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# MASITINIB IN ALZHEIMER'S DISEASE

*17 December 2020*

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# Participants

## Alzheimer's Disease Experts

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Chief Scientific Officer and Chaiman of Scientific Committee

# Masitinib Profile and Mechanism of Action

## Orally-administered kinase inhibitor selectively targeting mast cells and microglia

### Masitinib targets mast cells

- Masitinib is a selective inhibitor of c-Kit, Lyn, and Fyn kinases
- These kinases play critical roles in the activation of mast cells

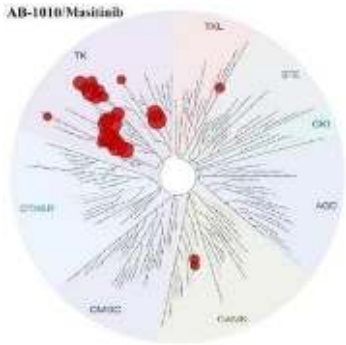
### Masitinib targets macrophages/microglia

- Masitinib is a potent and selective inhibitor of MCSFR-1
- This kinase plays critical roles in the modulation of microglia

### Masitinib is a tablet

- Oral route
- Morning and evening

| Kinase inhibition profile of masitinib | | | |
|---|---|---|---|
| **Cellular Target** | Molecular Target | $IC_{50}$ [nM] | Kd [µM] |
| **Mast cells** | KIT wild-type (WT) | 20 | 0.008 |
| | FYN | 240 | 0.14 |
| | LYN | 225 | 0.061 |
| **Microglia** | MCSFR-1 | 90 | 0.0076 |




Dubreuil 2009, PLoSONE.4(9):e7258; AB Science. Davis 2011, Nat Biotechnol; 29(11):1046

# Scientific Rationale in Alzheimer's disease (AD)

## The mode of action of masitinib in AD is based on four targets, which may have a synergistic effect

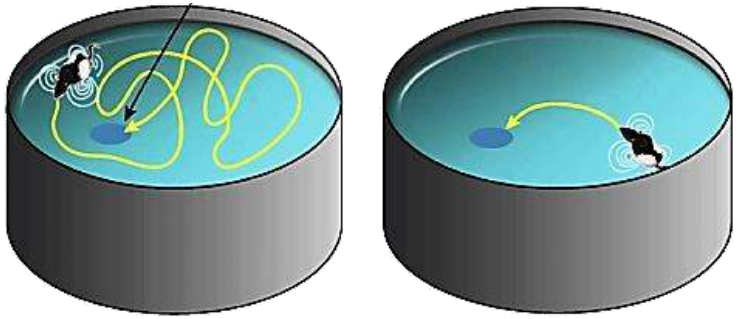
| | | |
|---|---|---|
| Modulation of Microglia | ▪ Microglia is involved in the neuro-inflammation in AD | ▪ Masitinib blocks microglia through inhibition of MCSFR-1 kinase |
| Protection of Synapses | ▪ Synapses are altered in AD | ▪ Masitinib promotes recovery of synaptic markers in mice model of AD |
| Inhibition of Tau protein | ▪ Tau protein aggregates in the physiopathology of AD | ▪ Masitinib inhibits FYN kinase, a kinase that is phosphorylasing Tau<br>▪ Masitinib prevent the accumulation of amyloid fibrill in hippocampus of young mice model of AD |
| Control of Mast Cell (MCs) activity | ▪ Mice depleted from MCs do not develop symptoms of AD | ▪ Masitinib blocks MCs activation through inhibition of c-Kit, LYN, and FYN kinases<br>▪ βeta-amyloid plaques activate mast cells<br>▪ Transgenic AD mice treated by masitinib are protected for cognition impairment |

# Pharmacology

## In a transgenic mouse model of AD, masitinib could restore/protect completely cognitive impairment

**Cognitive evaluation in a curative setting (APPXPS1DE9 mouse model)**

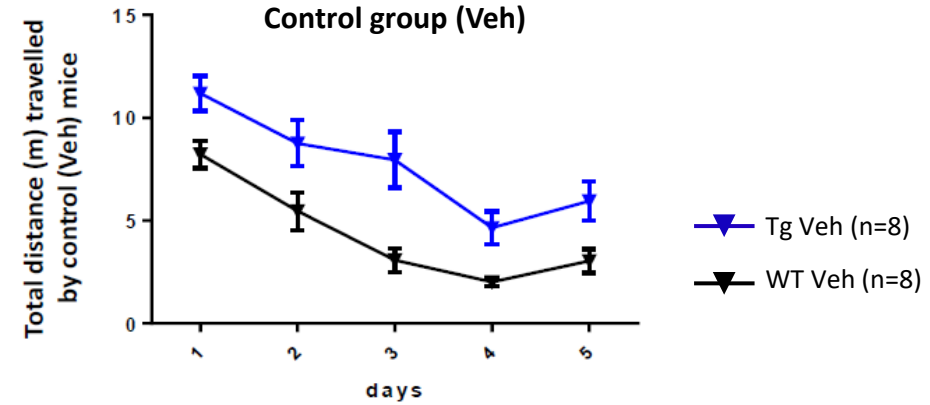
Hidden platform (target)



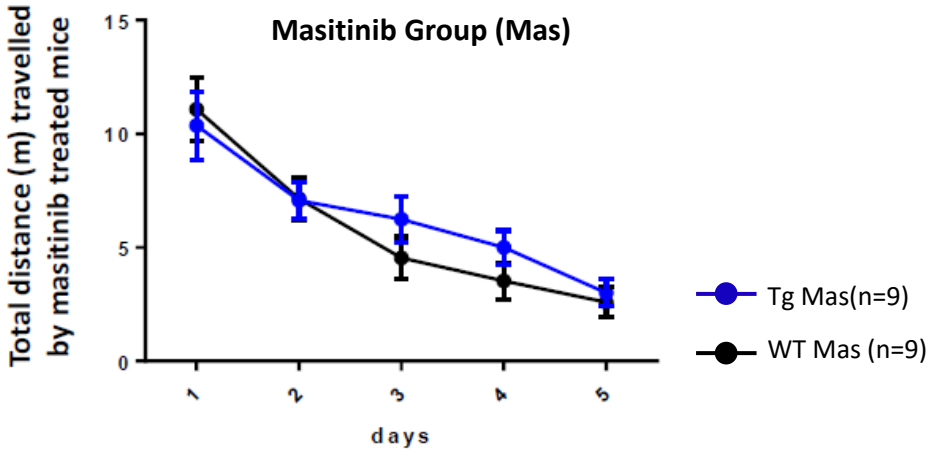
During learning — End of learning period

- Blinded study
- Masitinib was evaluated for its effect on memory deficit in AD mice (Tg) versus using the Morris Water Maze (MWM) in a curative setting (mice aged 12-14 months)
- The MWM test evaluates hippocampal-dependent learning, including acquisition of spatial memory and long-term spatial memory, which is often affected in AD.

**Morris Water Maze (MWM) – Improvement in Acquisition Phase**




**AD mice (Tg) have longer distance and no spatial memory improvement as compared with control mice (WT=wild-type)**




**AD mice (Tg) treated with masitinib improve cognitive function, with spatial memory returning to normal levels**

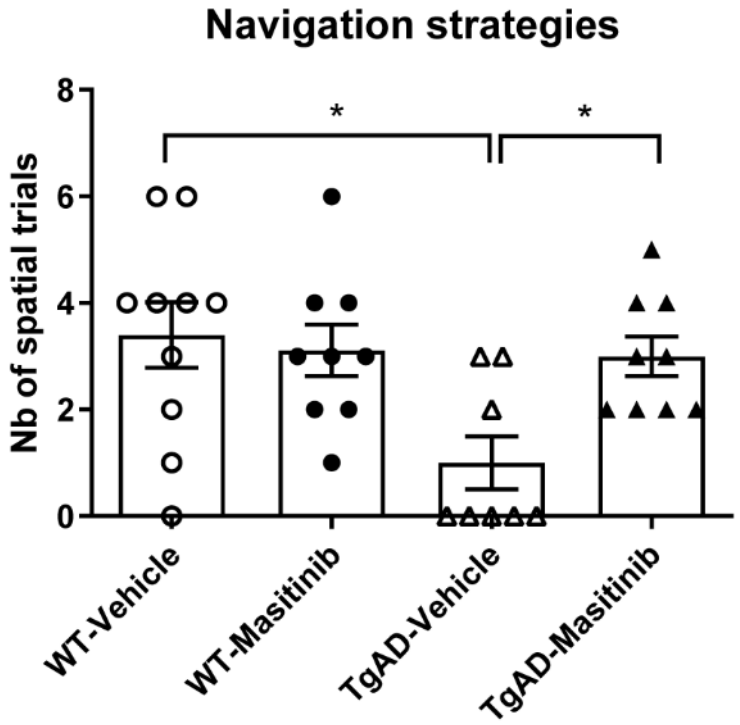
**References :** Courtesy from B Delatour. ICM – Brain Institute - France

# Pharmacology

## In a transgenic mouse model of AD, masitinib could completely protect/restore the ability to perform navigation strategy

**Morris Water Maze (MWM) – Improvement in Spatial Strategy**

A




| Group | p-value | Test |
|---|---|---|
| Tg Veh vs. Tg M | 0.034 | Treatment effect |

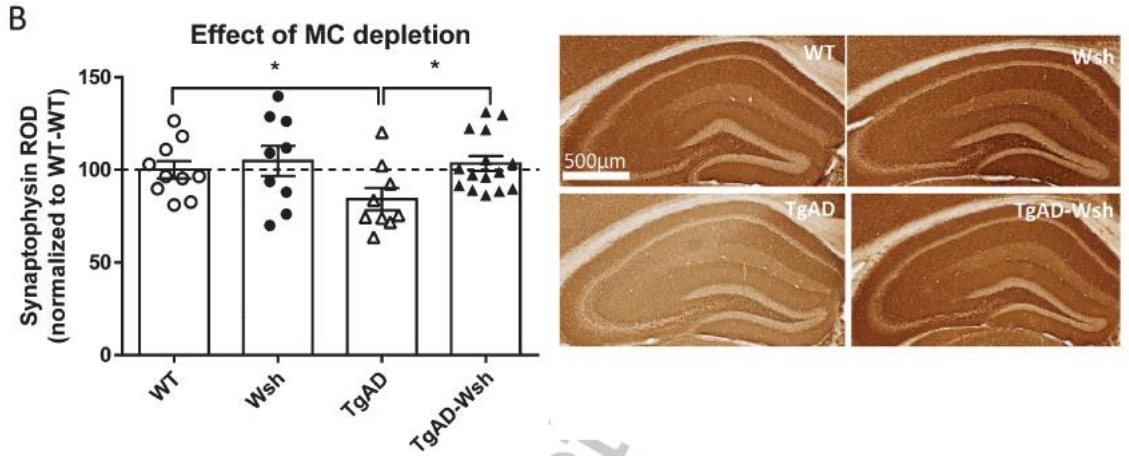
* p<0.05. WT = wild-type mice. Tg = APPxPS1dE9 mice. M = masitinib treatment. Veh = vehicle treatment.

**References :** Courtesy from B Delatour. ICM – Brain Institute - France

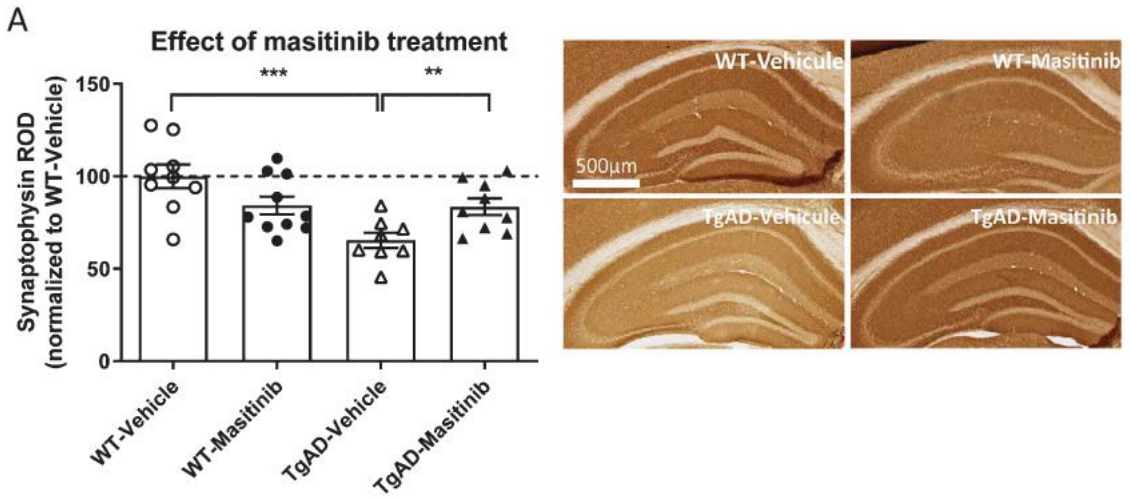
# Pharmacology

## In a transgenic mouse model of AD, masitinib could protect through mast cell inhibition against synaptic loss/destruction

**Mast cell-deficient transgenic AD mice show a recovery of synaptic markers**




**Likewise, masitinib induces a recovery of synaptic markers in transgenic mice model of AD**




WT = Wild-type mice. Wsh = Wild-type mice depleted in mast cells. TgAD = mice model of AD. TgAD-Wsh = mice model of AD depleted in mast cells. Veh = Vehicule

B. Relative optical density of synaptophys in immunoreactivity in the hippocampus of WT and TgAD mice with or without mast cells depletion induced by the Wsh mutation (left part) and representative microphotographs illustrating synaptophys in immunoreactivity levels in the four studied groups (right part).

A. Relative optical density of synaptophys in immunoreactivity in the hippocampus of WT and TgAD mice treated with Vehicle or masitinib (left part) and representative microphotographs illustrating synaptophys in immunoreactivity levels in the four studied groups (right part).

Data expressed as mean±SEM.***$p < 0.0001$, **$p < 0.01$, *$p < 0.05$.

B Delatour. Effects of Chronic Masitinib Treatment in APPswe/PSEN1dE9 Transgenic Mice Modeling Alzheimer's Disease. J Alzheimers Dis. 2020;76(4):1339-1345. doi: 10.3233/JAD-200466.

# Masitinib Clinical Development Plan in AD

## The development program in Alzheimer's disease is comprised of AB04024 proof of concept study *(published)*, and AB09004 phase 2B/3 study

| Phase | Study code | Design | Population | Primary endpoint | Patient target | Related publications |
|---|---|---|---|---|---|---|
| 2a | AB04024 (NCT00976118) | Double-blind, placebo-controlled, parallel-group study | Patients with mild to moderate Alzheimer Disease | Change on ADAS-Cog | 34 | Piette, 2011 |
| 2B/3 | AB09004 (NCT01872598) | Prospective, double-blind, placebo-controlled, parallel groups study | Patients with mild to moderate Alzheimer Disease | Change on ADCS-ADL<br>or<br>Change on ADAS-Cog | 720 | |

# Positioning in AD

## Masitinib is positioned in patients with mild and moderate dementia, which is different from other compounds

| Disease severity | MMSE Score (mini mental state examination) |
|---|---|
| Prodromal | > 25 |
| Mild | [21 – 25] |
| Moderate | [12 – 20] |
| Severe | < 12 |

**Aducanumab**

**Prodromal AD**
**> 22 / > 24**

**Masitinib**

**Mild & Moderate AD**
**[ 12 – 25]**

# Standard of care in AD

## There are currently four drugs used in the treatment of mild and moderate AD and approved 20 years ago

| Year of approval | Drug | Class |
|---|---|---|
| 1996 | Doneprazil | Cholinesterase inhibitors |
| 2000 | Rivastigmine | Cholinesterase inhibitors |
| 2001 | Galantamine | Cholinesterase inhibitors |
| 2003 | Memantine | NMDA Antagonist |

**Masitinib is used in add-on to Standard of Care**

# Primary clinical endpoints

## Evaluation of efficacy is based on two clinical endpoints

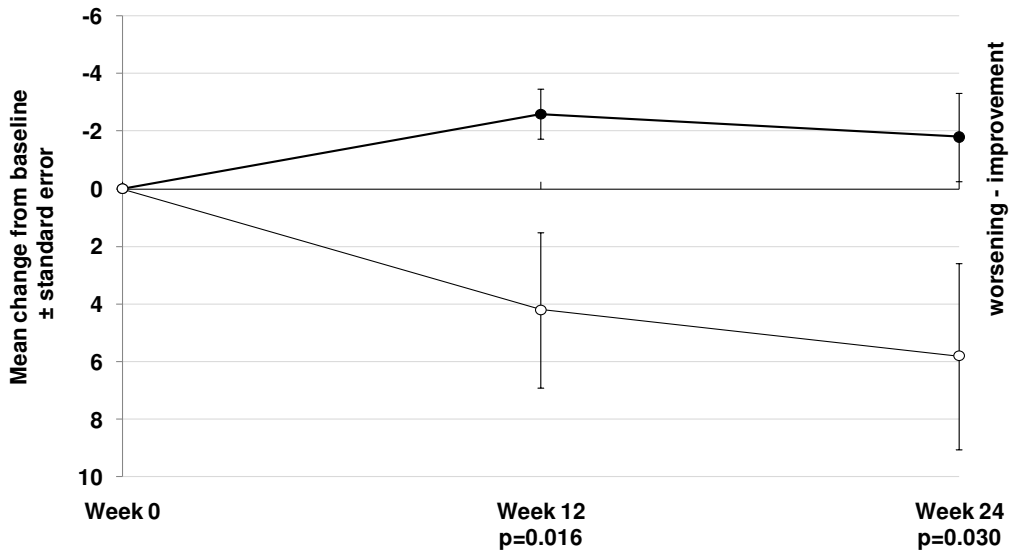
| Clinical endpoint | Objective | Assessment | Measurement | Outcome |
|---|---|---|---|---|
| ADAS-Cog | Measure the effect on cognition and memory | By patient | 11 Questions<br>Maximum 70 points | The lower the better |
| ADCS-ADL | Measure self-care and activities of daily living | By caregiver | 23 Questions<br>Maximum 78 Points | The higher the better |

# AB04024 study results in Alzheimer's disease

## A proof of concept study was published in 2011

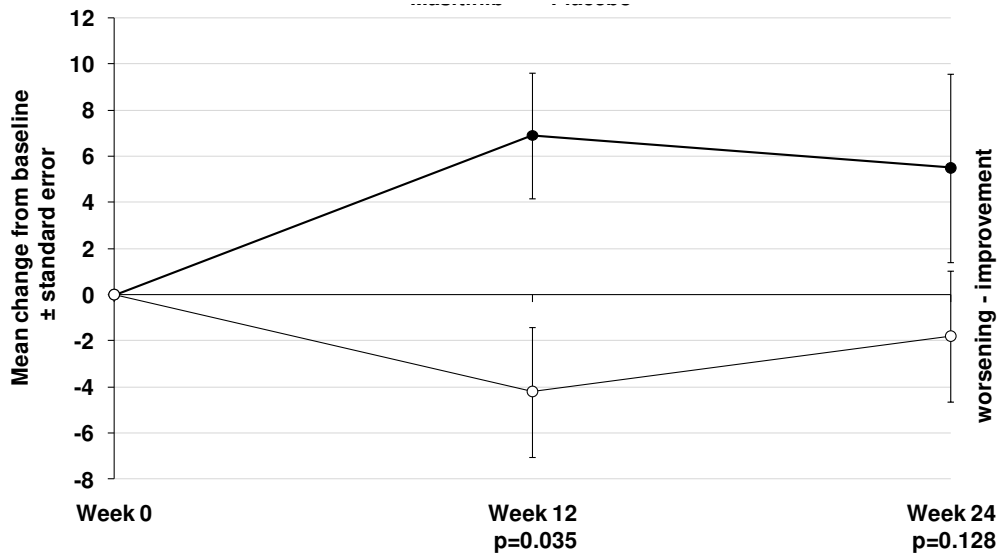
**Positive effect detected on cognitive function**

**Change in ADAS-Cog**




**Positive effect detected on Daily activity**

**Change in ADCS-ADL**




Phase 2a (n=34)

- ● Masitinib
- ○ Placebo

Piette et al., Alzheimers Res Ther. 2011 Apr 19;3(2):16. doi: 10.1186/alzrt75.

# AB09004 – Study Design

## Study AB09004 evaluated, in add-on to standard of care, three doses of masitinib, each dose having its own placebo control

### Design

**Design:**

Double-blind, Placebo-controlled, Randomized, Parallel-group Phase 3 Study to Evaluate the Safety and Efficacy of Masitinib in Patients With Mild to Moderate Alzheimer's Disease (AD), in add-on to Standard of Care

**Standard of Care (SoC):** Cholinesterase inhibitors, memantine

**Doses tested:**

- Masitinib 3 mg/kg/day (stopped early based on IDMC recommendation)
- Masitinib 4.5 mg/kg/day, randomisation 1:1
- Masitinib titration 4.5 to 6.0 mg/kg/day, randomisation 2:1

**Planned Enrolment:** 720 patients

**Primary endpoint:**

- Change in the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog)
- Change in the Alzheimer's Disease Cooperative Study Activities of Daily Living (ADCS-ADL)

**Duration:** 24 weeks

### Main inclusion criteria

1) Patient with dementia of Alzheimer's type, according to the Diagnostic and Statistical Manual of Mental Disorders criteria (DSM-IV)

2) Patient with probable Alzheimer' disease according to the NINCDS-ADRDA criteria (National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association)

3) Patient with MMSE ≥ 12 and ≤ 25 at baseline

4) Patient treated for a minimum of 6 months with a stable dose of cholinesterase inhibitors and/or a stable dose of memantine, with no changes foreseen in therapy throughout the study.

ClinicalTrials.gov Identifier: NCT01872598

# AB09004 – Study Design

## The study was successful if a significant improvement was reached on either ADAS-Cog or ADCS-ADL at a 2.5% level of statistical significance

**Statistical analysis:**

- Statistical risk Alpha (chance finding) splited between ADAS-COG (2.5%) and ADCS-ADL (2.5%).
- Study is successful if the treatment effect is established **in at least one of the two primary endpoints**

**Stratification factors**

- MMSE score at baseline
- Age at baseline
- ADCS-ADL total score at baseline
- ADAS-COG total score at baseline

**Populations analysed**

- Primary analysis : FAS (Full Analysis Set)

**Type I error was controlled at interim by the Haybittle-Peto alpha spending method**

The efficacy criteria was tested at a significance level which defined as follows –

- Stop at interim and reject null hypothesis on primary endpoint if p-value < 0.001
- If at interim p-value > 0.001, continue to final analysis and efficacy criteria at final analysis is tested at 2.499% level for each of the primary endpoints

# AB09004 – Population analyzed

## The study was comprised of two independent sub-studies testing two distinct dosing regimens

**Study AB09004 : N = 718 from 118 sites in 21 countries, 51.5% of patients enrolled in EU countries**

| ***Dosing 3.0 mg/kg/day*** | **Dosing Masitinib 4.5 mg/kg/day vs matching placebo** | **Dosing Masitinib 4.5 to 6.0 mg/kg/day titration vs matching placebo** | ***Dosing 6.0 mg/kg/day*** |
|---|---|---|---|
| *N=58* | **ITT population** N=370 (M=185 ; P=185) | **ITT population** N=278 (M=186 ; P=92) | *N=12* |
| *Stopped early in the study upon IDMC recommendation. Data not analyzed* | **Safety population** N=368 (M=185 ; P=183) | **Safety population** N=278 (M=186 ; P=92) | *Stopped early in the study by Sponsor decision and replaced with Masitinib 4.5 to 6.0 mg/kg/day titration. Data not analyzed* |
| *N= 58 is masitinib treated patients. Placebo treated patients are analyzed as part of the placebo arm versus masitinib 4.5 mg/kg/day* | **Full Analysis Set** N=358 (M=182 ; P=176) | **Full Analysis Set** N=277 (M=186 ; P=91) | *As a result, Group 4.5 mg/kg/day and Group titration up to 6.0 mg/kg/day were not conducted at the same time nor in the same centers* |

**Full Analysis Set :** Exclusion from ITT population of 13 patients

- Patients from sites with critical GCP violations at 2 sites as highlighted by audit report and internal report (n=6)
- Patients with no treatment intake (n=2)
- Patients with baseline Adl or Cog scores that do not correspond to the medical history, with documented letter from investigator to exclude them from primary analysis, validated by steering committee (n=3)
- Patients with caregiver that changed during the main period, with documented letter from investigator to exclude them from primary analysis, validated by steering committee (n=2)

# AB09004 – Baseline Characteristics

## Baseline characteristics were balanced

**Masitinib 4.5 mg/kg/day vs matching placebo**

| FAS | Masitinib + SoC (N = 182) | Placebo + SoC (N = 176) |
|---|---|---|
| **Age** (Years) | | |
| Mean (std) | 71.9 (8.28) | 71.7 (8.21) |
| Median | 73.0 | 73.0 |
| >=50 - <60 [n (%)] | 19 (10.4) | 17 (9.4) |
| >=60 - <70 [n (%)] | 44 (24.0) | 52 (28.9) |
| >=70 - <80 [n (%)] | 82 (44.8) | 76 (42.2) |
| ≥ 80 [n (%)] | 38 (20.8) | 35 (19.4) |
| **Sex** [n (%)] | | |
| Female | 114 (62.6) | 98 (55.7) |
| **MMSE** | | |
| 12-20 | 119 (65.4) | 115 (65.3) |
| 21-25 | 63 (34.6) | 61 (34.7) |
| Mean | 18.8 (3.73) | 18.6 (3.76) |
| Median | 19.0 | 19.0 |
| **ADCS-ADL** | | |
| Mean (std) | 51.8 (15.13) | 51.4 (14.95) |
| Median | 55.0 | 53.5 |
| **ADAS-COG** | | |
| Mean (std) | 26.1 (10.13) | 25.9 (9.67) |
| Median | 25.5 | 24.8 |

**Masitinib 4.5 to 6.0 mg/kg/day titration vs matching placebo**

| FAS | Masitinib + SoC (N = 186) | Placebo + SoC (N = 91) |
|---|---|---|
| **Age** (Years) | | |
| Mean (std) | 71.9 (8.29) | 71.2 (8.11) |
| Median | 72.0 | 72.0 |
| >=50 - <60 [n (%)] | 14 (7.5) | 10 (11.0) |
| >=60 - <70 [n (%)] | 54 (29.0) | 26 (28.6) |
| >=70 - <80 [n (%)] | 78 (41.9) | 41 (45.1) |
| ≥ 80 [n (%)] | 40 (21.5) | 14 (15.4) |
| **Sex** [n (%)] | | |
| Female | 118 (63.4) | 57 (62.6) |
| **MMSE** | | |
| 12-20 | 123 (66.1) | 57 (62.6) |
| 21-25 | 63 (33.9) | 34 (37.4) |
| Mean | 18.8 (3.62) | 18.7 (3.71) |
| Median | 19.0 | 19.0 |
| **ADCS-ADL** | | |
| Mean (std) | 52.4 (14.76) | 53.2 (13.65) |
| Median | 54.0 | 57.0 |
| **ADAS-COG** | | |
| Mean (std) | 24.9 (10.08) | 26.2 (10.64) |
| Median | 24.3 | 24.3 |

# AB09004 – Primary analysis - Cog - 4.5 mg/kg/day

## The study met its primary analysis, demonstrating a statistically significant reduction in Cognitive impairment based on ADAS-COG (p=0.0003)

**Significant effect on cognitive function after 24 weeks of treatment**

**Change in ADAS-Cog - ANCOVA Analysis (Full Analysis Set) - M4.5 vs Placebo**

| | Descriptive Statistics | | Model Summary - LSM | | Difference | | |
|---|---|---|---|---|---|---|---|
| Treatment | n | Mean (SD) | LS Mean | 95% CI | LS Mean (SE) | 97.51% CI | p-value |
| Masitinib 4.5 mg/kg/day + SoC | 182 | -1.51 (5.81) | -1.46 | (-2.46, -0.45) | -2.15 (0.59) | (-3.48, -0.81) | 0.0003 |
| Placebo + SoC | 176 | 0.63 (5.35) | 0.69 | (-0.36, 1.75) | | | |

**Imputation Model for missing Data**

For the primary analysis, missing values are imputed by using the patient's previous non-missing score and data from other similar patients (same cluster) that have continued treatment.

# AB09004 – Cog J2R sensitivity analysis - 4.5 mg/kg/day

## Cog sensitivity analysis based on Jump to reference imputation method remained positive, demonstrating a robust treatment effect

**Significant effect on cognitive function confirmed based on Jump to Reference analysis**

**Change in ADAS-Cog - ANCOVA Analysis (Jump to Reference) - M4.5 vs Placebo**

| | Descriptive Statistics | | Model Summary - LSM | | Difference | | |
|---|---|---|---|---|---|---|---|
| Treatment | n | Mean (SD) | LS Mean | 95% CI | LS Mean (SE) | 95% CI | p-value |
| Masitinib 4.5 mg/kg/day + SoC | 182 | -1.24 (5.86) | -1.04 | (-2.06, -0.03) | -1.89 (0.60) | (-3.06, -0.72) | 0.0016 |
| Placebo + SoC | 176 | 0.63 (5.35) | 0.85 | (-0.21, 1.91) | | | |

**The Jump to Reference (J2R) approach**

The Jump to Reference, which is the most conservation approach, imputes the Placebo estimates for all patients who prematurely discontinue due to *lack of efficacy* and *toxicity* (related TEAE) in the treatment arm.

# AB09004 – Adl - 4.5 mg/kg/day

## The study demonstrated a statistically significant improvement on daily activity based on ADCS-ADL (p=0.0381)

**Significant effect on daily activity after 24 weeks of treatment**

**Change in ADCS-Adl - ANCOVA Analysis (Full Analysis Set) - M4.5 vs Placebo**

| | Descriptive Statistics | | Model Summary - LSM | | Difference | | |
|---|---|---|---|---|---|---|---|
| Treatment | n | Mean (SD) | LS Mean | 95% CI | LS Mean (SE) | 97.51% CI | p-value |
| Masitinib 4.5 mg/kg/day + SoC | 182 | 0.51 (7.78) | 1.01 | (-0.48, 2.50) | 1.82 (0.87) | (-0.15, 3.79) | 0.0381 |
| Placebo + SoC | 176 | -1.09 (9.17) | -0.81 | (-2.36, 0.74) | | | |

**Imputation Model for missing Data**

For the primary analysis, missing values are imputed by using the patient's previous non-missing score and data from other similar patients (same cluster) that have continued treatment.

# AB09004 – Adl J2R sensitivity analysis - 4.5 mg/kg/day

## Adl sensitivity analysis based on Jump to reference imputation method showed a numerical advantage close to statistical significance in favor of masitinib

**Numerical advantage close to statistical significance on daily activity based on sensitivity analyses**

**Change in ADCS-Adl - ANCOVA Analysis (Jump to Reference) - M4.5 vs Placebo**

| | Descriptive Statistics | | Model Summary - LSM | | Difference | | |
|---|---|---|---|---|---|---|---|
| Treatment | n | Mean (SD) | LS Mean | 95% CI | LS Mean (SE) | 95% CI | p-value |
| Masitinib 4.5 mg/kg/day + SoC | 182 | 0.39 (7.79) | 0.81 (0.76) | (-0.68, 2.30) | 1.71 (0.87) | (-0.01, 3.43) | 0.0512 |
| Placebo + SoC | 176 | -1.09 (9.17) | -0.90 (0.79) | (-2.46, 0.65) | | | |

**The Jump to Reference (J2R) approach**

The Jump to Reference, which is the most conservation approach, imputes the Placebo estimates for all patients who prematurely discontinue due to *lack of efficacy* and *toxicity* (related TEAE) in the treatment arm.

# AB09004 – Cog and Adl analysis in mITT - 4.5 mg/kg/day

## mITT analysis shows that the Cog analysis remained positive and Adl analysis lost statistical significance

**Post-Hoc Analysis (ANCOVA) in mITT - M4.5 vs Placebo**

| | Descriptive Statistics | | Model Summary - LSM | | Difference | | |
|---|---|---|---|---|---|---|---|
| Treatment | n | Mean (SD) | LS Mean | 95% CI | LS Mean (SE) | 95% CI | p-value |
| **Change in ADAS-Cog** | | | | | | | |
| Masitinib 4.5 mg/kg/day + SoC | 183 | -1.49 (5.81) | -1.45 (0.51) | (-2.45, -0.45) | -2.10 (0.59) | (-3.25, -0.95) | 0.0004 |
| Placebo + SoC | 180 | 0.61 (5.30) | 0.65 (0.53) | (-0.39, 1.69) | | | |
| **Change in ADCS-Adl** | | | | | | | |
| Masitinib 4.5 mg/kg/day + SoC | 183 | 0.57 (7.79) | 1.09 (0.76) | (-0.41, 2.59) | 1.58 (0.88) | (-0.16, 3.31) | 0.07426 |
| Placebo + SoC | 180 | -0.76 (9.35) | -0.49 (0.79) | (-2.05, 1.08) | | | |

**mITT population :**

- Exclude 8 patients from sites with critical GCP violations at 2 sites as highlighted by audit report and internal report (n=6) and with no treatment intake (n=2)
- Retain patients with baseline Adl or Cog scores that do not correspond to the medical history, with documented letter from investigator to exclude them from primary analysis, validated by steering committee (n=3), and patients with caregiver that changed during the main period, with documented letter from investigator to exclude them from primary analysis, validated by steering committee (n=2)

# AB09004 – CIBIC - 4.5 mg/kg/day

## The study demonstrated a 71% improvement on CIBIC as compared with placebo, statistically significant (p=0.040)

**CIBIC (Improve) - Logistic Regression Analysis (Full Analysis Set) - M4.5 vs Placebo**

| | Descriptive Statistics | Count (percentage) | | Statistic | |
|---|---|---|---|---|---|
| Treatment | n | Improvement | Worsening/No Change | OR (95% CI) | p-value |
| Masitinib 4.5 mg/kg/day + SoC | 182 | 47 (25.82) | 91 (50.00) | 1.71 (1.02, 2.85) | 0.0400 |
| Placebo + SoC | 176 | 36 (20.45) | 119 (67.61) | | |

**Modified Last Observation Carried Forward (mLOCF)**

Comparison between treatment groups performed on the difference between improvement [1-3] and worsening [5-7] CIBIC-plus classes (improvement minus worsening) at Week 24 by using a chi square test for proportions comparison, using Modified Last Observation Carried Forward (mLOCF) methods for the management of missing data.

The mLOCF approach carries forward the last observed value for patients who prematurely discontinue due to *lack of efficacy* and *toxicity* (related TEAE).

# AB09004 – MMSE / CDR / NPI - 4.5 mg/kg/day

## The study showed a numerical advantage non statistically significant in favor of masitinib on MMSE, CDR, and NPI

**Summary of change from baseline (mLOCF) of All Secondary Endpoints Over Time by Treatment - Full Analysis Set - M4.5 vs Placebo**

| Parameter | Treatment | Statistics | Week 8 | Week 12 | Week 24 |
|---|---|---|---|---|---|
| Mini-Mental State Examination (MMSE) | Masitinib + SoC | n | 156 | 149 | 139 |
| | | Mean (SD) | 0.49 ( 2.67) | 0.79 ( 2.89) | 0.35 ( 3.04) |
| | Placebo + SoC | n | 170 | 163 | 155 |
| | | Mean (SD) | 0.09 ( 2.52) | 0.66 ( 2.77) | 0.22 ( 3.02) |
| | | **Diff. of M-P** | **0.40** | **0.12** | **0.13** |
| Clinical Dementia Rating (CDR) | Masitinib + SoC | n | 123 | 146 | 136 |
| | | Mean (SD) | -0.05 ( 0.42) | -0.03 ( 0.41) | -0.01 ( 0.49) |
| | Placebo + SoC | n | 116 | 162 | 155 |
| | | Mean (SD) | -0.01 ( 0.41) | 0.06 ( 0.48) | 0.01 ( 0.55) |
| | | **Diff. of M-P** | **-0.04** | **-0.09** | **-0.02** |
| Caregiver Distress (NPI) | Masitinib + SoC | n | 87 | 103 | 95 |
| | | Mean (SD) | -1.08 ( 3.58) | -0.50 ( 4.62) | 0.61 ( 4.88) |
| | Placebo + SoC | n | 77 | 120 | 108 |
| | | Mean (SD) | -0.66 ( 3.05) | -0.13 ( 3.73) | 0.85 ( 4.64) |
| | | **Diff. of M-P** | **-0.42** | **-0.38** | **-0.24** |
| Frequency and Severity (NPI) | Masitinib + SoC | n | 87 | 103 | 95 |
| | | Mean (SD) | -2.06 ( 7.51) | -0.72 ( 9.12) | 1.18 (10.20) |
| | Placebo + SoC | n | 77 | 120 | 108 |
| | | Mean (SD) | -0.66 ( 5.58) | -0.11 ( 7.81) | 2.19 ( 8.70) |
| | | **Diff. of M-P** | **-1.40** | **-0.61** | **-1.01** |

# AB09004 – Cog and Adl analysis – titration 6.0 mg/kg/day

## No significant treatment-effect was observed either on Cog or Adl for high-dose masitinib (titration up to 6.0 mg/kg/day)

**ANCOVA Analysis (Full Analysis Set) - M4.5 up to 6.0 vs Placebo**

| | Descriptive Statistics | | Model Summary - LSM | | Difference | | |
|---|---|---|---|---|---|---|---|
| Treatment | n | Mean (SD) | LS Mean | 95% CI | LS Mean (SE) | 95% CI | p-value |
| **Change in ADAS-Cog** | | | | | | | |
| Masitinib 4.5 to 6.0 mg/kg/day + SoC | 186 | **-0.54** (4.50) | -0.18 (0.47) | (-1.10, 0.73) | -0.43 (0.61) | (-1.81, 0.95) | 0.4828 |
| Placebo + SoC | 91 | **-0.26** (5.46) | 0.25 (0.60) | (-0.94, 1.43) | | | |
| **Change in ADCS-Adl** | | | | | | | |
| Masitinib 4.5 to 6.0 mg/kg/day + SoC | 186 | **0.53** (6.15) | 0.57 (0.62) | (-0.69, 1.80) | 0.20 (0.82) | (-1.64, 2.04) | 0.8073 |
| Placebo + SoC | 91 | **0.25** (6.98) | 0.37 (0.81) | (-1.22, 1.96) | | | |

**Improvement under placebo possibly influenced by low number for placebo (n<100)**

**Improvement in mean Cog**
(Mean = - 0.26)

**Improvement in mean daily activity**
(Mean = 0.25)

**No higher efficacy with masitinib titration to 6.0 vs 4.5 mg/kg/day**

**Cognitive function**
(Mean = - 0.54 with M6 vs -1.51 with M4.5)

**Daily activity**
(Mean = 0.53 with M6 vs 0.51 with M4.5)

**We can conclude that the effective dose in Alzheimer's disease for masitinib is 4.5 mg/kg/day**

# AB09004 – 4.5 mg/kg/day vs combined placebo

## In order to assess the impact of the divergent placebo effect, masitinib 4.5 mg/kg/day was compared with the pooled placebo arms and Cog analysis remained significant

**Significant effect on Cog with masitinib 4.5 versus combined placebo**

**ANCOVA Analysis (Full Analysis Set) - M4.5 vs Combined Placebo**

| | Descriptive Statistics | | Model Summary - LSM | | Difference | | |
|---|---|---|---|---|---|---|---|
| Treatment | n | Mean | LS Mean | 95% CI | LS Mean (SE) | 95% CI | p-value |
| **Change in ADAS-Cog** | | | | | | | |
| Masitinib 4.5 mg/kg/day + SoC | 182 | -1.51 (5.81) | -1.16 | (-2.12, -0.19) | -1.90 (0.53) | (-2.95, -0.85) | 0.0004 |
| Combined Placebo + SoC | 267 | 0.33 (5.40) | 0.74 | (-0.15, 1.63) | | | |
| **Change in ADCS-Adl** | | | | | | | |
| Masitinib 4.5 tmg/kg/day + SoC | 182 | 0.51 (7.78) | 1.00 | (-0.39, 2.39) | 1.33 (0.77) | (-0.18, 2.84) | 0.0838 |
| Combined Placebo + SoC | 267 | -0.64 (8.50) | -0.33 | (-1.61, 0.95) | | | |

# AB09004 – Severe Dementia - 4.5 mg/kg/day vs combined placebo

## There were significantly fewer patients reaching severe dementia stage (MMSE<10) and a significant decrease in time to severe dementia with masitinib 4.5 mg/kg/day compared with the pooled placebo arms

**Significant effect on severe dementia (MMSE<10) with masitinib 4.5 versus combined placebo**

**Dementia- M4.5 vs Placebo Pooled (FAS)**

| | | | | | | | p-value | | Hazard | |
|---|---|---|---|---|---|---|---|---|---|---|
| Treatment group | Total | No. of Events | Percentage Events | No. Censored | Percentage censored | Median [95% CI] | KM p-Value | Log Rank | Ratio (95% CI) | p-Value |
| Masitinib 4.5 mg/kg/day | 182 | 2 | 1.10 | 180 | 98.90 | Not reached [ ; ] | 0.0446 | 0.0403 | 0.19 (0.0,0.8) | 0.0276 |
| Pooled Placebo | 267 | 15 | 5.62 | 252 | 94.38 | 6.3 [5.9;6.3 ] | | | | |

| Baseline MMSE (FAS) | Masitinib + SoC (N = 182) | Pooled Placebo + SoC (N =267) |
|---|---|---|
| < 14 | 18 (9.9) | 30 (11.2) |
| < 17 | 54 (29.7) | 81 (30.3) |

# AB09004 – Safety Overview

## The safety of masitinib consistent with its known tolerability profile

**Summary of Adverse Events – Safety population - [W0-W24] period**

| | Masitinib 3.0 + SoC (N = 58) n (%) | Masitinib 4.5 + SoC (N = 185) n (%) | Masitinib 4.5 to 6.0 + SoC (N = 186) n (%) | Placebo + SoC (N = 280) n (%) |
|---|---|---|---|---|
| At least one AE | 53 ( 91.4) | 161 ( 87.0) | 160 ( 86.0) | 217 ( 77.5) |
| At least one serious AE (non-fatal) | 6 ( 10.3) | 24 ( 13.0) | 25 ( 13.4) | 15 ( 5.4) |
| At least one severe AE | 9 ( 15.5) | 49 ( 26.5) | 47 ( 25.3) | 54 ( 19.3) |

Among the 13% and 13.4% SAEs with masitinib (M4.5 and M6), 4.8% and 4.9 % were associated with mild or moderate adverse events, respectively

# AB09004 – Safety Overview

## The increase in Serious adverse events was equally distributed across all organ classes

**Non - Fatal Serious Adverse Events by System Organ Class – Safety population - [W0-W24] period**

| | Masitinib 3.0 + SoC (N = 58) n (%) | Masitinib 4.5 + SoC (N = 185) n (%) | Masitinib 4.5 to 6.0 + SoC (N = 186) n (%) | Placebo + SoC (N = 280) n (%) |
|---|---|---|---|---|
| At least one Serious Adverse Event | 6 ( 10.3) | 24 ( 13.0) | 25 ( 13.4) | 15 ( 5.4) |
| Skin and subcutaneous tissue disorders | 1 ( 1.7) | 3 ( 1.6) | 9 ( 4.8) | 0 ( 0.0) |
| Infections and infestations | 0 ( 0.0) | 6 ( 3.2) | 3 ( 1.6) | 3 ( 1.1) |
| Blood and lymphatic system disorders | 3 ( 5.2) | 4 ( 2.2) | 4 ( 2.2) | 0 ( 0.0) |
| Gastrointestinal disorders | 0 ( 0.0) | 4 ( 2.2) | 1 ( 0.5) | 1 ( 0.4) |
| Neoplasms benign, malignant and unspecified | 0 ( 0.0) | 3 ( 1.6) | 1 ( 0.5) | 2 ( 0.7) |
| Cardiac disorders | 0 ( 0.0) | 4 ( 2.2) | 1 ( 0.5) | 0 ( 0.0) |
| Injury, poisoning and procedural complications | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 5 ( 1.8) |
| Investigations | 1 ( 1.7) | 1 ( 0.5) | 2 ( 1.1) | 1 ( 0.4) |
| Hepatobiliary disorders | 0 ( 0.0) | 1 ( 0.5) | 1 ( 0.5) | 2 ( 0.7) |
| Nervous system disorders | 1 ( 1.7) | 1 ( 0.5) | 2 ( 1.1) | 0 ( 0.0) |
| General disorders and administration site conditions | 0 ( 0.0) | 0 ( 0.0) | 3 ( 1.6) | 0 ( 0.0) |
| Renal and urinary disorders | 0 ( 0.0) | 3 ( 1.6) | 0 ( 0.0) | 0 ( 0.0) |
| Respiratory, thoracic and mediastinal disorders | 0 ( 0.0) | 2 ( 1.1) | 1 ( 0.5) | 0 ( 0.0) |
| Immune system disorders | 0 ( 0.0) | 1 ( 0.5) | 0 ( 0.0) | 0 ( 0.0) |
| Metabolism and nutrition disorders | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.4) |
| Musculoskeletal and connective tissue disorders | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.4) |
| Reproductive system and breast disorders | 0 ( 0.0) | 1 ( 0.5) | 0 ( 0.0) | 0 ( 0.0) |

# Intellectual Property

**A new patent was filed based on results from study AB09004, which would permit AB Science to retain exclusive rights on the use of masitinib in Alzheimer's disease until 2041.**

| Protection | Item | Duration of protection | Status |
|---|---|---|---|
| **Patent on composition of matter and PTE** | Patent on composition of matter has been filed and delivered. It will be further extended until 2028 through patent term extension (PTE) | Until 2028 | Delivered |
| **Synthesis process patent** | A further protection until 2028 has been achieved through synthesis 'process' patent | Until 2028 | Delivered |
| **Phase 2/3 'Method of use' patents** | New patent based on results from study AB09004 | Until 2041 | Filed |

# Market potential

| Indication | Prevalence | Estimated number of potential eligible patients | | Annual cost of drugs registered in the indication |
|---|---|---|---|---|
| | | US Patients | EU Patients | |
| Alzheimer's Disease | 1,000 / 100,000[1] | 2,000,000 | 3,000,000 | No approved drug as an add-on to cholinesterase inhibitors or memantine |
| Mild and moderate forms of Alzheimer's Disease* | 60%[2] | | | |

* : expressed as percentage of Alzheimer's Disease

Source :
Population : https://data.worldbank.org/indicator/SP.POP.TOTL and https://ec.europa.eu/eurostat/web/population-demography-migration-projections/population-data/main-tables


1. Weili Xu et al. Epidemiology of Alzheimer's Disease. 2013.doi: 10.5772/54398
2. https://www.j-alz.com/editors-blog/posts/when-do-we-diagnose-severe-alzheimers-disease

# Q&A