Masitinib for the treatment of Alzheimer’s disease: Clinical and preclinical data

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Disclosure

Co-founder of AB science
Scientific consultant
Research grants
MAST CELLS AND DISEASES

- Cancer
- Allergy
- Autoimmunity
- Mastocytosis
- Inflammation fibrosis
- Alloreactivity acute chronic
MASTOCYTOSIS DEFINITION

- Mast cell accumulation in various organs (Skin, GI tract, Liver, Bone and Bone Marrow, etc)
- Myeloproliferative disorder; Aggressive vs indolent disease
- Association with hematological disorders
- Clinical heterogeneity (Infiltration vs Mediators release)

Photos Pr Bodemer et Dr Barete
IDENTIFICATION OF ALL SYSTEMIC MANIFESTATIONS IN PATIENTS SUFFERING FROM MASTOCYTOSIS

- From 2004, 363 mastocytosis patients and 90 controls in France were asked to rate their overall disability (OPA score) and the severity of 38 individual symptoms.

- A specific questionnaire (AFIRMM V1), encompassing these 38 symptoms, has been created and validated.


Case-Control Cohort Study of Patients’ Perceptions of Disability in Mastocytosis

Olivier Hermine\(^1\), Olivier Lortholary\(^3\), Phillip S. Leventhal\(^3\), Adeline Catteau\(^3\), Frédérique Soppelsa\(^3\), Cedric Baude\(^3\), Annick Cohen-Akenine\(^3\), Fabienne Palmérini\(^3\), Katia H année\(^3\), Ying Yang\(^4\), Hagay Sobol\(^6\), Sylvie Fraytag\(^5\), David Ghez\(^1,2\), Felipe Suarez\(^2\), Stéphane Barete\(^1,7\), Philippe Casassus\(^3,8\), Beatrice Sans\(^9\), Michel Arock\(^10\), Jean Pierre Kinet\(^3\), Patrice Dubreuil\(^3,4,6\), Alain Moussy\(^3\)
### Identification of All Systemic Manifestations in Patients Suffering from Mastocytosis

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Any disability</th>
<th>Severe or intolerable disability</th>
<th>n</th>
<th>Any disability</th>
<th>Severe or intolerable disability</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychological impact</td>
<td>9 (10%)</td>
<td>1 (1%)</td>
<td>363</td>
<td>261 (72%)</td>
<td>120 (33%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Asthenia</td>
<td>34 (38%)</td>
<td>3 (3%)</td>
<td>362</td>
<td>296 (82%)</td>
<td>102 (28%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Pruritus</td>
<td>25 (28%)</td>
<td>3 (3%)</td>
<td>363</td>
<td>299 (82%)</td>
<td>82 (23%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Food allergy/intolerance</td>
<td>9 (10%)</td>
<td>0 (0%)</td>
<td>363</td>
<td>222 (61%)</td>
<td>97 (27%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Erythematous crisis</td>
<td>17 (19%)</td>
<td>1 (1%)</td>
<td>363</td>
<td>293 (81%)</td>
<td>69 (19%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Muscle and joint pain, cramps</td>
<td>36 (40%)</td>
<td>3 (3%)</td>
<td>363</td>
<td>276 (76%)</td>
<td>71 (20%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Pollakiuria</td>
<td>58 (64%)</td>
<td>6 (7%)</td>
<td>362</td>
<td>263 (73%)</td>
<td>64 (18%)</td>
<td>0.12</td>
</tr>
<tr>
<td>Drug allergy</td>
<td>16 (18%)</td>
<td>0 (0%)</td>
<td>363</td>
<td>205 (56%)</td>
<td>70 (19%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Aerophagia/eructation</td>
<td>43 (48%)</td>
<td>1 (1%)</td>
<td>363</td>
<td>229 (63%)</td>
<td>62 (17%)</td>
<td>0.0080</td>
</tr>
<tr>
<td>Dyspnea/bronchoreactivity</td>
<td>15 (17%)</td>
<td>3 (3%)</td>
<td>362</td>
<td>154 (43%)</td>
<td>94 (26%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Headache</td>
<td>34 (38%)</td>
<td>4 (4%)</td>
<td>362</td>
<td>250 (69%)</td>
<td>48 (13%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Bone pain</td>
<td>16 (18%)</td>
<td>0 (0%)</td>
<td>363</td>
<td>196 (54%)</td>
<td>65 (18%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Reduced sexual relations</td>
<td>11 (12%)</td>
<td>4 (4%)</td>
<td>362</td>
<td>132 (36%)</td>
<td>65 (18%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Epigastric pain</td>
<td>35 (39%)</td>
<td>2 (2%)</td>
<td>362</td>
<td>249 (69%)</td>
<td>40 (11%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ocular discomfort</td>
<td>43 (48%)</td>
<td>1 (1%)</td>
<td>363</td>
<td>219 (60%)</td>
<td>55 (15%)</td>
<td>0.0309</td>
</tr>
<tr>
<td>Memory loss</td>
<td>32 (36%)</td>
<td>0 (0%)</td>
<td>362</td>
<td>240 (66%)</td>
<td>34 (9%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Tinnitus</td>
<td>29 (32%)</td>
<td>1 (1%)</td>
<td>363</td>
<td>166 (46%)</td>
<td>47 (13%)</td>
<td>0.0205</td>
</tr>
</tbody>
</table>
IDENTIFICATION OF PSYCHOPATHOLOGICAL MANIFESTATIONS IN PATIENTS SUFFERING FROM MASTOCYTOSIS

- Determine the prevalence and to describe features of depression in a large cohort of mastocytosis patients (n = 288)
- Use of 17 items Hamilton Depression Scale (Ham-D17)


Depression in Patients with Mastocytosis: Prevalence, Features and Effects of Masitinib Therapy

Daniela Silva Moura¹,², Serge Sultan²,³, Sophie Georin-Lavialle¹,⁴, Nathalie Pillet⁵, François Montestruc⁵, Paul Gineste⁵, Stéphane Barete⁶, Gandhi Damaj⁷, Alain Moussy⁵,⁸, Olivier Lortholary⁹, Olivier Hermine¹,⁴,⁵,⁸
IDENTIFICATION OF PSYCHOPATHOLOGICAL MANIFESTATIONS IN PATIENTS SUFFERING FROM MASTOCYTOSIS

- 64% of Patients are depressed (Hamilton Score)
  - Moderate 56%
  - Severe 10%

- Characteristics of the depression
  - Anxiety and depression
    - Depressed mood
    - Psychiatric and somatic anxiety
    - Impairement and weakness for social and professional interactions
  - Sleep disturbances

- NO CORRELATION WITH COGNITIVE FUNCTIONS
EVALUATION OF COGNITIVE IMPAIRMENT IN PATIENTS SUFFERING FROM MASTOCYTOSIS

- Describe the prevalence and features of cognitive impairment in a large cohort of patients with this rare disease (n=57)
- Explore the relations between memory impairment and depression
- Memory impairment evaluated using the 3(rd) edition of the Clinical Memory scale of Wechsler. Depression symptoms evaluated using the Hamilton Depression Rating Scale


Evidence for Cognitive Impairment in Mastocytosis: Prevalence, Features and Correlations to Depression

Daniela Silva Moura¹,²*, Serge Sultan⁷,⁸, Sophie Georquin-Lavialle¹,³,⁴, Stéphane Barete¹,³,⁵, Olivier Lortholary¹,⁶, Raphael Gaillard⁹,¹⁰, Olivier Hermine¹,³,¹¹,¹²*
EVALUATION OF COGNITIVE IMPAIRMENT IN PATIENTS SUFFERING FROM MASTOCYTOSIS

Cognitive dysfunctions in mastocytosis

Memory impairment is a symptom associated with Mastocytosis

Memory impaired patients are no more depressed than patients without cognitive impairment.

unpaired t-test to compare depression scores of patients with and without cognitive impairment

Hypoperfusion of the anterior Cingulum antérieur in 10 patients with depression and mastocytosis Vs. 18 patients with Mastocytosis but not depressed

Hyperperfusion of central grey nuclei : 11 patients with cognitive impairment vs 33 controls

p<0.001
HYPOTHESIS

Tryptophane → Kynurenine → Serotonin (5-hydroxytryptamine) → Low serotonin → Depression ?

Histamine
Others
ASL abnormalities
Proteases

+ IDO

TNFα

Acid xanthurenic
Acid quinolenic

Neurotoxicity
Oxidative stress
apoptosis

Cognition (?)
TRYPTOPHAN METABOLISM IS ALTERED IN MASTOCYTOSIS AND CORRELATES WITH PERCEIVED STRESS AND DEPRESSION, DEMONSTRATING MAST CELLS' INVOLVEMENT IN INFLAMMATION PATHWAYS LINKED TO DEPRESSION.

Georgin Laviale, Moura D et al Mol Psychiatry, 2016
MAST CELL ACTIVATION DISEASE

Mast cell activation disease: An underappreciated cause of neurologic and psychiatric symptoms and diseases

Lawrence B. Afrin\textsuperscript{a}, Dieter Pöhlau\textsuperscript{b}, Martin Raithel\textsuperscript{c}, Britta Haenisch\textsuperscript{d,e}, Franz L. Dumoulin\textsuperscript{f}, Juergen Homann\textsuperscript{f}, Uwe M. Mauer\textsuperscript{g}, Sabrina Harzer\textsuperscript{h}, Gerhard J. Molderings\textsuperscript{h,*}
SIMPLIFIED PATHWAYS OF HUMAN MC DIFFERENTIATION

**Bone Marrow**

- Stem Cell
  - CD34+
  - SCF
  - IL-10
  - IL-6

**Circulation**

- Tissues
  - MC<sub>TC</sub>
  - IL-4
  - SCF
  - IL-4
  - ?

- MC<sub>C</sub>

**Survival:**
- SCF
- NGF
- IL-4
- IFN-γ

---

**MC<sub>T</sub>**

- CD34+
- c-kit high
- FcεRI neg
- CD13+
MASITINIB: SELECTIVE TYROSINE KINASE INHIBITOR, INHIBITING MAST CELL SURVIVAL, DEGRANULATION AND MIGRATION VIA C-KIT INHIBITION

**Summary of Inhibitory Effects of Masitinib**

<table>
<thead>
<tr>
<th>Target</th>
<th>IC&lt;sub&gt;50&lt;/sub&gt; [nM]</th>
<th>Kd [µM]</th>
</tr>
</thead>
<tbody>
<tr>
<td>KIT wild-type</td>
<td>200</td>
<td>0.008</td>
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<tr>
<td>FYN</td>
<td>240</td>
<td>0.14</td>
</tr>
<tr>
<td>LYN</td>
<td>225</td>
<td>0.061</td>
</tr>
<tr>
<td>PDGFR-alpha</td>
<td>50</td>
<td>0.025</td>
</tr>
<tr>
<td>PDGFR-beta</td>
<td>110</td>
<td>0.008</td>
</tr>
<tr>
<td>CSF1R</td>
<td>90</td>
<td>0.008</td>
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</table>

Dubreuil 2009, PLoS ONE.4(9):e7258; AB Science
MASITINIB DEMONSTRATED EFFICACY IN IMPROVING HANDICAPS ASSOCIATED WITH MASTOCYTOSIS

Phase 3 AB06006 – efficacy analysis - W8-W24 period

<table>
<thead>
<tr>
<th>Primary Analysis</th>
<th>4H75% Cumulative 75% response rate on the handicaps of pruritus or flushes or depression</th>
<th>mITT/MDF</th>
<th>Masitinib</th>
<th>Placebo</th>
<th>p-value</th>
<th>Odd ratio (CI95)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mITT/MDF</td>
<td>18.7%</td>
<td>7.4%</td>
<td>0.0076*</td>
<td>3.63</td>
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</table>

<table>
<thead>
<tr>
<th>Secondary Analyses</th>
<th>3H75% Cumulative 75% response rate on the handicaps of pruritus or flushes or depression</th>
<th>mITT/MDF</th>
<th>Masitinib</th>
<th>Placebo</th>
<th>p-value</th>
<th>Odd ratio (CI95)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mITT/MDF</td>
<td>24.7%</td>
<td>9.8%</td>
<td>0.0071</td>
<td>3.06</td>
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</table>

<table>
<thead>
<tr>
<th>Secondary Analyses</th>
<th>2H75% Cumulative 75% response rate on the handicaps of pruritus or flushes</th>
<th>mITT/MDF</th>
<th>Masitinib</th>
<th>Placebo</th>
<th>p-value</th>
<th>Odd ratio (CI95)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mITT/MDF</td>
<td>27.2%</td>
<td>10.7%</td>
<td>0.038</td>
<td>2.63</td>
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</tr>
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</table>

<table>
<thead>
<tr>
<th>Secondary Analyses</th>
<th>Pruritus 75% Cumulative 75% response rate on the handicaps of pruritus</th>
<th>mITT/MDF</th>
<th>Masitinib</th>
<th>Placebo</th>
<th>p-value</th>
<th>Odd ratio (CI95)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mITT/MDF</td>
<td>22.0%</td>
<td>7.3%</td>
<td>0.0322</td>
<td>3.13</td>
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<table>
<thead>
<tr>
<th>Secondary Analyses</th>
<th>Flush 75% Cumulative 75% response rate on the handicaps of flush</th>
<th>mITT/MDF</th>
<th>Masitinib</th>
<th>Placebo</th>
<th>p-value</th>
<th>Odd ratio (CI95)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mITT/MDF</td>
<td>39.9%</td>
<td>19.0%</td>
<td>NS</td>
<td>3.03</td>
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</table>

<table>
<thead>
<tr>
<th>Secondary Analyses</th>
<th>Depression (Hamilton 75%) Cumulative 75% response rate on the handicaps of depression</th>
<th>mITT/MDF</th>
<th>Masitinib</th>
<th>Placebo</th>
<th>p-value</th>
<th>Odd ratio (CI95)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mITT/MDF</td>
<td>18.6%</td>
<td>7.6%</td>
<td>NS</td>
<td>2.71</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Other supportive analyses</th>
<th>Fatigue (FIS 75%) Cumulative 75% response rate on the handicaps of fatigue</th>
<th>mITT/MDF</th>
<th>Masitinib</th>
<th>Placebo</th>
<th>p-value</th>
<th>Odd ratio (CI95)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mITT/MDF</td>
<td>7.7%</td>
<td>3.2%</td>
<td>&lt;5%</td>
<td>4.84</td>
<td></td>
</tr>
</tbody>
</table>

* With 10,000 rerandomization
MAST CELLS AND DISEASES

- Cancer
- Allergy
- Autoimmunity
- Mastocytosis
- Inflammation
- Fibrosis
- Neurological and Psychiatric Diseases
  - Acute
  - Chronic
  - Alloreactivity
BRAIN BLOOD PERFUSION: SIMILARITY MASTOCYTOSIS AND ALZHEIMER’S DISEASE

Representative images from a control patient (Fig. A&B), an AD patient (Fig. C), and a mastocytosis patient (Fig. D), illustrating the impaired cognitive functions.

Measurement of cerebral blood flow using arterial spin labeling MRI reveals similar hypoperfusion patterns between mastocytosis patients with impaired cognitive functions (memory and/or attention) and AD patients.

BRAIN BLOOD PERFUSION: SIMILARITY MASTOCYTOSIS AND ALZHEIMER’S DISEASE

Representative images from mastocytosis patient comparing ASL-MRI before masitinib treatment (A) and after 6 month treatment (B)

Preliminary evidence suggests that masitinib may be able to reverse hypoperfusion in mastocytosis patients, with a concomitant improvement in cognitive functions.
PUTATIVE MECHANISM OF ACTION OF MASITINIB IN ALZHEIMER’S DISEASE

Masitinib for the treatment of mild to moderate Alzheimer’s disease

ANIMAL MODEL (APPXPS1DE9): COGNITIVE EVALUATION IN A CURATIVE SETTING

- 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.

- Blinded study
IN VIVO PROOF OF CONCEPT FOR MASITINIB’S EFFECT ON COGNITIVE FUNCTION IN AD HAS BEEN ESTABLISHED VIA A MOUSE MODEL (APPXPS1DE9) INDICATING IMPROVED SPATIAL MEMORY IN A CURATIVE SETTING

MWM Acquisition phase

- Genotype effect observed between wild-type (WT) and APPxPS1dE9 (Tg) mice treated with vehicle (Veh)
- Disappearance of genotype effect on mice treated with masitinib
- Masitinib treatment improves cognitive function, with spatial memory returning to normal levels

B Delatour et al ICM Paris
IN VIVO PROOF OF CONCEPT FOR MASITINIB’S EFFECT ON COGNITIVE FUNCTION IN AD HAS BEEN ESTABLISHED VIA A MOUSE MODEL (APPxPS1DE9) INDICATING IMPROVED SPATIAL MEMORY IN A CURATIVE SETTING

Percentage of spatial response increased through training for all mice except the Tg Veh group.

Tg mice treated with masitinib showed significant improvement compared with controls (Veh).

<table>
<thead>
<tr>
<th>Group</th>
<th>p-value</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tg Veh vs. Tg M</td>
<td>0.034</td>
<td>Treatment effect</td>
</tr>
<tr>
<td>Tg Veh vs. WT Veh</td>
<td>&lt;0.001</td>
<td>Genotype effect</td>
</tr>
<tr>
<td>Tg M vs. WT M</td>
<td>0.038</td>
<td>Genotype effect</td>
</tr>
<tr>
<td>WT Veh vs. WT M</td>
<td>1</td>
<td>Negative control</td>
</tr>
</tbody>
</table>
**IN VIVO PROOF OF CONCEPT FOR MASITINIB’S EFFECT ON AMYLOID LOAD IN AD HAS BEEN ESTABLISHED VIA A MOUSE MODEL (APPXPS1DE9) INDICATING REDUCED HIPPOCAMPAL AMYLOID LOADS IN A PREVENTIVE SETTING (MICE AGED 4-6 MONTHS)**

Masitinib treatment decrease the amyloid charges (Congo red +) in the hippocampus of young APP/PS1dE9 mice.
PROOF OF CONCEPT CLINICAL STUDY

Efficacy results in mild-to-moderate Alzheimer's disease
(Phase 2; n=34 patients)

Masitinib generated efficacy in phase 2 on ADCS-ADL.
PROOF OF CONCEPT CLINICAL STUDY

**Efficacy results in mild-to-moderate Alzheimer's disease**  
*(Phase 2; n=34 patients)*

Masitinib generated efficacy in phase 2 on ADAS-Cog.

![Graph showing efficacy results](image)

Week 12
p=0.016

Week 24
p=0.030
PROOF OF CONCEPT CLINICAL STUDY

Efficacy results in mild-to-moderate Alzheimer's disease  
(Phase 2; n=34 patients)

Masitinib generated efficacy in phase 2 on MMSE.

Week 12  
Week 24  
p=0.047  
p=0.031

Mean change from baseline ± standard error

Week 0  
Week 12  
Week 24  

-5  
-4  
-3  
-2  
-1  
0  
1  
2

MMSE

Masitinib  
Placebo

worsening - improvement
ON GOING PHASE 3 DESIGN

**Study design**
- Patients with mild to moderate Alzheimer’s disease
- Blinded, placebo controlled
- 24 week treatment period
- 675 patients

**Selection of patients**
- Patient with
  - dementia of Alzheimer's type, according to DSM-IV criteria
  - probable Alzheimer' disease according to NINCDS-ADRDA criteria
  - MMSE ≥ 12 and ≤ 25 at baseline
  - minimum 6 month treatment at baseline with a stable dose of cholinesterase inhibitors and/or a stable dose of memantine

**Clinical Endpoints**
- Effect on ADCS-ADL from Week 8 to Week 24.
- Effect on ADAS-Cog from Week 8 to Week 24

**Dosing**
- 3 doses
  - 3 mg/kg/day masitinib
  - 4.5 mg/kg/day masitinib
  - 4.5 mg/kg/day with a switch to 6 mg/kg/day masitinib
ON GOING PHASE 3 PASSED FUTILITY TEST

❖ Efficacy : DSMB performed a futility analysis with efficacy data
  - Definition of futility test : test the inability of a clinical trial to achieve its efficacy objective
  - Test performed on ADCS-ADL and ADAS-Cog
  - Test performed after about one third of the patients were enrolled into the study and had reached the 24 week treatment duration period
  - IDMC statement : Study Not Futile

❖ Safety : Independent Data and Safety Monitoring Board (DSMB) reviews every 6 months the safety data
  - On this basis, and before the futility analysis, the IDMC always recommended the continuation of the study
CONTACT ALZHEIMER STUDY PHASE 3

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Katia Hansen

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UPMC
Institut de la Moelle et du Cerveau
Tengfei Li
Cécile Delarasse
Benoit Delatour

Alain Moussy
Laurent Guy
Colin Mansfield
MISATINIB FOR THE TREATMENT OF ALZHEIMER’S DISEASE: CLINICAL AND PRECLINICAL DATA

E-mail: ohermine@gmail.com

Cognitive dysfunction is a hallmark symptom of Alzheimer’s disease (AD). Mastocytosis (MCO), a mast cell (MC) related disease, is also associated with
cognitive impairment. Around 40% of MCO patients (pts) present with impaired cognitive functions (memory and/or attention). We performed morphological and functional MRI in pts with MCO. Arterial spin labeling (ASL) MRI revealed an abnormal pattern of hypoperfusion in the brain when compared with healthy subjects, which correlated also with loss of cognitive functions. This pattern was similar to that observed in AD. In an open study, a few pts with MCO showed an improved blood flow in the brain that correlated with an increase in cognitive abilities following treatment with masitinib. Masitinib is an inhibitor of tyrosine kinases including c-Kit and Lyn, two kinases that may participate in the abnormal accumulation and activation of MCs in MCO. Hence, masitinib may also be efficient in AD. Proof of concept for masitinib in AD has been established via in vivo preclinical studies, with preliminary 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. In a phase 2 study, masitinib showed a consistent improvement in primary (ADAS-cog) and secondary (ADCS-ADLMMSE) endpoints. Although the mechanism of masitinib in AD is expected to be multi-faceted (e.g. through its dual actions as an inhibitor of the MC-glia axis and of Fyn kinase activity in the context of AD pathology) it is hypothesized that one plausible mechanism of action is its ability to maintain or reinforce the integrity of the blood brain barrier (BBB) via inhibition of MC function: reducing the accumulation of blood-borne Aβ peptides in the brain and pool of circulating pro-inflammatory mediators. These ALS-MRI data in MCO pts with cognitive impairment corroborate this hypothesis, demonstrating its pharmacological activity as a modulator of BBB permeability. Clinical development of masitinib in AD will be presented including details of the ongoing phase 3 trial, study futility analyses, additional preclinical data and mechanistic considerations.

Keywords: Alzheimer therapy, Blood brain barrier (BBB), Masitinib, Mast cells, Mastocytosis, Tyrosine kinase inhibitor