Chaiman of Scientific Committee

Principal Investigator of Study AB7002

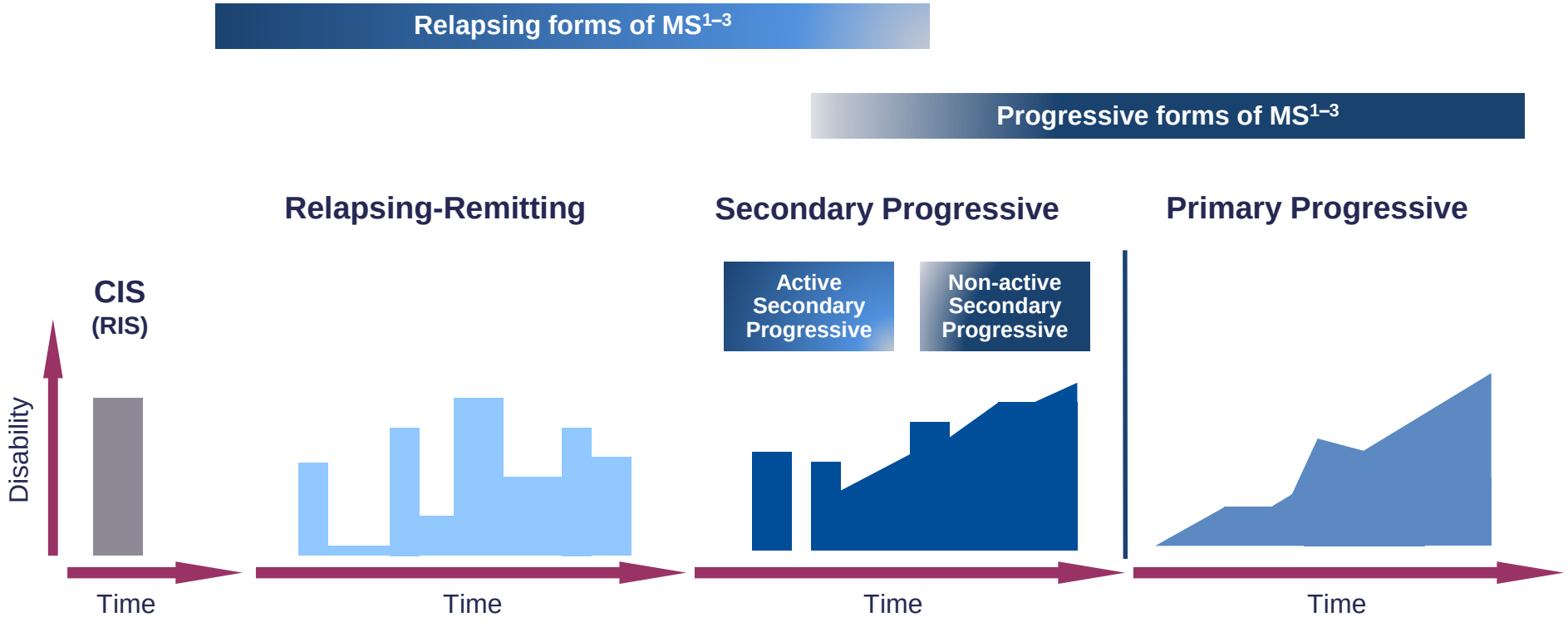
Patrick VERMERSCH, MD, PhD

- **About Patrick Vermersch**
  - Professor of Neurology at Lille University in France.
  - Vice-president for research in biology and health at the University of Lille
  - Board member of the European Charcot Foundation.
  - Author or co-author of 400 peer reviewed articles, reviews and monographs (Hi 60).
  - Areas of interest are prognostic markers of MS and neuroimmunology.
  - Participates in many therapeutic protocols on MS as member of steering committee.

- **Role in masitinib program**
  - Lead investigator of proof of concept study with masitinib (published in BMC Neurology).
  - Lead investigator of AB7002 study.

Clinical Forms of Multiple Sclerosis

Multiple sclerosis has two main forms, relapsing and progressive forms.

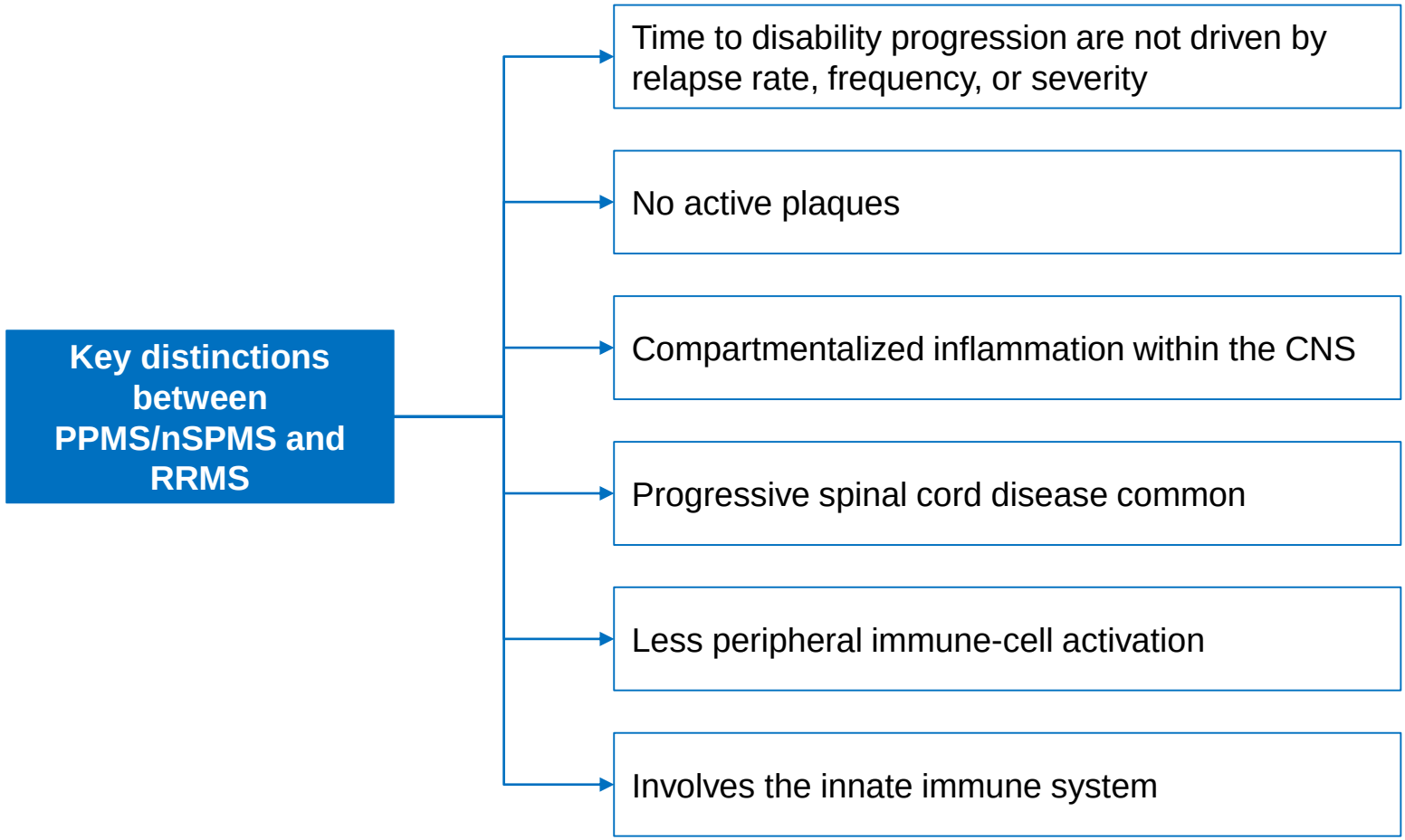


CIS, clinically isolated syndrome; MS, multiple sclerosis; RIS, radiologically isolated syndrome.

1. Lublin FD, Reingold SC. *Neurology* 1996;46:907–911; 2. Lublin FD, *et al. Neurology* 2014;83:278–286; 3. Antel J, *et al. Acta Neuropathol* 2012:123:627–638.

Difference between Progressive and Relapsing Forms of MS

PPMS and nSPMS are distinct from RRMS, which may explain why therapies targeting the peripheral adaptive immune system (T and B-cells) proven to be effective in RRMS have failed or had inconclusive results in PPMS and nSPMS.



New Scientific Rationale in Progressive Forms MS – Target Mast Cells and Microglia

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].**

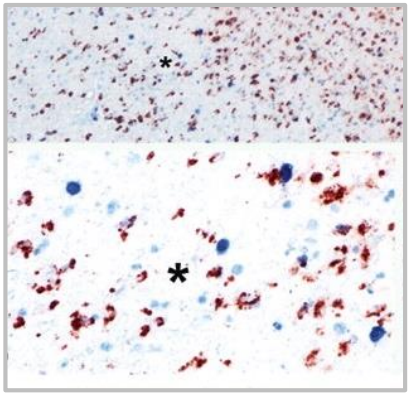
- **Targeting innate immunity-related MS disease progression via modulation of mast cells and activated macrophage/microglia may slow or prevent worsening of disability in progressive MS.**

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

New Scientific Rationale in Progressive Forms MS – Target Mast Cells and Microglia

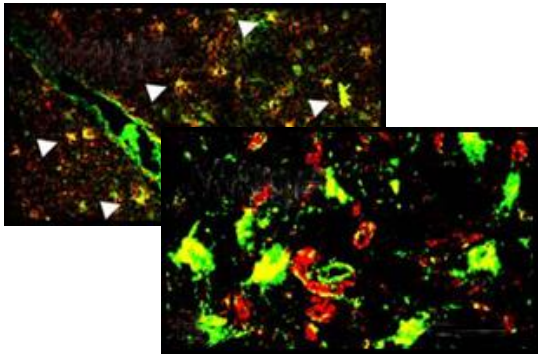
The innate immune system can play a critical role in the progressive forms of MS.

Macrophages/activated microglia can cause injury by releasing proteases and reactive oxygen species[1]



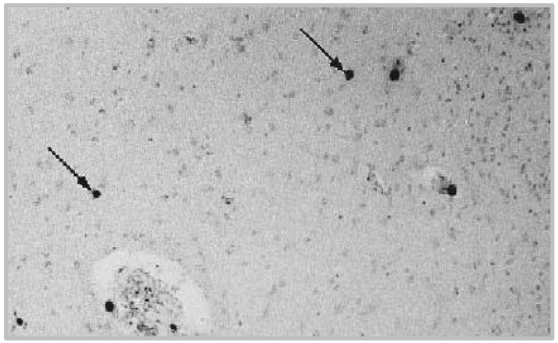
Oxidised DNA (blue) and activated microglia (brown) in PPMS patient[2]

Activated microglia and hypertrophic astrocytes found at the rims of chronic active MS lesions express chemokine receptors[3]



Chemokine and chemokine receptor expression in lesions from SPMS patients. Top: astrocyte (red); CXCL10 (green). Bottom: microglia (red); CCR2 (green). Both: co-stain (yellow).[3]

Mast cells release enzymes that can lead to demyelination and destruction of oligodendrocytes and neurons[4]



Mast cell tryptase (dark stain) on a chronic active lesion; arrows indicate mast cells[5]

Innate immune cells can directly contribute to neurodegeneration in MS[1-5]

1. Wu GF, Alvarez E. *Neurol Clin.* 2011;29:257-278. **2.** Haider L et al. *Brain*. 2011;134:1914-1924. **3.** Tanuma N et al. *Acta Neuropathol*. 2006;112:195-204. **4.** Sospedra M, Martin R. *Annu Rev Immunol*. 2005;23:683-747.
5. Ibrahim MZM et al. *J Neuroimmunol*. 1996;70:131-138.

Masitinib Inhibits Activated Mast Cells and Microglia

Masitinib targets selected kinases in mast cells and M-CSF1 receptor in microglia.

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
- Microglia are a target in amyotrophic lateral sclerosis and Alzheimer's disease.

Masitinib is orally administered

- Tablet in 2 dosage forms
- Morning and evening intake

Kinase inhibition profile of masitinib

Cellular Target	Molecular Target	IC_{50} [nM]	Kd [µM]
Mast cells	KIT wild-type (WT)	200	0.008
	FYN	240	0.14
	LYN	225	0.061
Microglia	MCSFR-1	90	0.0076

Notes

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

Masitinib Positioning in Progressive Forms of Multiple Sclerosis

Because of its mechanism of action targeting mast cells and microglia, Masitinib is aimed to treat patients with PPMS and non-active SPMS, which is a difficult to treat population representing around 50% of MS patients.

- **Primary progressive MS**
  - PPMS is characterized by steadily worsening function from the onset of symptoms, often without early relapses or remissions.
  - PPMS affects about 15% of people diagnosed with MS.

- **Non-active secondary progressive MS**
  - nSPMS 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.
  - nSPMS affects about 30-35% of people with MS.

Antel J, Antel S, Caramanos Z, Arnold DL, Kuhlmann T. Primary progressive multiple sclerosis: part of the MS disease spectrum or separate disease entity? Acta Neuropathol. 2012 May;123(5):627-38.
Paz Soldán MM, et al. Relapses and disability accumulation in progressive multiple sclerosis. Neurology. 2015 Jan 6;84(1):81-8.

Masitinib Positioning in Progressive Forms of Multiple Sclerosis

There is a tremendous unmet need, with no approved drugs for nSPMS and only one for PPMS.

Masitinib positioning

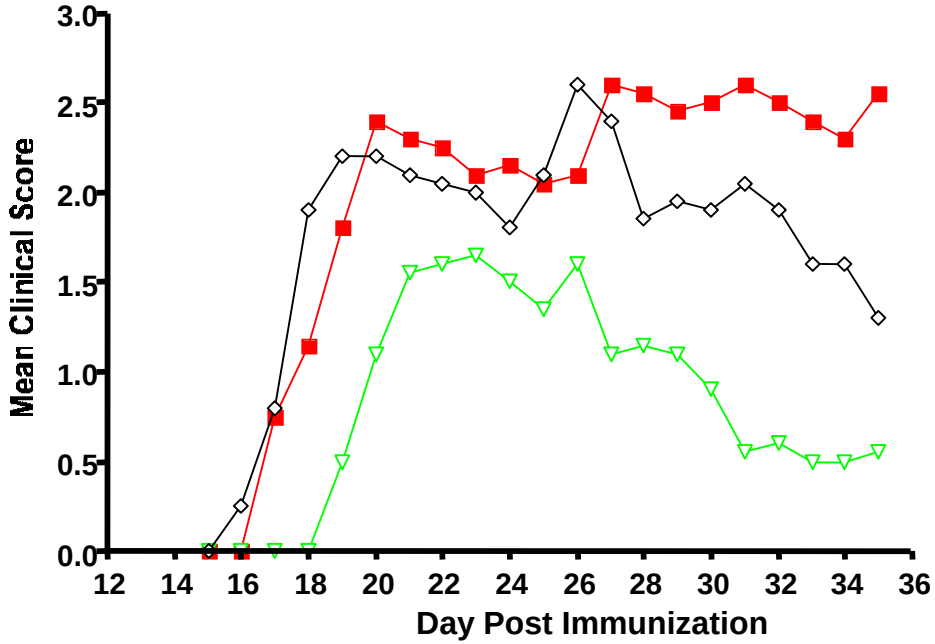
	Manufacturer	Label				First approved
		PPMS	Non-active SPMS*	Active SPMS	RRMS	
Distribution of patients *(Estimated Nbr of patients Europe + USA)*		**15%** *(~ 150 000)*	**35%** *(~ 350 000)*	**10%** *(~ 90 000)*	**40%** *(~ 400 000)*	
Total number of drugs registered		**1**	**0**	**15**	**16**	
Mayzent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

**: 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.*

Pharmacology Data - Masitinib improves MS Symptoms in Mice

In a 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 Clinical Development Plan in Progressive Forms of MS

The current development program in progressive forms of MS is comprised of one proof of concept study (*published*), and one pivotal study.

Phase	Study code	Design	Population	Primary endpoint	Patient Enrolled	IDMC recommendation	Study status	Related publications
2a	AB4011 (NCT01450488)	Double-blind, placebo-controlled, parallel-group study	Patients with primary progressive or non-active secondary progressive multiple sclerosis	Response on MSFC, which measures symptoms of patients on three aspects: movement of the lower limbs, movement of the upper limbs, and cognitive tests	35	NA	Study completed	Vermersch, 2012
2B/3	AB7002 (NCT01433497)	Prospective, double-blind, placebo-controlled, 2-parallel groups study	Patients with primary progressive or non-active secondary progressive multiple sclerosis	Change in EDSS (Expanded Disability Status Scale), which is a scale used for quantifying disability in multiple sclerosis	656	Continuation of the study without resampling option (based on interim analysis performed on one dosage and safety data)	Study completed	-

BMC Neurol. 2012 Jun 12;12:36. *Masitinib treatment in patients with progressive multiple sclerosis: a randomized pilot study*. Vermersch P.

Proof of concept study – 2012 Publication

Proof of concept in progressive MS has been established through a study evaluating masitinib effect on the multiple sclerosis functional composite score (MSFC).

- **Positive effect on MS-related impairment for PPMS and nSPMS patients.**
  - Improvement in MSFC scores with masitinib (+103% ± 189 relative change from baseline)

  Compared with
  - Worsening MSFC score with placebo (-60% ± 190 relative change from baseline) at month-12
- **This positive response was observed as early as month-3 and sustained through to month-18**
- **Similar trends seen in the PPMS and nSPMS subpopulations.**
- **Overall safety was acceptable.**
- **The study achieved its objectives with a limited sample population (n=35), warranting further evaluation of masitinib in progressive forms of MS.**
- **Results published in BMC Neurol. 2012 Jun 12;12:36. *Masitinib treatment in patients with progressive multiple sclerosis: a randomized pilot study*. Vermersch P.**

Study AB7002 - Phase 2B/3 Design

Study AB7002 evaluated two masitinib doses in patients with PPMS and non-active SPMS.

- **Double blind, placebo controlled, 2-parallel groups**
  - Two doses tested independently, each with its own placebo control group (i.e. 4 arms study)
    1. Masitinib 4.5 mg/kg/day versus its own placebo (300 patients randomization 2:1)
    2. Masitinib titration up to 6.0 mg/kg/day versus its own placebo (300 patients randomization 2:1). This titration scheme was introduced later in the study to replace through an amendment a fixed starting dose of 6.0 mg/kg/day and therefore had its own placebo control arm
  - Therefore, statistically, study AB7002 is treated as two independent sub-studies under a common study identifier, with alpha control set at 5% for each dose
  - Alpha spending function for interim analysis was based on Pocock, so the residual alpha risk for final analysis was 0.0296 after interim analysis
- **Main Inclusion Criteria**
  - Patient with Primary Progressive (PPMS) or Non-active secondary progressive multiple sclerosis (nSPMS) defined as:
    - No relapse (measured by EDSS progression, not by imaging) within 2 years before inclusion according to the revised McDonald's criteria
    - EDSS score progression ≥ 1 point within 2 years before inclusion
  - Must be EDSS and age requirements
    - EDSS score of [2.0 to 6.0] inclusive at baseline
    - Age 18 to 75 years old

Phase 2B/3 - Design

The primary endpoint was absolute change from baseline on Expanded Disability Status Scale (EDSS) averaged for all time points over 2 years, with a sensitivity analysis based on the ordinal EDSS change.

- **Pre-specified Primary Endpoint: Change from baseline in absolute EDSS value averaged over the two-year study**
  - Mean of all changes from baseline in EDSS measured at 8 time points for each patient (every 12 weeks from week 12 to week 96)
  - Primary analysis is calculated with GEE model (generalized estimating equation)
    - Allows for analysis of repeated measurements
    - Adjusts for correlation across variables and across time
    - Gives the true treatment effect over the two year study
  - The primary analysis in not a one-time ancova test of the last EDSS value measured at week 96
- **Pre-specified Sensitivity Analysis : Change from baseline in Ordinal EDSS score averaged over the two-year study**
  - Instead of the change in absolute EDSS, the change is measured with an ordinal score (+1 ; 0 ; -1)
    - -1 if worsening * in EDSS
    - +1 if improvement * in EDSS
    - 0 if EDSS is stable
  - The ordinal model allows to take into account the fact that the magnitude of EDSS necessary to define improvement or worsening over time depends on the EDSS score itself (not linear).
  - The evaluation is the mean of all ordinal EDSS changes from baseline measured at 8 time points for each patient (every 12 weeks from week 12 to week 96)
  - The analysis is calculated with a GEE model

** Worsening is defined as a change of at least +1 points from baseline if EDSS at baseline ≤ 5.5 and change of at least +0.5 points from baseline if EDSS at baseline > 5.5. Improvement is defined as a change of at least -1 points from baseline if EDSS at baseline ≤ 5.5 and change of at least -0.5 points from baseline if EDSS at baseline > 5.5*

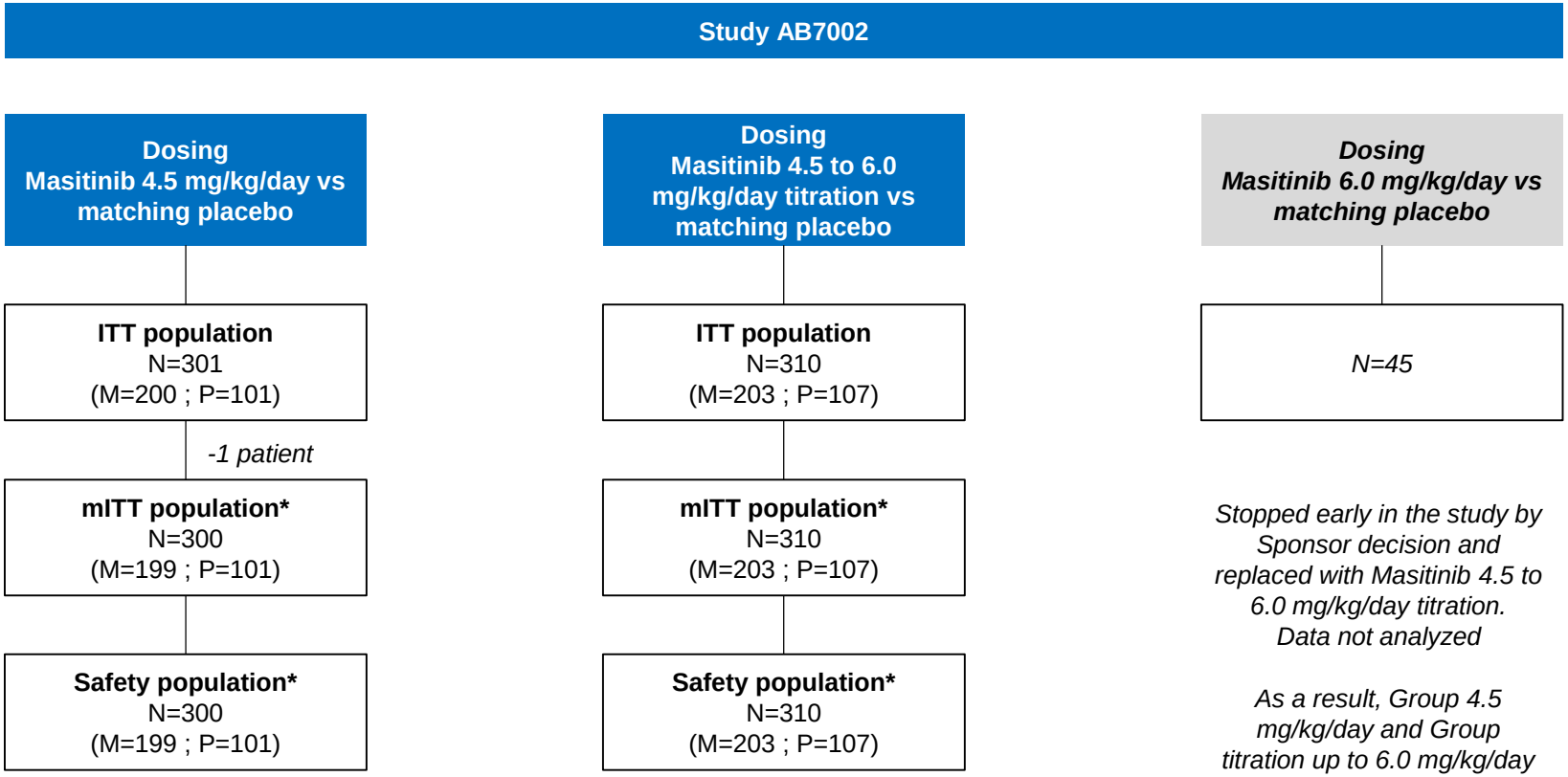
Phase 2B/3 - Design

Time to first EDSS progression and time to confirmed EDSS progression were pre-specified for sensitivity analysis although the study was not powered to detect an effect on these endpoints.

- **Pre-specified Sensitivity analysis based on time to first EDSS progression and confirmed (3 months) EDSS progression**
  - Study was not designed and powered to detect a significant effect on these endpoints
    - The expected % of events at week 96 based on literature is between 20% and 30% for EDSS progression and between 10% and 20% for confirmed EDSS progression [1;2].
    - Study AB7002 enrolled 300 patients per dose tested, meaning that the expected number of progressions was between 60 and 90 and the number of confirmed progressions was between 30 and 60.
    - To detect a statistically significant effect on this endpoint would have required >1,000 patients per dosing

Phase 2B/3 - Disposition of patients

The study was comprised of two independent sub-studies testing two distinct dosing regimens
Analyses were performed on the mITT* population.



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

Phase 2B/3 - Masitinib 4.5mg/kg/day - Baseline Characteristics

Patients were enrolled at an advanced stage of disease, reflecting a difficult-to-treat population.

Baseline Characteristics (M4.5 mg/kg/day vs placebo)

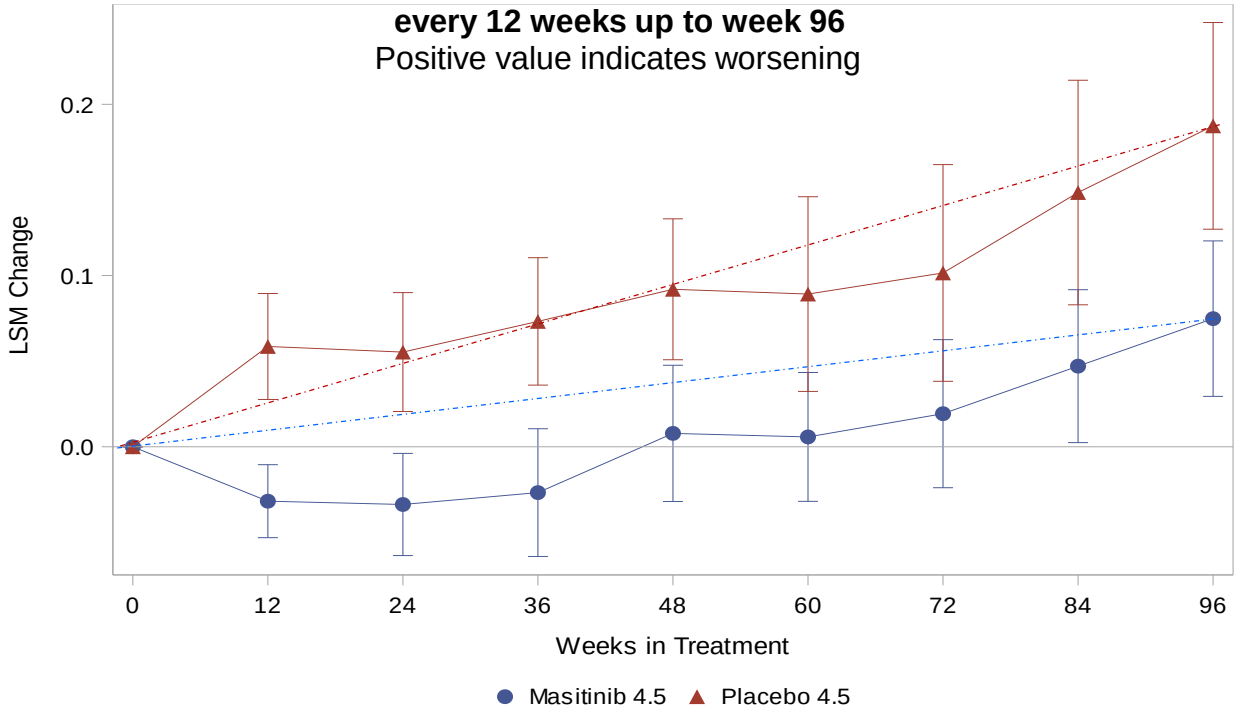
		Masitinib	Placebo
Number of Randomised Patients		200	101
Sex [n (%)]	Male	89 (44.5)	47 (46.5)
	Female	111 (55.5)	54 (53.5)
Age (Years)	Mean (SD)	49.8 (9.63)	49.7 (10.19)
	Median	50.0	50.0
Duration of First MS Symptom to Randomisation (Years)	Mean (SD)	14.0 (9.14)	12.6 (7.96)
	Median	12.4	12.2
EDSS Score at Baseline	Mean (SD)	5.2 (1.07)	5.1 (1.06)
	Median	5.5	5.5
Distribution of EDSS at Baseline	6	98 (49.0)	48 (47.5)
	5 and 5.5	41 (20.5)	21 (20.8)
	Less than 5.5	61 (30.5)	32 (31.7)

- **Baseline characteristics were balanced between the treatment arms**
- **Patients were enrolled at an advanced stage of the disease**
  - Close to 50% of patients with EDSS score 6.0
  - Median EDSS = 5.5
  - Mean and Median age close to 50

Phase 2B/3 - Met Primary Analysis at 4.5 mg/kg/day

The study met its primary analysis, demonstrating a statistically significant reduction in disability progression on EDSS (p=0.0256) .

Primary analysis – Visualization of absolute changes from baseline in EDSS measured at 8 time points every 12 weeks up to week 96



Primary analysis - Mean of absolute changes from baseline in EDSS measured at 8 time points every 12 weeks up to week 96

Treatment	N	Means	Means Difference	p-Value
Masitinib 4.5 mg/kg/day	199	0.001	-0.097	**0.0256**
Placebo	101	0.098		

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

Phase 2B/3 – Subgroup Analysis by Disease Category

This treatment-effect was consistent for PPMS and nSPMS, supportive of the case for registration of masitinib in the two populations.

Assessment of consistency of the primary endpoint for each population (PPMS and sSPMS)

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

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

Phase 2B/3 - Masitinib 4.5mg/kg/day - Ordinal EDSS

The sensitivity analysis based on ordinal EDSS change showed a significant 39% increased probability with masitinib of having either more disease improvements or fewer disease progressions.

Prespecified Analysis on EDSS – Ordinal EDSS

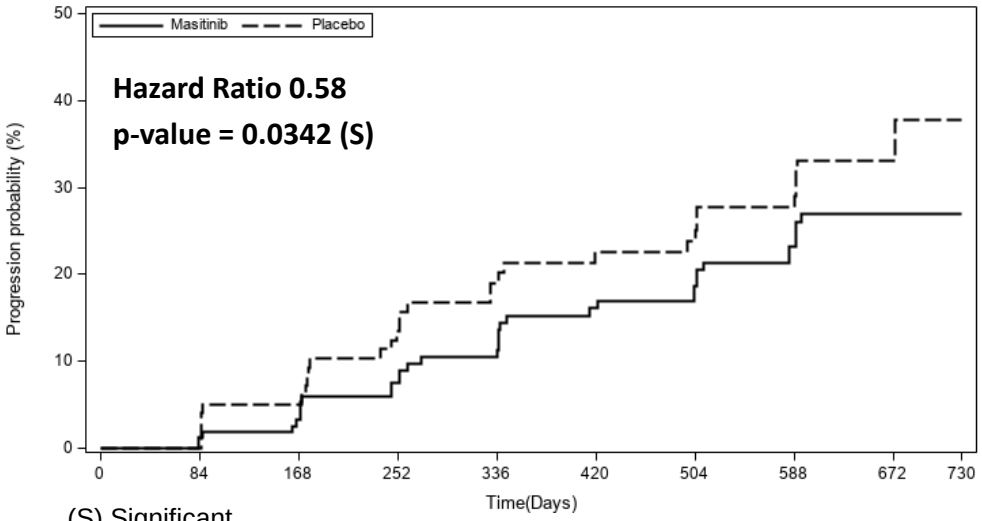
		Mean of 8 time points measured every 12 weeks up to week 96	
Treatment	**N**	**Masitinib vs. Placebo Odds ratio**	**p-Value**
Masitinib 4.5 mg/kg/day	199	0.61	0.0446
Placebo	101		

0.61 odds ratio corresponding to 39% increased probability with masitinib of having either more disease improvements or fewer disease progressions

Phase 2B/3 - Masitinib 4.5mg/kg/day - Time to EDSS progression

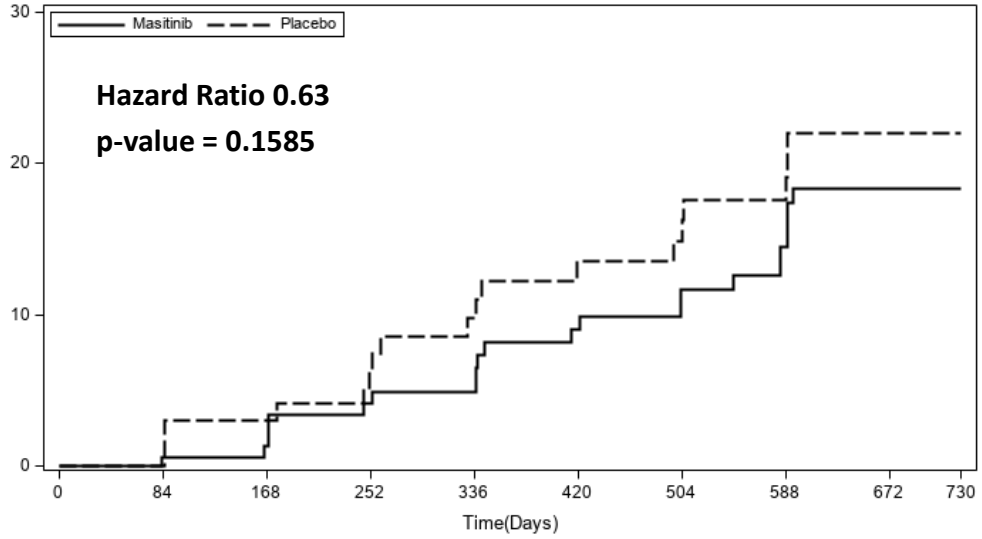
Masitinib reduced the risk of first disability progression by 42% and the risk of confirmed disability progression by 37%.

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



(S) Significant

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



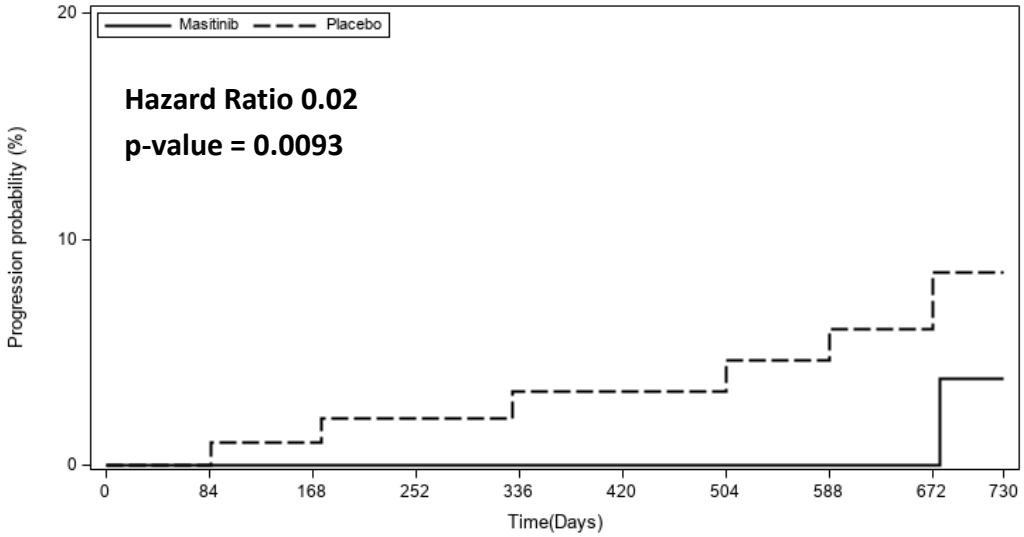
Significant 42% reduction of the risk of first disability progression

37% Reduction of the risk of confirmed disability progression

Phase 2B/3 - Masitinib 4.5mg/kg/day - Time to EDSS 7.0 (wheelchair)

Masitinib also significantly reduced the risk of reaching an EDSS score of 7.0, corresponding to disability severe enough that the patient is restricted to a wheelchair.

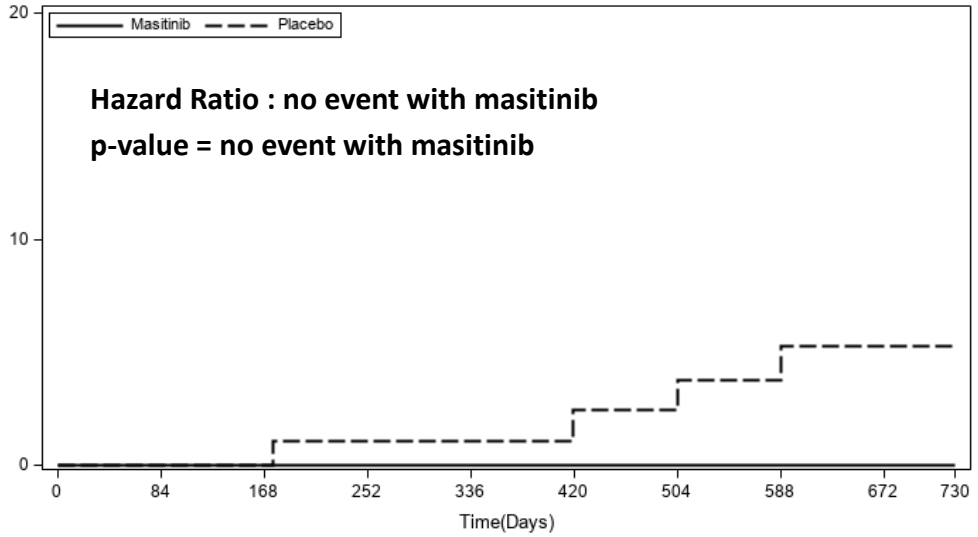
Kaplan Meier plot of Analysis of time to <u>First</u> EDSS score of 7.0



(S) Significant

Significant 98% reduction of the risk of reaching an EDSS score of 7.0 over timeframe of 96 weeks (first progression)

Kaplan Meier plot of Analysis of time to <u>Confirmed</u> EDSS score of 7.0



100% reduction of the risk of reaching an EDSS score of 7.0 over timeframe of 96 weeks (confirmed progression)

Phase 2B/3 - Masitinib 4.5mg/kg/day – Comparison to Other Drugs

Masitinib has the potential for a best-in-class profile for treating PPMS and nSPMS.

			Time to confirmed disability progression		Ordinal EDSS change	Average of Change in EDSS Treatment versus placebo
Drug	**Study Size (patients)**	**Type of Progressive MS**	**Hazard Ratio**	**Reduction in confirmed (3 months) disability progression**	**Probability to have more improvement or less progressions**	
Masitinib 4.5 mg/kg/day	300	PPMS and nSPMS	0.63	37% (NS)	39% (S)	-0.097 (2 years) (S)
Ocrelizumab	732	PPMS	0.76	24% (S)	na	na
Siponimod	1651	SPMS	0.79	21% (S)	na	na
Biotin	255	PPMS and SPMS	na	na	na	-0.100 (9 months) *Estimated based on publication*

S: Statistically Significant. NS : Not Statistically Significant

Phase 2B/3 study - Masitinib 4.5mg/kg/day - Safety

Safety was consistent with the known profile for masitinib.

- **Common treatment-emergent AEs were diarrhea, rash, edema, nausea and hematological assessments**
- **Most Frequent Severe Adverse Events were hematological assessments and rash**
  - **Most Frequent Severe Adverse Event (M-P≥1%) - Safety Population**

	Masitinib 4.5 (N=199)		Placebo (N=101)		M-P
PREFERRED TERM	Subjects n (%)	Events n	Subjects n (%)	Events n	Delta
Blood Phosphorus Decreased	9 (4.5)	11	0	0	4.5
Lymphocyte Count Decreased	6 (3.0)	7	1 (1.0)	1	2.0
Multiple Sclerosis Relapse	4 (2.0)	4	0	0	2.0
Blood Potassium Increased	3 (1.5)	3	0	0	1.5
Hyponatraemia	3 (1.5)	3	0	0	1.5
Neutropenia	3 (1.5)	3	0	0	1.5
Gamma-Glutamyl transferase Increased	4 (2.0)	4	1 (1.0)	1	1.0
Blood Sodium Increased	2 (1.0)	2	0	0	1.0
Lymphopenia	2 (1.0)	2	0	0	1.0
Rash Maculo-Papular	2 (1.0)	2	0	0	1.0

Phase 2B/3 - Masitinib 6.0mg/kg/day - Primary Analysis

No significant treatment-effect on EDSS was observed for high-dose masitinib (6 mg/kg/day).

- **Numerically, masitinib 6.0 mg/kg/day titration was comparable to masitinib 4.5 mg/kg/day**
- **However, the placebo comparator for the 6.0 mg/kg/day titration showed an abnormal improvement in EDSS change, driven by PPMS patients (while the placebo comparator for the 4.5 mg/kg/day dosing what in line with the literature)**
- **Consequently, the 6.0 mg/kg/day titration scheme is not conclusive**
- **Given the positive benefit/risk balance with 4.5 mg/kg/day, the 6.0 mg/kg/day titration scheme will no longer be pursued in MS.**

Next steps

- **AB Science intends to present detailed study results at one or more major scientific conference in the next 6 months.**

- **AB Science will consult with the FDA (through EOP2 meeting) and with the EMA (through Scientific Advice) to discuss the appropriate pathway forward for masitinib in the treatment of progressive forms of multiple sclerosis.**
  - Possibility to file based on study as single pivotal trial
  - Design of confirmatory study if required

Intellectual Property

Masitinib IP rights are secured up to 2031 in multiple sclerosis, and potentially until 2040 with patent recently filed based on AB07002 study results.

Protection	Item	Duration of protection	Status
Phase 2/3 'Method of use' patents	Multiple sclerosis	Until 2031	Delivered
Phase 2/3 'Method of use' patents	Progressive forms of Multiple sclerosis	Until 2040	Filed

Discussion

The clinical data are extremely encouraging and provide new hope for progressive MS patients.

Patrick Vermersch

- **There is a high unmet medical need for people with PPMS and nSPMS**
  - PPMS and nSPMS account for half of all MS patients.
  - Numerous treatments based on targeting of B-cells and T-cells of the adaptive immune system are available for patients with relapsing forms of MS.
  - These strategies have failed or had inconclusive results in PPMS and nSPMS.
- **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.
  - Masitinib compares favorably vis-à-vis ocrevus, siponimod, and biotin.

Discussion

Robert FOX, MD

- **About Bob Fox**
  - Staff Neurologist at the Mellen Center for Multiple Sclerosis.
  - Professor of Neurology at Cleveland Clinic Lerner College of Medicine
  - Vice-Chair for Research of the Neurological Institute, Cleveland Clinic
  - Board member of the European Charcot Foundation.
  - Published over 200 peer-reviewed papers, book chapters, and books.
  - Managing Director of the NARCOMS MS Patient Registry, which currently follows over 10,000 people with MS
  - Advisor for many phase I, II, III, and IV clinical trials.
  - Member of various advisory and review committees for the National MS Society (USA), International Progressive MS Alliance, the General Advisory Council for the Cleveland Clinic Clinical Research Unit, the Editorial Board of *Neurology* and *Multiple Sclerosis Journal*

- **Role in masitinib program**
  - Willing to take an active role for future steps of masitinib program in progressive forms of MS.

Discussion

These results represent a significant advancement for progressive forms of MS.

Robert Fox

- **There is a high unmet medical need for people with PPMS and nSPMS**
  - About half of MS patients have PPMS and nSPMS.
  - Numerous treatments target the adaptive immune system in relapsing forms of MS. These strategies have generally not worked well in PPMS and nSPMS.
- **The clinical data are supported by the mechanism of action of masitinib**
  - RRMS and active SPMS are predominantly driven by peripherally-driven, adaptive immunity (e.g. B cell and T cell lymphocytes). Progressive MS (PPMS and nSPMS) are predominantly driven by other mechanisms, notably the innate immune system and possibly other mechanisms.
  - Masitinib is the first drug targeting microglia, astrocytes, and mast cells, and thus has a distinctive and more relevant mechanism of action.
- **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

Discussion

Friedemann PAUL, MD

- **About Friedemann Paul**
  - Professor of Clinical Neuroimmunology and head of the neuroimmunology outpatient clinic at the Experimental and Clinical Research Centre (Berlin, Germany).
  - Co-chairs Charité's Clinical and Experimental Multiple Sclerosis (MS) Research Centre (Berlin, Germany)
  - Main research areas are novel imaging techniques in autoimmune disorders of the CNS, the visual system in neuroimmunological disorders, and fatigue and cognition in MS and related conditions.
  - Authored and co-authored more than 300 papers in the field of clinical and basic neuroimmunology.

- **Role in masitinib program**
  - Willing to take an active role for future steps of masitinib program in progressive forms of MS.

Friedemann Paul

The clinical results obtained with masitinib validate the relevance of targeting mast cells and microglia in progressive forms of multiple sclerosis.

Friedemann Paul

- **The medical need for people with PPMS and nSPMS is still very high**
  - Patients PPMS and nSPMS are severely disabled by the progression of there disease.
  - While significant progresses have been made in the relapsing forms of MS, PPMS and nSPMS remains in high need for effective and complementary therapies.
- **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.

Q&A Cession