AB SCIENCE

Emerging pharmaceutical company
in targeted therapies

MASITINIB IN THE TREATMENT OF AMYOTROPIC LATERAL SCLEROSIS (ALS)

20 MARCH 2017

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DESIGN OF ALS STUDY AB10015

RESULTS OF FINAL ANALYSIS

MECHANISM OF ACTION OF MASITINIB IN ALS

INTELLECTUAL PROPERTY IN ALS

NEXT STEPS

UPDATE ON OTHER STUDIES

ALS - STUDY DESIGN

Study AB10015 is a pivotal, placebo controlled study with close to 400 patients.

- **Blinded, placebo controlled**
- **3 treatment-arms, randomisation 1:1:1**
  - Masitinib 4.5mg/kg/day + riluzole
  - Masitinib 3mg/kg/day + riluzole,
  - Placebo + riluzole
- **Treatment duration : 48 weeks**
- **Patients enrolled : 394 patients**
- **Pre-planned interim analysis with 50% of patients enrolled treated for 48 week, which was positive**

ALS - STUDY DESIGN

The study tested 2 doses in a sequential manner based on endpoints validated by regulatory authorities.

- **Efficacy assessment was based on endpoints validated by regulatory authorities.**
  - Primary endpoint: Change in ALSFRS-R at week 48.
  - Secondary endpoint : PFS
  - Supportive endpoints : ALS-AQ40, FVC, CAFS, Survival
- **Sequential analysis :**
  - Masitinib 4.5mg/kg/day + Riluzole, and then
  - Masitinib 3mg/kg/day + Riluzole

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ALS – PRIMARY ANALYSIS

The study was a success based on pre-specified primary endpoint on ALSFRS-R at 4.5 mg/kg/day.

- **Primary Endpoint : ALSFRS-R** *(Amyotrophic Lateral Sclerosis Functional Rating Scale)*
  - ALSFRS-R includes 12 questions, each rated on a five-point scale from 0 = cannot do, to 4 = normal ability. Individual item scores are summed to produce a score of between 0=worst and 48=best
  - ALSFRS-R is the most widely used instrument to measure function in ALS clinical trials
  - ALSFRS-R is a validated rating score for monitoring the progression of disability in patients with ALS, which takes into account both quality of life and survival
  - Reference: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/12/WC500199241.pdf
- **Primary analysis in ITT population is successful**
- **Calculation of ALS-FRS-R based on Last Observation Carried Forward (LOCF) method**

ALS – PRIMARY ANALYSIS

The primary analysis was supported by sensitivity analyses on reasons for discontinuation.

- **Four different data censoring methods based on reason of discontinuation**
- **These analyses are differentiating methods of missing data imputation based on the reasons of discontinuation is in line with "Guideline . EMA/CPMP/EWP/1776/99 Rev. 1".**

  "An attractive approach for imputing missing data may be to employ a different pre-specified imputation technique for each different reason for withdrawal, rather than the same technique for all patients."

- **All four sensitivity analyses are significant**

ALS – PRIMARY ANALYSIS

The primary analysis was supported by key sensitivity analyses based on imputation model.

- **Calculation of ALS-FRS-R based on Imputation method**
  - Missing data at week 48 are imputed based on data available in clusters of patients with similar characteristics based on:
    - Stratification factors (Bulbar versus Non-bulbar, progression in ALSFRS-R, region)
    - Reason for discontinuation due to
      - Lack of efficacy
      - Toxicity
      - Other reasons: missing at random

- **Alternative method of imputation was used with penalty applied on missing data due to lack of efficacy**
  - Patients who withdraw for lack of efficacy are expected to have different efficacy from other patients.
    (Permutt, T. (2016). "Sensitivity analysis for missing data in regulatory submissions." Statistics in medicine 35(17): 2876-2879)

- **The two sensitivity analyses are significant**

ALS – SECONDARY ANALYSES

The study was positive based on PFS at 4.5 mg/kg/day.

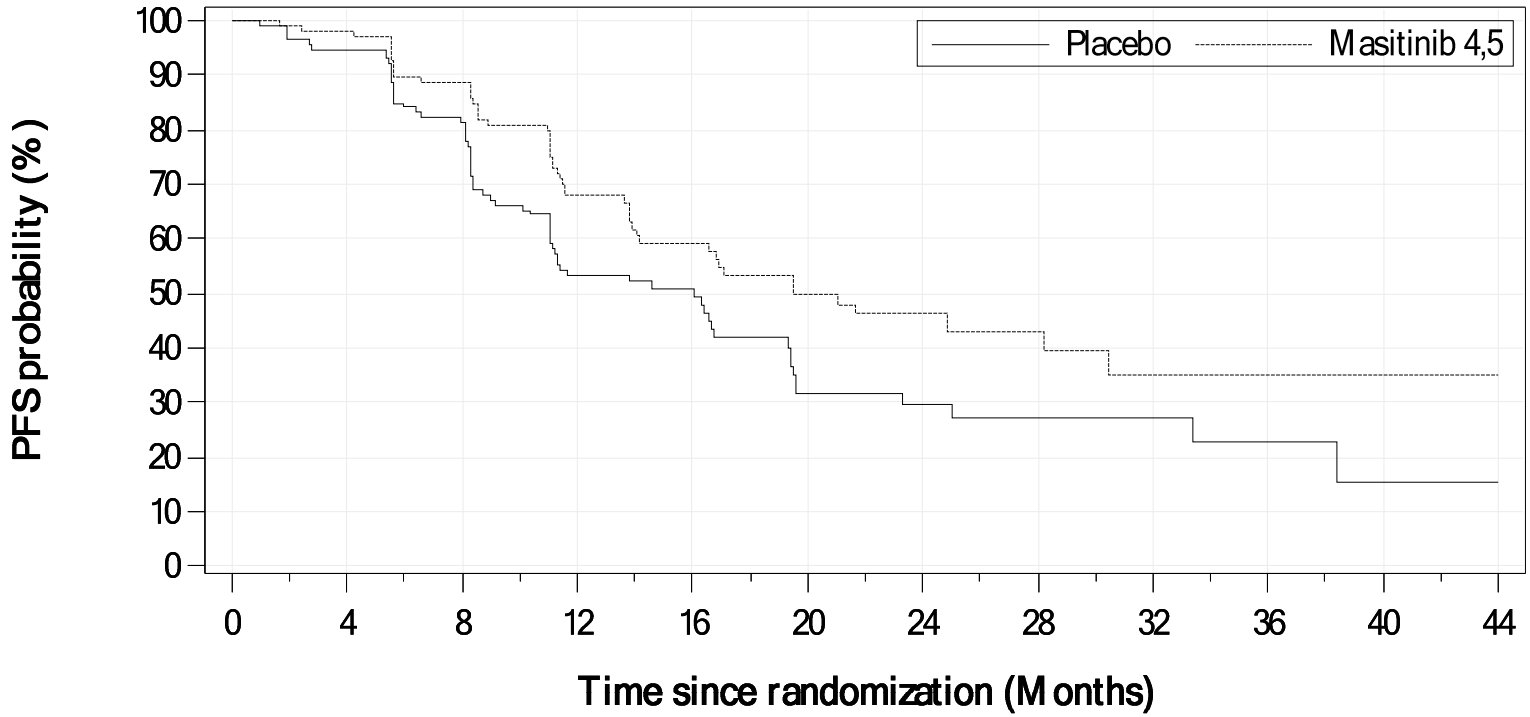
- **Significant benefit on key secondary endpoint PFS**
  - A time-to-event endpoint with the event defined as death or a predefined deterioration on the ALSFRS-R scale was recommended by EMA based on guideline for ALS
  - In AB10015 study, PFS is defined as the earliest event between ALSFRS-R deterioration of more than 9 points or death.
  - This endpoint is valid for registration
  - Reference: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/12/WC500199241.p

ALS – SECONDARY ANALYSES

The study was positive based on PFS at 4.5 mg/kg/day.

- The key secondary analysis on PFS was statistically significant

Figure 1: KM analysis of PFS: Masitinib 4.5 mg vs Placebo(mITT)



ALS – SUPPORTIVE ANALYSES

The study was positive based on ALS-AQ40 at 4.5 mg/kg/day.

- **The supportive analysis on ALS-AQ40 was statistically significant**
- **ALS-AQ40 is a questionnaire to assess the quality of life**
- **It is a ALS-specific health status measure in relation to 5 domains**
  - eating and drinking
  - Communication
  - ADL/independence
  - physical mobility
  - emotional functioning
- **Quality of life is recognized as a key endpoint given the high medical need**

ALS – SUPPORTIVE ANALYSES

There was no benefit on overall survival at 4.5 mg/kg/day.

- **No benefit on overall survival**
- **The main issue limiting use of survival is the fact that ALS trials are not of sufficient duration for many patients to reach this endpoint, severely reducing power.**
- **The only two options to resolve this problem are to increase study duration or sample size, both of which contribute to cost, and reduce trial efficiency.**

http://www.alsa.org/advocacy/fda/assets/als-drug-development-guidance-for-public-comment-5-2-16.pdf

ALS – SUPPORTIVE ANALYSES

At masitinib 3 mg/kg/day, there was a trend of benefit on the primary endpoint change in ALSFRS-R at week 48, a trend of benefit on PFS, and a significant benefit on quality of life.

- **Trend of benefit on change in ALSFRS-R at week 48**
- **Trend of benefit on PFS**
- **Significant benefit on Quality of life (ALSAQ-40)**
- **No benefit on overall survival**

ALS – SAFETY

The safety profile of masitinib in combination with riluzole appeared acceptable.

- The adverse events observed for masitinib in study AB10015 were consistent with its known safety profile.
- There were no new safety events at final analysis as compared with interim analysis.

ALS – PRESENTATION OF RESULTS

Full efficacy and safety data will be submitted for presentation at the European Network for the Cure of ALS (ENCALS) annual meeting.

- ENCALS is the leading network regrouping the key ALS centres in Europe
- ENCALS organizes a yearly scientific meeting
- 2017 Meeting location and date : Ljubljana, Slovenia (18 – 20 May, 2017)

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AMYOTROPHIC LATERAL SCLEROSIS - STUDY RATIONALE

- **It is now well-established in the scientific literature that proliferation and accumulation of microglial cells (microgliosis), in particular the emergence of aberrant glial cells, is a major neuropathological feature for ALS animal models.**
  - This disease mechanism is regulated by the CSF1/CSF1R signaling pathway, making it a viable target for regulating the activation of microglia cells in ALS.
  - Masitinib is a potent inhibitor (IC_{50} 90 nM) of CSF1R-dependent cell proliferation (albeit without completely depleting microglial cells). Doses of 3 or 4.5 mg/kg/day provide a concentration above the IC_{50}.
  - Hence, as a primary mechanism of action masitinib acts on neuroglia via inhibition of CSF1R.
- **The primary pharmacodynamic profile of masitinib in ALS has been investigated through a series of *in vivo*/*in vitro* studies.**
  - Findings have been published.

Trias *et al. Journal of Neuroinflammation* (2016) 13:177
DOI 10.1186/s12974-016-0620-9

Journal of Neuroinflammation

RESEARCH Open Access

Post-paralysis tyrosine kinase inhibition with masitinib abrogates neuroinflammation and slows disease progression in inherited amyotrophic lateral sclerosis

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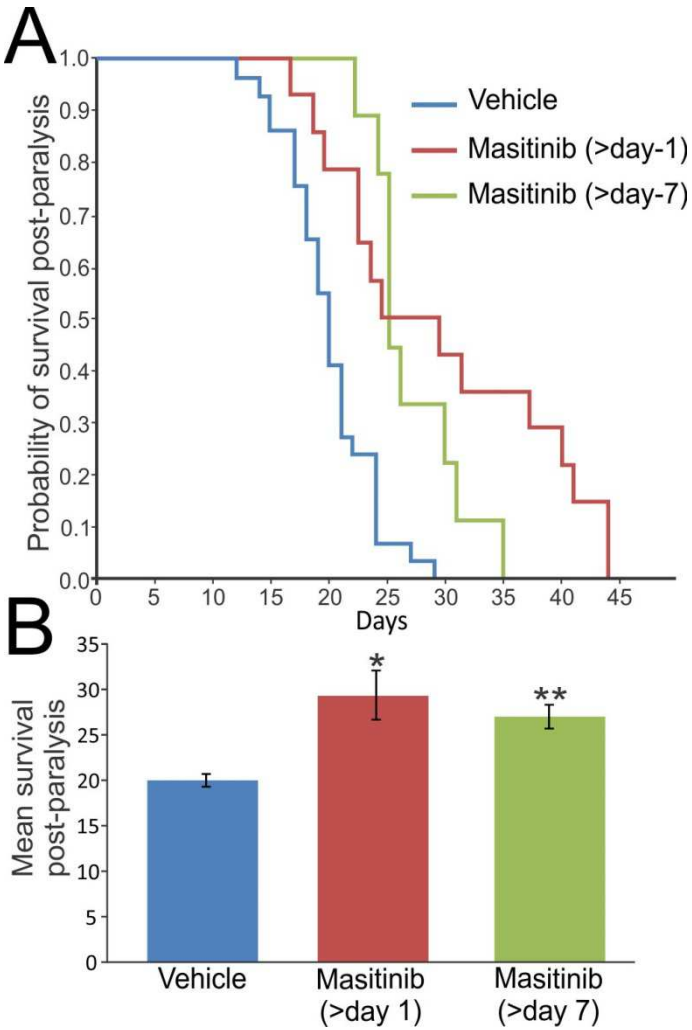
AMYOTROPHIC LATERAL SCLEROSIS – PRECLINICAL DATA

❖ **Masitinib has demonstrated an unprecedented protective effect in a relevant ALS model of post-paralytic SOD1^{G93A} rats** (according to both severity of the model being used and magnitude of treatment effect observed)



- Kaplan-Meier curves show a significant difference for both masitinib-treated groups when compared with the vehicle-treated group.
  - p<0.0006 for masitinib gait onset (>day-1)
  - p<0.00025 for masitinib 7d onset (>day-7)

Masitinib treatment initiated 7 days after paralysis onset prolonged post-paralysis survival by 40% with respect to vehicle-treated SOD1^{G93A} rats.

- Mean post-paralysis survival time also evidenced a significant retardation of disease progression
  - 30 ± 8 days; p<0.0016 for masitinib gait onset (>day 1)
  - 27 ± 4.3 days; p<0.00025 for masitinib 7d onset (>day-7)
  - 20 ± 3.8 days for vehicle-treated rats

AMYOTROPHIC LATERAL SCLEROSIS – PRECLINICAL DATA

❖ **Immunohistochemistry data additionally showed that masitinib treatment (Trias et al. 2016):**

- Prevented microglia proliferation, migration and transformation into aberrant glial cells.
- Reduced the number of aberrant glial cells in the degenerating spinal cord.
- Improved microgliosis and motor neuron pathology.
- Inhibited microgliosis along the degenerating spinal cord and microglia proinflammatory phenotype.

❖ **New data show protective effects of masitinib in the peripheral nervous system of SOD1^{G93A} rats after paralysis onset (Barbeito et al. ALS/MND Symposium, Dublin, Ireland, 2016):**

- Strong upregulation of CSF1 and IL-34 in the degenerating sciatic nerve has been observed for first time, as well as a high infiltration of macrophages and a moderate infiltration of mast cells.
- Masitinib reduces pathological changes in the sciatic nerve, with a sharp decrease of inflammatory infiltrates of CSF1R-expressing macrophages and c-Kit expressing mast cells.
- Masitinib was seen to delay neuromuscular junction (NMJ) denervation in fast skeletal muscles.
- Masitinib reduces pathological changes in the NMJ, with a decrease of inflammatory cells in these muscles.

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ALS – IP PROTECTION

Masitinib has been granted orphan drug designation by both EMA and FDA.

- **FDA: Exclusivity of 7 years**
- **EMA: Exclusivity of 10 years**

ALS – IP PROTECTION

IP rights for masitinib are secured in ALS until 2028 and potentially until 2036 based on a recently filed phase 3 patent.

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 patent	▪ Patent filed in 2014 on treatment of amyotrophic lateral sclerosis	Until 2034	Filed
Phase 3 patent	▪ Patent filed in March 2016 on treatment of amyotrophic lateral sclerosis	Until 2036	Filed

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REGULATORY STATUS

❖ **EMA : Application for conditional marketing Authorization**

- Filed in September 2016
- Decision expected in Q4 2017
- With conditional marketing Authorization, the drug can be marketed as for a full marketing authorization. There is no need to wait for the results of the confirmatory study

❖ **FDA**

- Communicate final data to the FDA to discuss future steps

CONFIRMATORY STUDY – TIMING & RECRUITMENT CONSIDERATIONS

A confirmatory phase 3 study is expected to begin in Q3 2017

- Estimated schedule:
  - Start date: Q3 2017
  - Recruitment period: Q3 2017 → Q3 2018
  - Final data readout: Q3 2019
  - Results by Q4 2019

- No interim analysis

ALS – TARGETED PATIENT POPULATION

ALS incidence is high but prevalence is low due to the rapid fatal outcome of the disease.

- **Epidemiology of ALS**
  - ≈50,000 prevalent cases in USA and Europe (prevalence was 5.98/100,000 population*)
  - ≈16,000 new cases in USA and Europe (incidence was 1/50,000 population)
- **High unmet medical need**

* meta-analysis from 7 studies

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(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
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Mastocytosis

- Claim : Treatment of adult patients with indolent or smouldering severe systemic mastocytosis unresponsive to optimal symptomatic treatments

- Phase 3 results were published in *The Lancet*
  Lancet. 2017 Feb 11;389(10069):612-620. doi: 10.1016/S0140-6736(16)31403-9. Epub 2017 Jan 7.

- EMA decision on marketing authorization is expected end of May 2017

UPDATE ON OTHER STUDIES

Severe asthma

- Status of study AB07015
  - Claim: Patient with severe asthma uncontrolled by oral corticosteroids
  - Status
    - 350 Assessable patients. Recruitment completed
    - Final results expected Q4 2017
  - Interim analysis performed by IDMC
    - No safety concern
    - Conditional power >80% because no resampling was requested by the IDMC
    - Efficacy in low eosinophilic patients because no stop of recruitment in these patients was requested, although IDMC had this option
- New study AB14001
  - Claim: Patient with asthma uncontrolled by high-dose inhaled corticosteroid and with elevated eosinophil level
- Third option for registration for masitinib
  - Severe asthma becomes a potential indication for masitinib