Masitinib in primary progressive (PPMS) and non-active secondary progressive (nSPMS) multiple sclerosis: Results from phase 3 study AB07002

P. Vermersch[1], O. Hermine[2] (on behalf of the AB07002 Study Group)

[1] University Lille, Inserm U1172, CHU Lille, FHU Imminent, Lille, France

[2] Imagine Institute, INSERM UMR 1163 / CNRS ERL 8254, Hôpital Necker, Paris, France

Rationale: The innate immune system plays a critical role in progressive forms of MS

- Emerging evidence indicates that *Primary Progressive MS* and *non-active Secondary Progressive MS* (nSPMS) are driven in part by activity of the innate immune system, compartmentalized within the CNS

- Microglia and mast cells are types of innate immune cells present in the CNS that are strongly associated with the pathophysiology of MS

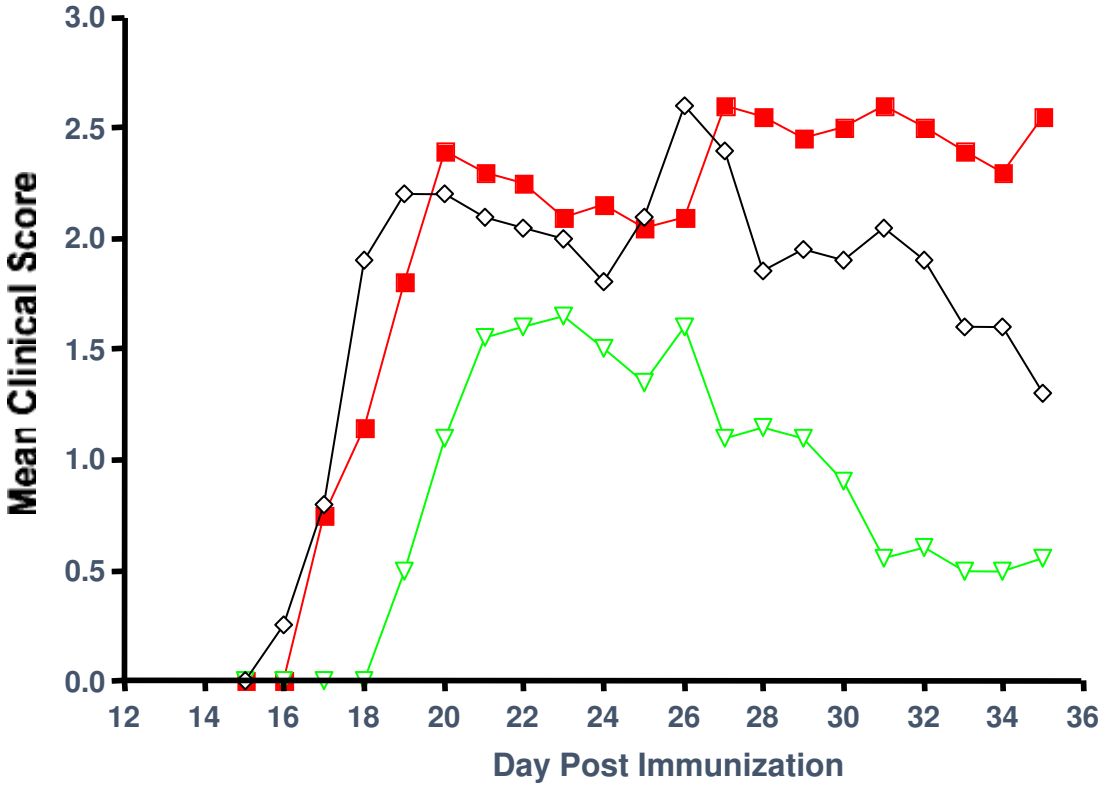
- Targeting innate immunity-related MS disease progression via modulation of mast cells and activated macrophage/microglia, may slow or prevent worsening of disability in progressive MS

- Masitinib, an oral tyrosine kinase inhibitor, selectively targets mast cell activity (c-Kit, LYN, FYN) and microglia activity (CSF1R). Masitinib has previously demonstrated neuroprotective action in preclinical models of various neurological conditions (amyotrophic lateral sclerosis and Alzheimer's disease [1−5]).

Ref: [1] Trias E, et al. Glia. 2020;68(6):1165-1181. [2] Trias E, et al. JCI Insight. 2018;3(19):e123249. [3] Trias E, et al. JCI Insight. 2017;2(20):e95934. [4] Trias E, et al. J Neuroinflammation. 2016;13(1):177. [5] Li T, et al. 1 Jan.2020:1–7.

Preclinical and clinical proof-of-concept

- The potential of masitinib in MS was explored using a MOG-induced experimental allergic encephalomyelitis (EAE) model, with a significant reduction in disease observed at a clinically relevant dose [1].
- It is established that mast cells are necessary for the full manifestation of disease in this model [2].



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

- Proof-of-concept that masitinib slows progressive forms of MS was also demonstrated in a small trial (n = 35) [1]

Ref: [1] Vermersch P, et al. BMC Neurol. 2012 Jun 12;12:36.
[2] Secor VH, et al. J Exp Med 2000;191(5):813–821.

Study AB07002 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-arm study)
  1. Masitinib 4.5 mg/kg/d versus its own placebo (300 patients randomization 2:1)
  2. Masitinib titration up to 6.0 mg/kg/d versus its own placebo (300 patients randomization 2:1)
- Statistically, study AB07002 is treated as two independent sub-studies under a common study identifier, with alpha control set at 5% for each dose

❖ Main inclusion criteria

- Patient with PPMS or nSPMS defined as:
  - No relapse, as measured by Expanded Disability Status Scale (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
- EDSS and age requirements
  - EDSS score of [2.0 to 6.0] inclusive at baseline
  - Age 18 to 75 years old

Study AB07002 key efficacy endpoints

- **Primary endpoint: Change from baseline in absolute EDSS value averaged over the 2-year study**
  - Mean of all changes from baseline in EDSS, measured at 8 time points for each pt (every 12 weeks from W12−W96)
  - Primary analysis calculated using a GEE model (generalized estimating equation)
    - Allows for analysis of repeated measurements and adjusts for correlation across variables and across time
    - Gives the true treatment-effect over the 2 year study
  - The primary analysis *is not* a one-time ANCOVA test of the last EDSS value measured at week 96

Study AB07002 key efficacy endpoints

- **Sensitivity analysis of the primary endpoint**
  - **Change from baseline in ordinal EDSS score averaged over the 2-year study**
    - Gives the probability of a patient having either more improvements in EDSS or fewer worsening EDSS scores with masitinib treatment relative to placebo
    - Change over time is measured using an ordinal score (+1 improvement; 0 stable; -1 worsening). Mean of all ordinal EDSS changes from baseline measured at 8 time points for each pt (every 12 weeks from W12−W96)
  - **Jump-to-reference imputation method.** Missing data related to discontinuation of masitinib treated patients due to lack of efficacy or a safety event were replaced by placebo imputed data.
  - **Risk of EDSS progression (time-to-event) - First onset and 3-month confirmed (Kaplan-Meier analysis)**
  - **Risk of progression to an EDSS score of 7.0 - First onset and 3-month confirmed (Kaplan-Meier analysis)**

Baseline Characteristics - Masitinib 4.5 mg/kg/d

- **Patients were enrolled at an advanced stage of disease, reflecting a difficult-to-treat population**
- **Baseline characteristics were balanced between the treatment-arms**

		Masitinib	Placebo
Number randomized		200	101
Sex [n (%)]	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 randomization (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 baseline EDSS	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)

- **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

Primary Endpoint Results - Masitinib 4.5 mg/kg/d

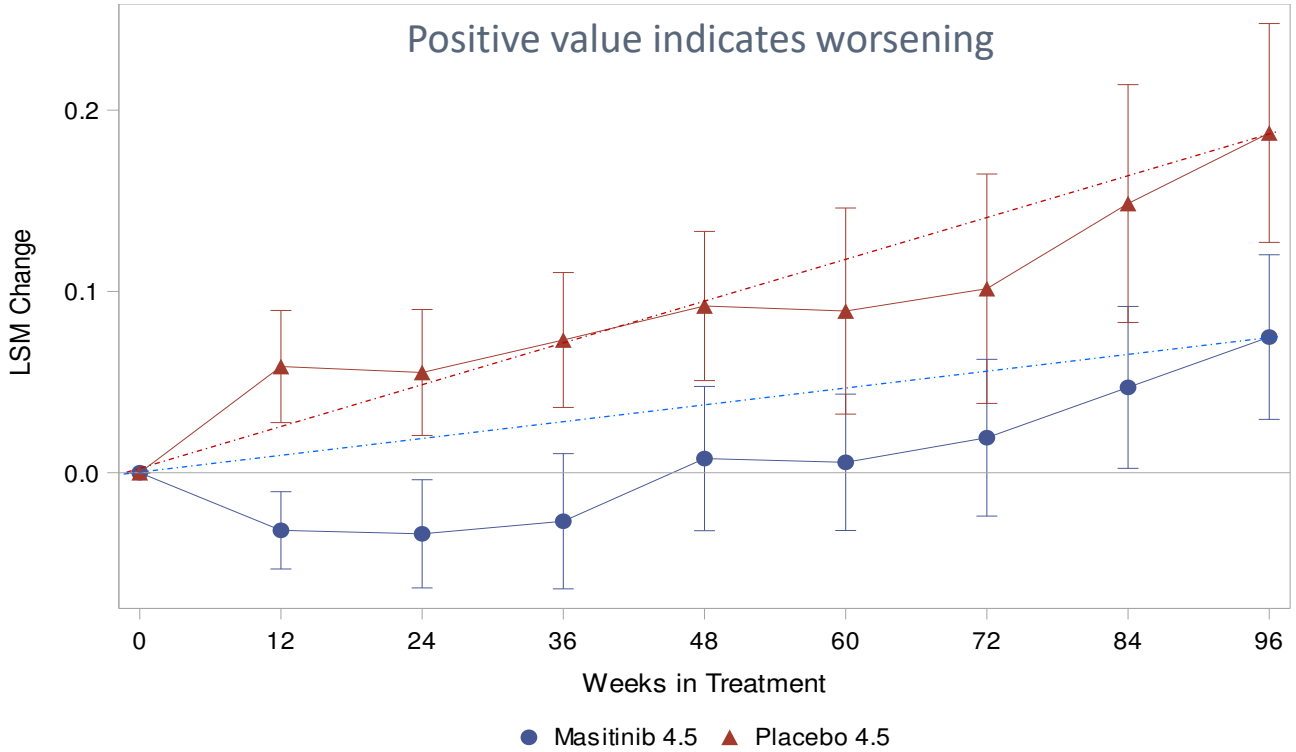
Study AB07002 met its primary analysis, demonstrating a statistically significant reduction in disability progression on EDSS (p=0.0256)

❖ **Primary analysis - Mean of absolute changes from baseline in EDSS measured every 12 weeks up to week 96**

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

Treatment	N	Means	Means Difference	p-value
Primary Analysis				
Masitinib 4.5 mg/kg/d	199	0.001	-0.097	0.0256
Placebo	101	0.098		
PPMS subgroup				
Masitinib 4.5 mg/kg/d	79	0.029	-0.128	
Placebo	45	0.158		
nSPMS subgroup				
Masitinib 4.5 mg/kg/d	120	-0.052	-0.104	
Placebo	56	0.051		

❖ **Visualization of absolute changes from baseline in EDSS measured every 12 weeks up to week 96**



Primary Endpoint - Sensitivity Analyses

The positive primary outcome was corroborated by numerous sensitivity analyses

- **This included the conservative multiple imputation technique known as 'Jump-to-Reference'**
  - Primary analysis maintained a significant reduction in disability progression on EDSS (p=0.0367) even when missing data related to discontinuation of masitinib treated patients due to lack of efficacy or a safety event were replaced by placebo imputed data

Mean of absolute changes from baseline in EDSS measured every 12 weeks up to week 96

Treatment	N	Means	Means Difference	p-value
Jump-to-Reference Sensitivity Analysis				
Masitinib 4.5 mg/kg/d	199	0.015	-0.089	0.0367
Placebo	101	0.105		

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

Ordinal EDSS Results - Masitinib 4.5 mg/kg/d

Sensitivity analysis based on ordinal EDSS change showed a significant, 39% increased probability of having either more improvements in EDSS or fewer worsening EDSS scores with masitinib

- **Instead of the change in absolute EDSS, change is measured with an ordinal score:**
  - -1 if worsening in EDSS*
  - +1 if improvement in EDSS†
  - 0 if EDSS is stable

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

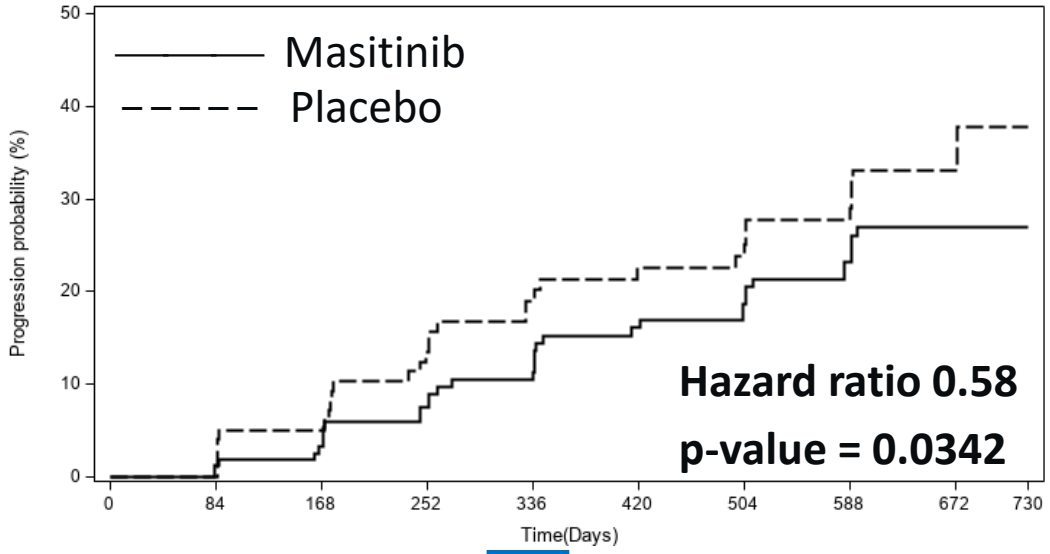
Treatment	N	Odds Ratio	p-value
Masitinib 4.5 mg/kg/d	199	0.61	0.0446
Placebo	101		

- **0.61 odds ratio (masitinib vs placebo)**
- **Corresponds to a 39% increased probability with masitinib of having either more improvements in EDSS or fewer worsening EDSS scores**

Risk of EDSS progression - Masitinib 4.5 mg/kg/d

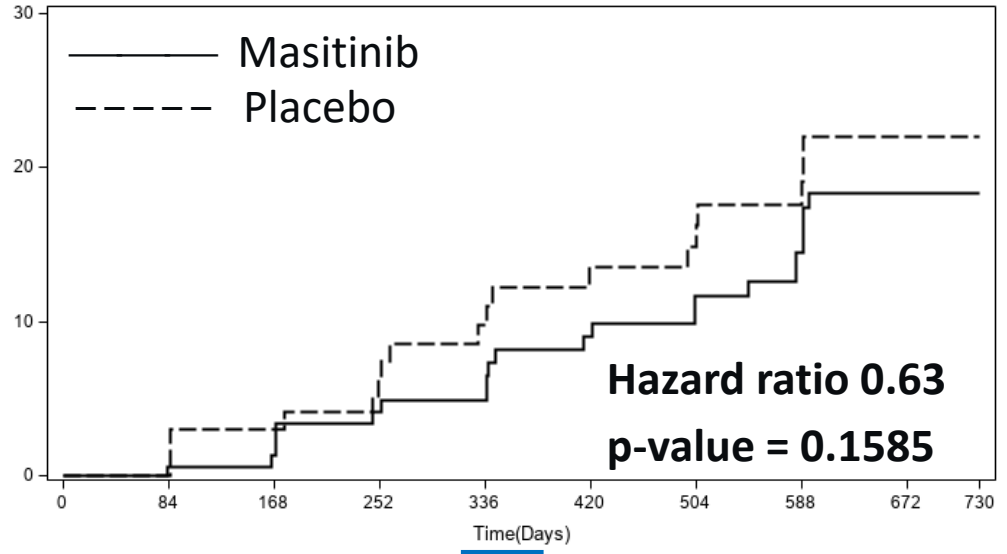
Masitinib reduced the risk of first disability progression by 42% and the risk of confirmed (3-month) disability progression by 37%

❖ **Kaplan-Meier analysis - cumulative probability of reaching first EDSS progression**



Significant 42% reduction in the risk of first disability progression over a timeframe of 96 weeks

❖ **Kaplan-Meier analysis - cumulative probability of a confirmed EDSS progression**

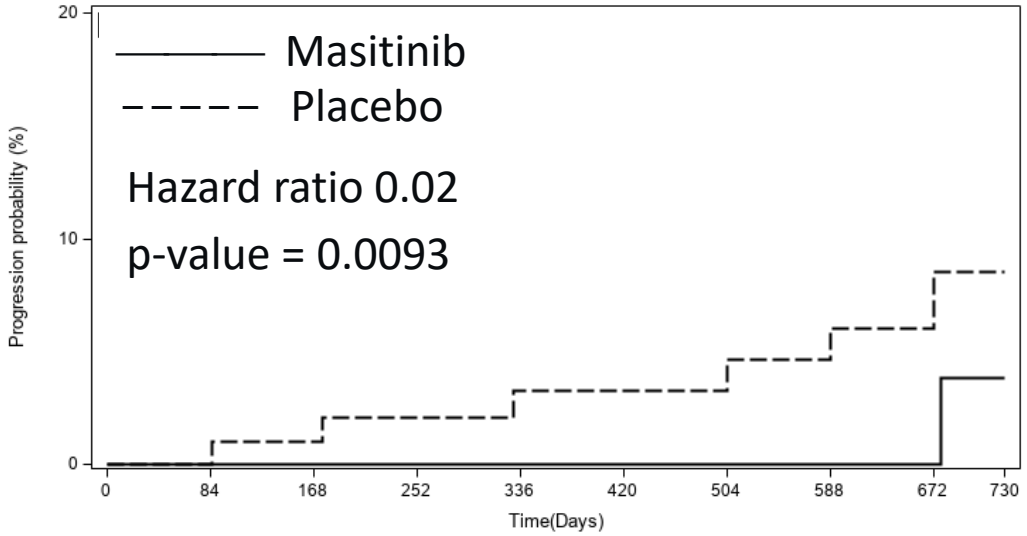


37% reduction in the risk of confirmed disability progression over a timeframe of 96 weeks

Risk of progression to EDSS[7.0] - Masitinib 4.5 mg/kg/d

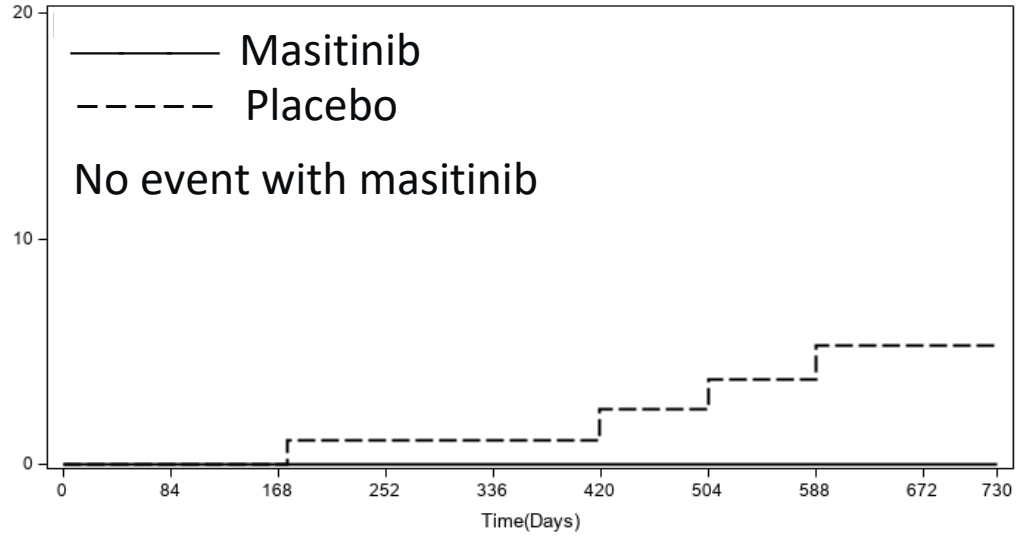
Masitinib also significantly reduced the risk of reaching an EDSS score of 7.0, corresponding to disability severe enough that the patient is restricted to a wheelchair

❖ **Kaplan-Meier analysis - cumulative probability of reaching an EDSS score of 7.0**



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

❖ **Kaplan-Meier analysis - cumulative probability of a confirmed (3-month) EDSS score of 7.0**



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

Safety - Masitinib 4.5 mg/kg/d

Safety was consistent with known masitinib profile with no new safety signals observed

- Safety dataset excluded 1 patient from ITT population because of no intake of study drug
- Adverse events (any grade) occurring most frequently for masitinib (MAS) compared with placebo (PBO) were: diarrhea, maculopapular rash, nausea/vomiting, peripheral edema, pruritus and various laboratory assessments

❖ **Safety summary of treatment-emergent adverse events (AE) over the 96-week treatment period**

Patients with ≥1 event	MAS (n=199)	PBO (n=101)
AE (any grade)	**94.5%** (188)	**87.1%** (88)
AE leading to death	**0%** (0)	**2.0%** (2)
Serious AE (non-fatal)	**21.1%** (42)	**12.9%** (13)

❖ **Non-fatal serious adverse events occurring in ≥2 patients over the 96-week treatment period**

Patients with ≥1 event	MAS (n=199)	PBO (n=101)	Δ[M–P] (%)
Rash Maculo-Papular	**1.5%** (3)	**0%** (0)	**1.5%**
Erythema Multiforme	**1.0%** (2)	**0%** (0)	**1.0%**
GGT Increased	**1.0%** (2)	**0%** (0)	**1.0%**
Neutropenia	**1.0%** (2)	**0%** (0)	**1.0%**
PP Erythrodysesthesia	**1.0%** (2)	**0%** (0)	**1.0%**
Urinary Tract Infection	**1.0%** (2)	**1.0%** (1)	**0%**
MS Relapse	**2.0%** (4)	**3.0%** (3)	**-1.0%**

Masitinib 6.0 mg/kg/d - Primary Analysis

Results from the second parallel group, with a titrated target masitinib dose of 6.0 mg/kg/d, did not show any significant difference between treatment-arms

- Numerically, masitinib 6.0 mg/kg/d titration change in EDSS was comparable to the masitinib 4.5 mg/kg/d result; therefore, only the masitinib 4.5 mg/kg/d dose will be pursued further in MS
- Placebo-arm of the masitinib 6.0 mg/kg/d titration cohort unusually showed an improvement relative to baseline after 96 weeks (conversely, the placebo comparator for the 4.5 mg/kg/d cohort was consistent with the literature and expected worsening in EDSS score over 96 weeks)
- No new safety signal was observed

Conclusions

Masitinib, a first-in-class tyrosine kinase inhibitor targeting the innate immune system via inhibition of mast cell and microglia/macrophage activity, may provide a new treatment option for PPMS and non-active SPMS

- **Study AB07002 demonstrated a sustained and significant benefit for masitinib (4.5 mg/kg/d) in EDSS change over a 2-year duration**
- **The 37% reduction in risk of confirmed disability progression is relevant from a medical standpoint**
- **Benefit was demonstrated across a broad population**
  - Little or no restriction on age, duration of disease or baseline disability
  - Inclusive of both progressive MS phenotypes (PPMS and nSPMS)
  - Irrespective of baseline active inflammation status
- **Masitinib safety profile is suitable for long-term administration in this population**

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