Masitinib Mechanism of Action

Tyrosine Kinase[1]

- Activated via either transmembrane receptor or intracellularly
  - 58 known mammalian receptor tyrosine kinases (RTKs)
- Tyrosine kinase inhibitors (TKIs) – primarily used in cancer treatment
  - Currently being studied for a variety of neurologic conditions, including ischemic stroke, Alzheimer's, ALS, and MS

Differences Between Masitinib and BTK Inhibitors

Masitinib[1]

- Selective tyrosine kinase inhibitor (TKI) with strong affinity for c-kit receptor (an RTK)
  - Also binds to RTK growth factor receptors PDGRF and FGFR3, as well as non-receptor TKs (NRTKs) Lck/Lyn and FAK
- Inhibits activity of mast cells, microglia, and macrophages

BTK inhibitors[2]

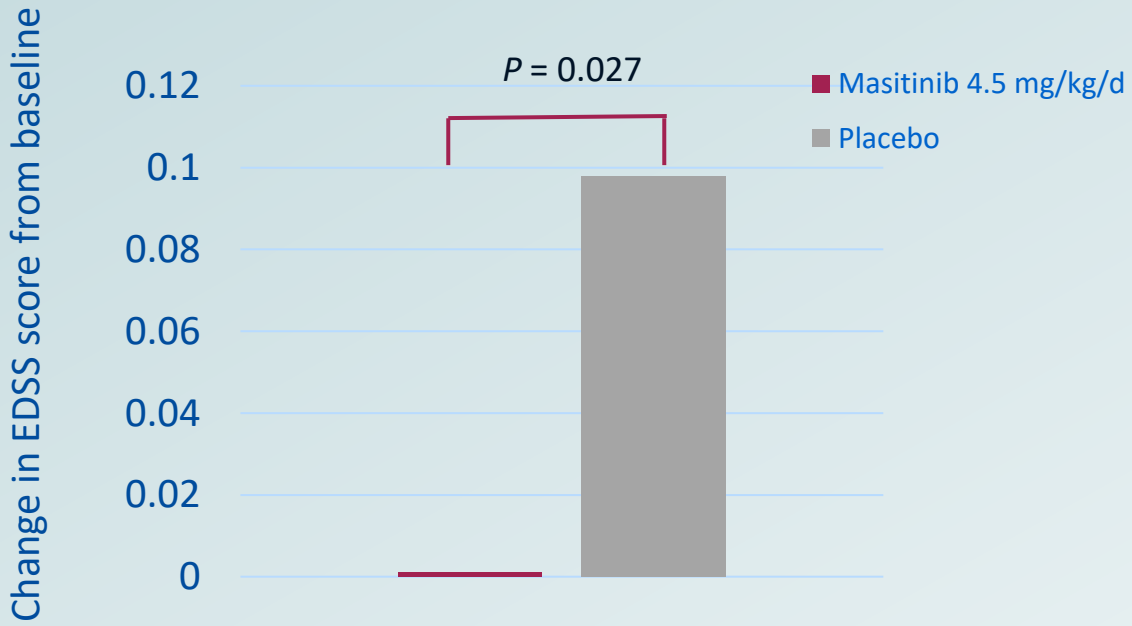
- Inhibit a nonreceptor tyrosine kinase with increased expression in autoreactive cells – Bruton's tyrosine kinase
- Crosses the blood brain barrier

ALS, amyotrophic lateral sclerosis; BTK, Bruton's tyrosine kinase.

1. Gągało I et al. *Curr Neuropharmacol*. 2015;13:836-844; 2. Garg N et al. *J Clin Med*. 2022;11:6139.

Masitinib Efficacy in PPMS and nonactive SPMS: Results from Phase 3 Placebo-Controlled Trial

Primary Endpoint: Change in EDSS scores from baseline, 96-week trial*



Note: A parallel group, titrated to masitinib 6.0 mg/kg/d, showed no significant masitinib effect. Results were complicated by an uncharacteristic early and robust response to placebo.

Secondary Endpoints: Change from baseline, 96-week trial*

Endpoints*	Overall	nSPMS	PPMS
MSFC	NS	NS	NS
Timed 25-foot walk test	NS	NS	NS
9-hole peg test	*P* = 0.039	*P* = 0.02	NS
PASAT-3	NS	NS	NS
MSQOL-54 physical and mental health subscores	NS	NS	NS
EQ-VAS	NS	*P* = 0.029	NS

A second phase 3 clinical trial is needed to

- Collect MRI data
- Establish efficacy for secondary endpoints

*Adjusted using generalized estimating equation using time points at 12-week intervals, for 96 weeks

EDSS, Expanded Disability Status Scale; EQ-VAS, health state visual analogue scale; MSFC, multiple sclerosis functional composite; MRI, magnetic resonance imaging; MSQOL-54, multiple sclerosis quality of life; NS, non-significant; nSPMS, nonactive secondary progressive multiple sclerosis; PASAT-3, paced auditory serial addition test-3; PPMS, primary progressive multiple sclerosis. Vermesch P et al. *Neurol Neuroimmunol Neuroinflamm*. 2022;9:e1148.

Masitinib Safety Profile in nSPMS and PPMS Clinical Trial

- Masitinib was not associated with increased risk of infections or serious infections
- Treatment-related discontinuation greater for masitinib groups than placebo
  - Most AEs leading to discontinuation could be managed with dose reduction or temporary interruption
- Rate of SAEs greater for masitinib groups than placebo
  - Most common SAEs were maculopapular rash, erythema multiforme, elevated gamma-glutamyl transferase, neutropenia, and palmar-plantar erythrodysesthesia syndrome

	Masitinib 4.5 mg/kg/d		Masitinib titrated to 6.0 mg/kg/d	
	Masitinib (n = 199)	Placebo (n = 101)	Masitinib (n = 203)	Placebo (n = 107)
SAEs	21.1%	12.9%	23.2%	10.3%
AEs leading to permanent discontinuation	20.6%	2.0%	21.2%	8.4%

AE, adverse event; nSPMS, nonactive secondary progressive multiple sclerosis; PPMS, primary progressive multiple sclerosis; SAE, serious adverse event.

Vermesch P et al. *Neurol Neuroimmunol Neuroinflamm*. 2022;9:e1148.