AB SCIENCE

Emerging pharmaceutical company
in targeted therapies

MASITINIB IN AMYOTROPHIC LATERAL SCLEROSIS (ALS)

11 May 2015

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HIGH UNMET MEDICAL NEED

ALS is an orphan condition with high unmet medical need.

- **Life threatening and orphan disease**
  - Life-threatening neurological disease that causes muscle weakness, disability and eventually death.
  - 80% of patients die within 5 years, and only around 10% of patients live past 10 years.
  - ≈50.000 prevalent cases in USA and Europe (prevalence was 5.98/100,000 population*).
- **Lack of satisfactory treatment**
  - Only drug registered in this indication is Riluzole, which was registered in 1996.
  - All studies in this indication failed.

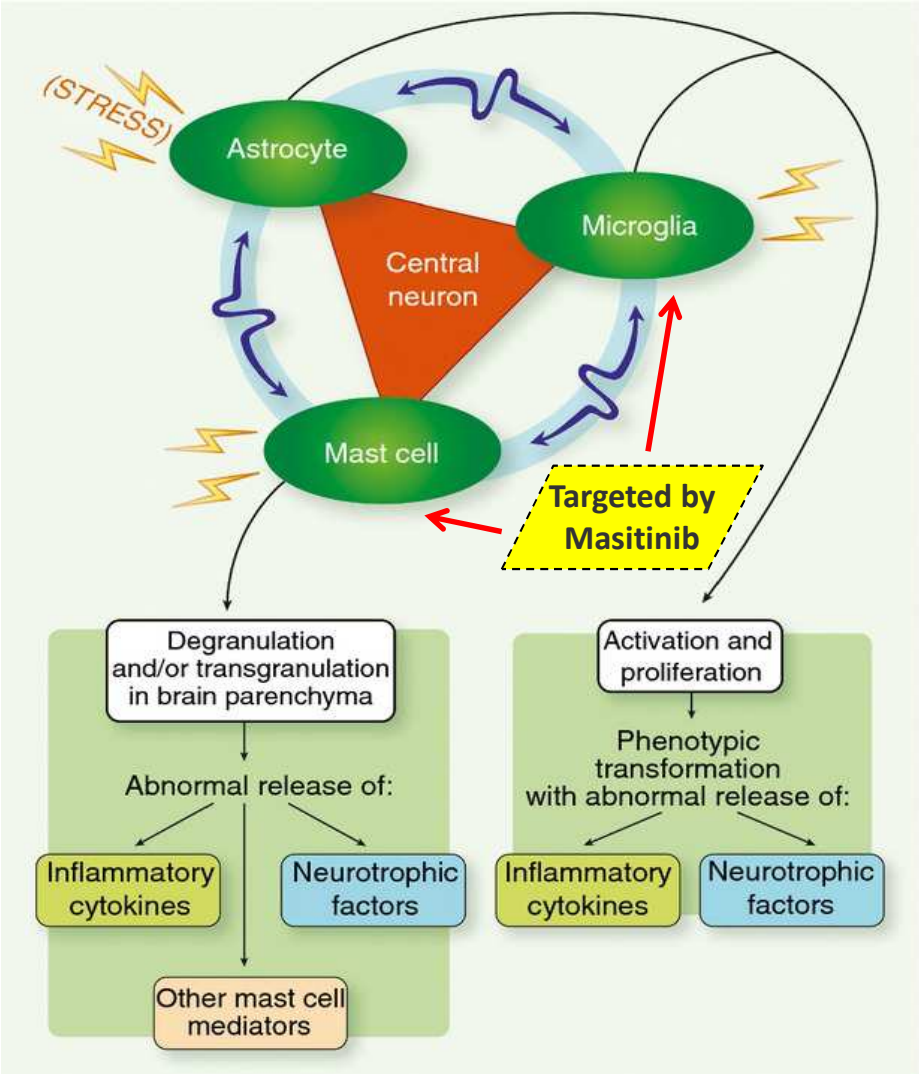
* meta-analysis from 7 studies

(1) Logroscino G *et al*. EURALS. Incidence of amyotrophic lateral sclerosis in Europe. *J Neurol Neurosurg Psychiatry*. 2010; 81:385-90
(2) Huisman MH *et al*. Population based epidemiology of amyotrophic lateral sclerosis using capture-recapture methodology. *J Neurol Neurosurg Psychiatry.* 2011; 82:1165-70
(3) Ragonese P *et al*. Incidence of amyotrophic lateral sclerosis in Sicily: A population based study. *Amyotroph Lateral Scler*. 2012; 13(3):284-7
(4) Abhinav K *et al*. Amyotrophic lateral sclerosis in South-East England: a population-based study. The South-East England register for amyotrophic lateral sclerosis (SEALS Registry). *Neuroepidemiology*. 2007;29:44-8
(5) Imam I *et al*. The epidemiology of motor neurone disease in two counties in the southwest of England. *J Neurol*. 2010; 257:977-81
(6) Hoppitt T *et al*. A systematic review of the incidence and prevalence of long-term neurological conditions in the UK. *Neuroepidemiology*. 2011; 36:19-28
(7) Gundersen MD *et al*. Incidence and Clinical Features of Amyotrophic Lateral Sclerosis in Møre and Romsdal County, Norway. *Neuroepidemiology.* 2011;37:58–63

ALS - STUDY RATIONALE

Several publications suggest that ALS is a neurodegenerative disorder in which cross-talk between microglia, mast cells and astrocytes may destroy motor neuron.

- Excessive and/or persistent exogenous and/or endogenous stimuli.
- Microglia–astrocyte–mast cell cross-talk and disregulation of these non-neuronal cells
- Neuroinflammation
- Damaging of central nervous system neurons

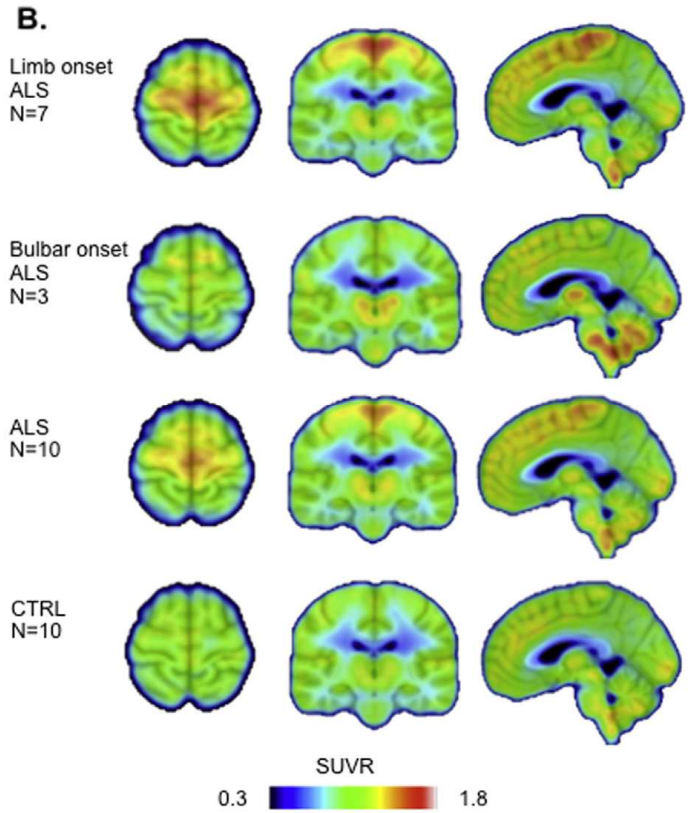


Immunology. 2014 Mar; 141(3): 314–327. Published online 2014 Feb 10. doi: 10.1111/imm.12170

ALS - STUDY RATIONALE

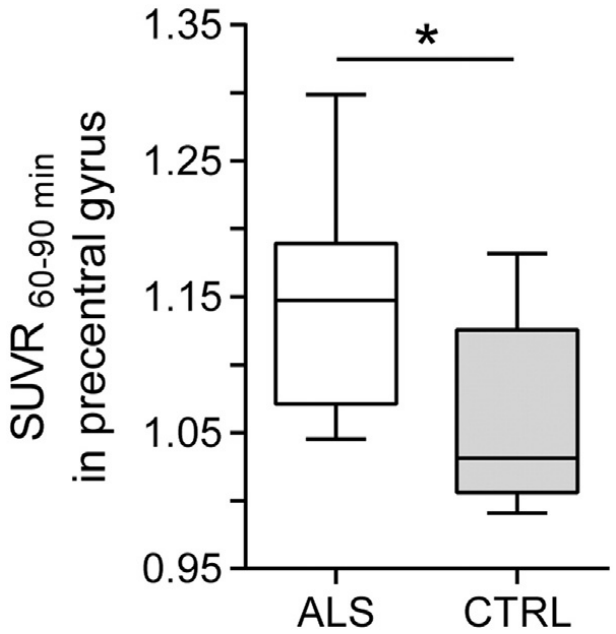
PET imaging using SUVR as a marker of glia confirms the activation of glia in patients with ALS.

PET Scan of ALS patient's brain versus control, using SUVR as a marker of glial activation



Mean [11C]-PBR28 SUVR60–90 min images for the ALS and control groups, including comparisons between limb- and bulbar-onset patients, shown at MNI coordinates x=−2, y=−20, and z=+64.

Measure of increased glial activation through SUVR marker in primary motor cortex in ALS patients.

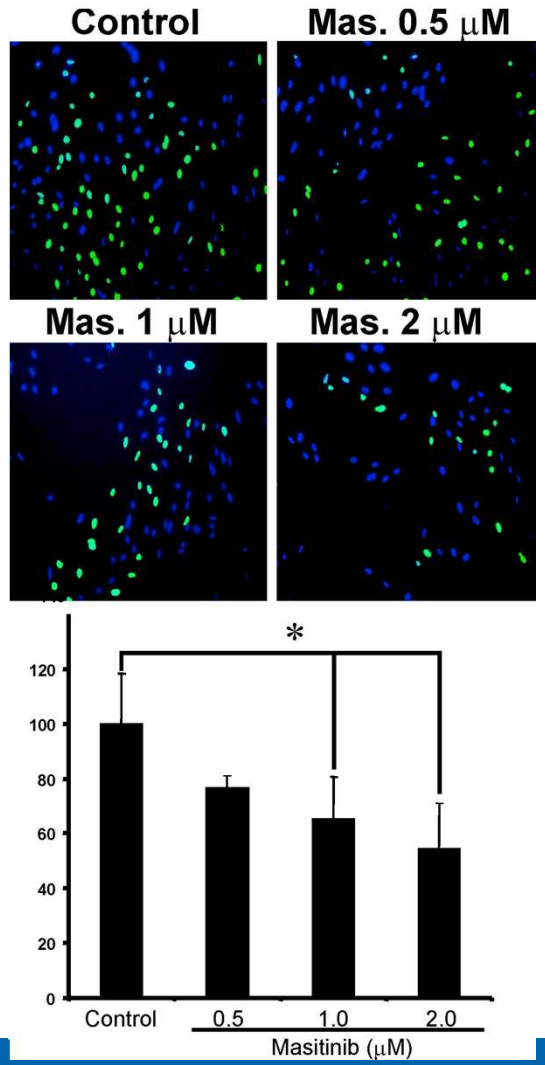


Boxplots for [11C]-PBR28 SUVR60–90 min for the precentral gyrus a priori ROI for individuals with ALS and healthy controls.
Patients with ALS exhibit significantly increased binding in the motor cortex compared to healthy controls, *p b 0.05.

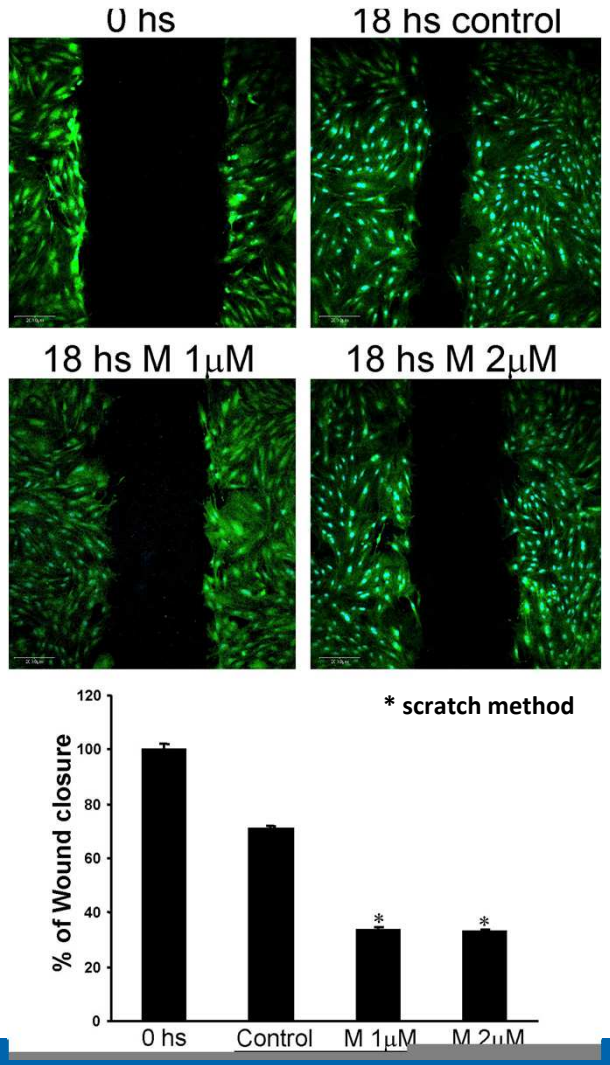
ALS - STUDY RATIONALE

Masitinib decreases cultured SOD1^{G93A} rodents microglia proliferation and astrocytes migration.

Masitinib decreases proliferating of microglial cells measured with Ki67+ , a marker of cells mitosis



Masitinib decreases the migration of SOD1^{G93A} astrocytes *, as illustratred in this monolayer visual



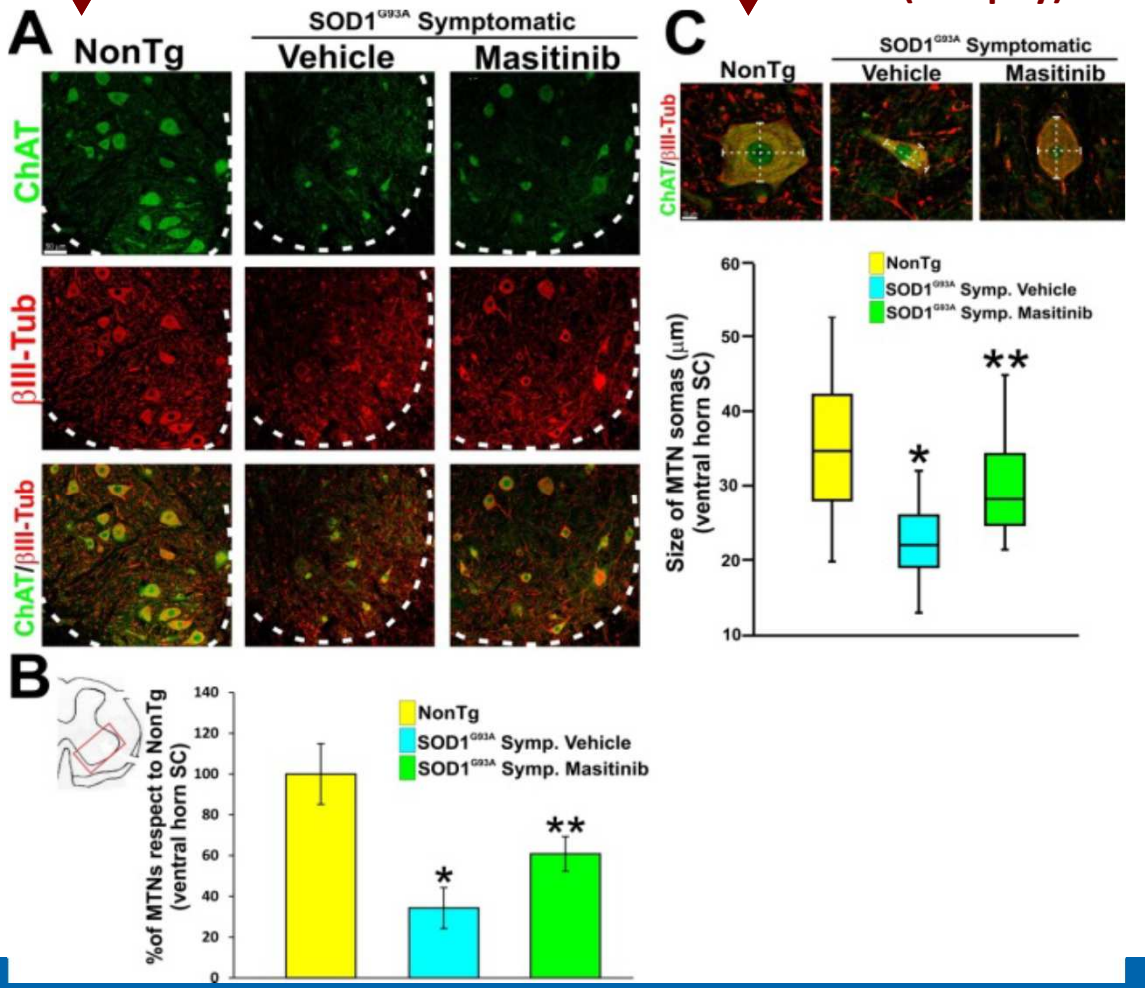
ALS - STUDY RATIONALE

Masitinib reduces motor neurons death and protects motor neuron atrophy in SOD1^{G93A} rats

Preclinical trial on SOD1^{G93A} rats treated during 25 days with Masitinib (30mg/kg) or vehicle, <u>starting after paralysis onset</u>

Number of motoneurons*

Motoneurons size (atrophy)



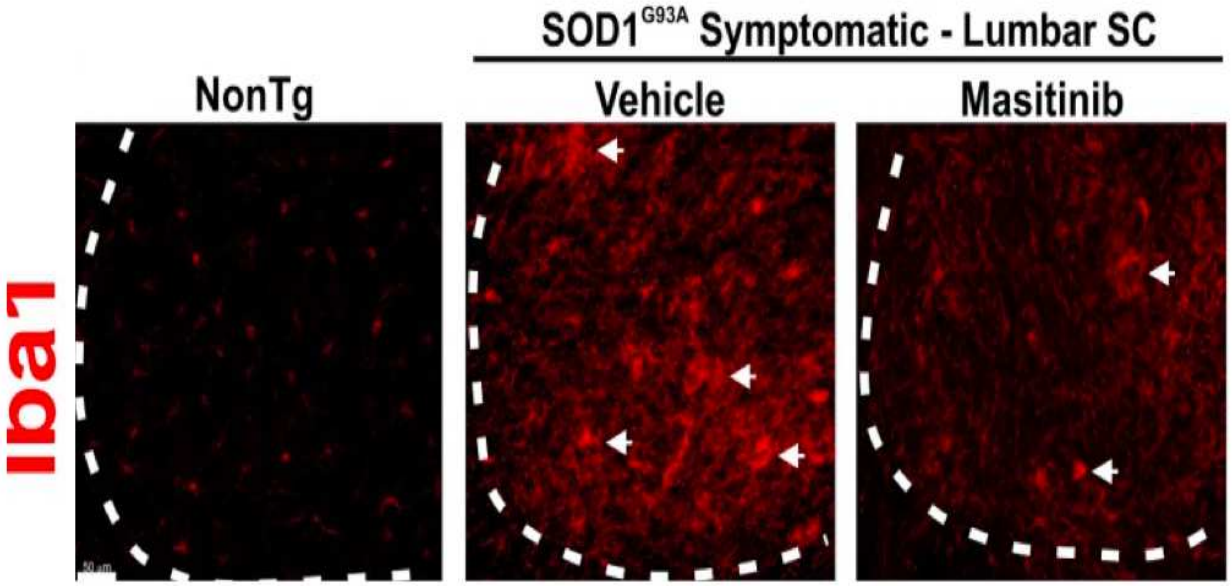
* Number of motor neurons assessed by ChAT, an enzyme of motor neurons, and Tubuline, another marker of motor neurons A) Representative confocal image of ChAT (green) and bIII-Tubulin (red) in lumbar spinal cord sections from non-transgenic (NonTg) and two groups of SOD1G93A symtomatic rats, treated during 25 days with vehicle and masitinib. Note that the number of motor neuron somas in the masitinib group is higher than that in the vehicle group. A white dotted line indicates the border between white and grey matter. B) Note the reduction of approximately 70% of motor neuron number at the end-stage animals in the vehicle treated rats as compared with 40% in masitinib treated rats. In comparison, animals treated with 30 mg/kg of masitinib there is a reduction of approximately 50%. C) Quantitation of the motor neuron soma diameter. Note the generalized-decreased diameter of surviving motor neurons in vehicle-treated rats and the protective effect of masitinib. Data are expressed as mean ± SEM *p<0.05. Respect to NonTg rats, ** p<0.05 with respect to symptomatic vehicle rats.

Personal communication from Dr. Luis Barbeito (Institut Pasteur de Montevideo)

ALS - STUDY RATIONALE

Masitinib potently reduces microgliosis (accumulation of microglia cells) in SOD1^{G93A} rats

Preclinical trial on SOD1^{G93A} rats treated during 25 days with Masitinib (30mg/kg) or vehicle, <u>starting after paralysis onset</u>

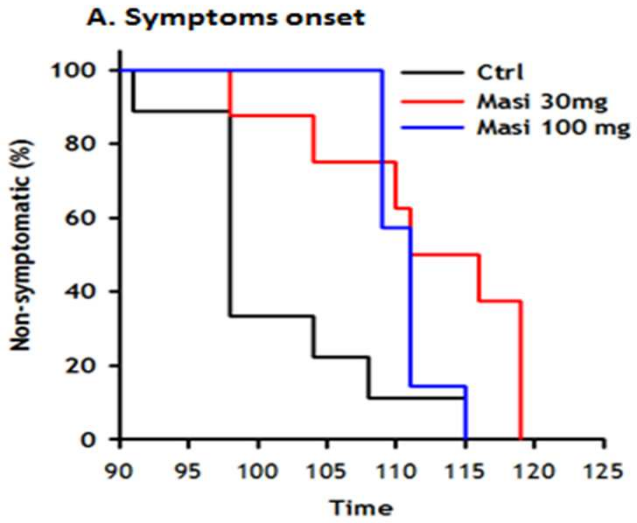


Masitinib reduces microgliosis in the degenerating spinal cord (A) Representative confocal image showing Iba1 (red) expression in the ventral horn of the lumbar spinal cord (white dotted lines indicate separation of white from grey matter in the upper panel and motoneurons in the lowe panel). After 25-days with Masitinib treatment the number of Iba1-postive microglia showed a marked decrease.
Note the fewer typical microglia clusters compared with what observed in vehicle-treated animals (white arrows indicate microglial clusters).

ALS - STUDY RATIONALE

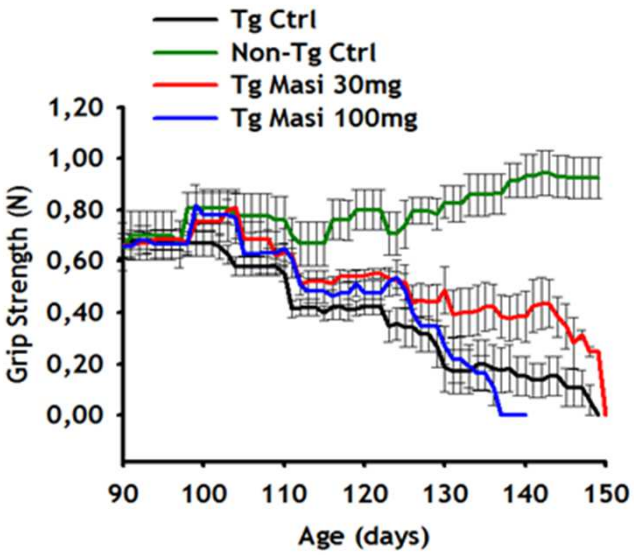
Masitinib delays the onset of symptoms and improved grip strength in ALS SOD1^{G93A} mice at therapeutic dose.

Effect of masitinib treatment* (30mg/kg) *on symptoms onset in SOD1^{G93A} female mice



Administration of masitinib alone by oral gavage to SOD1^{G93A} female mice, significantly delayed age of symptoms onset (111 days vs 101 days, for masitinib 30 mg/kg/ and control, respectively; p-value: 0.025

Effect of masitinib treatment* (30mg/kg) *on Grip strength in SOD1^{G93A} female mice



Administration of masitinib alone by oral gavage to SOD1^{G93A} female mice improved grip strength and weight loss compared to control SOD1^{G93A} animals

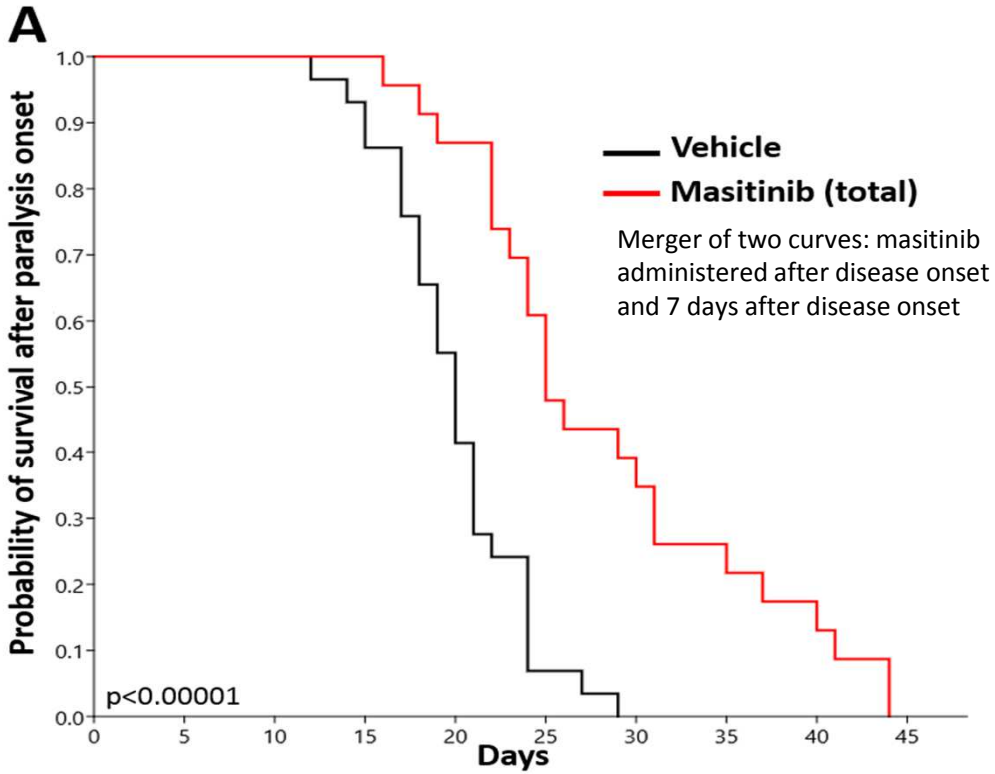
- 30mg/kg in mice is equivalent to around 3 mg/kg/day in human
- 100mg/kg in mice is equivalent to around 10 mg/kg/day in human
- Doses used in phase 3 are 3 mg/kg and 4.5 mg/kg

24 animals with SOD1G93A mutation were treated with masitinib and formed the basis to evaluate efficacy of masitinib as single agent.
The methodological approach for the therapeutic interventions in SOD1G93A mice that has been previously validated in reports published in prestigious journals [Miquel et al., 2012; Cassina et al., 2008].

ALS - STUDY RATIONALE

Masitinib improves significantly survival, even when treatment was started 7 days after paralysis onset

Preclinical trial on SOD1^{G93A} rats treated with Masitinib (30mg/k) or vehicle, <u>starting after paralysis onset</u>



Kaplan-Meier analysis showing the survival curves of both Masitinib trials (n=23 SOD1^{G93A} rats) compared with Vehicle-treated rats (n=29). There was a statistically significant difference in the probability of survival for both Masitinib-treated groups (after disease onset and 7 days after disease onset) when compared with vehicle-treated group, according to the Log-rank test of the Kaplan-Meier analysis with p<0.00001.

According to the authors, the survival finding from this study on SOD1^{G93A} rats is compelling because masitinib improves survival when:

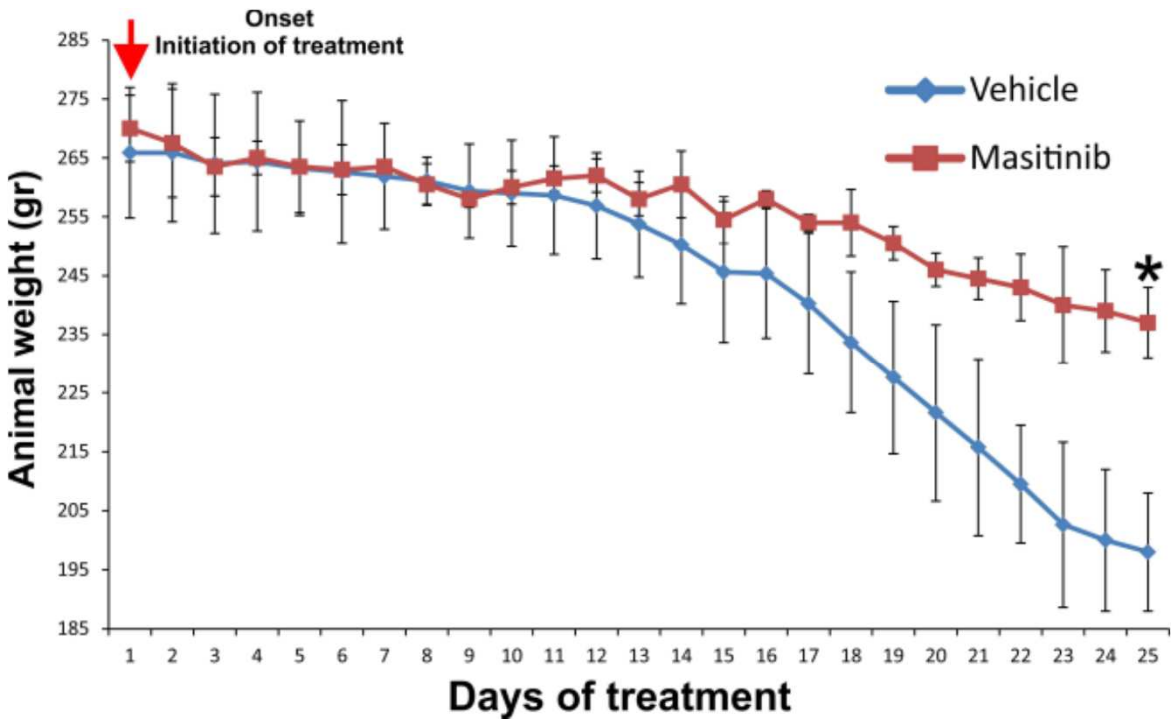
- Masitinib was started after disease onset.
- Masitinib was started 7 days after paralysis onset.

This is unique among all previous studies in the literature.

ALS - STUDY RATIONALE

Masitinib treated rats lost on average half as less weight in comparison to rats treated with vehicle.

Preclinical trial on SOD1^{G93A} rats treated with Masitinib (30mg/k) or vehicle, <u>starting after paralysis onset</u>



A preclinical study was conducted in SOD1^{G93A} female rats aged 120 days to assess the effect of masitinib on motor neuron pathology, neuroinflammation and mast cell infiltration in the spinal cord.
Five pairs of female SOD1^{G93A} rats developing hind legs paralysis were used. For each pair, one rat was randomly assigned to receive vehicle and the other 30 mg/kg masitinib for 25 days. For each individual rat, treatment started immediately after clinical diagnosis of disease onset.
The effect of masitinib was assessed at the end of the 25-days trial

***± SD of rats submitted to treatment with Masitinib (p.o. 30 mg/k, n=5) or vehicle (n=5). Data are expressed as mean ± SEM.**
***p<0.05 respect to vehicle.**

Personal communication from Dr. Luis Barbeito (Institut Pasteur de Montevideo)

PHASE 3 AB10015 - DESIGN

Phase 3 study on-going.

Study design	▪ Patients with Amyotrophic Lateral Sclerosis (ALS) ▪ Blinded, placebo controlled ▪ 48 week treatment period ▪ 381 patients
Clinical Endpoint	▪ Change from baseline to week 48 in Amyotrophic Lateral Sclerosis functional rating scale (ALSFRS)-Revised
Primary hypothesis	▪ Detect a difference of a couple of points in ALSFRS between masitinib and placebo at week 48
Dosing	2 doses versus placebo ▪ 3 mg/kg/day masitinib + riluzole ▪ 4.5 mg/kg/day masitinib + riluzole

PHASE 3 AB10015 – SAFETY REVIEW

Phase 3 study AB10015 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, the last review being performed in December 2014
  - On this basis, the IDMC recommended the continuation of the study

PHASE 3 AB10015 – FUTILITY ANALYSIS

Phase 3 study AB10015 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 with one third of patients enrolled (≈120 patients) and having reached the 48 week treatment duration period
  - Performed on primary endpoint, ALSFRS-R
  - Data set is extrapolated based on the first one-third of patients
  - P-value is set <5%
  - Take into consideration the observed standard deviation with the first third of patients enrolled
  - Conditional power (predictive probability of success) is set around 20%

PHASE 3 AB10015 – FUTILITY ANALYSIS

This futility test was supported by 4 sensitivity analyses provided to the DSMB.

- Purpose of sensitivity analysis
  - To ensure the robustness of the primary analysis through additional converging measures of efficacy
- Primary analysis
  - ALSFRS-R change from baseline to week 48 using Last Observation Carried Forward (LOCF) method for patients who discontinued
- Sensitivity analyses performed
  - ALSFRS-R change from baseline to week 48 using Observed cases (no carry forward)
  - Combined Assessment of Function and Survival (CAFS*) for masitinib versus placebo
    - CAFS ranks each patient based on survival time and change in ALSFRS-R score
    - The higher the score, the better the outcome for the patient
    - All patients ranking are added for each treatment group
    - The significance between treatment group is tested statistically.
  - Number of failures (defined as a 9-point drop in ALSFRS-R from baseline or death) considering as failure the missing data for discontinued patients
  - Number of failure (defined as a 9-point drop in ALSFRS-R from baseline or death) using Observed Cases method

* CAFS, JAMES D. BERRY & al 2013. The Combined Assessment of Function and Survival (CAFS): a new endpoint for ALS clinical trials.

PHASE 3 AB10015 - INTERIM ANALYSIS

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

Interim analysis

- Performed with 50% of patients
- Possibility to stop the study in case of success, with potential filing for registration
- 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 AB10015 - INTERIM ANALYSIS

Given the re-sampling option, the probability that the study succeeds for final analysis with non futility passed with 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%
30%	64%
40%	80%

PHASE 3 AB10015 – TIMING OF NEXT STEPS

Phase 3 study interim analysis is planned in Q1 2016 and is certain.

- **Interim analysis**
  - Planned with 50% of patients recruited
  - Planned in Q1 2016
  - This date is certain as the number of patients required to perform the interim analysis have already been enrolled
- **Final analysis without resampling (if study not stopped at interim analysis)**
  - With 100% of recruitment
  - Expected Q4 2016
- **Final analysis with resampling (if study not stopped at interim analysis and increase in sample size required)**
  - With a maximum of 200% of recruitment (between 101% and 200%)
  - Q3 2017 if resampling 150%
  - Q1 2018 if resampling 200%

IP PROTECTION

IP rights for masitinib are secured in ALS until 2028 and potentially until 2034.

Protection		Duration of protection	Status
Patent on Composition of matter and PTE	▪ Composition of matter has been file and delivered and will be further extended until 2028 through patent tem extension (PTE).	Until 2028	Delivered
Synthesis process patent	▪ A further protection until 2028 has been achieved through synthesis'process' patent already granted.	Until 2028	Delivered
Phase 2 patents	▪ Patent filed in 2014 on treatment of amyotrophic lateral sclerosis	Until 2034	Filed
Orphan Drug Status	▪ Masitinib has been granted orphan drug status in ALS by FDA (filing at EMA pending)	Exclusivity of 7 years in USA and 10 years in Europe	

Questions