

Masitinib for the treatment of Alzheimer's disease: a randomized phase 3 trial

Olivier Hermine^{1,2}, Tengfei Li³, Cecile Delarasse³, Alain Moussy², Colin Mansfield², Patrice Dubreuil^{2,4}, Grégory Fenaux⁴, Benoît Delatour³

Corresponding author: Olivier Hermine MD, PhD. E-mail: ohermine@gmail.com

¹Service d'hématologie and IMAGINE Institute, Necker Hospital, Paris; ²AB Science, Paris; ³Sorbonne Universités, UPMC Univ Paris 06 UMR S 1127, Inserm, U 1127, CNRS UMR 7225, ICM, Paris; ⁴CRCM [Signaling, Hematopoiesis and Mechanism of Oncogenesis], Inserm, U1068; Institut Paoli-Calmettes; Aix-Marseille Université, UM105; CNRS, UMR7258; F-13009, Marseille, France.

Introduction

➤ **THE RATIONALE** for evaluating masitinib in Alzheimer's disease (AD) is based on masitinib's inhibition of the c-Kit, Lyn, Fyn and CSF1R kinases.

Neuroinflammation plays a critical role in AD [1,2,3] and mast cells present in the brain play a central role in the inflammatory process

AD is characterized by the loss of blood brain barrier (BBB) integrity. Mast cells participate in the regulation of the BBB's permeability [1]

Protein tau is phosphorylated by tyrosine kinase Fyn [5]

The proliferation and activation of microglial cells is a hallmark of AD. This mechanism is regulated by the activation CSF1R [6]

Masitinib targets mast cells by inhibiting c-Kit Lyn and Fyn [4]

Masitinib inhibits Fyn

Masitinib inhibits CSF1R and aberrant microglia cells

➤ **CLINICAL AND PRECLINICAL DATA**

- Proof of concept for the evaluation of masitinib in AD was established by a phase 2 study. Masitinib showed a consistent improvement of disease in primary (ADAS-cog) and secondary (ADCS-ADL, MMSE) endpoints [7]
- An ancillary imaging study in mastocytosis has revealed that masitinib is an effective modulator of blood-brain barrier permeability with a concomitant increase in cognitive abilities *
- *In vivo* proof of concept established via results from a APPxPS1dE9 mouse model of AD, indicating improved spatial memory in a curative setting and reduced hippocampal amyloid loads in a preventive setting *
- New evidence shows that masitinib targets proliferating aberrant microglia by inhibiting macrophage colony stimulating factor (CSF1R), a key target for amyotrophic lateral sclerosis (ALS), but also a valid target in AD [6] *

(*See related oral presentation on Friday, March 11 during the 'Emerging Novel Therapeutic Targets' session)

Overall, these data provide provide strong medical and biological plausibility for masitinib in the treatment of AD

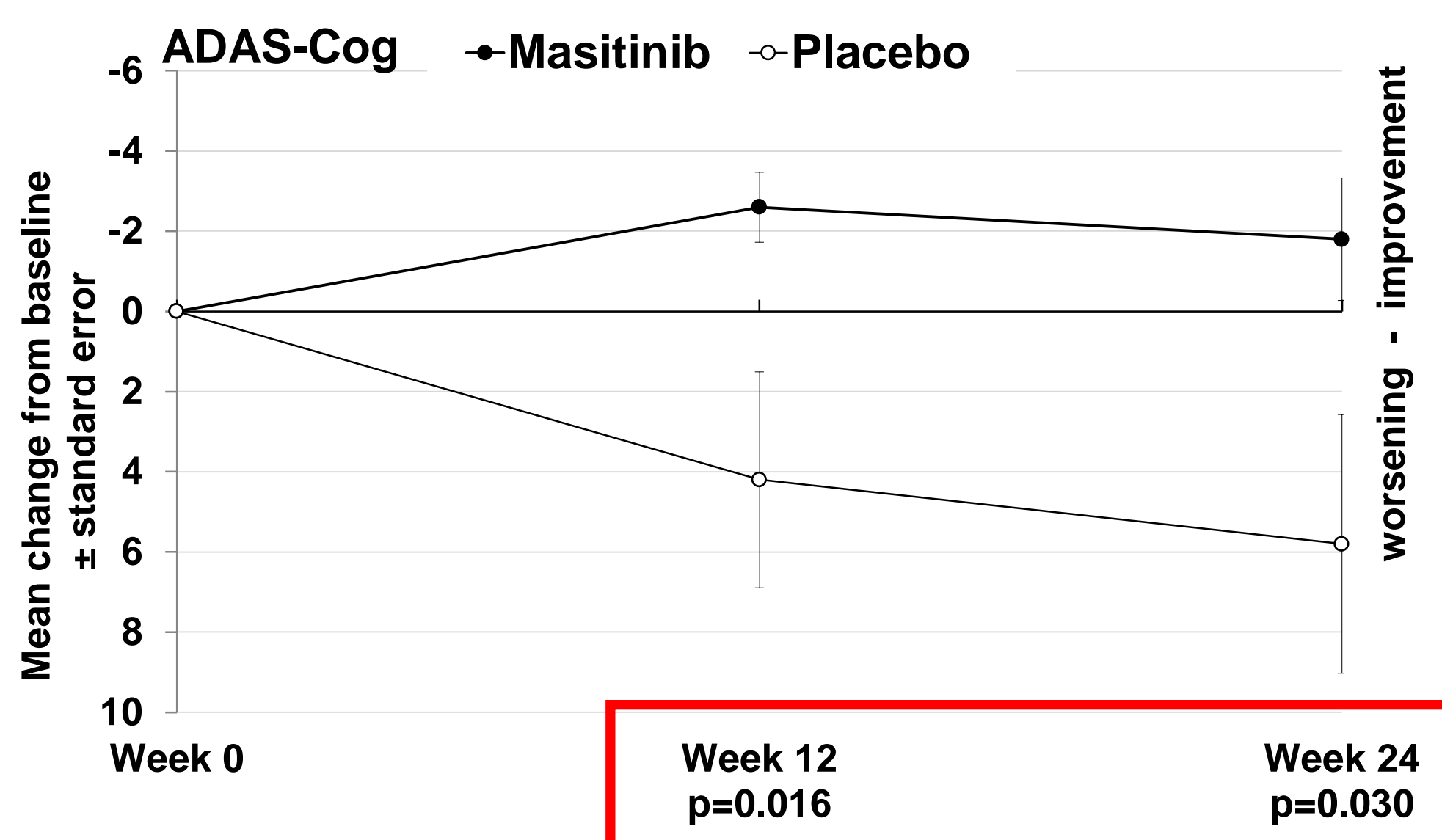
Phase 2 of masitinib in mild to moderate AD

➤ **MASITINIB IS AN INNOVATIVE AVENUE OF TREATMENT IN AD**

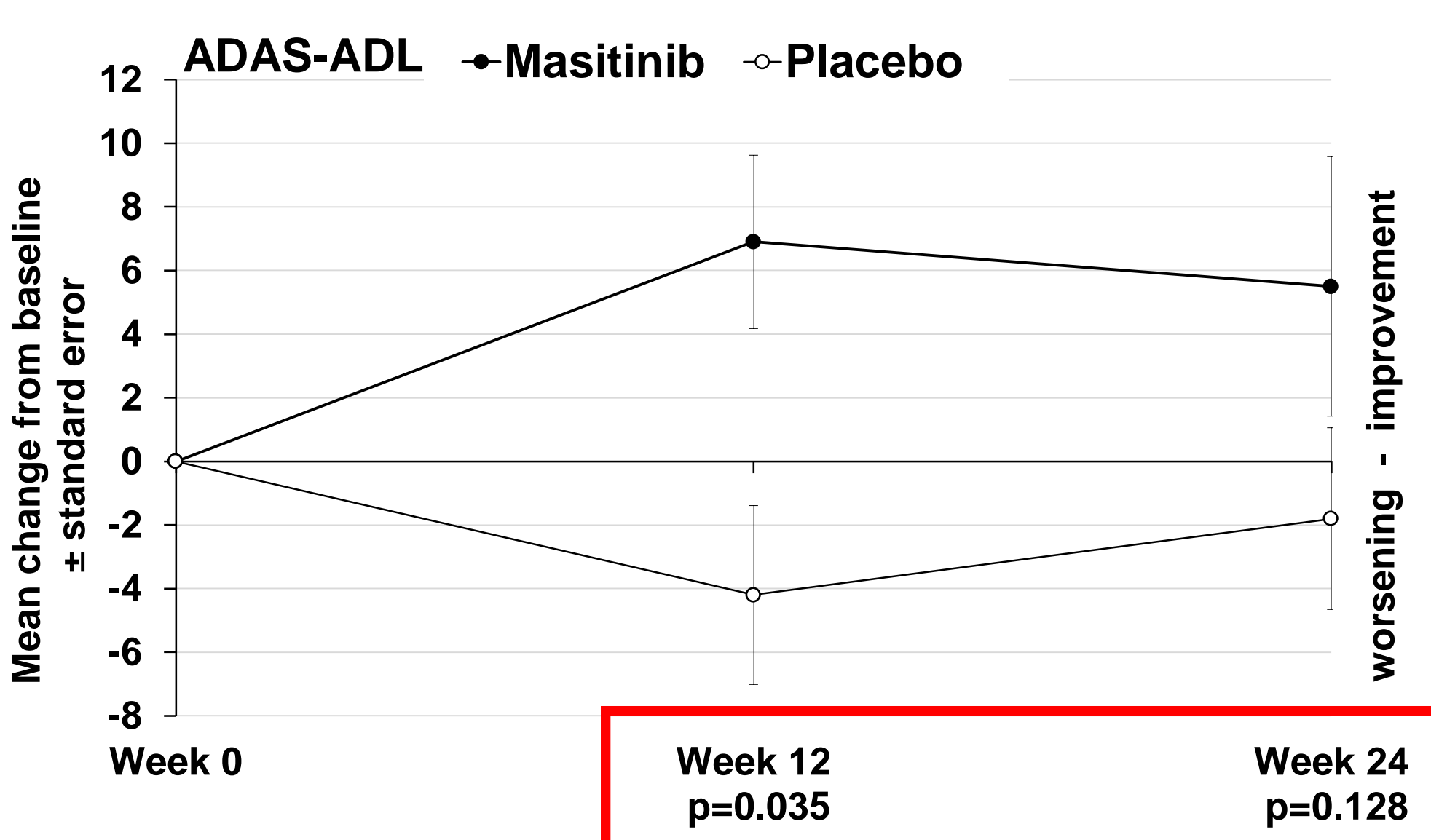
PHASE 2 STUDY DESIGN

- Patients with mild to moderate AD
- Masitinib starting dose of 3 or 6 mg/kg/day
- Adjunct to cholinesterase inhibitor or memantine
- 24-week treatment period
- 34 patients (26 masitinib, 8 placebo)

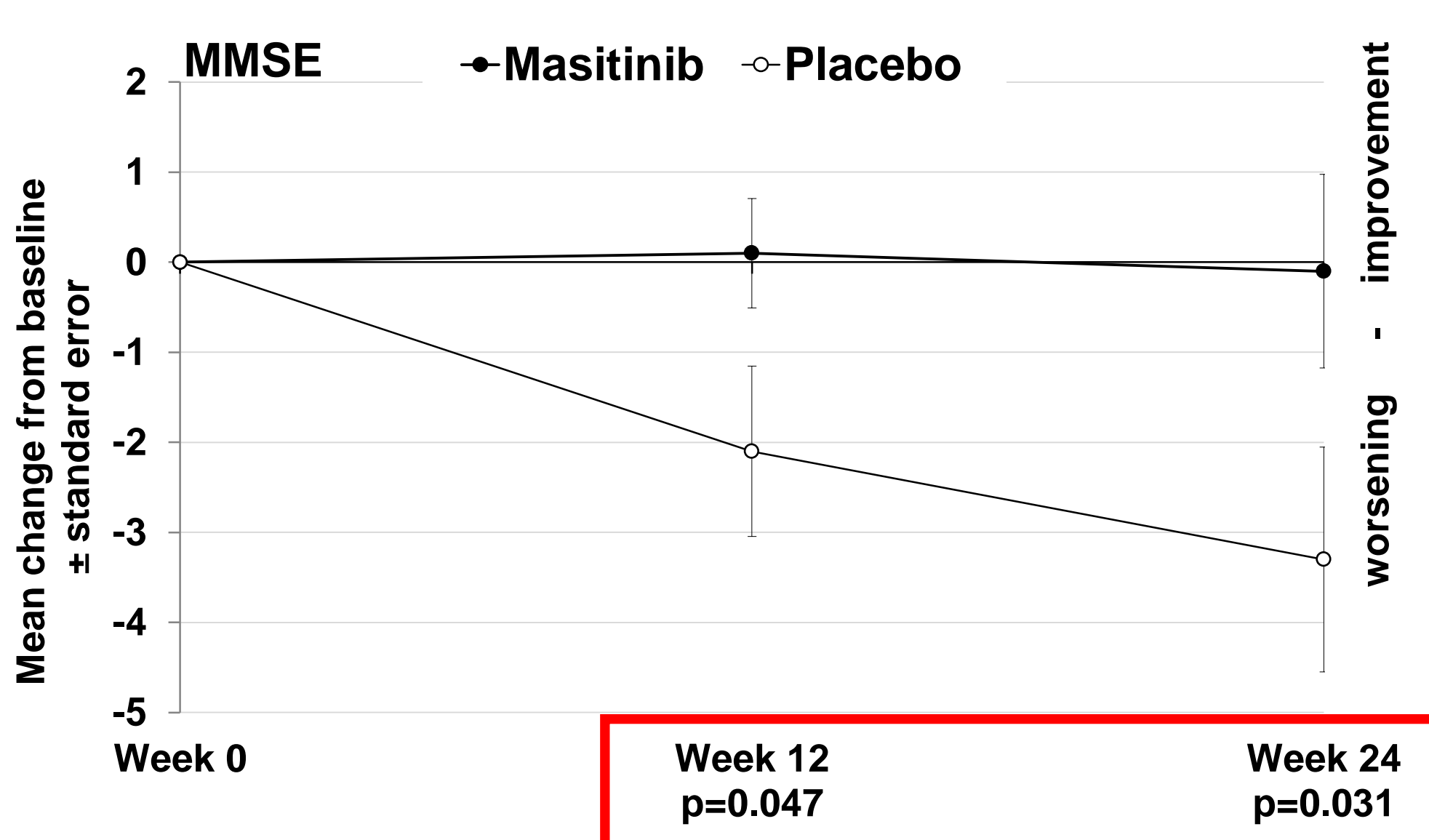
➤ **MASITINIB GENERATED EFFICACY ON ADAS-COG**



➤ **MASITINIB GENERATED EFFICACY ON ADCS-ADL**



➤ **MASITINIB GENERATED EFFICACY ON MMSE**



Phase 2 results have been published in Piette F et al. Alzheimer's Res Ther. 2011 Apr 19;3(2):16

Phase 3 (AB09004) – On-going

PHASE 3 STUDY DESIGN

- 675 patients with mild to moderate AD
- Blinded, placebo controlled
- 24-week treatment period

SELECTION OF PATIENTS

- Dementia of Alzheimer's type, DSM-IV criteria
- Probable AD according to NINCDS-ADRDA criteria
- MMSE ≥ 12 and ≤ 25 at baseline
- Minimum of 6 months treatment with a stable dose of cholinesterase inhibitors and/or memantine

CLINICAL ENDPOINTS

- Effect on ADCS-ADL from week 8 to week 24
- Effect on ADAS-Cog from week 8 to week 24

DOSING OF MASITINIB

- 3 mg/kg/day
- 4.5 mg/kg/day
- 4.5 mg/kg/day with a switch to 6 mg/kg/day

STATUS: RECRUITING

- Study sites are currently open for patient recruitment in 14 countries.

➤ **SUCCESSFUL FUTILITY TEST**

- In February 2015, study AB09004 was assessed as non futile by the Independent Data Monitoring Committee (IDMC)
- Test performed on ADCS-ADL and ADAS-Cog after about one third of the patients were enrolled into the study and had reached the 24 week treatment duration of the study
- Conclusion: given the data available at that time, study AB09004 is on track to achieve its stated efficacy objective
- Regular assessments of safety parameters by the IDMC have not revealed any major or unexpected safety concerns
- Together these assessments suggest that the benefit-risk balance of study AB09004 is positive based on currently available data

These findings are a significant milestone because to date no other phase 3 study has been reported as non futile in patients with mild to moderate AD

➤ **PRE-PLANNED INTERIM ANALYSIS**

- Planned at around 50% of recruitment
- Anticipated in 2017

For further details of this phase 3 study contact: investigateurs@ab-science.com

References: [1] Skaper SD, et al. Immunology. 2014 Mar;141(3):314-27. [2] Silver R, et al. Trends Neurosci. 2013 Sep;36(9):513-21. [3] in t'Veld BA, et al. N Engl J Med 2001;345:1515-21. [4] Dubreuil 2009, PLoSONE.4(9):e7258. [5] Folch J, et al. Expert Rev Neurother. 2015 May 11:1-10. [6] Olmos-Alonso A, et al. Brain. 2016 Jan 8. [7] Piette F et al. Alzheimer's Res Ther. 2011 Apr 19;3(2):16