AB SCIENCE

Emerging pharmaceutical company
in targeted therapies

MASITINIB IN PROGRESSIVE FORMS OF MULTIPLE SCLEROSIS

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HIGH UNMET MEDICAL NEED

Multiple Sclerosis (MS) in its progressive forms is a prevalent disease that continues to remain a high unmet medical need.

- **Large prevalent disease**
  - Characterized by continuous disease progression of disease, i.e. without relapses and remissions.
  - Prognosis is considered as poor due to the relatively rapid development of advanced disability as compared with relapsing remitting MS.
  - Progressive forms of multiple sclerosis represent around 60% of patients.
  - ≈400.000 prevalent cases in USA and Europe.
- **Lack of satisfactory treatment**
  - No drug registered progressive forms of MS.
  - All drugs registered in relapsing forms of MS and developed in progressive forms of MS have failed so far to demonstrate efficacy.

MS - STUDY RATIONALE

Data from the literature show that mast cells can actively participate in the pathogenesis of MS.

- Multiple sclerosis (MS) is an inflammatory disease of the central nervous system (CNS).
- The presence of mast cells (MCs) and increased concentration of MCs constituent have been reported in MS plaques. MCs are clustered close to the wall of venules and capillaries [1].
- Growing evidences suggest that MCs play a crucial role in the inflammatory process and the subsequent demyelination observed in patients suffering from MS. Recent results from animal models clearly indicate that MCs act at multiple levels to influence both the induction and the severity of disease.
- MCs are involved in experimental model of demyelination including experimental allergic encephalomyelitis (EAE).
  - Inhibitors of mast cells (hydroxyzine) have been found to effectively inhibit the progression and severity of clinical signs of EAE, and the extent of mast cells degranulation [2].
  - Nedocromyl sodium, a mast cell stabilizer, have also successfully delayed and prevented the development of EAE [3].
  - Last, the EAE model in mast cell-deficient W/Wv mice exhibited significantly reduced disease incidence, delayed disease onset, and decreased mean clinical scores [4].

  These data suggest that MCs degranulation is crucial to the development of this model and that MCs inhibition could be a therapeutic approach in the treatment of MS.

[1] P. G. Krüger and al. Mast cells and multiple sclerosis: a quantitative analysis. Neuropathology and Applied Neurobiology. 2001;27:275-280.
[2] V. Dimitriadou et al. Hydroxyzine inhibits experimental allergic encephalomyelitis (EAE) and associated brain mast cell activation.International Journal of Immunopharmacology. 2000;22:673-684.
[3] P. A. Seeldrayers and al. Treatment of experimental allergic neuritis with nedocromil sodium. Journal of Neuroimmunology 1989;25:221-226.
[4] V. H. Secor and al. Mast Cells Are Essential for Early Onset and Severe Disease in a Murine Model of Multiple Sclerosis. The Journal of Experimental Medicine 2000;191(5):813–821.

MS - STUDY RATIONALE

Masitinib has been designed to be a selective blocker of mast cells (through c-kit, Lyn and Fyn tyrosine kinases) and is well profiled for multiple sclerosis.

Masitinib potency

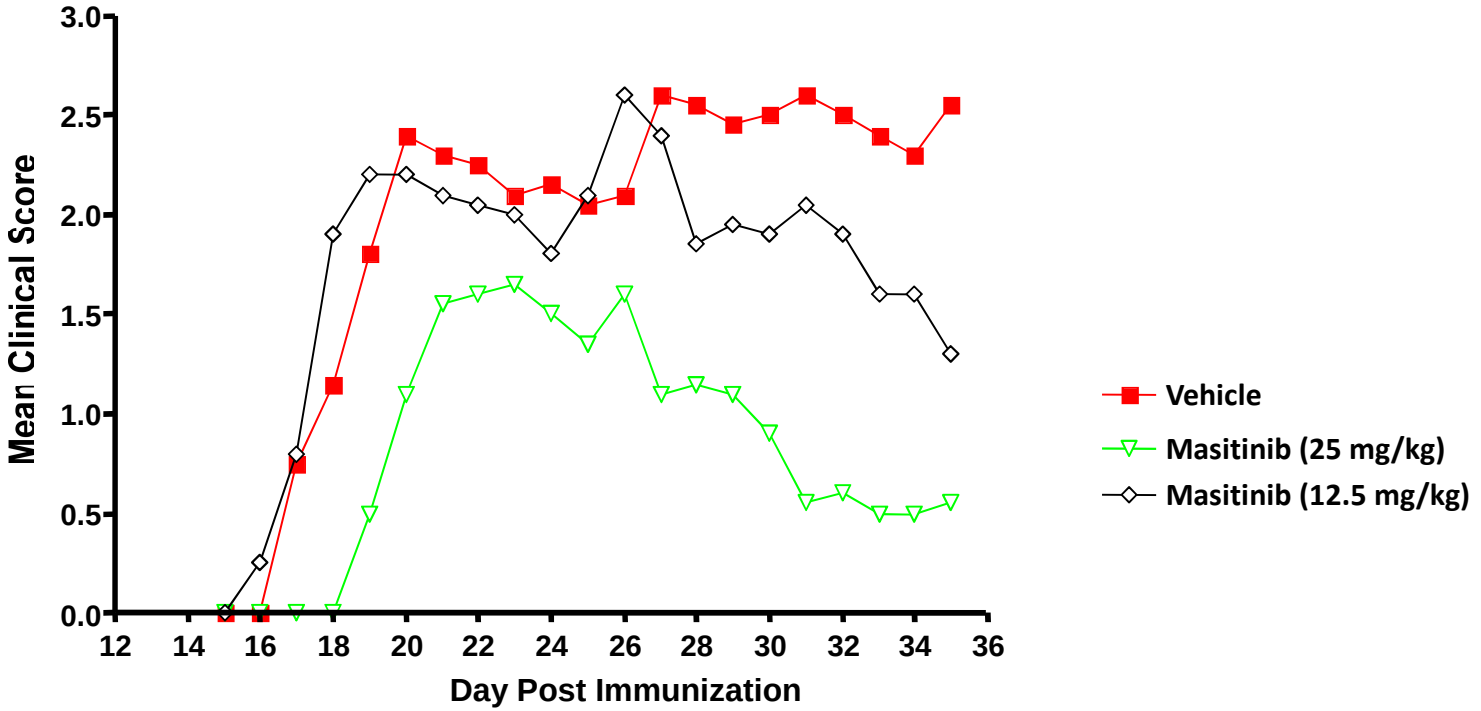
Target / IC50 [µM]	Enzymatic Assay
c-KIT Wild type	0.02
FYN	0.24
LYN	0.225

1. PLoS One. 2009 Sep 30;4(9):e7258. doi: 10.1371/journal.pone.0007258.
2. Nat Biotechnol. 2011 Oct 30;29(11):1046-51. doi: 10.1038/nbt.1990.

MS – PRE-CLINICAL PROOF OF CONCEPT

Masitinib induces significant delay in the onset of multiple sclerosis symptoms in EAE mice model.

Results in an experimental allergic encephalomyelitis (EAE) murine model



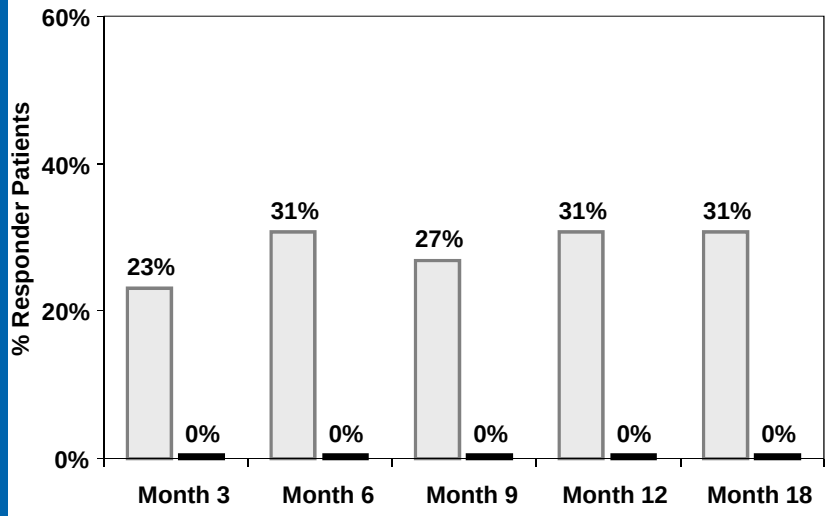
treatment starts day 0

MS - CLINICAL PHASE 2A PROOF OF CONCEPT

Signs of activity in clinical proof of concept phase 2a has been established.

MSFC

Percentage of Responder Patients at Each Time-point



legend

Masitinib **Placebo**

Definition of responder :

Patient with an increase in MSFC score ≥ 100% from baseline

MSFC

Change in % between baseline and Time-point

		M3	M6	M9	M12	M18
ALL	AB1010	24	24	24	24	24
		146±360	152 ± 286	123±296	124±256	116±257
	Placebo	6	6	6	6	6
		-20±112	-15±130	-15±114	-25±113	-26±113
Primary progressive	AB1010	10	10	10	10	10
		218±490	147±309	139±382	140±313	141±313
	Placebo	4	4	4	4	4
		22±38	23±86	21±29	15±51	15±51
Secondary progressive	AB1010	14	14	14	14	14
		95±237	155±280	111±232	111±218	99±220
	Placebo	2	2	2	2	2
		-103±195	-89±214	-88±215	-104±193	-107±189

PHASE 3 AB07002 - DESIGN

Phase 3 study on-going.

Study design	▪ Patients with primary progressive or relapse-free secondary progressive multiple sclerosis ▪ Blinded, placebo controlled ▪ 96 week treatment period ▪ 600 patients
Clinical Endpoint	▪ Change in MSFC ▪ Change in Multiple Sclerosis Quality of Life 54 items (MSQOL-54) ▪ Change in EDSS
Primary hypothesis	▪ Superiority of masitinib over placebo ▪ p-value < 0.05
Dosing	Randomization 2:1 2 doses versus placebo ▪ masitinib at 4.5 mg/kg/day or placebo ▪ masitinib at 4.5 mg/kg/day with a dose escalation to 6 mg/kg/day after three months of treatment, or placebo

PHASE 3 AB07002 – SAFETY REVIEW

Phase 3 study AB07002 passed Safety review from the DSMB.

- **Safety : Independent Data and Safety Monitoring Board (DSMB) reviews every 6 months safety data**
  - DSMB reviewed twice the safety data of the study in the past 12 months, the last review being performed in June 2015
  - On this basis, the IDMC recommended the continuation of the study

PHASE 3 AB07002 – FUTILITY ANALYSIS

Phase 3 study AB07002 passed successfully futility test performed by the DSMB.

- Definition of the futility test
  - Test the inability of a clinical trial to achieve its efficacy objective
  - Not aimed to stopped study for early efficacy (different from interim analysis)
  - Sponsor has no access to the data, only DSMB has access to the data
- Futility test
  - Performed after approximately one third of the planned study population had reached the 48 week treatment duration period
  - Hypothesis that all the remaining patients to be enrolled in the study will follow the trend observed on the patient already enrolled at the time of futility analysis.
  - P-value below 5%
  - Conditional power (predictive probability of success) of 20%

Importantly, the IDMC highlighted that the study was not futile on the three main assessment criteria, MSFC, MSQOL-54, and EDSS.

A second futility analysis will be done once 33% of patients have reached the 96 week time point

PHASE 3 AB07002 - INTERIM ANALYSIS

An interim analysis is pre-planned in the protocol and includes a resampling adaptative option

Interim analysis

- Will be performed with 50% of patients
- Possibility for filing for conditional registration and continue in parallel recruitment of phase 3
- Adaptative option to increase the sample size of the study for the final analysis by a factor of up to 2 if there is a trend of efficacy but more patients are needed to achieve statistical significance
- Consequently : 4 possible outcomes
  a. Interim analysis is a success. Depending on discussion with agencies and ethical committee there is a possibility that study could be stopped and a registration dossier filed.
  b. Interim analysis fails but study continues without re-sampling. This implies that the study is expected to be a success following recruitment of the 50% remaining patients, based on projected trends.
  c. Interim analysis fails but study continues with re-sampling. This means that by increasing the sample size by a maximum factor of 2 the study is expected to be a success.
  d. Interim analysis fails and study stops. This means that even by doubling the sample size, the study is expected to fail. This scenario, which corresponds to stating that the study is futile, is however less likely to occur since the study has successfully passed the futility test with one third of the patients enrolled.

PHASE 3 AB07002 - INTERIM ANALYSIS

Given the re-sampling option of the interim analysis, the probability that the study succeeds for final analysis, with non futility passed with conditional power 20% and 33% of patients recruited, is more than 46%

If the study passes the futility test with 33% of patients recruited and with a predictive probability of success of	Then, with the predictive probability of success for final analysis with a resampling of x2 becomes :
20%	46%

Questions